David W. Hollar

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ISBN 978-3-319-59625-9 e-ISBN 978-3-319-59626-6
https://doi.org/10.1007/978-3-319-59626-6

Library of Congress Control Number: 2017944366

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

For our daughter, Brooke Hollar, future clinician, courageous follower of Christ, and leader by example.

Preface

The objective of this book is to introduce health researchers, epidemiologists, health policy makers, and clinicians to Trajectory Analysis , a term that I use to refer to the nonlinear analysis of processes. This science was developed by a number of scientists, most notably the French mathematician Henri Poincare and the Russian mathematician Aleksandr Lyapunov during the late 1800s. During the twentieth century, the science gained traction in the physical sciences with the development of quantum mechanics and mathematical descriptions of fluid mechanics , further applied during the latter part of the century to Chaos Theory and the analysis of defects in nanoparticles and crystals.

Trajectory Analysis relies heavily on the measurement of continuous change, which is measured using differential equations, although phase transitions across critical transition points are generally non-integrable. I have kept the mathematics to a minimum, but several central equations and rough derivations are provided to demonstrate importance and applicability to health research. Health research and epidemiology currently enjoys many powerful statistical tools, but few address process and change, to which I constantly refer to Rene Thom's work on Catastrophe Theory , where he emphasized the topology of patterns, processes, and change and criticized statistical analyses that involved "clouds of points." Health research also suffers from the lack of consistent, longitudinal data on the physiology and behaviors of people as well as the endless variables that impact health.

Most importantly, I stress a systems perspective on change, process, and analysis, and particularly using these tools to effect positive health change. Chapter 1 provides an overview of the physical principles and universality of nonlinear dynamics in health and our environment. Chapter 2 represents a needs assessment of health research, particularly the need for comprehensive, multiple variable, and longitudinal analyses to demonstrate long-term health care conditions, contributing variables, and ultimate outcomes. Decision-making models are emphasized, along with an introduction to Thom's Catastrophe Theory and Ilya Prigogine's work on non-reversibility in changing systems. Chapter 3 addresses the major problem in health research, recidivism , and introduces the nonlinear approaches to countering this recurring issue for health interventions.

Chapter 4 provides a very general overview of epidemiological methods. I refer the reader to the several cited excellent references and textbooks for more comprehensive discussions of these methods. Nevertheless, Chap. 5 provides an introduction to two valuable statistical methods, structural equation models and hierarchical linear models , and it discusses the importance of Sewall Wright's pioneering work on path coefficients and the role of direct and indirect variable effects/associations in multiple variable statistical regression analyses leading up to these modeling approaches.

Chapter 6 provides a more detailed discussion of the problems involved in processes and trajectories, focusing on Prigogine's research contributions. Chapter 7 illustrates the importance of energy potentials in all living processes and in the necessary transitions to better health. Chapter 8 diverges somewhat but illustrates a different viewpoint on probability : negative probability and the role of both actions and non-actions among variables in a process. Along these lines, I present chaos theory , the systems perspective , ecological examples, and Poincare's return maps and " sensitive dependence on initial conditions" in Chaps. 9 and 10 .

Continuing from Chap. 10 , I introduce topological aspects of Trajectory Analysis by considering health behaviors as processes that operate on physical as well as conceptual surfaces as they evolve over time. Chapter 12 derives the important Jacobian matrix and its characteristic roots , the Lyapunov exponents , that directly measure trajectory changes. Connected with these equations, Chap. 13 describes phase transitions that are necessary for physiological and health behavior change, using the physical principle of the Rankine-Hugoniot Jump conditions .

Chapter 14 provides applied examples of nonlinear dynamics for cardiology and neuroscience interventions, although many of the latter primarily involve animal models. Chapter 15 represents another divergence but illustrates again the universality and intricacies of nonlinear causes and effects across large time scales that ultimately contributed to our current existence and health scenarios.

Chapter 16 illustrates straightforward computations and simulations of nonlinear trajectory changes using Wilensky's freeware NetLogo , an Agent-Based Modeling platform. Finally, Chap. 17 pulls everything together with perspectives and eight central principles of Trajectory Analysis that apply directly to health care.

I use many non-health references from diverse scientific disciplines to support the described methods and theory, so be prepared for somewhat of a wild ride. Nevertheless, I trust that these sources will be informative and illuminating, and that you will freely explore these fascinating works. There are many other excellent sources that unfortunately had to be omitted for purposes of brevity and clarity. This is a rich subject area with so many possibilities for advancing health research.

David W. Hollar
Morrisville, NC, USA
January 27, 2017

Acknowledgments

I thank my wife, Paige, and daughter, Brooke, for their tremendous support during the writing of this book. For Brooke, it was a true team effort in extraordinary ways! I also thank Virginia Dean and my good colleagues Dr. Barnett Parker, Dr. Nur Onvural, and Dr. Jennifer Rowland. I also thank my many colleagues with Pfeiffer University and the Billy Graham Evangelistic Association. The journey in writing this work was seeded by a March 1989 National Science Foundation Chautauqua short course on Cellular Automata taught by Professor Max Dresden at SUNY-Stony Brook. It was further motivated during my doctoral coursework under the supervision of Professors Bert Goldman, John Hattie, Mary Olson, Sam Miller, and Jim Lancaster at the University of North Carolina—Greensboro and through later interdisciplinary research in Disability and Children's Genetics at Wright State University and the University of Tennessee. I thank Janet Kim, Acquisitions Editor at Springer, for encouraging this project. I thank Paramasivam Vijay Shanker for manuscript styling and proofing. In all good things, we give thanks to God.

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is an Associate Professor of Health Administration at Pfeiffer University. He received his Ph.D. in Curriculum and Teaching from the University of North Carolina at Greensboro, where he was awarded the graduate school's Outstanding Dissertation Award. He has B.S. and M.S. degrees in Biology. He successfully completed postdoctoral research in community health at the NIDILRR-funded Rehabilitation Research and Training Center on Substance Abuse and Employment at Wright State University in Dayton, Ohio. In 2004, he wrote and supervised a University of Tennessee $2 million AHRQ grant-funded project to develop electronic health records for children with genetic or metabolic conditions. He also has a Graduate Certificate in Public Health Entrepreneurship. His specialties include multivariate statistics, structural equation models, mathematical models, disability policy, and decision-making. He has numerous peer-reviewed publications on health risk factors, allostatic load, behavioral genetics, and disability policy, along with presentations at numerous national conferences. He edited and coauthored the *Handbook of Children with Special Health Care Needs* and *Epigenetics, the Environment, and Children's Health Across Lifespans* , both published by Springer in 2012 and 2016, respectively. He serves on the editorial board of the *Maternal and Child Health Journal* , he is a member of the American Public Health Association and the American Association on Health and Disability, and he volunteers with the Billy Graham Evangelistic Association Rapid Response Team. He and wife Paige have one daughter and they are members of Collide Church.

David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_1

1. Introduction: The Universality of Physical Principles in the Analysis of Health and Disease

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All events in the universe involve energy potential differences. Whether it is the flow of light photons and other electromagnetic energy from the sun through the solar system, a lightning bolt, the bioenergetic proton motive force across the dynamic mitochondrial inner membranes within our cells, or interactions between individuals, energy potential differences drive the creation of order. This phenomenon exists in all health conditions, good and bad, even though it is rarely recognized. This failure too often comes from the rigid silos of academic hubris even when there is considerable consilience between all areas of knowledge. In this volume, we explore these applications for epidemiology and health care.

This phenomenon of energy potentials across all aspects of living and nonliving systems at many orders of magnitude merits its place not as an anomaly but as a basic physical principle. In their book on scale invariance in phase transitions , Lesne and Laguës (2012) cited Pierre Curie's 1895 doctoral thesis, in which Curie keenly observed that, comparing the magnetic state of a metal to the density of an ordinary fluid, the intensity of magnetization I is proportional to density D, and magnetic field strength H is proportional to pressure P:

$$f(I,H,T) \propto f(D,P,T) \tag{1.1}$$

While this relationship remains poorly explained, scientists such as Rene Thom (1972) attempted to understand similarity in patterns across seemingly unrelated processes: a topology of reality. Such similarities rely strongly on basic physical processes that operate on multiple levels. Furthermore, whereas such processes can be measured with high precision in molecules, cells, and tissues, they are far more difficult to evaluate in thinking beings and in dynamic, complex social systems.

Nevertheless, we have identified several physical principles that can be applied to

disease, epidemiology , public health , and health behaviors . These principles include the use of return maps to previous time-dependent phenomena, measured using Lyapunov exponents and other entropy -related mathematical tools, the uses of negative probabilities in terms of linked events, and a strong emphasis on longitudinal , continuous processes and monitoring of these events in real time. The latter point is critical, as too many epidemiological studies rely on arbitrary classifications, often for research convenience, as well as lack of clarity on cause-and-effect relationships for associated variables, not necessarily time sequence independent and subsequent dependent variables as should be practiced.

Furthermore, behaviors and physiological processes are cyclical phenomenon, being driven by multiple interacting cycles (e.g., Manfred Eigen and Peter Schuster's (1979) Hypercycle model), daily Circadian rhythms associated with melatonin and other hormonal levels, lunar cycles, and multiple levels of solar cycles. We even see transgenerational epigenetic effects such as Marcus Pembrey's group (Pembrey et al., 2006) discovery that individual morbidity and mortality correlates with same sex grandparental pre-pubertal nutrition . All of these relations bring into play another basic physical phenomenon: resonance effects of one system upon another.

Morbidity and aberrant behaviors often result from disturbances to such cycles and resonances . The cyclical beating of the heart, with its characteristic pause then PQRST wave electrical pattern in association with the sinoatrial and atrioventricular nodes for precision timing of ventricular contractions, is one prominent example of obvious health research, given that so many factors can disturb this rhythm and lead to a cascade of effects throughout the body. The heart further is influenced by the actions of sympathetic and parasympathetic nerves with their stress-related and regulatory electrical activity from the central nervous system and its interface with both internal and external environments. The central nervous system itself represents a further cyclic phenomenon with its electrical activity based upon ion exchange across axons , dendrites, and neurotransmitter/hormonal releases across trillions and neural synapses and hundreds of thousands of neuromuscular junctions. Resonances within these physiological systems with light, ultimately solar/earth rotation-driven Circadian rhythms occur in cyclic processes from the molecular and cellular levels to multi-organ physiological systems .

On a planetary scale, the Jovian moons Io , Europa , and Ganymede exhibit a 1:2:4 Laplace-Lagrange orbital resonance such that tidal forcing of Io's crust between the moons and Jupiter creates substantial volcanic activity on Io. The earth's moon exhibits a 1:1 rotational: orbital resonance such that one hemisphere always faces earth (Zeebe, 2015) , with less traumatic tidal forcing on the oceans. The planets Mercury and Jupiter exhibit a secular eccentricity resonance (Batygin and Laughlin, 2008) that could affect the inner solar system stability . Consequently, basic physical principles of resonance operate at both biological and planetary scales.

The task for the health researcher is to identify and apply these phenomena in

measurements and models of human behavior and health conditions. Some conditions will require maintenance or restoration (e.g., phase resetting arrhythmias) of a resonance pattern, whereas other conditions might warrant the disruption of undesired patterns. Thom (1972) stressed the importance of pattern identification in data and the topology of complex systems, in the process identifying seven elementary catastrophes. He studied these catastrophes both from the perspective of system collapse but also from the potentiality for the emergence of order, the latter point demonstrated with his models for morphological development of organisms. Most importantly, the topic of system stability emerges from elementary catastrophes, as well as the concept of processes as topological surfaces or manifolds .

Healthy People 2010 and 2020 Goals for the American population (National Center for Health Statistics, 2012; U.S. Department of Health and Human Services, 2010) outline a variety of measured outcomes (e.g., cardiovascular, disability, exercise , and nutrition) that are assessed using national databases (e.g., National Health and Nutrition Examination Survey). These approaches have a longitudinal focus, but they have few multiple data points on each variable. Besides the Baltimore Longitudinal Study on Aging, Gallacher and Hofer (2011) called for greater use of large, longitudinal data sources to study aging across populations . Ben-Shlomo and Kuh (2002) earlier had advocated more realistic and complex conceptual model epidemiological testing of multiple variables to more accurately measure the life course of chronic conditions, an approach that would incorporate expertise from diverse academic disciplines. Nesse and Stearns (2008) suggested applications of evolutionary theory to public health studies and interventions, and Luke and Harris (2007) promoted the use of network analysis to study the intricate relationships of many variables in public health research.

The Healthy People goals for the nation are highly important to reduce occurrence of new diseases and conditions as well as to reduce the prevalence of already existing conditions, disease, and disability that affect much of the population to varying degrees. As a composite for the entire nation, the goals do not necessarily address substantial geographic variations across multiple demographic groups that are continuously changing. Furthermore, the goals may be limited by our current knowledge and attitudes on health conditions, where we do not fully see all of the many variables that may be involved in the epidemiological cause-and-effect measures for these conditions. A commonly used analogy is the iceberg model, where most of the iceberg (i.e., problems) is underwater and unseen. Sometimes, contributing factors that impact a problem might be beyond current scientific approaches, might exist only in theory, or could be missed due to one’s lack of awareness, training, or consideration during analysis. Innovation and systems thinking are important aspects of studying health problems. Decision making must be comprehensive, systems-oriented, based on scientific evidence, while willing to entertain novel perspectives that run counter to established viewpoints.

Therefore, we seek to energize public health research and epidemiology with basic

principles from the natural and physical sciences, principles that have wide ranging applications beyond single disciplines to the complexity of living systems, health, physiology , and behavior . The injection of novel approaches to health research has been marginal, but its importance is necessary given the need for innovation and entrepreneurship following decades of progress in some health areas but simultaneous lingering weaknesses in certain areas, particularly health behaviors, the obesity epidemic, birth defects, substance abuse, continued major killers such as cancer , heart disease, and violence , the re-emergence of bacterial diseases now with antibiotic resistance, and the failure to find a single cure for any viral disease.

Epidemiological methodology shares many commonalities with similar approaches in the biological, physical, and educational research sciences, and similar research problems exist across these disciplines. For instance, the rigor of research studies has been called into question across many disciplines (Ioannidis, 2005). Therefore, the public health researcher needs to focus on appropriate research design, avoiding shortcuts at the expense of rigor, and using the most suitable methodology to attack a given problem. Many researchers are versed in specific methodologies, but one must expand their research horizons to apply the best methodology that will analyze the data and validly test the correct research questions or hypotheses. Too often, researchers quickly assemble a set of variables to measure, find a small convenience sample, perform a quick pretest , brief intervention, and posttest , ignore any follow-up data collection months later to see if the intervention effect persisted, then pass the data along to a statistician to determine what the research questions should have been and if/how the analysis can be performed. This is a recipe for disaster, but somehow such studies receive grant funding and are actually published. What is even more annoying are “health outcomes” studies that measure training interventions but never address actual outcomes for the recipients of health services, or where the study shows significant relationships between health variables without any mention for how the findings could be applied to help people. There also exists an ever-growing tendency for extraneous agendas to merge with public health research despite limited evidence of causal connections/associations.

Our approach here seeks to demonstrate not only the application of physical principles to health research, but most importantly the need for consilience across the sciences (Wilson, 1998), the utilization of the entrepreneurial strategy of benchmarking across disciplines to gain competitive edge, and to illustrate the logic and ease of taking a few extra steps to generate a powerful research concept and study instead of mediocre research whose only goal is to get published and secure a promotion (Gold, 1975). With respect to the energetic potentials central to all life processes that are mentioned above and will be stressed later in this book, there is a tendency for researchers to become too focused on one area without respecting the applicability of diverse scientific areas to the problem. For instance, organic chemistry and biochemistry are required courses for

many professional academic programs, most notably medical schools, although they are seen as measures of academic achievement that never will be used instead of powerful tools (e.g., biochemical pathways such as the Krebs cycle) that have direct clinical applications. Such nonsense illustrates the lack of innovation and interdisciplinary thought that is needed to advance the health of people everywhere, Healthy People goals not only for Americans but worldwide. Yes, we do need to understand cellular respiration and biochemical pathways, not only because these processes drive all life on earth but because they have genuine, powerful applications in medicine and general health care. For a physician facing a newborn infant with a newborn screening profile of presumptive classical galactosemia, knowing the biochemical pathways makes the difference between life and death for that infant.

Along similar lines to Gold (1975) and Wilson (1998), the theologian and philosopher Francis Schaeffer argued the historical break with a higher purpose from the natural world at the beginning of the Renaissance, countered for only a time by the Reformation. Both of these events in Western Civilization led to tremendous advances in science, technology, and all aspects of society, although Schaeffer (1976) argued that the preeminence of the Renaissance led to overall cultural decline and loss of meaning. Science has a major role to play in society, even from the Reformative perspective, just that it has failed to deliver beyond materialistic objectives and has devolved into separate disciplines that rarely collaborate despite occasional superficial attempts. Our approach to Trajectory Analysis , with an emphasis on the universality of basic principles, resonance , and order emerging from chaos , is to demonstrate new applications across disciplines into health care that provide meaning and improved understanding of biological and behavioral processes. Joseph Fourier, in his 1878 introduction to *The Analytical Theory of Heat*, stated that mathematics "…attest the unity and simplicity of the plan of the universe, and to make still more evident that unchangeable order which presides over all natural causes" (Fourier, 2009; also cited in Bhatia, 2005, p. 116).

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_2

2. Longitudinal and Nonlinear Dynamics "Trajectory" Analysis in Health Care: Opportunities and Necessity

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Abbreviations

E_{Pl} Planck energy

$f(x(t))$ Function of variable x at time t

I_{Pl} Planck length

RNA Ribonucleic acid

ROC Receiver operator characteristic curve

Twentieth century science provided explosive discoveries that transformed societies and improved the lives of many people across the planet. The discoveries of antibiotics, vaccines, nutrient-fortified foods, and public health monitoring and outreach across the globe, coupled with technological breakthroughs from the space programs that were distributed into the public sphere transformed the planet. Tens of millions of lives were saved and hundreds of millions were lifted out of poverty, despite the fact that tens of millions died in the world wars and through totalitarian oppression. The sciences reached every aspect of human life, mostly in a positive way, although mistakes and lack of adequate research or product oversight did produce some negatives. In recent years, the development of antibiotic-resistant bacteria and the continuing elusiveness of many viruses to treatment have somewhat slowed the process of medication discovery, although new technologies offer potential new breakthroughs (Lewis, 2012; Novoselov et al., 2012; Tao et al., 2008).

Trajectory analysis in health care involves the mapping of sequences of events and

multiple variables contributing to health outcomes for individuals. As such, the term "trajectory" is used in a stochastic, approximate sense, because we can never perfectly predict the future for any process. Watching a cardinal fly from one tree to another, we can map the approximate path, but we cannot predict the slight shifts in the flight path, from a shifting breeze to the bird's sudden interest in a worm spotted on the ground below, or a predator near the target tree. Even more so, we cannot monitor changes in the bird's heart rate, mental status, eyesight, or basic cellular processes to high precision.

Nobel physicist Ilya Prigogine (1982) discussed Einstein's dissatisfaction with the "arrow of time , arguing that irreversible processes (i.e., directional time) are consistent not only with the macroscopic classical physics of observable reality but also with microscopic quantum physics at dimensions smaller than the Planck length ($l_{Pl} = 1.62 \times 10^{-33}$ cm) or energy ($E_{Pl} = 1.22 \times 10^{19}$ Giga electron volts). Prigogine's (1982, p. 48) primary point is that, contrary to high entropy equilibrium systems where "structures are destroyed" and "systems are immune to perturbation ," unstable "far from equilibrium " systems, particularly living systems, can become stable or unstable, generating structures for the former situation, in response to disturbances . Probability , entropy , and energy are central throughout these events. In conjunction with these observations, human aging researcher Leonard Hayflick (2007, p. 2353) identified six principles of aging that have no disease parallel:

1. Aging occurs in multicellular animals that stop growth at maturity.

2. Aging is similar across species.

3. Aging begins following reproductive maturation.

4. Aging occurs in all domesticated animals that previously never lived long enough to age in the wild.

5. Aging occurs in all matter, living and nonliving.

6. Aging always involves "thermodynamic instability " of molecules.

Human health from conception through old age follows a relatively "predictable" trajectory for overall populations that receive similar levels of health care and socioeconomic conditions, albeit there are invariably major events that might shorten, lengthen, or complicate individual pathways along this trajectory. As Prigogine

emphasized, each of us represents a system that experiences various events/disturbances , each having a certain probability of occurrence, and systems within systems of the body react in different ways to these disturbances . In general, the human body is highly resilient, more so up until Hayflick's first and third principles of aging beginning at the cessation of growth (i.e., distinguished from tissue replacement), then declining irreversibly with the arrow of time . Additionally consistent with Prigogine, Hayflick's fifth and sixth principles illustrate the role of probability, entropy , and energy in human aging as well as disruptions to health (i.e., illness) across the lifespan. Every person endlessly confronts physical, psychological, and environmental insults that leave an epigenetic footprint on our genome, indirectly or directly, that is unique for each of us (Hollar, 2016a, 2016b; Pembrey et al., 2006).

2.1 Background

Even with the many advances in science, medicine, and health during the past century, most fields from business to health lag behind in the research and evaluation of complex systems to establish true cause and effect. For example, the sequencing of the human genome was heralded as a major breakthrough, although this achievement was only a tenuous first step. The next stage is far more daunting: trying to decipher the incredibly complicated ways and in what situations genes are transcribed, messenger RNA is modified and translated, and then how proteins interact with each other, various other molecules, and changing cellular and intercellular conditions. We have come a long way since Francois Jacob and Jacques Monod's discovery of the lactose operon regulatory system in the bacterium Escherichia coli, but we have much further to go to understand complex epigenetic controls of gene expression and biochemical pathways. One should visit the ever-growing gene expression pathway depositories located at the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov), the online Mendelian Inheritance in Man (http://www.omim.org; also linked to NCBI), or summaries at any major biotechnology company to understand the staggering array of potential molecular interactions within the cells of living organisms.

There is much discussion of personalized genomic medicine, but little has been put into actual clinical practice. The overwhelming public health and clinical research literature continues to focus on brief interventional studies with a snapshot in time of a narrow list of variables, often focusing only on arbitrary demographic categories that fail to address the complexity of unique individuals, their genetic and epigenetic backgrounds, and their lifelong social and environmental experiences/exposures. What is further left out of these studies are critical moments, events, or psychological/physiological thresholds that re-directed people into specific directions. I often hear clinicians state that we need less telemetry data. Actually, we need more so that we can better understand critical cause-and-effect events. Certainly, we already are

inundated with exponentially increasing data that overwhelms server capacities and creates the desire for less.

Over 50 years ago, Nobel laureate Nikolaas Tinbergen cited this need for responsible, comprehensive data collection without becoming deluged with irrelevant details. Tinbergen (1963, p. 412) stated, “Description is never, can never be, random; it is in fact highly selective, and selection is made with reference to the problems, hypotheses, and methods the investigator has in mind;” and “the variety of behaviours in the animal kingdom is so vast…that selectiveness of description will become increasingly urgent.”

What we need is smarter collection, storage, and analysis of multiple variable and many time points for individual and group studies, along with training and employment of highly skilled analytics professionals to examine the data patterns and who will be recognized for their value to improved health care. With respect to the latter point, we are calling for analytics as a new profession. This includes the ability to translate the data into actual use for other health professionals and clinicians to help the people whom they serve. Mandl et al. (2014) have questioned the usable information: cost ratio of electronic medical records, which are extremely expensive but which the authors argue could be made user-friendlier for improved patient outcomes.

Consequently, there is a clear need for longitudinal data analysis to improve health care. Likewise, researchers and practitioners need to understand that there usually are no simple relationships or that any given association between variables is linear in nature. Complexity and dynamics are the major terms that we must keep in mind as we move forward with in-depth studies of behavioral , metabolic, and clinical data.

2.2 Necessary and Sufficient Conditions

Longitudinal analysis clearly involves the collection of similar data at baseline and many subsequent temporal points. Along similar lines, independent variables must precede dependent variables for a true cause-and-effect assessment. All relevant variables must be included in the longitudinal model in order to support or refute current theory. Simplistic models rely on readily available data, a situation that exists with the preponderance of secondary data analyses of existing data sources, as these sources almost never include all relevant variables, given that their purpose was for some other study. As a result, researchers and dissertation students often go to secondary data sources, often out of necessity due to lack of funding or time, to test research questions.

The concept of necessary and sufficient conditions (Rothman & Greenland, 1998) is relevant in epidemiological research because one’s theoretical model should maximize the number of relevant variables that are tested. A variable is necessary if it is required to contribute to a given condition or outcome, although it might not directly be the

"cause" of the condition or outcome. A variable that is sufficient by itself to cause the outcome is termed accordingly. The researcher should attempt to include all variables that are both necessary and sufficient to explain the dependent variable.

Due to convenience samples and data availability, researchers and practitioners can commit fallacies in their interpretation of cause-and-effect relationships. A fallacy is an error in argumentation, often a statement that sounds logical but contains an inconsistency that leaves open a mistake in drawing conclusions. Too often, individuals accuse someone with whom they disagree of committing a fallacy because they are "wrong;" unfortunately, being incorrect is not a fallacy, but the accusation thereof is a fallacy termed an Ad Hominem. Examples of fallacies were extensively documented by Aristotle in his *Prior Analytics* and other works; more recent examples of fallacies in health care that can contribute to medical errors have been documented by Croskerry (2003) and Redelmeier (2005).

Daniel Kahneman (2002), through his previous extensive work with Amos Tversky (e.g., Tversky & Kahneman, 1974), demonstrated that most people engage in fallacies and poor decision-making practices, despite wide variations in individual educational and occupational levels. Specifically, Kahneman (2002) argued that humans cognitively are "wired" for rapid, low effort, associative, intuitive (Type 1) thinking when making decisions, making them more prone to make cognitive errors. This phenomenon occurs across all types of decision-making processes, and it is very applicable to the health researcher and health practitioners in research design as well as in the interpretation of research results. Besides avoiding fallacious reasoning , Kahneman (2002) stressed the need for greater reasoning (Type 2) thinking, which requires effort, rules, and greater mental networking.

Decision-making in the research process requires the combination of these methods to develop realistic models of processes that can be tested. Fallacious reasoning or attempts at quick studies with readily available data, but not the necessary and sufficient variables, lead to inaccurate models that might be significant but are failures when applied to interventions to help people.

Figure 2.1a illustrates a simple cause-and-effect model: A causes B. Such a model can be tested with a correlation coefficient or several inferential statistical methods if groups are compared. However, is variable A necessary and sufficient by itself? Are other variables involved? Could B precede A if the data are collected at the same time point? Is the researcher limiting the focus, thereby committing the fallacy of assuming the consequent (i.e., Post Hoc Ergo Propter Hoc—"After this variable, therefore because of this variable.")? It is obvious that numerous issues come into play during the research design. Internal threats to study validity include testing, instrumentation, selection of participants, and selection interactions (Gay, 1992). Many epidemiological studies test A–B relationships using odds or risk ratio analysis, and such studies examine the effects of each independent variable on the dependent variable separately;

this process unfortunately inflates the likelihood of statistical significance for each comparison. For ten independent variables, the Type 1 error rate, the probability of finding at least one significant comparison, balloons from the standard .05 level to $(1-0.95^{10}) = 0.40$! Besides using a Bonferroni correction in such studies, the researcher should consider examining multiple variables together in a multivariate regression analysis (see Chap. 4).

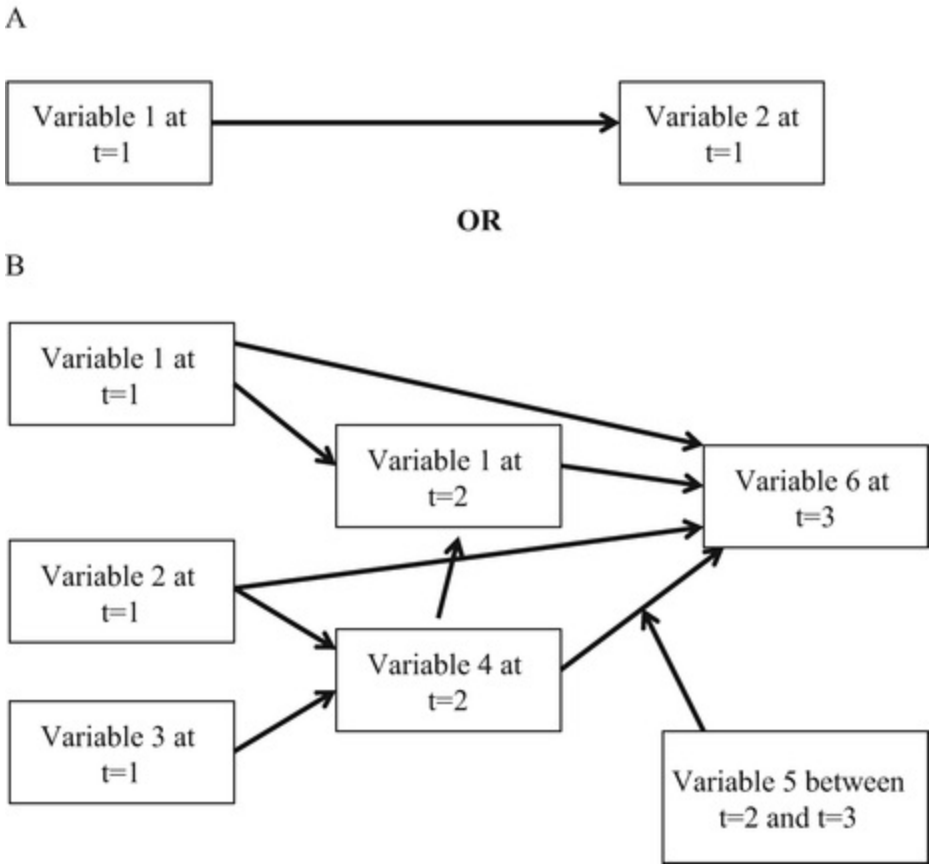

Fig. 2.1 "Causal" Pathways . Simple unrealistic models (snapshots at arbitrary times) versus temporal Necessary & Sufficient models. (**a**) Simple. (**b**) Less simple

Figure 2.1b shows a less simple model that better attempts to capture reality. We use the term "less simple" instead of "complex" because even our "less simple" model in all likelihood will not be fully measuring reality. In this more comprehensive model, there are multiple variables 1–5 that contribute directly and/or indirectly to the dependent variable 6, which is measured at a third data collection point. Variable 1 is measured at times 1 and 2, and variable 5 moderates the direct effect of variable 4 at time 2 onto variable 6 at time 3. Multiple variables and data collection points, based on theory and previous research, help the researcher to establish improved models of reality that can be tested.

2.3 Decision-Making in Longitudinal Research

Following Kahneman and Tversky's work , Swets, Dawes, and Monahan (2000a, 2000b) illustrated the usefulness of the basic statistical decision matrix (Table 2.1) to make improved decisions. The goal of sensitivity analysis is to match one's decision diagnostics as closely as possible to reality. In other words, the researcher wishes to use a predictive tool that is correct most if not all of the time. With this goal, the researcher and decision maker wishes to correctly state that something is true (or positive) when it really is true, therefore achieving a "True Positive." Likewise, one wants to correctly state that something is false (or negative) when it really is negative, thereby achieving a "True Negative."

Table 2.1 Sensitivity chart comparing reality versus evaluation/measurement (see Glass & Hopkins, 1984; Last, 2001; Swets et al., 2000a, 2000b)

		"Reality"	
Measurement or Perception of "Reality"		Positive	Negative
	Positive	True positive	False positive (type II error)
	Negative	False negative (type I error)	True negative (statistical power 1-β)

However, errors occur when one makes a false statement that does not match reality. Concluding that someone is lying to you when they really are telling the truth, or vice-versa, are examples of False Negatives and False Positives, respectively. As one can surmise, a good decision maker collects as much information as possible to try to maximize the True Positives and True Negatives. Nevertheless, many individuals engage in poor decision-making strategies by not engaging the Type 2 reasoning heuristics that Kahneman (2002) advocated or by falling for fallacious arguments/situations. Too many leaders have made disastrous decisions that impacted many people because they became too focused on a limited set of data or a specific theory despite strong alternative evidence contradicting their false beliefs. Some leaders even engage in hearsay evidence to drive research and policy, even when just a little homework can yield a better program to operate with dramatically improved results.

Clearly, strong decision-making skills are important in the design of longitudinal research activities, the ethical conduct of the research, and in the interpretation of the study results and analyses. It all begins with accurate information to drive the study and a willingness to collect the data at multiple data points, thereby obtaining a truer trajectory or pattern for how the measured phenomenon might be occurring, and testing this pattern against the prevailing scientific evidence and theories.

Swets et al. (2000a, 2000b) examined several clinical diagnostic examples to illustrate their points, including diagnostic tests for glaucoma and prostate cancer . What

they found was that no single test is optimal, for there will be individuals with high intraocular pressures who do not have glaucoma as well as individuals with low/normal intraocular pressures who do have this condition. Likewise, not all males who have a high Prostate Specific Antigen (PSA) test or enlarged prostate gland have prostate cancer, and conversely, there are males with prostate cancer who had normal PSA test results and/or normal prostate gland morphologies. Swets et al. (2000a, 2000b) concluded that for best results, researchers and clinicians should triangulate the results from multiple measurements, looking for consistencies before making the diagnostic decision. This makes perfect sense from reasoning heuristics if multiple, reliable, and valid measurement tools are available. When accurate and precise tools are not available, such as in interviews or psychological testing, decision-making becomes much more challenging.

Mathematically, sensitivity and specificity of decision tables are defined as follows (Dawes, 1988, 2000; Rothman & Greenland, 1998; Swets et al., 2000b):

$$\text{Sensitivity} = \text{true positives} / (\text{true positives} + \text{false negatives}) \tag{2.1}$$

$$\text{Specificity} = \text{true negatives} / (\text{true negatives} + \text{false positives}) \tag{2.2}$$

Sensitivity and specificity each have values from zero to 1.0. These two values for repeated tests of a diagnostic instrument are plotted against each other (Fig. 2.2) as part of Receiver Operator Characteristic (ROC) curve analysis , a validation technique developed by radar experts during the Second World War. The objective of ROC analysis for clinical diagnosis is to maximize sensitivity and specificity, thereby reducing the numbers of false positive and negative conditions. Examining Fig. 2.2, a poor test (diagonal) indicates decision-making that is no better than flipping a coin (50:50 probability). The steeper the curve, approaching 1.0 sensitivity for all values of (1—specificity), the better the decision-making tool.

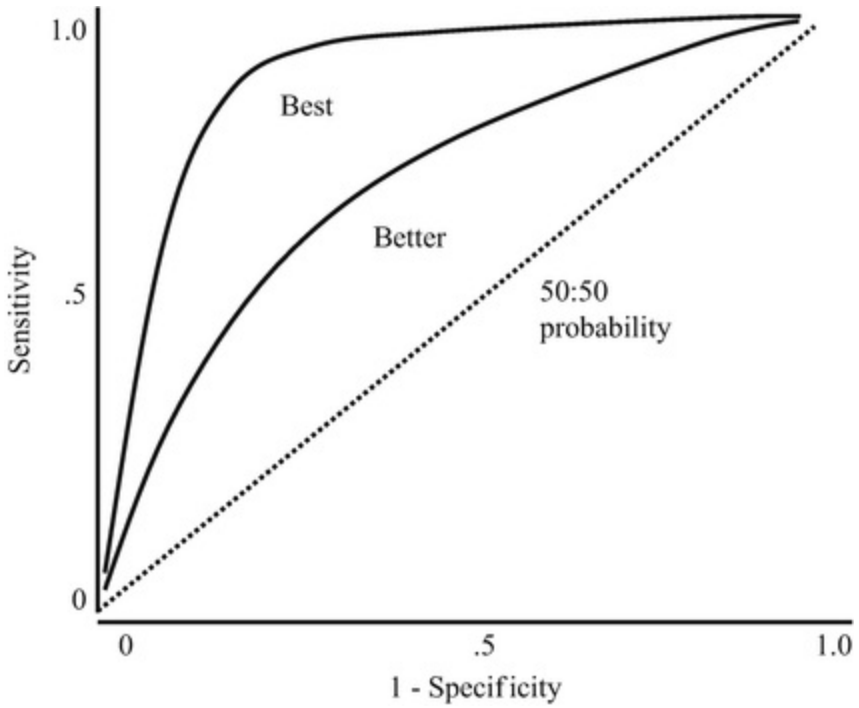

Fig. 2.2 Receiver Operator Characteristic (ROC) curves for sensitivity analysis. The steeper the curve, the better the diagnostic or other measurement tools used in the decision-making study. See Lalkhen and McCluskey (2008), Swets et al. (2000a, 2000b), and Wray, Yang, Goddard, and Visscher (2010) for further descriptions and specific applied examples

Longitudinal analysis requires considerable planning to make the study meaningful. This means using logical reasoning and accurate, precise data collection at all phases of the project, including extended measurement beyond the end of the study to assess the long-term effectiveness of interventions while controlling for extraneous variables. Sensitivity (ROC) analysis illustrates the importance of multiple measurement tools to corroborate each other.

2.4 Nonlinear Dynamics

In nonlinear dynamics, we measure the pathway of a system as a point located on a surface . The point changes over time and, therefore, can be represented by a vector. Each point on the surface represents a possible state of the system, and the vectors for all of these states constitute a vector field. “The collection of all possible states is called the phase space of the system” (Tufillaro, Abbott, & Reilly, 1992, p. 11). From an arrow of time directional perspective, the systems that we will consider are semi-deterministic because only the future state can be predicted from the present state. This approach does not necessarily preclude the interpretation of reversible deterministic events or systems (i.e., those that can predict the past and the future), which can occur in the chemical reactions of cells and even of major physiological processes. Our focus will follow Prigogine (1982) and Hayflick (2007) because the life course strictly is

directional and irreversible.

Henri Poincare first observed the nature of nonlinear dynamics in the observation of return maps that described processes (see Chap. 3). Analyses of vector fields on such maps require the use of ordinary differential equations. For a vector field of changing states of a system of points, Poincare identified four possible types of motion: (a) source (repeller), (b) sink (attractor), (c) saddle, and (d) limit cycle (Ruelle, 1989; Tufillaro et al., 1992). These four types of motion are possible if the system continues independent of time. Again, for our purposes, motion is time-dependent, so these four systems are modified somewhat, and we add a fifth outcome: (e) chaos (strange attractor). The five motions are shown in Fig. 2.3.

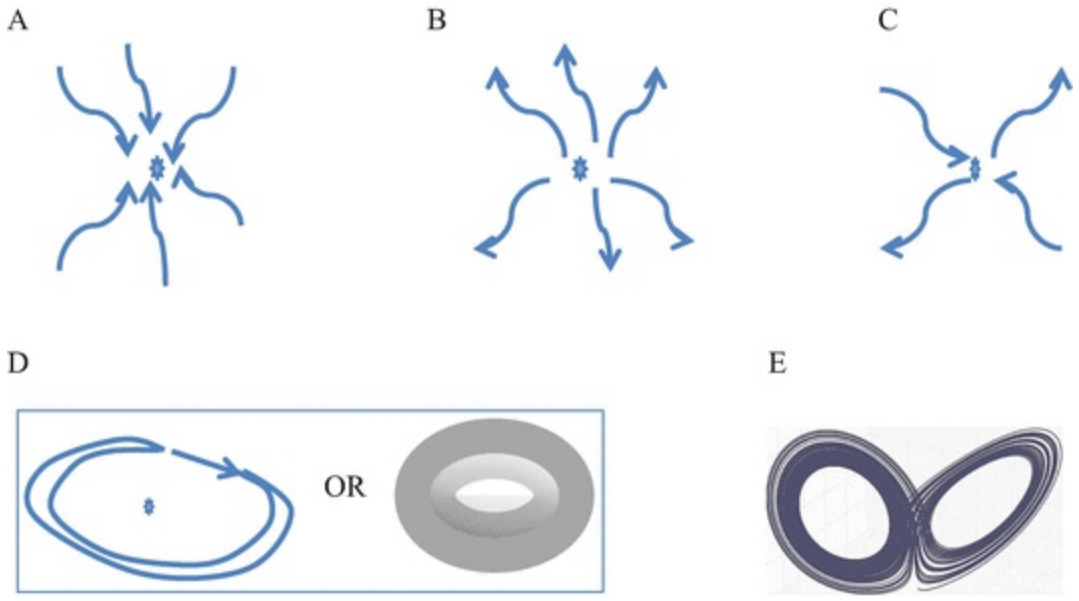

Fig. 2.3 Types of motion on a planar vector field. See Devaney and Keen (1989), Eigen and Schuster (1979), Glass and Mackey (1988), Ruelle (1989), Shaw (1981), and Tufillaro et al. (1992) for more discussion and examples. (**a**) Attractor . (**b**) Repeller . (**c**) Saddle. (**d**) Periodic Cycle. (**e**) Strange Attractor (Chaos)

What the five motions show are possibilities for the directional change in a given condition or behavior . A system may converge to a single point that is difficult to reverse. Conversely, the system might repel, a situation equally difficult to reverse. The system might alternate attracting and repelling in a saddle topography, depending upon the impact of independent variables acting upon the system. The system might orbit a given point, either periodically or quasiperiodically (e.g., multiple points of oscillation). Finally, the system might shift from point to point with no coherent pattern.

Ruelle (1989) demonstrated the evolution of a system using ordinary differential equations, following the form:

$$dx(t)/dt = f(x(t)) + \delta x(t) \tag{2.3}$$

where $\delta x(t)$ represents some type of correlating/resonating variable(s) that shifts the

system away from its normal trajectory $f(x(t))$. Ruelle (1989) demonstrated that differential resonance effects on hypothetical "identical" systems can yield drastically different trajectories, including chaotic motions (Fig. 2.4).

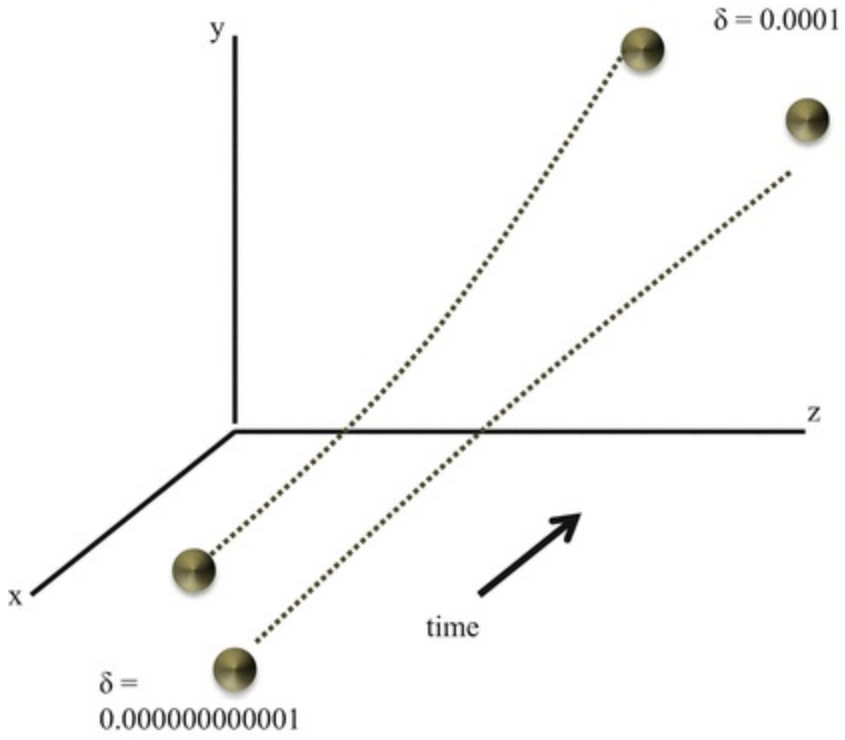

Fig. 2.4 Sensitive dependence on initial conditions. See Ruelle (1989, pp. 6–8) for another detailed example. Note the $\delta = 0.000000000001$ at the beginning of the divergence between the two trajectories

Petrosky and Prigogine (1993) demonstrated that eliminating resonance divergences in Large Poincare Systems (i.e., observable classical systems) yields chaotic motion. Specifically, they concluded that time symmetry is broken, yielding directional (present to future), irreversible processes, and that the systems are better explainable by statistical ensembles (i.e., probabilistic descriptions) instead of true trajectories. Their findings suggest that nonequilibrium systems, which would include living organisms, attain stability via dissipative processes driven by perturbations , although significant perturbations could send the behavior into chaos . Thus, systems have the potential to oscillate between states of stability, instability, and chaos depending upon driving forces (e.g., independent variables).

Along these same lines, Rene Thom (1972) defined an "ordinary catastrophe point" as a point y on a four-dimensional space $\mathbf{B} \times \mathbf{T}$ "if the intersection of the catastrophe set K and the ball $b_r(y)$ of center y and sufficiently small radius r has … a nonempty embedded semianalytic polyhedron without interior point…." (p. 42). Thom (1972) proceeded to classify seven elementary catastrophe s on manifolds M within four-dimensional space-time coordinates, most notably the parabolic and hyperbolic

umbilics, in which regional fluctuations about catastrophe points (i.e., region of catastrophe set K) lead to bifurcations as cusps that collapse the system to a lower energy , different and perhaps more stable state. These bifurcations can lead to changes of state such as the periodic, aperiodic , and chaotic behavioral trajectories shown in Fig. 2.3. Such systems likewise can be triggered by sensitive initial conditions (Fig. 2.4).

In his famous paper that delineated the sensitive dependence of initial conditions on weather systems, Lorenz (1963) discussed the forces involved in stability and instability, noting (p. 132) that systems define a "phase space Γ in which a unique trajectory passes through each point, and where the passage of time defines a continuous deformation of any region of Γ into another region." Lorenz (1963, p. 132) further stressed that "a trajectory $P(t)$ will be called stable at a point $P(t_1)$ if any other trajectory passing sufficiently close to $P(t_1)$ at time t_1 remains close to $P(t)$ as $t \rightarrow \infty$." Therefore, maintaining a stable trajectory can be extremely difficult given the many forces that influence any system. Nevertheless, biological systems employ multiple redundant systems such that they are extremely resilient for much of the lifespan until structural and functional collapses lead to system declines and vulnerability to pathogens. With this context, we can see that maintaining desirable phase states or stable spaces can be accomplished through facilitating forces and energies. At the same time, altering an undesirable but stable phase space may require a carefully timed perturbation to drive the system to a different stable state (see conditions in Fig. 2.3). Symmetry breaking (Petrosky & Prigogine, 1993) involves such phase shifting of resonance states.

Thom (1972, p. 134) concluded, "This competition of resonances has never been studied mathematically, even though it seems to be of the greatest importance." Thom 's model of resonance competition, similar to Lorenz' (1963) and Petrosky and Prigogine's (1993) models, is illustrated in Fig. 2.5. A system , represented by a ball, occupies varying levels of thermodynamic potential (e.g., hills and valleys). The natural tendency is for the system to descend to its lowest ground potential, or perhaps to reach a middle peak of intermediate stability . A supply of energy can maintain the system at a higher potential. If competing resonances exist, where two systems interact at different potentials, the interference can be destructive and release energy , with the systems coexisting or merging at a lower, stable energy potential.

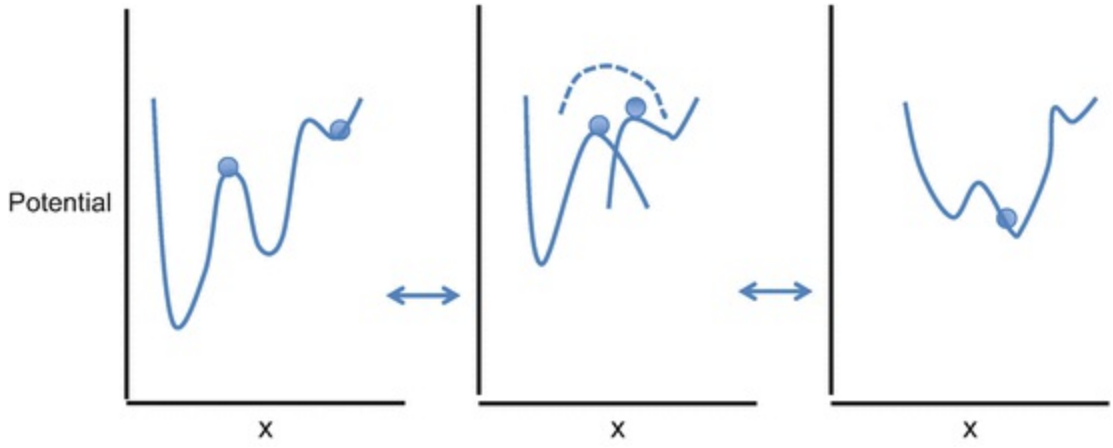

Fig. 2.5 Thom's (1972, pp. 60–64) concept of the competition of resonant states of the phase space such that the systems superimpose and "collide," leading to a shock burst of energy and relaxation to a stable, lower potential state

Ruelle extends this same concept with the shifting of trajectories on the phase space yielding a topological shift in the system. In his original model, increasing eccentricity of the sphere leads to decreased resolution between two initially adjacent points. An analogous three-dimensional deformation (Fig. 2.6) relates to Poincare's return map (Chap. 3) and to Lorenz' (1963) discussion of stability above. We will expand upon these concepts in subsequent chapters as we demonstrate the utility of these approaches in epidemiological analysis.

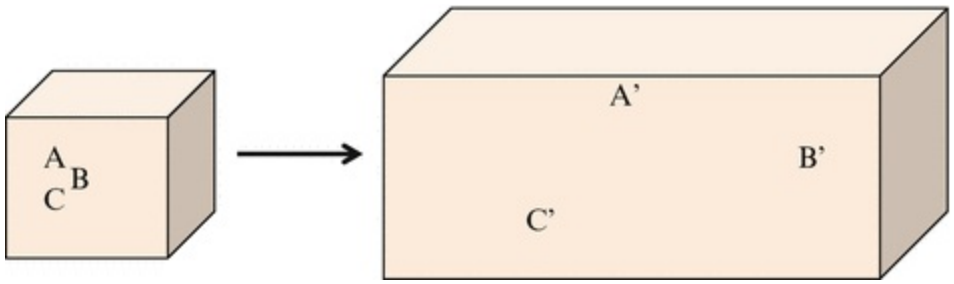

Fig. 2.6 Trajectory change as the deformation of a manifold by a disturbance such that initially adjacent points *A*, *B*, and *C* become stretched over time, losing resolution between the points as their phase states separate, and Poincare time-dependent trajectories move further apart from the initial state. See Ruelle (1989, pp. 72–73) for further discussion

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_3

3. The Problem of Recidivism in Healthcare Intervention Studies

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Abbreviations

ADL Activity of daily living

ATP Adenosine triphosphate

IADL Instrumental activity of daily living

ICF International Classification of Functioning, Disability and Health

PQRST Wave peaks and troughs of an electrocardiogram

R^2 Coefficient of variation

One of the major problems of preventative health programs and other health intervention programs is the problem of recidivism , where individuals and/or conditions return to their pretreatment levels. Often, this situation arises due to the lack of adherence to guidelines provided by clinicians and health educators during the treatment program, including lack of proper exercise , nutrition , and/or compliance with medications. More likely with conditions that are beyond behavioral control, pathologies and/or secondary conditions can occur/recur due to many unknown reasons, including random events and other conditions that are persistently occurring within the body. The growing biopsychosocial health research literature also shows that lack of family, friend, and peer social supports, one's environment, and the ability to be included in communities as well as participating in social activities can severely impact health outcomes, including the will to get well (Hollar, 2013; Hollar & Lewis, 2015; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Ryff, Love, & Levy-Storms, 2002). In fact, Seeman et al. (2001, 2002) demonstrated that people with fewer than three friends were at significantly increased risk for morbidity and mortality compared to people with

three or more friends. These findings follow Selye's (1950) description of the general adaptation syndrome to stress , which Seeman et al. (2001) termed "allostatic load ."

3.1 Periodic Behavior

For recurrence of conditions and/or actual behavioral recidivism , we invoke the resonance comparison again. A given system or behavior has a characteristic periodicity or wave-like behavior (Fig. 3.1a). The phenomenon repeats itself in a predictable fashion such that the researcher can reliably measure it at subsequent time points, at each measurement usually finding a characteristic amplitude and frequency for each occurrence. A heartbeat has a specific amplitude and frequency when shown on an electrocardiogram . The orbital resonance patterns of the inner Jovian satellites have characteristic frequencies as the inner satellites orbit faster and precess past the frequencies of the next outer satellites. Seasonal weather cycles are semi-periodic with overall patterns based upon solar and lunar driving of the upper atmosphere and jet stream, although specific regions may encounter varied patterns over time such that weekly weather remains only partially predictable. Disturbances reign in many systems so that most systems exhibit sensitive dependence on initial conditions (Ruelle, 1989). Some systems are much more resistant to disturbances than others.

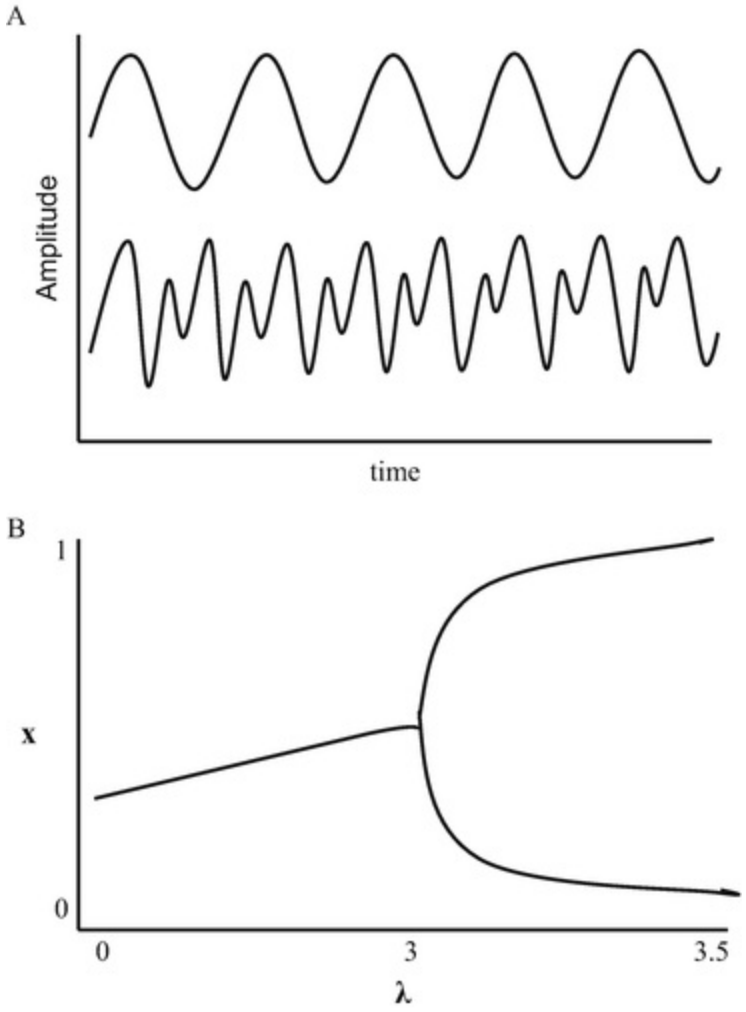

Fig. 3.1 Period 1 and Period 2 cycles (**a**); Bifurcation shift from period 1 to period 2 (**b**), with *x* indicating fixed points during a cycle, and λ indicating the Lyapunov number, which is positive for the expansion of the trajectory. See Glass and Mackey (1988) for examples

Human behaviors can be recurrent, such as wake/sleep cycles, eating patterns, and engagement in specific activities. Returning to Fig. 3.1a, cycles can be repetitive in a sinusoidal wavelike pattern, with predictable high and low points over time. Such periodic behaviors have a single spectral peak and can be broken down into harmonic frequencies, much like musical frequencies, by a mathematical process called Fourier analysis (Bracewell, 1986, 1989; Loy, 2006). Fourier analysis is available in many statistical and mathematical software programs, although it clearly requires repetitive, longitudinal data on participant behaviors or conditions over many time points.

Figure 3.1a illustrates two types of periodic behavior , a period 1 cycle with a single maximum amplitude and a period 2 cycle where there are two different behavior peaks that alternate and repeat again and again. The period 2 cycle could represent multiple related behaviors, or two different levels of the same behavior. What is most relevant to the complexity health researcher is the shift in behaviors from a period 1 cycle to a period 2 cycle, a bifurcation disturbance that is mapped in Fig. 3.1b. We will

explore the mathematics of bifurcations in Chaps. 7–12, but the primary point here is that disturbances can alter a system substantially and sometimes permanently. Obviously, some cyclic systems (e.g., heart wave patterns, brain wave patterns) should be maintained, so disturbances that disrupt and create abnormal rhythms should be studied so that they can be reversed or prevented. Alternatively, undesirable behaviors (e.g., substance abuse, various mental health conditions) potentially could be altered by bifurcation disturbances, perhaps to stable, healthy levels, if such procedures are ethical and do no harm to the patient. Consequently, Fig. 3.1 illustrates a central concept in trajectory analysis that we seek to map, understand, and perhaps regulate for improved health outcomes.

In a similar fashion , a Poincare Return Map (Fig. 3.2) illustrates a process that repeats over time, albeit altered slightly due to random noise or other disturbances to the system. The circle represents a surface , or manifold , perhaps a measuring device. The process occurs and returns near its starting point following a period of time. The difference in return points is subject to the pathway and a mathematical construct termed a Jacobian matrix (described in Chaps. 9 and 12). Clearly, orbits that return near the starting point are convergent and have little change in overall behaviors , whereas return points that are far away illustrate divergent behaviors. Again, the researcher is interested in the factors that keep desirable behaviors convergent, and those factors that cause undesirable behaviors to become divergent onto perhaps more stable pathways.

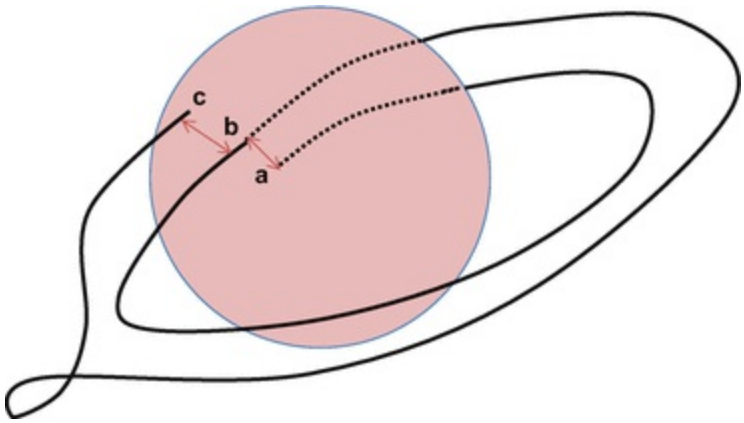

Fig. 3.2 Poincare Return Map , starting at point a on a manifoldmanifold, then cycling over time back to later equivalent point b, then a second "orbit" back to later equivalent point c, etc. See Devaney (1989, pp. 1–4) and Tufillaro, Abbott, and Reilly (1992, pp. 191–195) for further discussion

In health behavior interventions, recidivism or recurrent behaviors often occur following the removal of the treatment intervention. Examples of such recurrent behaviors include patients correctly following medications, especially antibiotics, individuals trying to lose weight, expectant mothers using tobacco products or alcohol during pregnancy, adolescents engaging in risk-taking behaviors, individuals attempting to stop smoking or using alcohol, individuals attempting to pursue exercise programs,

etc. In most cases, people fail to reach their objectives. Experimental studies of treatment or educational interventions often show improvements in people's health behaviors. Unfortunately, many such programs do not provide adequate follow-up evaluations to determine if there are long-term effects. The studies that do measure performance on follow-up usually find that individuals return to their bad habits in the absence of continued intervention supports. While no two individuals will necessarily respond in the same fashion to a treatment, whether pharmacological or behavioral/educational, many individuals require continued support to motivate their performance and will to succeed at improving their health. We know from biopsychosocial and stage of change models that social supports and the person's immediate environment have substantial impacts on healthy behaviors.

3.2 Stages of Change Models

Prochaska, DiClemente, and Norcross (1992) developed the transtheoretical model for motivating individual behavioral change (Fig. 3.3a). The model is designed to help public health and behavioral scientists to develop programs that change individual behaviors. The model begins with the standard epidemiological latent period, when a problem begins and persists, perhaps for very long periods, but individuals are unaware that a problem exists or discount the significance of the problem. Additionally, from a biopsychosocial perspective, the individual's social environment is unsupportive and/or unresponsive to the behavior . Of course, the existence of a "problem" often is defined by others, it might/might not be significant, and it might/might not be a valid problem depending upon the intentions of the others who identify the problem.

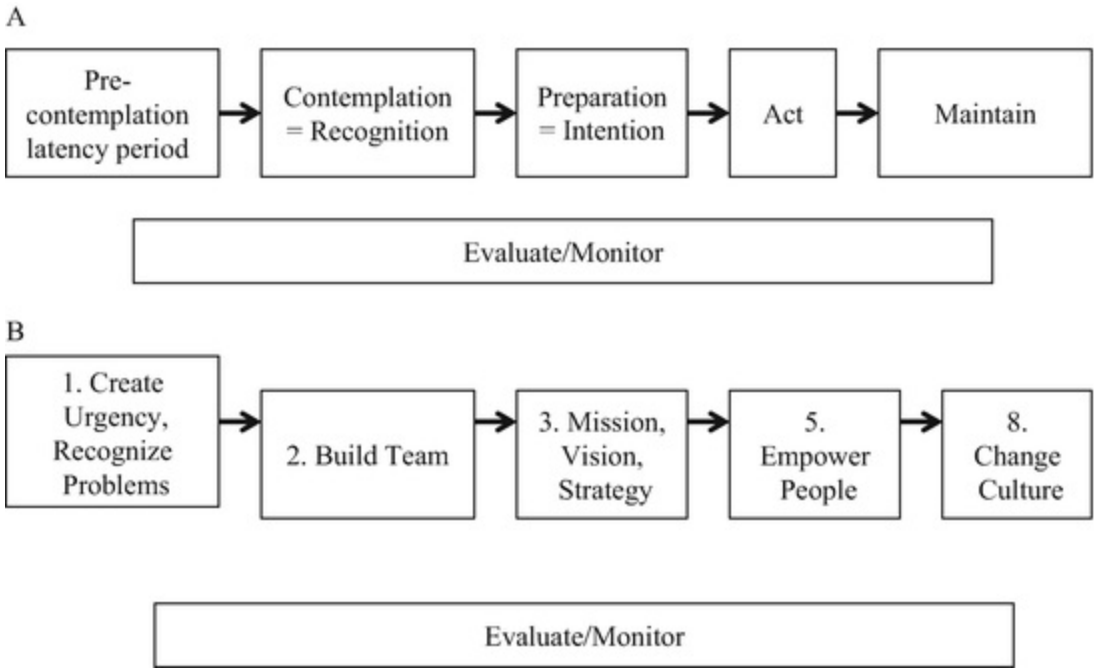

Fig. 3.3 Stage of Change Models . (**a**) Transtheoretical Model (Prochaska, DiClemente, & Norcross, 1992; Prochaska, Norcross, & DiClemente, 2013). (**b**) Kotter (1995, 1996, see also Kotter & Rathgeber, 2005a, 2005b, 2016) Eight Stages of Change, five shown here

Regardless, the next step in the transtheoretical model is to help the individual to recognize the problem, then to be motivated to consider how to proceed with changing the behavior (Fig. 3.3a). Each of these issues can be a substantial obstacle to overcome, and even more so are the last two steps: action and maintenance of the change. One can think of the exercise , weight loss, or household repair that people consider on a daily basis. The efforts just to start may be sporadic, sometimes successful, then stopped by a myriad of situations that compete for one's attention. Oriented toward psychotherapy, Prochaska, Norcross, and DiClemente (2013) described multiple approaches to effecting the full change cycle, including self-evaluation and re-evaluation exercises, role-play exercises , advocacy for the individual, remodeling one's environment to avoid stimulus exposure, substitution of alternatives for the problem behaviors , self-behavior contracts, rewards, etc. A variety of these and other approaches are practiced by therapists dealing with many different types of behavior change issues.

At the organizational level , John Kotter's Eight Stages of Change model (Kotter, 1995, 1996; Kotter & Rathgeber, 2005, 2016) is widely used in business entrepreneurship advocacy and in public health, the latter most strongly in patient safety teamwork models. Kotter's model, summarized in Fig. 3.3b, strongly mirrors the transtheoretical model , albeit at the organizational/group level. It starts with a period of urgency where a problem exists or needs to be clearly defined and addressed. A team has to be assembled, followed by setting the team's mission, vision, and strategies to attack the problem. Kotter's approach has the added advantage of emphasizing and building a dedicated team, indicating the need for mutual supports at all times. Empowerment is another common feature with the transtheoretical model , although Kotter's (1995, 1996) model acknowledges that there will be setbacks. Nevertheless, he stresses persistence to create innovative change in organizations.

Unfortunately, behavior change models have been attempted and tested in many different settings, often with mixed results. Few such models have been subjected to rigorous randomized clinical trials. Even when studies of these approaches have yielded positive results, the lack of long-term monitoring leads one to question whether the maintenance of the change actually occurred. Many studies where change supports have been withdrawn show a consistent return to pre-intervention behaviors for most study participants. The validity of the behavioral construct and its many necessary and sufficient variables (see Chap. 4) also must be considered. Kotter (1995, 1996) points out that over 70% of businesses fail or fall short of expectations due to lack of innovative change. We see some organizations that are highly innovative and successful, only to fail when they are not persistent and do not adapt to changing economic conditions. Timing and chance probably are important factors, so no clear combination

of measurable variables provides a valid model of organizational success.

Furthermore, individuals, and even organizations , vary across so many variables such that an intervention might generically work to some degree for a period of time for most participants, but individual persistence will be different for almost everyone. Both individuals and organizations can have very fixed behavioral patterns and cultures, resulting in considerable resistance to change, even when the facts indicate that change is needed. Each person's unique genetic and epigenetic profiles represent one major fact that illustrates this point. This is why we need greater data collection, wherever possible and with consent, on so many additional factors to map performance change trajectories at both the individual and group levels.

We included evaluation and monitoring for both models shown in Fig. 3.3. This approach is a needed, although not often properly implemented, component of any process, for it enables the researcher or leader to modify and make improvements to the process. This approach also falls into trajectory measurement for healthcare approaches because we can measure recursive and non-recursive relationships between measured variables. A recursive pathway is unidirectional from one variable to another, whereas a non-recursive pathway can follow multiple pathways and even reversible pathways in terms of relationships. The versatility of these models (see Chap. 4) enables improved simulations of reality that may yield predictive capabilities for the health policy decision maker.

3.3 Education, Race, Socioeconomics

Many public health studies focus on the role of demographic variables, particularly race, sex, educational level, and sometimes socioeconomic status, at predicting poor health outcomes. This approach is central to much of the health disparities and health promotion research efforts. Unfortunately, many of these studies do not explore beyond the boundaries of demographics to consider the many personal, social, and environmental contextual variables that interconnect with basic demographics. Whereas much of this research does show substantial associations between race, educational level, teen birth rates, and single parent households with negative health outcomes and social opportunities, these variables tend to strongly correlate with each other. Even more so, they tend to strongly correlate with socioeconomic status. Therefore, much of the public health poor outcomes tend to be associated with low socioeconomic class and its entailed lower access to health care, opportunities, and environments that increase one's probability of success and positive health outcomes.

At the same time, people are unique with their genetic and epigenetic profiles . This aspect results in variation of genetic and metabolic health conditions that occurs across socioeconomic classes. Furthermore, specific chance environmental exposures and chosen behaviors can cross this socioeconomic divide as well. Multiple factors across

different domains contribute to how people may or may not respond to a given health intervention. Educational and pharmacological interventions may help to promote change, but a myriad of experiences and factors, some within the person's control, can lead to positive or negative change.

3.4 Biopsychosocial Models

Along these lines, comprehensive biopsychosocial models have gained considerable use in public health research design and policy. These models extend beyond traditional medical models that identify only a given condition involving a body structure or function. Blum's model of health (Blum, 1983; Longest & Darr, 2014, p. 5) incorporates an extensive array of factors and variables that contribute to individual health and is representative of most biopsychosocial models that are used in health care and health stages of change models. Blum's model is concentric, with population, culture, and natural resources driving genetic, environmental, lifestyle, and health services that impact health and its various components (e.g., life expectancy, health behaviors, etc.).

As a variation on Blum's model, the International Classification of Functioning, Disability and Health (ICF; World Health Organization, 2001) expanded upon a previous medical model of handicaps to provide an advocacy model for the health and functioning of people with disabilities (Fig. 3.4). The ICF goes beyond body functions and structures to include the impact of personal, social, and environmental variables (e.g., attitudes of people, employers) on an individual's condition and/or disability, as well as the impact of the condition and all of these variables on a person's functional capacity as evaluated through activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ICF conditions are coded across four broad domains: Body Functions, Body Structures, Activities and Participation, and Environmental. Sub-codes address specific areas within a domain, although a given condition might be impacted across multiple domains. The ICF codes are intended to apply to anyone with a medical condition, with disability being acute or chronic, and the codes can be crosslinked to the standard ICD-9 and ICD-10 medical codes for conditions and billing. The ICF includes relatively similar coding for infant, youth, adolescent, and adult versions.

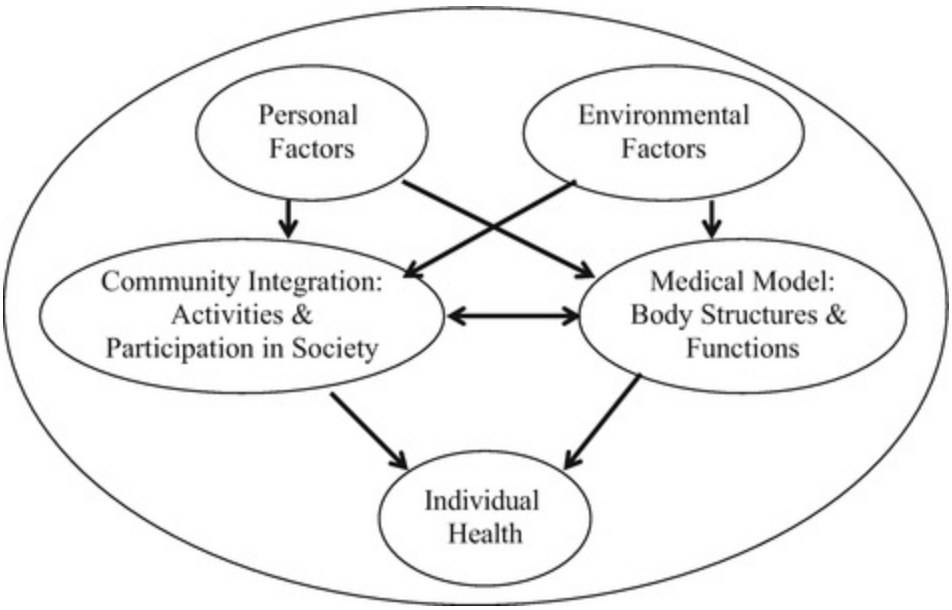

Fig. 3.4 Biopsychosocial Models: International Classification of Functioning, Disability and Health, adapted from World Health Organization (2001, p. 26); see also Hollar and Rowland (2015)

For example, low vision would be categorized under Body Functions code b210 ("Seeing functions"). The condition could be rated on a 0–4 scale (0 = "No problem," 4 = "complete problem), so this example could be listed as b210.3 for a severe vision problem (i.e., 50–95% functional limitation). Additionally, a severe vision problem will involve other domains, including Body Structures: b220.353, the b220 for "structure of eyeball, 0.3 for "severe problem," 0.05 for "discontinuity," and 0.003 for "both sides (eyes)." The condition will impact the Activities and Participation categories d110.3 ("Watching," "Severe difficulty"), d475.4 ("Driving," "Complete Problem"), and d485.2 ("Acquiring and keeping a job," "Moderate difficulty"), the latter depending on a variety of Environmental variables, including e310+3 ("Immediate Family support," "Substantial *Facilitator* ") and perhaps e330.2 ("People in Positions of Authority support," "Moderate problem *Barrier* ").

As a result, biopsychosocial models and tools such as the ICF can serve both as precision assessment tools that simultaneously can be used as statistical tools for continuously scoring and monitoring the many system components of a health condition or behavior, plus whether the driving force is a facilitator (i.e., positive helper) or a barrier (i.e., negative hindrance). Therefore, biopsychosocial models can go beyond merely providing a qualitative assessment of a health problem and its associated factors, something that will be very important for path analysis regression models in Chap. 4. Biopsychosocial models can provide a ranking method for the strengths of forces that are driving conditions in a positive or negative manner. The models can be informative to both the researcher and the applied practitioner who is working with customers to identify the best set of treatment parameters, including social support

measures and longitudinal supports to maintain treatment or behavioral adherence as well as to prevent a return to previous negative conditions.

3.5 Health Literacy Issues in Recidivism

Ratzan and Parker (2000, cited in Hernandez, 2009, p. 1) defined health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (Hernandez, 2009, p. 1; Ratzan & Parker, 2000). The U.S. Department of Health and Human Services (2008) estimated that 77 million American adults have minimal or low health literacy. This figure represents over one-third of the U.S. adult population, and health researchers have cited this statistic as a primary reason for the lack of adherence to health treatment programs and interventions.

Unfortunately, health literacy is broadly defined, and even the most specific criteria merely assess literacy as the ability to follow written health directions or to follow a prescription. The degree of health literacy/illiteracy is questionable as a result. In the absence of biopsychosocial models, the failure to address all variables and contextual factors can lead to simplistic explanations for health problems, and that possibly could be the case with the broad topic of "health literacy." Hollar and Rowland (2015) argued that more precise, valid, and consistent definitions of health literacy should be established, focusing on the tremendous variety of health conditions and associated medications, procedures, and other treatments. Using the ICF biopsychosocial model, such approaches would involve the entire healthcare team, including the patient, in the decision-making process. Hollar and Rowland's (2015) suggestion would be better health literacy across situations by improved communication and trust by all individuals involved in the health treatment process. This type of approach mirrors participatory action research, where study participants are involved in the design of the research procedures.

Trajectory analysis can address the recidivism problem by identifying variables and factors that maintain positive health conditions and behaviors via comprehensive data collection across multiple time points. Mapping trajectories can assess facilitators that move conditions or behaviors away from negative situations while also addressing declines in positive behaviors when supports might be limited or when treatments are withdrawn at the end of a study.

3.6 Examples

Many studies have examined brief follow-up studies of patient outcomes. Bacon and Aphramor (2011) noted that obese or high BMI individuals who engage in weight loss programs usually experience only short-term weight losses, only to regain weight, and

the process is cyclic . Furthermore, reviewing several clinical trials, they found that this cyclic repetition tended to produce negative health outcomes, including loss of self-esteem, eating disorders, and other secondary health conditions, leading the authors to conclude that weight-neutral control activities might be more beneficial. Hollar and Moore (2004) used longitudinal national data on people with disabilities from high school entrance through four follow-up periods over 12 years, finding that this sample was at increased risk for substance use and poor educational and employment outcomes.

At the physiological level, substantial chronobiological research has utilized longitudinal data to demonstrate the effectiveness of melatonin in managing a variety of circadian rhythm linked behaviors, including sleep disorders, jet lag, work shifts, but also cancer management, depression reduction, and the progression of Alzheimer's disease (Burke et al., 2013; Kostoglou-Athanassiou, 2013). Burke et al. (2013) specifically showed the nonlinear dynamic forcing of phase shift in the human circadian clock using melatonin administration with and without sessions of bright light exposure.

Ganesh et al. (2011) longitudinally monitored changes in gene expression patterns from blood samples of patients who experienced arterial changes impacted by stent implantation, finding significant changes in cellular growth patterns. Henly, Wyman, and Findorff (2012) argued for comprehensive longitudinal studies of changes in patient health to better understand the effectiveness of interventions. The Pembrey et al. (2006) study of multigenerational longevity, morbidity , and mortality to demonstrate transgenerational epigenetic effects of pre-adolescent famine on the germ-line and descendant health represents a remarkable study of truly longitudinal "cause-and-effect" health patterns.

3.7 Behaviors Locked in Periodic Patterns

Regardless of the reason why individuals cannot change behaviors , the idea of trajectory analysis maintains that we can track these behaviors, with individual consent for data collection, at the individual level, otherwise at the population level. The behaviors are repetitive over time, there are decision-making, behavioral , biological, or social/environmental contributors/predictors of these recurrent behaviors, and we potentially can identify the triggers and overall scheme/model for the behavior process.

We hypothesize that many behaviors will be periodic or semi-periodic, per Fig. 3.1a. The researcher who seeks to determine the trajectory of behaviors cannot rely on arbitrary time points for snapshot data collection. Many time points and events need to be mapped along a time continuum so that relevant possible predictor variables can be evaluated for a causal trajectory and potential "major" events that serve as behavioral thresholds .

Many "normal" behaviors are periodic. Therefore, we are interested in triggers that bifurcate (Fig. 3.1b) a normal trajectory into an alternate periodic or chaotic cycle.

Besides factors that trigger such bifurcations, we also are interested in the reinforcers/facilitating variables that maintain desirable behaviors. For undesirable behaviors or conditions, we seek to determine the variables that lock the behavior into a particular cycle, plus events, triggers, or even medicines that can phase shift the behavior to a near normal or improved state. For psychological states, variables can be both biological and cognitive in nature. For health conditions such as cardiovascular disease, tissue decay, or cancer , mostly biological variables will be the foci of research efforts. Glass and Mackey (1988) provide numerous examples of mostly biological conditions and their facilitator/barrier variables.

3.8 Tinbergen's Four Questions and Ethology

While rarely invoked in human psychology , Nikolaas Tinbergen's (1963) four principles of ethology are relevant to our longitudinal trajectory analysis of human behaviors: (a) causation (i.e., mechanism); (b) survival value (i.e., function/adaptation); (c) ontogeny (i.e., developmental course); and (d) evolution (i.e., phylogeny). Causation and ontogeny represent proximate (i.e., immediate) explanations for behaviors, whereas survival value and evolution represent ultimate (i.e., encompassing) global explanations for behaviors. As we attempt to understand behaviors, we must develop comprehensive sets of hypotheses that specifically and separately address each of these four questions (MacDougall-Shackleton, 2011).

For an individual returning to previous bad health behaviors, there must be mechanisms (variables) that drive the return to these behaviors instead of maintaining the intervention "good" health behaviors. These driving forces could be psychological (e.g., depression; lack of confidence), involve poor peer supports, or be socioeconomic , for instance, all measurable with the ICF and other biopsychosocial tools. Similarly, trajectory analysis comes into play to evaluate the development of the behavior with respect to the driving forces. These are proximal behavioral questions.

For questions of ultimate explanations for behaviors , few health studies have considered possible survival values/adaptations for bad health behaviors. It is possible that while such behaviors might be detrimental to one's health in one area, they might be beneficial psychologically or in some other aspect of individual health that has not been considered by the researcher. Likewise, the theory of evolution maintains that wide variations in human phenotypes are selected by the environment, and a behavior or characteristic that confers survival value in one environment might be lethal in another environment, and vice-versa. Therefore, a bad behavior might have some benefit in the possible universe of environments that is unbeknownst to the researcher.

The considerations of these issues can help the researcher to more comprehensively evaluate the nature of the scientific process and the procedures needed to approach a given public health research problem. It is likely that we do not fully understand

recidivism due to the tremendous diversity of humans as well as the many driving forces that impact behaviors. Trajectory analysis can help us to make these studies relevant for more effective, lasting interventions. In another review, Calhoun, Conner, Miller, and Messina (2015) likewise found a lack of rigorous clinical trials and longitudinal follow-up studies to evaluate factors affecting child and adolescent outcomes from parents engaging in substance abuse. Most existing studies have indicated that programs focusing on improved parenting practices can be effective, although these findings remain inconclusive with the lack of rigor in such studies and the multiple correlating factors that also affect child health and behavioral outcomes.

3.9 The Issue of Creating Bifurcations

To symmetry break the equilibrium situations where an undesirable condition or behavior is cycling (Figs. 3.1a and 3.2), we must provide a disturbance to the system. Such a disturbance would be energetic in nature so that the chemical conditions of a cell, electrical transmission along nerves, and/or cognitive processes are driven to change into a different pattern or direction. We illustrate such a change in Fig. 3.5, where a motivational impulse moves a behavioral pattern from one level to another. We know that such phase transitions or phase shifts occur in chemistry with substance transitions from solid to liquid, liquid to gas, or vice-versa, and such shifts involve a significant input or loss of energy (directionally) to get past the transition barrier . Similarly, using the chemistry analogies, we know that enzymes act as catalysts to lower the activation energy of a chemical reaction that has low probability of occurring by itself, thereby helping the reaction to proceed, often at rates a million-fold greater than in the absence of the enzyme. In reality, it is the enzyme structure that fits a chemical reactant shape that facilitates this process, sometimes with the help of a mineral or vitamin cofactor, sometimes with energy molecule bond breaking such as adenosine triphosphate (ATP).

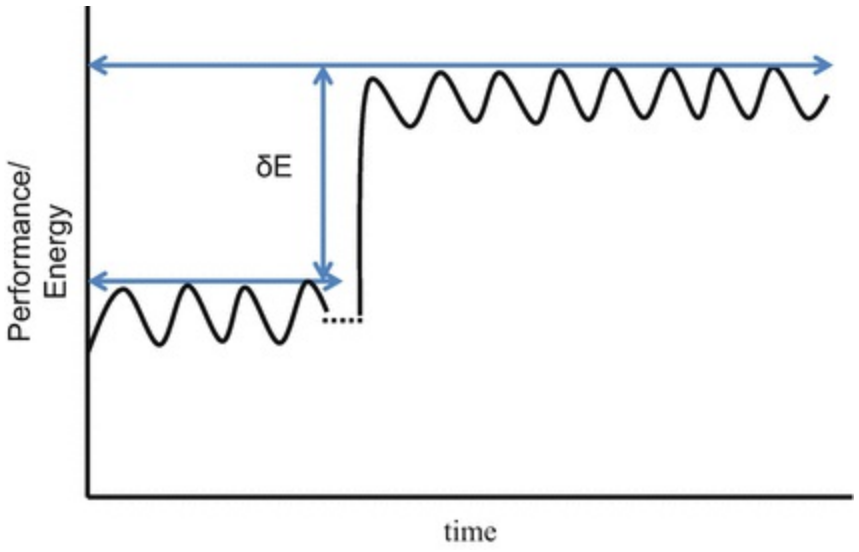

Fig. 3.5 The Jump

Likewise, we have to energetically jump a system to an alternative pattern, a phase shift that we will describe in more detail in Chaps. 7–11. Behaviorally, the jump requires intensive educational interventions, social supports, environmental reconstruction, and long-term reinforcements for behavioral change, sometimes involving medication at increasing and later decreasing levels. For biological conditions, the phase reset may involve electrical stimulation for nerve and/or heart/muscular conditions, but often it will involve precision medication delivery to specific cells or globally to several tissues.

Figure 3.6 shows normal (Fig. 3.6a) versus atrial fibrillation (Fig. 3.6b) electrocardiograms . The normal electrocardiogram measures typical electrical stimulation of the heart along the sinoatrial and atrioventricular nodes so that the ventricles contract in unison to force blood out of the heart, either to the lungs or to the rest of the body. The characteristic electrical signature follows a repeating triplet wave bulge that we term PQRST waves , with the R wave being the middle spike in the triplet. There should be a relatively quiescent interval between each heartbeat of almost 1-s duration, then electrical stimuli from the brain repeat the cycle, every second or so, billions of times, for the life of a person. The abnormal atrial fibrillation pattern (Fig. 3.6b) often results from the formation of electrically active ectopic foci on the ventricles, foci that trigger conflicting/chaotic stimulation of the cardiac muscle. The pattern characteristically lacks a P wave, and the time interval between beats may alternately and aperiodically increase or decrease in length.

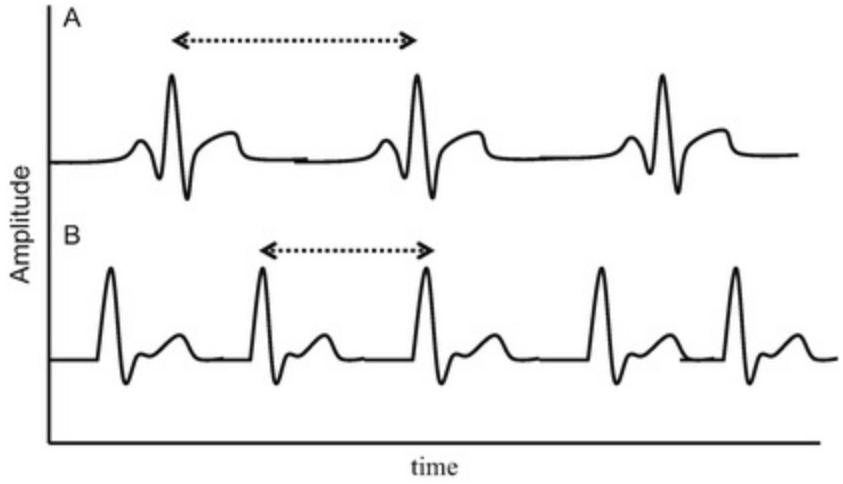

Fig. 3.6 Typical (**a**) versus atypical atrial fibrillation (**b**) electrocardiograms

Correction of the atrial fibrillation or other heart stimulus abnormalities may involve artificial electrical stimulation or heart stoppage/starting to shift the heart to an improved cycle for optimal ventricular forcing of blood flow (Glass & Mackey, 1988). More such examples will be described in detail in Chap. 14. Such phase shifts in trajectory analysis represent a direct intervention in both biological and behavioral cycles. Jumps represent one opportunity to alter undesired, unhealthy trajectories. It is extremely important that we understand relatively full causal trajectories (high R^2) and the effects of sensitive disturbances on these variables so that interventional jumps in physiological behaviors can be properly implemented.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_4

4. Epidemiological Methods

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Abbreviations

ANCOVA Analysis of covariance

ANOVA Analysis of variance

FDA U.S. Food and Drug Administration

ICF International Classification of Functioning, Disability and Health

NHANES National Health and Nutrition Examination Survey

NIH National Institutes of Health

RCT Randomized Clinical Trial

SAS Quantitative statistical package published by SAS, Inc., Cary, North Carolina

SPSS Statistical Package for the Social Sciences, published by IBM

WHO World Health Organization

Epidemiological methods have been developed and practiced for several hundred years. These methodologies helped clinicians and researchers to evaluate the extent of disease and methods of treatment. Epidemiological concepts date back at least to the Greek physiocratic school of philosophy (Fears, 2004; Tountas, 2009). Severe plagues were documented during the Roman Empire (Sabbatani & Fiorino, 2009). Some of the most famous early epidemiological studies included John Snow's mapping of infected London wells and the spread of cholera (Snow, 1849, 2002), Pasteur's studies of anthrax and rabies spread, Robert Koch's infectious criteria, and Florence Nightingale's mapping of hospital-based infections and military surgical outcomes (Davis et al., 2008; Longest & Darr, 2014, pp. 338–341; Madigan, Martinko, & Parker, 2000).

As epidemiology seeks to study the etiology, distribution, and control of disease and health conditions, it mirrors ecology , the study of the distribution and abundance of

organisms (Krebs, 1978), as well as Tinbergen's (1963) four principles of evolutionary ethology (see Sect. 3.8). The commonalities across these disciplines, as well as additional academic fields such as educational research, illustrate the common statistical language of these research fields. Besides medical, veterinary, and genetic epidemiological foci in those disciplines, public health epidemiology has branched into many specialty foci, including maternal and child health (MCH) epidemiology, infectious disease epidemiology, population health, etc. Clinical trials of new devices, treatments, or pharmaceuticals utilize epidemiological approaches.

4.1 Types of Studies

Types of epidemiological studies can range from experimental to non-experimental . Obviously, experimental studies are the most rigorous for establishing necessary and sufficient "causal" effects with representative samples of study participants. Experimental studies include clinical trials, field trials , community intervention trials , and cluster randomized trials that utilize one of three true experimental study designs: (a) Pretest-Posttest control group design; (b) Pretest-only control group design; or the more rigorous (c) Solomon Four-Group design (Gay, 1992, pp. 320–323; Rothman & Greenland, 1998, pp. 67–69). In contrast, quasi-experimental studies include non-equivalent control group designs, time series designs, and counterbalanced designs (Gay, 1992). Finally, non-experimental designs include one shot case or cohort studies, one group/cohort pretest-posttest design without a control, static group/cohort comparisons, case-control studies , cross-sectional studies , ecologic studies , and proportional morbidity/mortality studies (Fletcher et al., 1996; Gay, 1992; Last, 2001; Popper, 2002; Rothman & Greenland, 1998; Rothman et al., 2012).

Any of these studies can be longitudinal in nature with multiple data points for trajectory analysis . It is the existence of control versus treatment groups and ordering effects of tests and interventions that determines the experimental design status. With more experimental designs, there are fewer internal and external threats to study validity (see Chap. 5).

4.1.1 Experimental Studies

4.1.1.1 True Experimental Designs

The pretest-posttest control group design involves two groups of individuals who are randomly selected to either group, preferably in a "blinded" arrangement (i.e., the participant and researcher are unaware of group assignment until the conclusion of the experiment), followed by pretesting (e.g., questionnaires, demographic interview, physical, mental, biochemical measures, etc.) of dependent variables relevant to the study. The dependent variables cannot be altered by the researcher. At some time point

soon after the pretest, individuals in the respective groups receive a different intervention treatment. One group receives a standard treatment. The second, experimental group receives a novel treatment that involves the independent variable that is being manipulated by the researcher. Finally, a posttest (identical to the pretest), and preferably multiple posttests over time, is given soon after the intervention to capture any immediate (or delayed) treatment effects over time (Fletcher et al., 1996; Gay, 1992; Rothman & Greenland, 1998; Rothman et al., 2012). The timing of pretests and posttests around the intervention is important to avoid historical and maturation confounding threats and other threats to validity (see Chap. 5).

The posttest only control group design is identical to the pretest-posttest design except that there is no pretest. The obvious limitation is the lack of baseline information on the dependent variables for each study participant prior to the intervention, with only a significant difference between the treatment and control group performances on the dependent variables suggesting that the treatment made (or did not make) a difference. This design is weaker than the pretest-posttest design in that it opens up more questions on the effects of unknown exogenous variables to the study.

The most rigorous true experimental design is the Solomon Four-Group Design , which combines the features of the pretest-posttest and posttest only designs such that pretest-posttest effects can be measured. Most threats to internal and external test validity (Chap. 5) are controlled. Four groups are randomly selected; two groups receive the pretest and two groups do not; one of the pretested groups and one of the non-pretested groups receive the experimental intervention (likewise for two alternating groups receiving the standard, control routine); and all groups are posttested.

The Solomon Four-Group Design can be strengthened with repeated posttest measures at multiple time points up to many years following the intervention in order to determine the positive, negative, or neutral effects of the intervention upon the physiological, psychological, knowledge, attitudinal, and other behavioral trajectories . This rigorous design is widely used in randomized clinical trials (RCTs). Clinical trials generally involve recruitment of participants who have been diagnosed with a specific condition or focused set of common conditions, followed by testing of control and experimental treatments of the randomly assigned groups. The goal is to objectively determine whether or not the experimental, intervention treatment prevents or reduces the occurrence of negative secondary conditions that are associated with the primary patient condition or that have a reasonable probability of occurring (i.e., risk) due to the primary condition. It is important that study participants comply with all necessary procedures during the course of the intervention, along with data collection at pretest and posttest periods. Additionally, from an ethical viewpoint, the researcher should offer the intervention to the members of the control group following the conclusion of the study if the treatment is shown to be genuinely beneficial and safe, per National Institutes of Health (NIH) and United States Food and Drug Administration (FDA)

guidelines.

4.1.1.2 Field Trials

Field trials are very similar to clinical trials with two major exceptions: (1) participants do not have the specific condition that is the focus of the study; and (2) sample sizes must be considerably larger for the population -based study, along with close matching of participant characteristics across the experimental and control groups. The objective of a field trial is to experimentally determine health surveillance efficacies in areas such as the incidence (e.g., rates of new condition events in a population) of diseases or conditions, the effectiveness of preventative health interventions for targeted populations, and general population health (Rothman & Greenland, 1998; Rothman et al., 2012). Just as with clinical trials, where participants actually have the condition of interest, the experimental setup may use any of the three designs that were described above. Field trials provide information that enables the researcher and policy planner to proactively plan health programs for people nationwide, regionally, or in human factors-identified risk geographic regions.

4.1.1.3 Community Intervention Trials

Community Intervention Trials involve the administration of a health intervention to everyone in a defined geographic or governmental area or to specific group entities (e.g., schools, churches, etc.). Certain communities or groups may receive the intervention, whereas others receive standard, control (i.e., routine) treatments. Regardless, all three experimental designs are applicable to this group-oriented approach.

4.1.1.4 Group Randomized Trials

Group Randomized Trials represent an extension of Community Intervention Trials in that the participating communities are carefully matched on membership and are randomly selected to be in the control or experimental treatments. Similarly, the study can be blinded so that both the researcher and the participants do not know which groups are receiving the treatment until the conclusion of the data collection and analysis period. Thus, the Group Randomized Trial represents a merger of the Field Trial and the Community Intervention Trial.

4.1.2 Quasi-Experimental Studies

Quasi-experimental studies include non-equivalent control group designs, time series designs, and counterbalanced designs (Gay, 1992).

4.1.2.1 Non-equivalent Control Group Design

This particular quasi-experimental study involves nonrandom selection of participants to two or more groups, one group serving as a control group. The treatment group receives the experimental intervention, or several groups receive varying treatment types or levels of a treatment. The researcher pretests and posttests all groups. Therefore, the non-equivalent control group design is analogous to the experimental Pretest-Posttest Control Group Design except that there is no random selection of participants to the various groups, and the groups may not be matched such that they vary somewhat. The result can include threats to internal study validity such as regression of participant results to the mean and study selection bias interactions.

4.1.2.2 Time Series Designs

Time Series Designs are widely used in epidemiological research. This approach involves multiple pretests and posttests at staggered time intervals before and after a treatment intervention. The design can be operated with single or multiple groups.

4.1.2.3 Counterbalanced Designs

Counterbalanced designs involve the same number of multiple groups and treatments, with each group receiving each treatment, albeit in different orders, with all order permutations being addressed. For example, Group 1 could receive Treatment A, then Treatment B, then C, then D, etc. Group 2 could receive Treatment B, then A, C, and D; and Group 3 could receive Treatment B, then C, then A, then D, etc.; and so on. Pretesting and posttesting can occur between each of the treatments. This approach allows all the groups to receive all treatments. However, limitations of this approach include external threats to study validity , most notably test-treatment interactions, ordering effects with selection of participants, and interactions of the multiple treatments. Counterbalanced designs can operate more simply if only two treatments are used (e.g., control and experimental) in a true experimental design, followed by the control group receiving the experimental treatment if the researcher has found the experimental treatment to be beneficial to the participants. Such an approach sometimes is used at the conclusion of randomized trials in accordance with research ethics guidelines.

4.2 Non-experimental Studies

Non-experimental designs include one shot case or cohort studies, one group/cohort pretest-posttest design without a control, static group/cohort comparisons, case-control studies , cross-sectional studies , ecologic studies , and proportional

morbidity/mortality studies (Gay, 1992; Rothman & Greenland, 1998; Rothman et al., 2012).

4.2.1 One-Shot Case/Cohort Studies

A One-Shot Case or Cohort Study involves a single group treatment and posttest measurement. Such studies can be conducted if the goal is to construct and validate a particular behavioral model, treatment, or instrument. Generally, such groups should have a large sample size and be representative of the overall population . The groups may or may not be randomly selected, although random selection obviously strengthens the likelihood of having a representative sample. For a true one case study, some researchers will study individual clinical cases as comprehensive studies to inform other researchers who might encounter patients exhibiting similar clinical symptoms. In child development, Jean Piaget is famous for developing his widely used stages of cognitive development, mirrored by other researchers, by studying convenience samples of Parisian children (Miller, 1989). This approach is limited by internal threats to validity , including maturation and historical events affecting the individual participant(s).

4.2.2 One Group/Cohort Pretest-Posttest Design

This study design merely adds a pretest to the One-Shot Case/Cohort Study. Like the One shot design, this study is limited by participant history and maturation effects, but it is further weakened by testing, instrument, and regression to the mean effects, all threats to internal validity . Furthermore, the addition of the pretest can threaten external study validity due to pretest-posttest interaction effects (Gay, 1992).

4.2.3 Static Group Comparisons

Static group comparisons are similar to the one-shot case/cohort studies except that there are multiple groups, each treated with a specific intervention and then are measured with a posttest . Historical threats to internal validity are eliminated, but individual maturation effects can occur, along with mortality if significant numbers of individuals withdraw or disappear from the study. If there is no random sampling, then selection bias and selection/treatment interactions could occur (Gay, 1992).

As a general rule, if more than 20% of a sample do not respond or withdraw, it should be the duty of the researcher to re-sample these individuals to verify that they are not significantly different from true participants/respondents in terms of demographics and specific conditions.

4.2.4 Case-Control Studies

Case-control studies involve the identification of a study population , followed by sampling of the population to select control and exposed/symptomatic individuals for two comparison groups. Following the two groups enables determination of condition rates and progression in the overall population. Depending on the sampling protocol, threats to validity include potential sampling bias, mortality from the study, and historical/maturation effects.

4.2.5 Cross-Sectional Studies

Cross-sectional studies involve the determination of condition prevalence within a population at a given time. They do not truly measure causal trends from one time point to the next. Instead, they represent a frozen time perspective of condition prevalence. For example, Healthy People 2010 and 2020 measures involve these snapshot measures of condition prevalence in nationally representative measures such as the National Health and Nutrition Examination Survey (NHANES, approximately n = 10,000 participants randomly selected from the American population every 2 years).

4.2.6 Ecologic Studies

Ecologic studies examine aggregate counts/estimates for specified study units, such as schools, systems, governmental units, counties, states, provinces, etc. A typical example involves geographic information system spatial regression of disease conditions (Hollar, 2016b) using the County Health Rankings (University of Wisconsin Population Health Institute; www.countyhealthrankings.org).

4.2.7 Proportional Morbidity/Mortality Studies

Proportional morbidity/mortality studies involve subjects/participants who already are deceased or who have a specific condition. The statistical measure is to determine the rate of the cause of death/condition for the specific localized or overall population . With respect to cause of death, the determination is subject to error based upon autopsy or death certificate classifications, which can widely vary depending upon the level of expertise or multiple causal factors entered at the time of death/assessment.

4.3 Demographic Considerations

Whereas many public health epidemiological studies seek to address health disparities based upon a myriad of group classifications, some of which are obvious (e.g., sex), others which are more arbitrary (e.g., type of disability, race/ethnicity), few analyses comprehensively attempt to get at the complex genetic , environmental, individual behavioral, socioeconomic , and other contextual issues surrounding health. Advances

in human genomics currently are limited to a few hundred gene patterns that can be evaluated by personalized genomics microarray analysis per limited regional tissue samples, which can vary from region to region even within a tissue, leave alone the entire individual. Such assessments are limited, expensive, often not covered by insurance, and usually focused upon specific conditions such as aggressive cancers . Nevertheless, personalized genomics will be necessary to better assess the true uniqueness of each individual. Furthermore, even monozygotic twins will be progressively more unique, per Fig. 2.4 and the epigenetic environmental insults that progressively accumulate changes in gene expression in complex ways across different cells and tissues of each individual across the lifespan (Hollar, 2016a). The International Classification of Functioning, Disability and Health (ICF; WHO, 2001) represents a biopsychosocial model (Fig. 4.1) that attempts to map these varied unique circumstances for individuals within the context of their biological and environmental experiences. The ICF model (Fig. 4.1) goes beyond mere medical conditions to consider personal and environmental contextual factors, activities and participation in society, etc. that act as facilitators and barriers to an individual's optimal independent living.

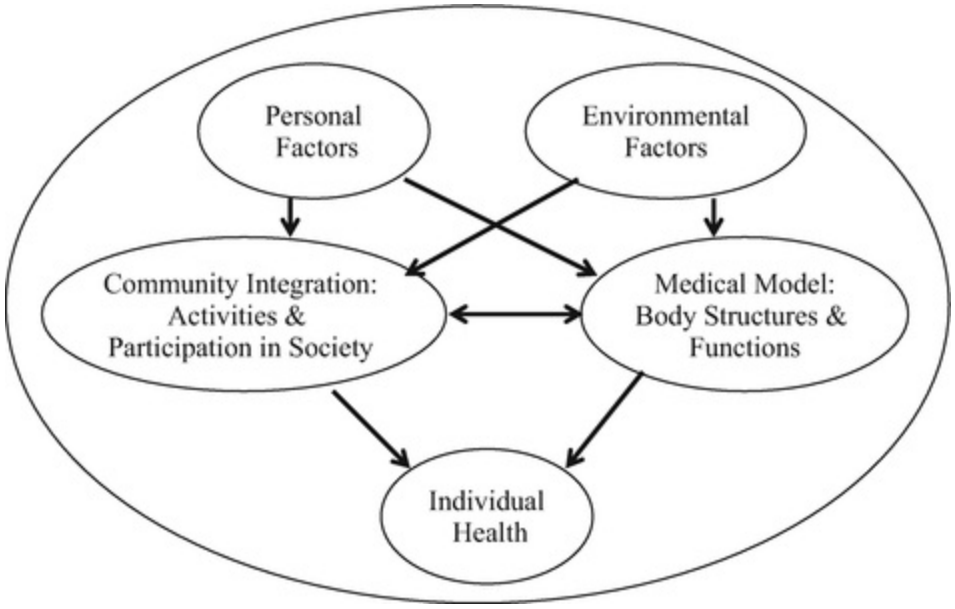

Fig. 4.1 The biopsychosocial international classification of functioning, disability, and health (ICF; WHO, 2001) incorporates medical condition, personal, and environmental contextual factors, including genetics and levels of functioning of individuals across a broad array of unique differences for independent social activities and participation in society

Even race/ethnicity represents an arbitrary concept when we consider the vast genetic and epigenetic differences between individuals. Cavalli-Sforza, Menozzi, and Piazza (1994; see also Cavalli-Sforza, 2001) have mapped multiple gene systems, particularly the highly polymorphic Major Histocompatibility Complex (MHC) on

chromosome six to demonstrate dramatic admixture of human groups and "races" over the course of recorded human history. For practical purposes, everyone is multicultural/multiracial due to the dynamic migration of human groups even over the past few thousand years (Cavalli-Sforza, 2001; Gurdasani et al., 2015; Nei and Roychoudhury, 1972; Tishkoff et al., 2009).

4.4 Methods of Analysis

A number of statistical packages are available for the types of studies covered in Sects. 4.4.1 and 4.4.2. For quantitative analysis, the primary statistical packages include SAS, STATA, and SPSS, although a number of other statistical vendors have entered the market with health epidemiological approaches. For qualitative analyses, NVIVO is a widely used analytical package, although there are other competitive software options here as well.

Quantitative tests have utilized odds ratios, relative risk ratios, and logistic regression analyses for categorical data (e.g., gender, race, socioeconomic categories). Additional statistical analyses are available for continuous data (e.g., blood pressure, weight, cholesterol levels) that do not take on categorical values. Such analyses add strength with objective data that are not biased by the researcher's classification of subjects or errors to individual responses to questionnaires and interviews. Such continuous data can include t-tests, analyses of variance (ANOVA), analyses of covariance (ANCOVA), and multiple regression analysis .

For trajectory analysis , time series trends and hierarchical linear models are effective tools for continuous data. For the approach outlined in this book, we are employing simplified applications of partial differential equations and Jacobian matrix analysis as borrowed from nonlinear dynamics and physics research.

4.5 Summary

The epidemiologist has multiple research study approaches to utilize when planning a research study. The research setup for assigning participants to groups determines the approach and ultimate methods of analysis. Too often, care is not taken to appropriately specify groups and to ensure proper data collection and follow-up data collections for study validity . Trajectory analysis will examine nonlinear effects from multiple data points in longitudinal studies.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_5

5. The Method of Path Coefficients

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Abbreviations

ABM Agent-Based Model
ANOVA Analysis of variance
HDL High density lipoprotein cholesterol
HLM Hierarchical Linear Model
IBM Individual Based Model
LDL Low density lipoprotein cholesterol
LISREL Linear structural relations, a software program
NAD Nicotinamide Adenine Dinucleotide
NetLogo Simulation software program (freeware)
SEM Structural Equation Model
SUD Substance use disorder

Sewall Wright (1918, 1920, 1921, 1934, 1960a, 1960b) developed the method of path coefficients as a comprehensive approach to study the direct and indirect relationships between multiple independent variables and a dependent variable. The approach builds upon traditional regression analysis by building models that incorporate all hypothesized necessary and sufficient conditions and that better address temporal "cause-and-effect " associations . Wright (1934, p. 193) stressed that this method does not address true causal inference from the correlation matrix of dependent and independent variables, but it instead allows for a qualitative interpretation of possible relations in a tested model.

5.1 Background

The classical simple linear regression model involves one independent (predictor or manipulated) X variable and one dependent (outcome) variable Y:

$$Y = a + BX + e \tag{5.1}$$

where a is the intercept, B is the regression coefficient or slope, and e is the residual error from other sources. Data are collected on each individual or situation for both the X and Y variables for a large sample and entered into the model. Analysis estimates the percentage variation in Y values that are associated with or can be explained by the X variable, a statistic referred to as the coefficient of variation (R^2), which is the square of the correlation between X and Y. The residual error e represents variation in Y that cannot be explained by the model. Together, R^2 and e should total 1.00, or 100% (Pedhazur, 1982).

The classical linear regression model requires adherence to the following nine assumptions involving variables and the research study design that was used to test the model. First, X is a fixed variable whose values would be used again if the study was replicated. Second, X is measured without error. Third, the regression of dependent variable Y on independent variable X is assumed to be linear. Fourth, the values of Y can vary, and each value can be assigned a probability of occurrence for a normal (Gaussian) distribution. Fifth, errors for each measured Y value are independent of other measurements. Sixth, the mean of errors for each Y measurement is zero. The seventh assumption is homoscedasticity , where the error variance remains constant regardless of each X measurement. The eighth and ninth assumptions are that errors are not associated with X and that the errors follow a normal (Gaussian) distribution (Pedhazur, 1982, pp. 33–34).

Too often, some epidemiologists refer to a series of independent single independent: single dependent variable linear regression models (or equivalent odds ratio analyses) as multivariate, which is incorrect. A true multivariate regression model involves the regression of a dependent variable on two or more independent variables:

$$Y = a + B_1X_1 + B_2X_2 + \cdots + B_nX_n \quad + e \tag{5.2}$$

where each B represents the corresponding regression coefficient (slope) for each independent variable. The same nine assumptions hold if the relationships of the independent to dependent variables are linear, and the coefficient of determination can be calculated for the overall model and for each contributing independent variable.

It should be noted that public health epidemiologists generally regard multivariate regression to involve multiple dependent variables being regressed upon a single set of predictor variables, including longitudinal , repeated measures, and nested data (Hidalgo & Goodman, 2013). However, Pedhazur (1982, p. 8) argues that the multivariate distinction that we use merely represents a stylistic issue that varies across

scientific disciplines and considers "multivariate analytical techniques as extensions of multiple regression analysis," as we describe here.

The power of multivariate regression analysis lies in the simultaneous evaluation of many independent variables, which enables the analysis of typical health and behavioral situations where there are many necessary and sufficient conditions (Rothman & Greenland, 1998). A necessary independent variable is the one that must occur for the dependent variable (outcome) to happen, but not by itself: other independent variables may be necessary as well in conjunction with this particular independent variable. Consequently, the combination of independent variables to "cause" the occurrence of the dependent variable represents the necessary and sufficient conditions. For example, smoking by itself may not cause lung cancer . It is the combination of smoking with other variables such as personal genetic risk factors, other environmental exposures, depth of inhalation during smoking, etc. that are the necessary and sufficient conditions.

The multivariate regression model leads directly to the method of path coefficients when we consider that the various independent variables are likely to correlate with each other. Consequently, we must consider the "causal " effects not only of the independent variables on the dependent variable, but also the interaction effects of the independent variables on each other. This approach helps the researcher to arrive at more realistic scenarios for how health conditions and behaviors occur and to test various competing models. Such an approach is consistent with deductive models of the scientific process (Popper, 2002; Rothman & Greenland, 1998) and with biopsychosocial models of health behaviors (Blum, 1983; World Health Organization, 2001). Kothari (1975, p. 5) stated, "The simple fact is that no measurement, no experiment or observation is possible without a relevant theoretical framework" (also cited in Prigogine, 1982, p. 59).

5.2 Path Coefficients

The multiple interactions between independent and dependent variables are illustrated in Fig. 5.1. The dependent variable is Variable 5, and four independent variables either directly and/or indirectly contribute to Variable 5. There are nine direct regression paths between the five variables:

(a) B_{51} B_{52} B_{53} B_{54} for the dependent variable from each independent.

(b) B_{31} B_{32} B_{41} B_{42} B_{43} for the independent variables.

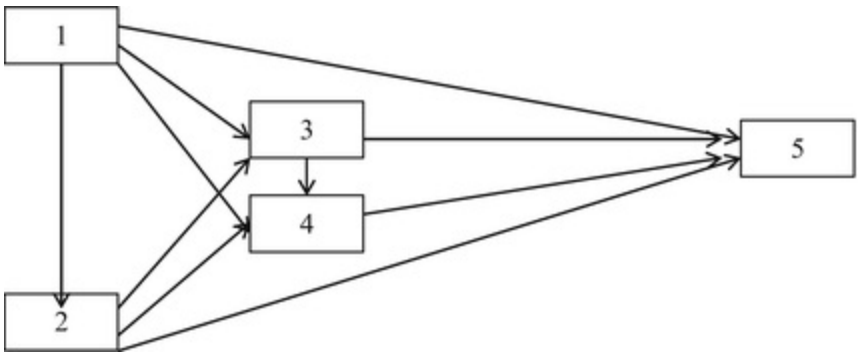

Fig. 5.1 Hypothetical Path Analysis Model with regression of outcome dependent variable 5 on independent variables 1–4. Direct and indirect path regression coefficients are represented by *arrows*

As a result, there are four direct regression path coefficients that predict the dependent variable. However, the direct paths are not the total effects of the independent variables on the dependent variable. At the same time, the interactive regression paths between the independent variables must be considered. The indirect effects of each independent variable on the dependent variable are as follows:

Variable 1: $B_{21}B_{52} + B_{31}B_{53} + B_{41}B_{54} + B_{31}B_{43}B_{54} + B_{21}B_{32}B_{53} + B_{21}B_{42}B_{54} + B_{21}B_{32}B_{43}B_{54}$.

Variable 2: $B_{32}B_{53} + B_{42}B_{54} + B_{32}B_{43}B_{54}$.

Variable 3: $B_{43}B_{54}$.

Total effects of each independent variable are equal to the sum of the variable direct and indirect effects. Additionally, residual errors can be computed from the partial correlations for the dependent variable and for the three intermediate variables 2, 3, and 4. The regression path coefficients are computed from the correlation matrix of all five variables and the variable standard deviations.

The path model (Fig. 5.1) represents one of many possible relationships between variables that could be hypothesized by the researcher. It is critically important that the researcher bases a model on previous research findings so that a logical, supported model is tested. Similarly, the relationships between variables should follow a temporally ordered sequence for the specified paths. Relationships can be positive or negative.

The multiple regression paths that are evident in a model such as Fig. 5.1 illustrate the strength of path analysis. A typical multiple regression model would be:

$$\text{Variable 5} = B1\,(\text{Variable 1}) + B2\,(\text{Variable 2}) + B3\,(\text{Variable 3}) + B4\,(\text{Variable 4}) + \text{Error} \quad (5.3)$$

We could glean some perspective on the strongest predictor variable(s) from this approach, as well as the approximate amount of variation in the dependent variable that is accounted for by the four independent variables (i.e., coefficient of determination, or

R^2). However, path analysis goes well beyond the standard regression model to approach a truer representation of the complex interactions between multiple variables, thereby obtaining an improved measurement of reality.

Wright (1960a, 1960b) would go further to describe reciprocal effects in path analysis models, such as if we had specified a path from variable 4 to variable 3 as well as from 3 to 4 in Fig. 5.1. Wright (1960b, p. 433) specifically examined a model of respiratory homeostasis with reciprocal interactions between lung alveolar carbon dioxide levels and depth of respiration. Wright (1960a, p. 190) also observed that path analysis is a linear relations methodology, although nonlinear variables can be linearly transformed using methods such as powered vector or logarithmic conversions prior to analysis. As mentioned earlier, Thom (1972) and others have emphasized the importance of patterns in data, including nonlinear patterns, instead of just automatically calculating means, standard deviations, and linear relationships. Whereas path analysis is limited in its linear approach, more powerful extensions of path analysis can incorporate nonlinear patterns.

The relevance of path models to trajectory analysis and epidemiology lies in the following observations:

1. Path models enable the measurement and testing of directionality for variables from past to present and even to future scenarios.

2. The incorporation of relevant necessary and sufficient conditions strengthens the validity of models so that realistic interventions can be implemented to solve problems, thereby improving conditions and/or redirecting behaviors.

3. Understanding the complex interrelationships between the myriad variables involved in any system promotes knowledge and identifying variables for targeted interventions.

With respect to observation 1, Fig. 5.2 illustrates the temporal evolution of a system, where initial events ("Beginning" sphere) offer isotropic possibilities and interactions between variables for future events. Nevertheless, specific events, decisions, or random noise cause only a subset of these possibilities to be realized ("Epoch 1" sphere). Epoch 1 also is isotropic, but again, only a subset of possibilities actually occurs and survives to the next future stage, ad infinitum. The result is a repeated, progressively reduced locking of specific trajectories for conditions or behaviors as well as the elimination of an increasingly large universe of conditions or behaviors that will never have happened. Some excluded conditions could reappear via mutation within the existence trajectory. Additionally, with imagination, innovation, and care/responsibility,

the researcher could introduce some of these unlocked, unrealized possibilities in controlled environments. Along these lines, author Stanislaw Lem's (1978) essay "Odds" illustrated the astronomically small probabilities of human uniqueness given chance events and this locking phenomenon, contrary to statistical views on probabilities of events.

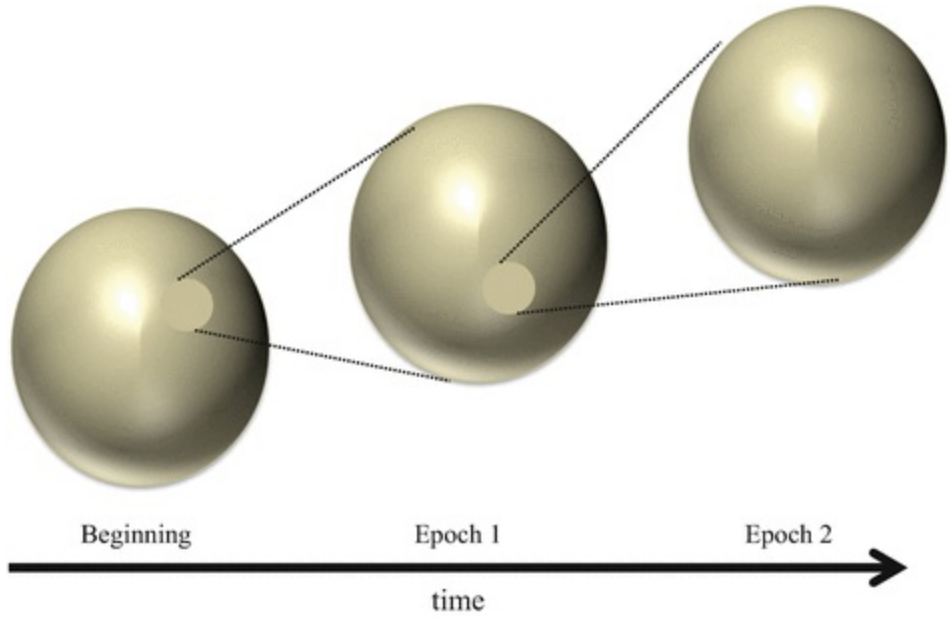

Fig. 5.2 The temporal evolution of a system, starting with isotropic potential, then only a small subset "surviving" and founding the next generation (Epoch 1), with only a tiny subset of Epoch 1 yielding Epoch 2, etc. The process illustrates the progressive locking of characteristics in subsequent iterations

Mathematically, Fig. 5.2 can be represented by the following iterative equation:

$$\mathbf{E}_n = f(\mathbf{E}_{n-1}) \tag{5.4}$$

where $f(\mathbf{E}_{n-1}) = \mathbf{E}_{n-1}\mathbf{X}_n$, and $\mathbf{E}_n$ represents a current matrix of all current situations for a set of individuals/conditions, $\mathbf{E}_{n-1}$ represents the same for the previous time period, and $\mathbf{X}_n$ represents a proportional matrix of selection elements that act on the elements of $\mathbf{E}_{n-1}$ to yield $\mathbf{E}_n$. It is the $\mathbf{X}_n$ matrix that the researcher seeks to understand to identify the factors/variables that affect a health condition or individual health outcomes, thereby affecting that condition or person's future trajectory. Zero elements in $\mathbf{X}_n$ lead to the elimination of that particular element in $\mathbf{E}_n$.

This leads to the second and third observations, the identification of necessary and sufficient conditions to address health conditions and behaviors, coincident with the applications of complex interactions between these variables. Path models attempt to examine these relationships from a cause and effect trajectory viewpoint. However, it is important that the researcher specifies a logical model to be tested, preferably through the actual scientifically controlled manipulation of variables for hypothesis refutation.

However, much of public health research relies upon post hoc analyses of previously collected data in contrast to true experimental approaches (e.g., Randomized Controlled Trials). Both Cliff (1983) and Messick (1988) stressed the importance of ethics in the development and testing of research models. In particular, Messick (1988) provided a comprehensive description of the various types of validity , including content, concurrent, construct, and predictive validities. Valid models and responsible research models play important roles in path and trajectory analyses, including the next step beyond path analysis: structural equation models .

5.3 Structural Equation Models

Structural Equation Models (SEM), also termed the analysis of covariance structures, represents a more comprehensive statistical approach to model development, testing, and validation. SEM provides a new causal approach to mathematical and statistical modeling in that it introduces latent factors as well as measured variables in the theoretical development, model specification, and testing stages. Theoretically, a researcher presents a hypothesized model of interrelating factors and variables that also are hypothesized to regress, or load, onto these latent factors, then collects data on these measured variables. The collected data, via the covariance matrices of all measured variables, are forced onto the hypothesized model of latent factor constructs, and SEM tests the fit of the data variable covariances to the hypothesized latent factor structure and variable loadings. Thus, SEM enables validated testing of complex relationships in prior specified models and alternative (competing models).

Figure 5.3 illustrates a generic SEM model. There are 13 measured variables, shown as rectangles, that load onto specific latent factors, shown as ovals. Six variables load onto two independent latent factors, labeled "ξ," and are termed exogenous variables. Seven variables load onto two endogenous, dependent factors, labeled "η," although η_1 actually is a mediator variable between the two exogenous factors and the true outcome latent factor, η_2. Each variable has an associated error residual term, "δ's" for exogenous variables and "ε's" for endogenous variables. The error contributions are shown as gray arrows that are oriented toward the corresponding variable (Fig. 5.3).

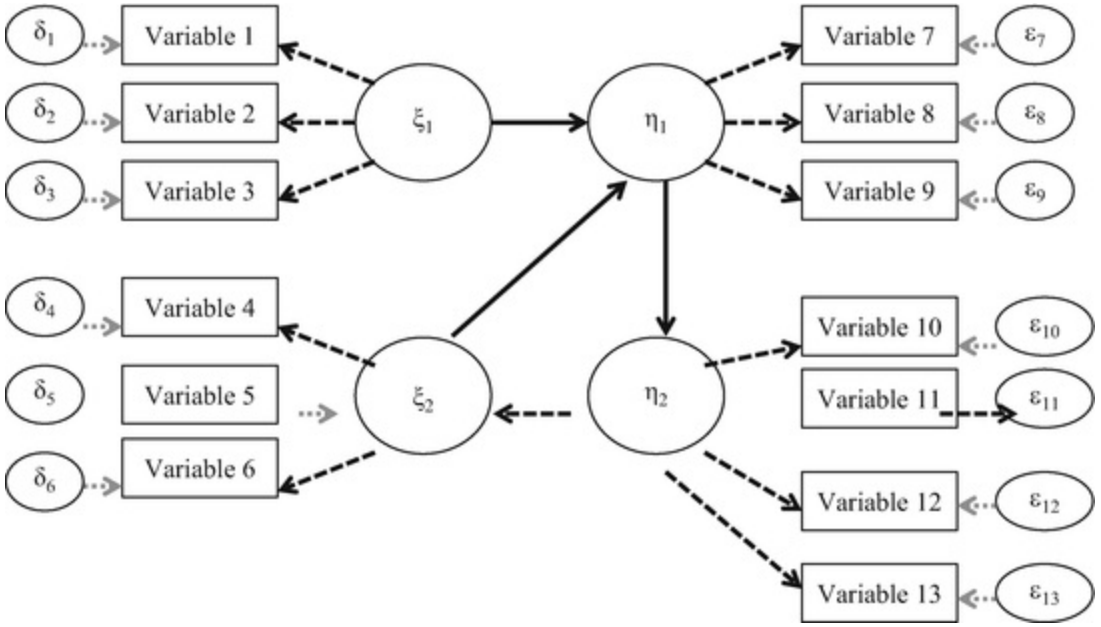

Fig. 5.3 Generic Structural Equation Model

In contrast, the variable loadings onto each latent factor are represented by dotted arrows that are oriented from the latent variable toward each of its loading variables. These arrows are the path regression coefficients, and are designated with the Greek symbol lambda (λ) but are not shown in Fig. 5.3. Thus, path regression coefficients λ_{11}, λ_{12}, and λ_{13} describe the regression strengths for variables 1, 2, and 3 onto latent factor ξ_1, for example. These λ errors are not to be confused with the Lyapunov exponent λ to be described in later chapters.

There are three path regression coefficients between the four latent variables. Two gamma (γ) coefficients, γ_{11} and γ_{12}, describe the regression of mediator endogenous latent variable η_1 onto the two exogenous latent variables ξ_1 and ξ_2, respectively. The final direct regression path from outcome exogenous latent variable η_2 onto mediator endogenous latent factor η_1 is represented by a beta (β) coefficient, in this case β_{21}. Furthermore, each endogenous η variable has a residual error component, ζ_1 and ζ_2 in this example. These additional, important symbols are not shown in Fig. 5.3 to avoid confusion.

Consequently, we have an overall model of "unseen" hypothesized latent variables that the researcher associates with specific measured variables. Obviously, these latent variables logically should be paired with reasonable associated variables. The researcher prepares a conceptual model such as Fig. 5.3 and specifies latent variables, error terms, variable and/or factor correlations, and direct regression paths (i.e., gammas and betas) between the exogenous and endogenous latent variables. The overall structural equation model can be summarized with three equations, two of which

describe the measured variables, and one combined structural equation to describe the latent factors. For the endogenous variables (Hayduck, 1987, p. 91; see also Hayduck, 1996), the measurement followed is:

$$\mathbf{y} = \Lambda_y \eta + \varepsilon \quad (5.5)$$

where **y** is a vector of measured endogenous variables, $\mathbf{\Lambda}_y$ is a matrix of regression path coefficients for each variable onto its latent factor, **η** is a vector of endogenous latent factors, and **ε** is a vector of residual errors for each endogenous variable. Similarly, for the exogenous variables (Hayduck, 1987, p. 91), the measurement model is:

$$\mathbf{x} = \Lambda_x \xi + \delta \quad (5.6)$$

where **x** is a vector of measured exogenous variables, $\mathbf{\Lambda}_x$ is a matrix of regression path coefficients for each variable onto its latent factor, **ξ** is a vector of exogenous latent factors, and **δ** is a vector of residual errors for each exogenous variable.

Finally, the full structural equation model examines the relations between the exogenous and endogenous latent factors (Hayduck, 1987, p. 91):

$$\eta = \beta\eta + \Gamma\xi + \zeta \quad (5.7)$$

where **η** is the vector of endogenous latent factors that are being tested in the SEM, **β** is the matrix of beta regression path coefficients between the latent factors, **Γ** is the matrix of gamma regression path coefficients from the exogenous latent factors to the endogenous latent factors, **ξ** is the vector of endogenous latent factors, and **ζ** is a vector of model errors associated with each endogenous latent factor.

The development of structural equation models begins with the researcher envisioning a conceptual model and building its components based upon evidence provided in the research literature. Therefore, SEM is theory driven. The relationships between variables and latent factors should match what other researchers have found, or they should address an unresolved relationship if conflicting studies indicate. Optimally, each latent factor should have 3–5 loading variables, although this number can be less or greater if the model is carefully specified. Sample sizes for the measurement models are critical, as model validation can fail if adequate statistical power is not achieved. As a rule of thumb, 20 times the number of variables should be the minimum sample size.

Study design and data preparation are of obvious importance. The researcher needs to identify specific data issues, such as use of dichotomous, polychotomous, or continuously scored variables, and consistently address these data issues when data analysis begins. Particularly for discrete versus continuous variables, the appropriate correlation coefficients (e.g., Pearson's, tetrachoric, etc.) should be used in order to obtain meaningful analytical results. Whereas structural equation modeling programs such as LISREL and Amos rely principally upon covariance matrices of measured

variables to test models, correlation matrices will suffice.

Temporally, exogenous variables should precede endogenous variables in order to provide a true causal pathway. While ideal, this approach rarely is practiced, thereby limiting the interpretation of true cause-and-effect . The primary reason why most SEM studies do not follow a temporal sequence is that many studies collect all data in a single data collection due to study design and/or participant attrition, or the goal of the study is to validate a questionnaire on a psychological construct, thereby not necessitating predictive validity , etc. Most nationally representative studies are single data collection studies, with the exception of longitudinal studies such as the National Education Longitudinal Study of 1988–2000, the Baltimore Longitudinal Study of Aging , etc. Rothman and Greenland (1998, pp. 24–27) identified nine criteria for cause-and-effect relationships: (a) temporal sequence; (b) strength of association; (c) repeated observations; (d) a single effect is produced; (e) a dose-response gradient exists; (f) plausible hypothesis; (g) coherence of association with the condition; (h) experimental evidence; and (i) analogy with comparable situations.

Model specification is critical. All relevant variables should be included in the conceptual model. Likewise, irrelevant variables should be excluded. Variables must be appropriately assessed for linearity or nonlinearity prior to inclusion in the model. For the first item, inclusion of relevant variables, this may not be achievable if the study did not measure all relevant variables, a common pitfall in research due to poor initial research design, lack of accurate measurement on variables, missing data, etc. but especially in post hoc SEM studies of existing data sets, where someone else prepared the study design. In public health research, a plethora of research studies unnecessarily become locked into common sets of demographic variables while ignoring genetic , social, and environmental variables. Many tortured studies have attempted to glean meaningful results from secondary analyses of datasets. Some researchers attempt to include irrelevant variables for exploratory purposes even though such variables are not supported in the research literature. Variables that change with age or situationally in a nonlinear pattern should be adjusted using powered vector modification, although following Thom's (1972) suggestions, we will describe nonlinear methodologies later in this volume. The results of misspecified models that do not address these issues are models that have poor fit and that, therefore, fail to describe the relationships between independent and dependent factors/variables. Pedhazur (1982, p. 230) appropriately stated, "No amount of fancy statistical acrobatics will undo the harm that may result by using an ill-conceived theory, or a caricature of a theory."

Similarly, model identification also is critical. A just identified model has all variables interconnected, or the number of estimated parameters is equal to the number of model equations (Pedhazur, 1982, p. 615). Underidentified models lack sufficient information or variable relationships to yield a convergent solution of parameter estimates, whereas an overidentified model contains too many restrictions for

convergence. To avoid over- or underidentification, the researcher must carefully prepare the conceptual model (e.g., Fig. 5.3), clearly specifying which variables are correlated or that contribute to specific latent factors. The researcher must also free variables to load onto other variables as necessary to evaluate multiple effects. Thus, the careful, theory-driven preparation of conceptual models during the research design is the most important step to insure model identification. Later steps during data analysis will include maximum likelihood, oblique factor analyses (Gorsuch, 1983) of variable loadings onto hypothesized factors, plus subscale reliability analyses prior to SEM analysis. Programs such as LISREL also include pre-SEM assessments (i.e., PRELIS) for assessment of measurement models. LISREL reports identification problems, and "correlations between estimates that exceed +/−0.9 may signify identification problems" (Hayduck, 1996, p. 142).

Figure 5.3 is a mediational model because endogenous latent factor η_1 mediates the relationship between exogenous latent factors ξ_1 and ξ_2 onto endogenous outcome latent factor η_2. The structural equation model regression paths go through η_1, then to η_2. An alternative model specification might be a moderational model, where a latent factor or variable modulates the strength of a regression path coefficient between two latent factors. The path analysis model (Fig. 5.1) also is a mediational model, albeit a partial mediational model of variable 3 and 4 effects due to the direct and indirect paths from variables 1 and 2 to variable 5. A moderational model would show a variable acting upon a specific regression pathway between two other variables or factors. Therefore, a mediational variable is responsible for the actual relationship between antecedent and postcedent variables, whereas a moderational variable only affects the strength of the relationship.

Given model specification, identification, and other considerations, the researcher will test one or several competing hypothetical conceptual models using SEM. The models might vary based upon the relationships between variables, latent factors, and mediational/moderational specifications in each model. Again, all models must be based upon theory. Typically, structural equation models are confirmatory in nature, thereby validating the current theory on the relationships between variables and factors. Generally, structural equation modeling is not suitable for exploratory analyses, where theory is less developed and variable/factor relationships are less clear. However, exploratory and confirmatory factor analyses using factor analysis first then SEM second on identically restricted models (i.e., no changes in variable/factor relationships) can be carefully conducted with large sample sizes (Hollar, 2016; Marsh et al., 2009, 2010).

For either exploratory or confirmatory factor analysis, preliminary factor analyses should utilize Generalized Least Squares or Maximum Likelihood factor analyses with oblique rotation (Gorsuch, 1983). The factor pattern and structure matrices can be

studied to verify the strengths of loadings for the hypothesized variables associated with each hypothesized latent factor. Similarly, the strength of the coefficient of determinations (R^2) for the latent factors having eigenvalues greater than 1 represents an important indicator for each factor subscale model. To accompany the factor analysis, a reliability analysis for the strength of relationships between each set of factor variables can be used in this initial assessment. Variables that load poorly or that increase the subscale Cronbach's alpha when they are deleted can be removed from the model if such a move does not seriously disturb the overall theoretical conceptual model. Factor and reliability analysis can be useful to improve model identification and to better understand relationships of variables across the hypothesized latent factors prior to the SEM analysis.

Measurements of fit for SEM models include chi-square (X^2), X^2/degrees of freedom (X^2/df), and X^2 difference between models. The X^2 estimate should be nonsignificant. The X^2/df ratio should be less than 5 but greater than 1. The X^2 difference between models should be significant. The Goodness of Fit Index (GFI) should be greater than 0.90, likewise for the Non-Normed Fit Index (NNFI; also termed Tucker-Lewis Index). The Root Mean Square Error of Approximation (RMSEA) the Root Mean Square Residual (RMSR) should be less than 0.05 (Browne & Cudeck, 1993; Byrne, 1998; Fassinger, 1987; Hayduck, 1987, 1996; Hollar, 2016; Hollar, Paxton, & Fleming, 2012; Long, 1983). Using these statistics, the researcher tests the strength of the conceptual model against the actual collected data. Even if the SEM supports a strong model, bear in mind that all models are incorrect, just that they seek to more clearly explain reality (Box, 1976, p. 792). Furthermore, Cliff (1983) challenges us to interpret these models with great caution.

5.4 Hierarchical Linear Models

Along the same lines as structural equation modeling , Hierarchical Linear Models (HLM) allow the researcher to address time trajectory patterns with nesting effects (e.g., variables impacted by different locations, etc.). Bryk and Raudenbush (1992) illustrated the analytical problem that variances of individual behaviors within groups may be smaller than variances of individuals between groups, and even more so of groups within larger groups. Specifically, some disturbance variables "…vanish into the error term of the linear (regression) model, causing correlation between disturbances….The disturbances have a group and an individual component" (Bryk & Raudenbush, 1992, p. xiv).

In developing Hierarchical Linear Models (HLM), Bryk and Raudenbush (1992) emphasized multilevel hierarchical models that connected with each other, with, for example, longitudinal repeated measurements for individuals at Level 1, groups of

individuals at Level 2, larger conglomerates of groups at Level 3, etc. Mathematically, HLM regression models can be represented as follows (Singer & Willett, 2003, pp. 50–51, 97–99):

$$\text{Level 1}: Y_{ij} = \pi_{0i} + \pi_{1i}\left(\text{TIME}_{ij}\right) + \varepsilon_{ij} \tag{5.8}$$

where Y_{ij} represents the dependent (outcome) variable value for individual i at time j. The parameter π_{0i} represents the y-intercept (i.e., value of Y at starting time 0), whereas π_{1i} represents the slope (i.e., change) in individual i's score on variable Y based upon the independent variable TIME. With the standard slope interpretation from algebra, π_{1i} is the amount of change (positive, negative, or neutral) in dependent variable Y per one unit increase in the independent variable (TIME in this case). As usual, ε_{ij} represents residual errors.

For a second level model within Level 1:

$$\begin{aligned}\text{Level 2}: \pi_{0i} &= \gamma_{00} + \gamma_{01}(\text{VAR1})_i + \gamma_{02}(\text{VAR2})_i + \cdots + \gamma_{0n}(\text{VAR}n)_i + \zeta_{0i} \\ \pi_{1i} &= \gamma_{10} + \gamma_{11}(\text{VAR1})_i + \gamma_{12}(\text{VAR2})_i + \cdots + \gamma_{1n}(\text{VAR}n)_i + \zeta_{1i}\end{aligned} \tag{5.9}$$

~~where π_{0i} and π_{0i} are from the Level 1 model for individual~~ intercept and slope, respectively. The parameter γ_{00} is the mean of the Level 1 intercepts. The parameter γ_{01} is the "mean difference in the Level 1 π_{0i} intercept for a one-unit difference" in independent variable 1 (Singer & Willett, 2003, p. 53), likewise for parameter γ_{02} for independent variable 2, etc. to γ_{0n} for the nth independent variable. Likewise, the parameter γ_{10} is the mean of the Level 1 slopes, whereas γ_{11} is the "mean difference in the Level 1 π_{1i} intercept for a one-unit difference" in independent variable 1 (Singer & Willett, 2003, p. 53), likewise for parameter γ_{12} for independent variable 2, etc. to γ_{1n} for the nth independent variable. The parameters ζ_{0i} and ζ_{1i} represent the Level 2 residual errors for intercept and slope, respectively.

Thus, for a two-level model, Level 1 provides the basic equation for repeated outcomes measurements from each study participant over time, which is supported from a predictive stance by the two equations in the Level 2 model, one equation for the intercept, the other equation for the slope. For the Level 1 model, the Y_{ij} dependent variable could be HDL/LDL cholesterol ratios measured at different time points for various participating individuals for the research study. At Level 2, independent variable 1 could be the individual's sex, while independent variable 2 could be high versus low socioeconomic status. In this way, multiple groupings of HDL/LDL ratios organized across four groupings can be achieved.

Now, this situation would not be much different from a Generalized Linear Model (GLM) repeated measures Analysis of Variance (ANOVA). HLM goes beyond this when the second and higher levels examine nesting effects over time, such as using

Level 2 and 3 variables such as neighborhood, then county, then region, etc. Furthermore, Singer and Willett (2003) emphasize the importance of standardizing reference starting points to zero, thereby linear converting the TIME variable.

For discontinuous events (i.e., discontinuities), Singer and Willett (2003, pp. 193–199) illustrated how the HLM model could be modified to address sudden or gradual changes in independent variables that also substantially impact the dependent variable Y_{ij} . For example, suppose we have the following hypothetical Level 1 model for substance use:

$$\text{Level 1 : SUD}_{ij} = \pi_{0i} + \pi_{1i}\left(\text{TIME}_{ij}\right) + \varepsilon_{ij} \tag{5.10}$$

Introduction of an additional Level 1 variable, PREVENT (e.g., a substitute or prevention program that "stops" or substantially reduces the behavior), we would code this variable as a dichotomy (0 = no treatment; 1 = treatment):

$$\text{New Level 1 : SUD}_{ij} = \pi_{0i} + \pi_{1i}\left(\text{TIME}_{ij}\right) + \pi_{2i}\left(\text{PREVENT}_{ij}\right) + \varepsilon_{ij} \tag{5.11}$$

Introduction of the PREVENT dichotomous variable could yield a noticeable shift down in SUD for individuals receiving the treatment (i.e., PREVENT = 1), assuming that the treatment is valid and effective.

Alternatively, if the change is not immediate, but gradual, Singer and Willett (2003, p. 197) stress the importance of a clearly specified model that links the TIME variable to an Elapsed Time (e.g., ELAP-T) variable so that the dependent variable can be measured at the equivalent time point on both the continuous TIME and ELAP-T variables, thus enabling mapping of the difference onto the slope:

$$\text{Alternative Level 1 : SUD}_{ij} = \pi_{0i} + \pi_{1i}\left(\text{TIME}_{ij}\right) + \pi_{2i}\left(\text{ELAP} - \text{T}_{ij}\right) + \varepsilon_{ij} \tag{5.12}$$

Combinations of these two abrupt and gradual models of discontinuous change can be incorporated as well.

These previous models illustrated linear change, even with shifts and discontinuities . Both Bryk and Raudenbush (1992) and Singer and Willett (2003) provided examples of nonlinear applications. Quadratic and cubic representations of the Eq. 4.10 Level 1 model would be (Singer & Willett, 2003, pp. 214–216; see also Eigen & Schuster, 1979, pp. 28–32):

$$\text{Quadratic Level 1 : SUD}_{ij} = \pi_{0i} + \pi_{1i}\left(\text{TIME}_{ij}\right) + \pi_{2i}\left(\text{TIME}_{ij}\right)^2 + \varepsilon_{ij} \tag{5.13}$$

$$\text{Cubic Level 1 : SUD}_{ij} = \pi_{0i} + \pi_{1i}\left(\text{TIME}_{ij}\right) + \pi_{2i}\left(\text{TIME}_{ij}\right)^2 + \pi_{3i}\left(\text{TIME}_{ij}\right)^3 + \varepsilon_{ij}. \tag{5.14}$$

As with structural equation models , the researcher must carefully specify the variable composition, discontinuities , and linearity/nonlinearity in multilevel HLM models during the research design process, based upon theory and the research literature, but not arbitrary or "after-the-fact." The discontinuity models described in

Singer and Willett (2003, pp. 193–199) and above also can be applied to the recidivism /recurrence problems described in Chap. 2, such that positive as well as negative "jumps" in behaviors can be more accurately represented and studied. This approach is consistent with trajectory analysis , as we seek to achieve more realistic models for predicting outcomes and providing relevant interventions.

5.5 Examples

Examples of structural equation models abound in the research literature, including for health care and clinical research. Stanger et al. (2002) studied the effects of parent and family problems on children's internalizing and externalizing problems for the children of $n = 91$ fathers and $n = 120$ mothers. For the independent variables, the latent factor Parent Problems included drug, medical, and psychiatric problems as measured by the validated Addiction Severity Index (McLellan et al., 1985), whereas the latent factor Family Problems included family communication, roles, affective behavior, and behavior control as measured by the validated Family Assessment Device (Epstein, Baldwin, & Bishop, 1983). For children latent factors, Internalizing Problems included withdrawal, somatic complaints, and anxiety/depression, whereas Externalizing Problems included attention problems, aggressive behavior, and delinquency as measured by the validated Child Behavior Checklist (Achenbach, 1991).

Stanger et al. (2002) carefully prepared an overall model of child internalization/externalization and tested competing constrained and unconstrained models. Whereas the two exogenous latent factors, Parent and Family Problems, were strongly correlated, only Family Problems had significant regression path coefficients to the two latent endogenous variables, Child Internalizing and Externalizing Behaviors. Separate father and mother models were tested, with Family Problems significantly predicting Child Internalization and Externalization Behavior problems. Interestingly, the correlation between Parent Problems and Family Problems was weak for fathers but was strong (significant) for mothers. This study illustrates the power of carefully planned and tested models that yield information to practitioners to implement appropriate therapies and interventions that can be targeted to different populations /groups.

Similarly, hierarchical linear or multilevel models have been extensively applied to behavioral science studies, particularly in educational settings where students can be exposed to high or low performance within and across classes, schools, and school districts, thus introducing a variety of nesting effects for study designs. These models also allow temporal change assessments that are consistent with our trajectory analysis approach.

Raudenbush and Bryk (1986) and Bryk and Raudenbush (1992) provided an extensive re-analysis of the famous Coleman report (Coleman et al., 1966) on academic

achievement among over 600,000 students in Chicago Catholic versus public schools. Achievement was higher for Catholic schools than public schools, although the slope of achievement with increasing socioeconomic status was steeper for the public schools, indicating that academic achievement was more socially equitable in Catholic schools. Several researchers had argued that the Coleman report had not addressed additional confounding variables. From a trajectory perspective, Raudenbush and Bryk appropriately addressed the idea that the intercepts and slopes of academic performance change between the school types could be used as outcome measures, and that the errors of the slopes and intercepts are correlated.

Lee and Bryk (1989) compared Catholic versus public schools in the longitudinal , nationally representative High School and Beyond study. They used a two-level model to examine the effects of academic background, minority gaps, socioeconomic differentiation, and academic differentiation on achievement at the student level (Level 1) and at the school level (Level 2). They found that academic background was positively associated with achievement, and this relationship was significant for socioeconomic status across Catholic and public schools, although stronger for the latter. Additionally, the minority gap was more negative for academic achievement, and Catholic high social class schools were less differentiating (Bryk & Raudenbush, 1992; Lee & Bryk, 1989).

Both structural equation models and hierarchical linear models enable improved evaluations of multiple independent variables and their interaction effects with respect to the outcome variables. They offer substantial versatility in terms of temporal effects, nesting of groups, variable interactions and correlations across levels, nonlinear as well as linear effects, and longitudinal data points for measuring trajectory slope changes, including errors and interactions between slopes and intercepts.

5.6 Agent-Based Models

Agent-Based Models (ABMs), also termed Individual Based Models (IBMs), are simulations of complex systems and processes from which emergent behaviors and patterns can be detected. A behavior is emergent if it is unique compared to the actors and variables described in the model, it cannot be predicted from actor or variable characteristics, and it is “not simply the sum of the properties” of actors and other elements specified in the model (Grimm & Railsback, 2005, p. 392). Grimm and Railsback (2005, p. 14) identified four criteria for a simulation model to be an ABM/IBM: (a) demonstrated complexity of described “life cycle;” (b) provision for realistic “dynamics of resources” that are used by model actors; (c) specification of “real or integer numbers” for the modeled population ; and (d) representation of realistic variances in actor characteristics based upon actor age. Agent-Based Models have a strong history in the ecological modeling of complex species interactions,

distributions, and changes in response to population and environmental characteristics. Hundreds of peer-reviewed research papers have utilized ABMs. Increased computer and graphical platforms have supported these ABMs , whose history was strongly influenced by early computer simulations in mathematics and physics.

Dresden and Wong (1975) described the mathematical basis of John Conway's Game of Life, one of the first cellular automaton simulations. Conway's simple programming game enables the user to apply specific decision rules for survival, death, or reproduction based upon the number of adjacent occupied cells of a matrix. Based upon initial specifications set by the researcher/programmer, the system can evolve toward expansion, sustainability, or collapse. Consequently, the model served as the basis for further model and software development to increase simulation capabilities, including classic ecological models such as the Lotka-Volterra predator-prey cycles.

Gilbert and Troitzsch (2005) described a number of simulation programs for social science applications that can be extended to health models. They provided relevant examples and code, such as a STELLA software model of the popular hawk-dove-law abider model and its adaptations. Major simulation programs include NetLogo , Swarm, STELLA, MIMOSE, POWERSIM, SIMPLE, SIMPLEX, etc., and there are numerous robotic, neural network , and systems dynamics groups that use these models to study hypothesized variable/population relationships. Simulation software platforms have developed sophisticated graphical capabilities for visualizing the model in progress and for plotting group variable trajectories. Some programs, such as NetLogo (Wilensky, 1999), can import actual data for modeling of future predictive patterns.

Wilensky (1999) invented and offers NetLogo as a freeware available from Northwestern University (http://ccl.northwestern.edu/netlogo/). The interface includes an extensive models library that can be run, along with source code that can be manipulated to create new models, control, display, and output features. The lengthy but user-friendly programming manual also is available from the website. The Cooperation game (Wilensky, 1997) is shown in Fig. 5.4. Grimm and Railsback (2005) included NetLogo among many strong ABM platforms, including SORTIE, PSPC+3, and Swarm as well.

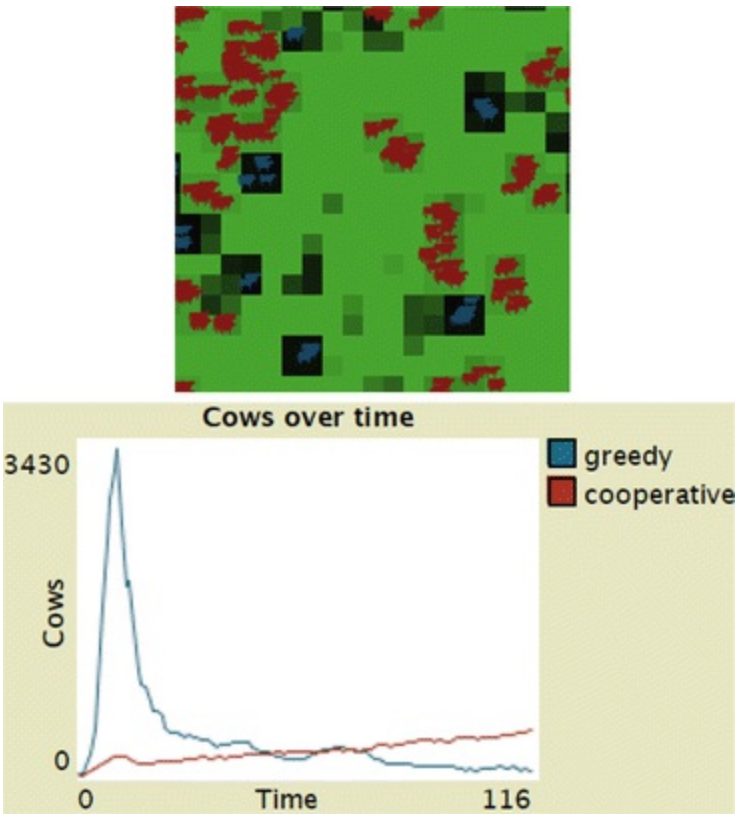

Fig. 5.4 Sample experimental run of an Agent-Based Model, using the open source software NetLogo 5.0.4 and Wilensky's Agent-Based Model of Cooperation, both developed by Wilensky (1997, 1999)

While limited compared to actual field-collected data, Agent-Based Models offer the researcher a powerful simulation tool for testing theories based upon existing collected data, current hypothesized variables, and when extensive field observation data might not be available. Most importantly, ABMs emphasize the research design process and can be used as a preliminary exploration to help establish the research program for actual data collection and analysis. As with all models, the ABM only will be as valid in its predictive power as the thought and background work prepared by the researcher.

5.7 Nonlinearity

Given the assumption of linearity in classical regression analysis (Pedhazur, 1982), violations of linearity in variable relationships can be tested so that the researcher can take the necessary steps to correct the hypothesized model under scrutiny. For example, many medications have a dose-response relationship that is curvilinear, with low effects at low dosage and perhaps low effects at very high dosages. Clinical trials should establish the proper relationship so that physicians can prescribe the correct dosage given the patient condition. Likewise, most ingestible substances have a measureable lethal dose LD_{50}, where there would be a fifty percent probability of a user dying at that

dosage. There is an unusual health phenomenon called hormesis, where very low levels of certain "toxic" chemicals and radiation actually promote growth, vitality, and immune function, although the physiological mechanisms are not understood and the novice should not attempt at home!

For nonlinear situations, the researcher pursuing trajectory analyses of longitudinal data should appropriately adjust the nonlinear variables to operate in an adjusted "linear" fashion with the linear variables in the model. These approaches will involve logarithmic or quadratic conversions of the nonlinear variables. Conversion methodologies are part of the data preparation for standard regression, structural equation models , hierarchical linear models , and Agent-Based Models. Nonlinear variables should be presented to the research audience, but they should be appropriately modified for the analysis when linear variables are involved. Nonlinear variables and variable relationships are to be expected as part of any attempt to model reality.

5.8 Causal Inference and Complexity

If carefully planned, the research process can establish evidence supporting "cause-and-effect " variable relationships, although research does not "prove" that one variable truly causes another in all situations. Research tests and supports the validity of plausible and analytically supported associations between variables, and the strengths of the associations provide the researcher, clinician, and policy maker with "evidence" to make decisions (see Chap. 2). As with the residual errors described in the sections on structural equation and hierarchical linear models , some extraneous variables always will be missing from our conceptual models, and some variables might be unique to specific individuals. As a result, it is important not to throw out outlier data, but instead to examine how and why these individuals are different.

Similarly, having statistically significant results does not necessarily mean that the association between two or more variables truly is significant. Sometimes, small sample sizes and the effects of treatments (see threats to eternal and internal validity under Validity below) can bias results. Non-representative or small samples invariably impact the statistical power of an experiment, so it is important that the researcher perform a straightforward power analysis (Cohen, 1988; Faul, Erdfelder, Lang, & Buchner, 2007) prior to conducting the experiment.

The complexity of trajectories and pathways in health conditions is most clearly demonstrated by biochemical pathways. Advances in genomics and biochemistry (see Preface) have uncovered thousands of experimentally verifiable causal relationships between proteins and other molecules. Continuing discoveries add new relationships to these models. One simplified biochemical pathway related to aging and cellular protection from free radical damage is the Sirtuin pathway shown in Fig. 5.5. We call this model simplified because additional pathway factors are left out for purposes of

clarity. There are two parts to the Fig. 5.5 pathway that are separated by the one negative relationship. First, free radicals (i.e., reactive oxygen species) positively promote DNA repair proteins because the free radicals damage DNA. The DNA repair protein Poly-ADP-Ribose Polymerase uses up the oxidized form of nicotinamide adenine dinucleotide (NAD^+), an essential ingredient to promote the NAD^+-dependent deacetylase Sirtuin 1. The Sirtuin 1 deacetylase modifies histone proteins to free inactive chromosomal regions for gene expression. NAD^+ is a necessary and sufficient effector of Sirtuin 1 (Guarente, 2014; Rodgers et al., 2008). Likewise, resveratrol and polyphenols are compounds found in red grapes and many vegetables (e.g., cloves, blueberries), respectively, that also are necessary conditions, but not sufficient by themselves. A calorie restrictive ketogenic diet, the amino acid tryptophan, and nicrotinamide mononucleotide are indirect effectors/facilitators of Sirtuin 1 activity. Subsequently, Sirtuin 1 triggers a pathway of sequential reactions leading to the transcription of mitochondrial genes, leading to proper mitochondrial functioning (Guarente, 2014; Picard et al., 2015).

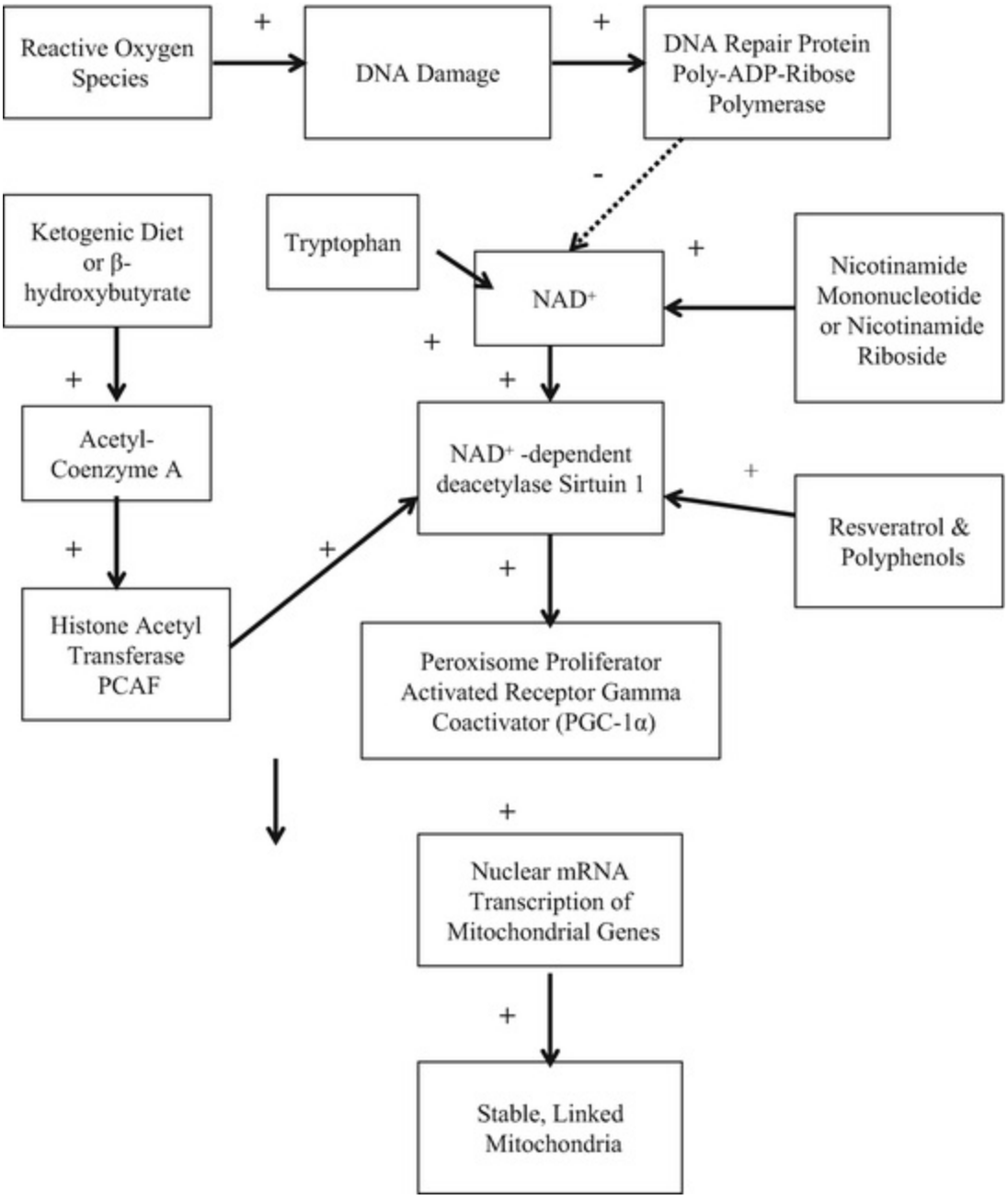

Fig. 5.5 NAD$^+$-Sirtuin pathway, adapted and expanded from Guarente (2014, p. 706) and Rodgers, Lerin, Gerhart-Hines, and Puigserver (2008, p. 48). All factors positively contribute to other factors, with the single exception of poly-ADP-ribose polymerase, which depletes NAD$^+$ necessary for Sirtuin 1 and subsequent processes

5.9 Validity and Reliability (Accuracy and Precision)

Including relevant theoretical and measurable variables related to a health outcome helps to achieve experimental validity and reliability. Too many researchers falsely confuse these two terms. Validity refers to accuracy, meaning that you are hitting the target with your study, that you are actually measuring what you claim to be measuring, not some correlated variable similar to your target outcome variable. Think of the

decision matrix (Table 2.1) with the true positives and true negatives for the situation at hand. For example, if you wish to measure posttrauma depression, make sure that you have the proper design and measurement tools pretested to measure that specific psychological construct and not something closely related, such as anxiety.

Reliability also is called precision, meaning that you are consistently hitting the same point on the same target with little error. However, reliability is not validity because you might be aiming at and hitting the wrong target! You might have a wonderful instrument that invariably measures something that you call self-esteem, but you might be precisely measuring another closely related attitudinal concept. There are many copycat psychometric personality inventories that proclaim to gauge one's personality profile, similar to the Meyers-Briggs Inventory, although some of them generically measure loose personality attributes, even when individuals respond randomly to the questions. Likewise, there are proponents of body language interpretation, yet Paul Ekman (1992) maintains that even with expert training, one can at most achieve about 80% precision, leaving a whopping 20% error rate. For many decades and even today, ethologists maintained that Hamilton's (1963) rule explained altruistic behaviors of individuals: an individual is willing to sacrifice their own fitness and reproduction and help another individual to reproduce if their genetic relatedness is greater than the cost/benefit ratio of the behavior. However , Nowak, Tarnita, and Wilson (2010) received heavy criticism when they demonstrated that most eusocial species utilize diplodiploid, not the theory-expected haplodiploid (e.g., honeybee *Apis mellifera*) sex determination. Furthermore, none of over "70,000 parasitoid and apocritan *Hymenoptera* (e.g., wasp species), all of which are haplodiploid," (pp. 1057–1058) are eusocial, thoroughly questioning Hamilton's rule of genetic relatedness and altruism. Nowak, Tarnita, and Wilson (2010, p. 1059) concluded that "something," not genetic relatedness, is greater than the cost/benefit ratio for eusocial behavior to occur.

Mulling over a valid construct should be a carefully planned process. Samuel Messick (1988) provided an extensive treatise on the types and approaches to validity : (a) face validity, (b) content validity, (c) construct validity, (d) concurrent validity, and (e) predictive validity. We arrange these types in order of increasing strength. Face validity is the easiest and is sometimes appropriate: the measure appears to truly assess the concept, at face value (e.g., obvious to an objective viewer). Content validity often is determined by a panel of experts, who reach agreement on the specific criteria and measures that are necessary to identify the given construct. Construct validity evaluates the various variables and factor loadings that are predicted by theory to represent a psychological construct; factor analysis and structural equation models often are used to evaluate construct validity. Concurrent validity is established by correlating a new measurement instrument with an existing measurement tool that already has been validated. Predictive validity is the strongest validity, as the measurement tool accurately predicts behavior (i.e., high sensitivity and specificity). For example, an

instrument that measures aggressive behaviors actually predicts aggressive acts, although this is an important but ethical issue given that we want to limit/eliminate such acts in actual society.

The approaches to testing your measurement instrument are complementary but distinctively different, neither very complicated, but researchers often shortchange their study preparation by just measuring reliability , which is not validity (Crocker & Algina, 1986; Messick, 1988). Reliability of similar measurement items is assessed via Cronbach's alpha. If various raters are used for all or grouped subjects, then a decision type study is used, and the consistency of rater agreements can be evaluated using coefficient kappa or the intraclass correlation coefficient (Crocker & Algina, 1986). For validity studies, factor analysis (Gorsuch, 1983) is used to evaluate the loadings of measurement variables onto a construct and/or subscales of the construct. Path analysis, structural equation models , hierarchical linear models , and even Generalized Linear Model repeated measures ANOVA can test whether measurement variables predict a given health outcome for predictive validity.

Experimental design validity also comprises external and internal study validity, and there exist design weaknesses that can become threats to the validity of the study design (Gay, 1992). Internal threats to validity include bias in the selection of study participants (e.g., convenience samples); maturation of participants, including acclimation to study procedures and retesting; Hawthorne effects (e.g., behavior change just due to the fact of the participant being observed); historical events impacting participants; natural regression of participant behaviors toward the population mean; and problems with the measurement instruments. External threats to validity include whether or not the study sample is representative of the overall population and whether or not the study results will generalize to other situations, the latter being affected by interactions between the testing and treatment, participant selection, and other tests used in the study. Further details on study validity and experimental designs can be found in Gay (1992).

5.10 Summary

The net result of the method of path coefficients is the realization that many variables, some seemingly insignificant, may contribute directly or indirectly to given health and behavioral outcomes. Along the same lines, any decision or action we take, or do not take, has immediate direct effects on others and potential indirect effects long-term. The Pembrey et al. (2006) demonstration of transgenerational epigenetic pre-pubertal nutritional effects of grandparents on grandchild morbidity /mortality represents one prominent example out of the approximately infinite interactions in the universe, leave alone the thousands of actions that each of us makes every day.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_6

6. Stability and Reversibility/Irreversibility of Health Conditions

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Abbreviations

DNA Deoxyribonucleic acid

FDA U.S. Food and Drug Administration

ICF International Classification of Functioning, Disability and Health

WHO World Health Organization

Most physiological processes are extremely stable for many decades of the human lifespan. Neural stimuli from the sinoatrial node pacemaker reliably trigger a heartbeat approximately once every second for years with little deviation outside of sympathetic and parasympathetic nerve feedback from other body systems (e.g., blood oxygen levels). The velocity of the heartbeat is modulated by stress , exercise , and relaxation stimuli from the sympathetic and parasympathetic nervous systems. The digestive system reliably moves food and absorbs nutrients through smooth muscular and neuroendocrine feedback mechanisms, even rebounding and phase resetting quickly from the occasional stomach virus or Salmonella bacterial infection. We conduct daily activities with fairly regular routines in sleep/wake cycles and levels of cognition/awareness.

Therefore, the complex human body exhibits exceptional stability and resiliency toward this stability via myriad feedback mechanisms at the molecular, cellular, tissue, and extracellular matrix levels. As will be described in subsequent chapters, these systems operate at far-from-equilibrium conditions in that they involve organized information and chemical processes for efficient energy and structural formation (Nicolis & Prigogine, 1981). Pure equilibrium systems would be random and chaotic with the equal distribution of energy, information, etc. Living organisms and the

processes within life require complex structure, organization of information flow, reliable copying of this information for cell and tissue maintenance, as well as reproduction of the entire organism. The compartmentalization of information and the molecular shuttling of energy and molecules to needed locations are staggering and efficient.

6.1 Irreversible Change and the Arrow of Time

Nevertheless, errors occur that lead to gradual, sudden, and/or long-term deviations from optimal functioning. These events can occur anywhere in the life cycle, although they are more pronounced as environmental and epigenetic changes accumulate past risk threshold levels with age, coupled with body system declines that reduce the ability to rebound from these changes. Elskens and Prigogine (1986) and Prigogine (2002) described these events as temporal "symmetry breaking" and the "arrow of time ."

The arrow of time refers to the fact that, at least for macroscopic systems that we can observe, there is a broken symmetry in the bidirectional orientation of time such that it only moves to the future. This seemingly obvious statement stems from the second law of thermodynamics , the law of entropy that maintains the inevitable collapse of potential states to a zero energy ground state, where there is maximum entropy with a random distribution of information. There is no organization at the ground state.

Different systems move to the ground state at varying rates. Whereas most entities fall within a Gaussian or Normal distribution (i.e., Bell Curve), the Poisson distribution is a lopsided estimate of the probability of an event occurring, sloping downward with increasing time, such that most events occur within proximate time. In aging , humans live many decades such that the decline and death generally occurs on average in the eighth or ninth decade for individuals living in developed nations. For canines, longevity is much shorter. For box turtles, it is longer. Using a different analogy, a breaking wave on a beach lasts for but a few seconds, but the rippled landscape from an earthquake represents a similar sinusoidal wave that may last for thousands of years, withstanding wind and water erosion.

Consequently, time moves forward. It cannot move backward without the exact reconfiguration of every minute piece of information content in the system at the preceding moment and the moment before that, etc. To do so would require staggering amounts of energy as well as currently unachievable capacities to measure every aspect of a system. Furthermore, Heisenberg's uncertainty principle would preclude us from ever achieving this task because the act of observation would interfere with the task.

Chemical reactions catalyzed by enzymes to lower the activation energy can convert a combination of reactants to thousands of products within seconds. Without the enzymes, the reactions might not occur by themselves for a thousand years, if at all. The coupling of interacting systems and energy is essential to the organization and

complexity of living systems, an important concept for health care and trajectory analysis that will be discussed in Chap. 7.

Nevertheless, chemical reactions are systems that can be reversed. The direction of the reaction can slowly or strongly proceed toward formation of products, depending upon multiple factors such as the concentration of reactants, available energy, catalyzing enzymes and cofactors that optimize enzyme functioning, pH, temperature, ionizing radiation, etc. However, the products of the reaction can reverse to the formation of the original reactants (although not the exact atoms involved in their original combinations) given alternative enzymes and changes in these same factors. In the middle, the reaction can be balanced, with some reactants converting to products, some products converting to reactants (Fig. 6.1). For biochemical reactions in living cells, many far-from-equilibrium living processes (see Preface and Chap. 7) utilize this balance. Think referent standard ranges for various laboratory examination results. Gradual genetic and epigenetic changes in the information systems (i.e., DNA) over many years lead to aging and eventual structural/systems collapse for these processes. More acute events (e.g., disease or injury) can disrupt these events at any age and may accelerate the gradual genetic and epigenetic changes.

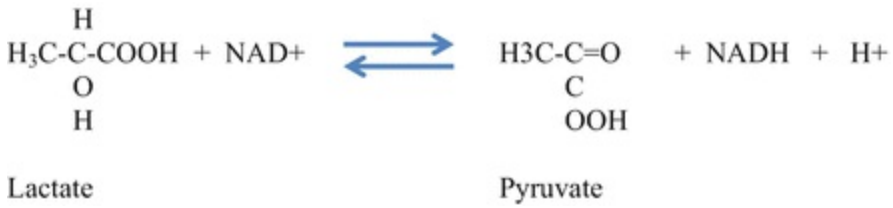

Fig. 6.1 A Standard Chemical Reaction, the end-glycolytic product lactate reacting with oxidized Nicotinamide Adenine Dinucleotide (NAD+), a large molecule that becomes reduced to NADH and simultaneously forming pyruvate, which is transported across the inner mitochondrial membrane for the Citric Acid Cycle and aerobic production of energy . The specific reaction shown here can move to the right or to the left depending upon the pH of the cytoplasm

For health care, these events manifest themselves in the many conditions that our medical and health programs attempt to prevent and/or to treat. We find similar types of situations with biochemical reactions in the human body (cyclical), environmental and epigenetic changes (directional), behavioral changes (cyclical), and outcomes of health behavior decisions (directional), etc. Prevention activities alter the course of events for a given patient by reducing the likelihood or time of occurrence of specific maladies, perhaps preventing their ever happening, thus altering a possible future path (see Chap. 8). This is the primary goal of health policy and interventions: to change the future. Hopefully, the prevention activities, programs, treatments, and other interventions will yield positive outcomes. We can never be certain, because the alternative futures/trajectories will never have existed. Having the best validated evidence for health outcomes from basic and applied research, proper decision making in policy

development, and delivering equitable treatments to everyone should produce positive outcomes.

Decision-making (Chap. 2), experimental validation, and the method of path coefficients (Chap. 5) are essential to applying health programs and medical treatments that yield the most optimal outcomes for every individual. Nevertheless, we must be aware that the method of path coefficients also applies to actions not taken and their positive or negative outcomes (see Chap. 8). Additionally, the interference of politics, flawed decision-making heuristics (e.g., fallacies ; see Chap. 3), and bad science into public health can yield terrible outcomes. Even medications that endure the rigorous and expensive U.S. Food and Drug Administration (FDA) approval process may have negative side effects (due to the complexities of linked cellular biochemical reactions) and may ultimately be shown to have negligible or even harmful effects.

The result is that we have an imperfect system that strives for improvement with better science and policy. Many conditions can be treated, and people can return to a relatively normal level of functioning. Few conditions can be reversed or even improved beyond the original physical situation or design. Therefore, except for isolated chemical reactions within cells, the trajectory of events and, hence, the arrow of time move forward, dependent upon past events and non-events that have established the pattern for the present (Fig. 5.2).

6.2 Levels of Functioning

For a given health condition, we can establish levels of functioning that have been estimated from population averages, bearing in mind that some individuals will be outliers from the normal distributions of such functioning due to genetic/epigenetic uniqueness and environmental exposures unlike that of any other person. Using the International Classification of Functioning, Disability and Health (ICF; World Health Organization, 2001) as an example, we can examine health variables as diverse as Immune Response (ICF b435) or Individual Attitudes of Health Professionals (e450). If either or both of these conditions are barriers to improved health, we can rate them as follows:

0. b435.0 or e450.0: No barrier to improved health (0–4%)

1. b435.1 or e450.1: Mild barrier to improved health (5–24%)

2. b435.2 or e450.2: Moderate barrier to improved health (25–49%)

3. b435.3 or e450.3: Severe barrier to improved health (50–95%)

4. b435.4 or e450.4: Complete barrier to improved health (96–100%)

Conversely, if either or both of these conditions facilitate/help to improve health, we can rate them as follows on degree of positive contribution:

0. b435.+0 or e450.+0: No facilitator for improved health (0–4%)

1. b435.+1 or e450.+1: Mild facilitator for improved health (5–24%)

2. b435.+2 or e450.+2: Moderate facilitator for improved health (25–49%)

3. b435.+3 or e450.+3: Severe facilitator for improved health (50–95%)

4. b435.+4 or e450.+4: Complete facilitator for improved health (96–100%)

The same goes for hundreds of body functions, body structures, activities and participation in society, and environmental factors. The WHO ICF coding system easily could have negative scores for the barriers , such that we truly have a continuum of scores from complete barriers to complete facilitators , the probabilities of which will be addressed in Chap. 8.

The ICF is not intended just to evaluate the level of functioning or degree of disability for people with disabilities. It can apply to the holistic health evaluation of any person at any time. Every person experiences ups and downs in various health and mental evaluations on a daily basis, even for conditions as simple as fasting for a day or not getting enough sleep. Virtually every person will encounter at least an acute, temporary disability and probably some chronic disability in some body structure or function during their lives. The makers of the ICF intended for the tool to complement the ICD-9 and ICD-10 diagnostic/billing codes for medical conditions.

Using the biopsychosocial ICF model (Fig. 4.1), we can develop health procedures and monitoring systems to follow individual conditions over time, even using smartphones and other technological applications for daily assessments. The goal is to maximize human performance and to minimize barriers across the physiological and environmental/personal factors that impact various aspects of health. All of these efforts are forward directed in time. We cannot reverse conditions, only treat and modify for optimal functioning.

6.3 Measuring Disturbances to Functioning

Prigogine (1977) showed that disturbing a system near equilibrium yields:

$$S = S_0 + \delta S + 0.5\delta^2 S \tag{6.1}$$

where S is the total entropy of a dynamical system, S_0 is the initial entropy, δS is the first-order partial derivative or change in entropy, and $\delta^2 S$ is the second-order change in entropy. Glandsdorff and Prigogine (1971) had shown that $\delta^2 S$ is a Lyapunov function near the equilibrium that dampens fluctuations in a system. Furthermore, the time derivative $\delta/\delta t$ of $\delta^2 S$ is equivalent to the entropy production, a phenomenon also noted by Ruelle (1989). Prigogine (1977, 2002) argued that entropic fluctuations near non-equilibrium points lead to "dissipative structures" that are "sources of order," following the above entropy equation and the Helmholtz free energy equation:

$$F = E - TS \tag{6.2}$$

where F is the free energy, E is the internal energy, T is temperature, and S is the system total entropy . At equilibrium , $F \sim 0$ and E balances TS. At low temperatures, E dominates, whereas at high temperatures, TS dominates (Lesne & Laguës, 2012)

The directional and irreversible shift in a system's properties occurs at a non-equilibrium critical point around which disturbances create vortices or tori fluctuations in the system. The system will be stable if $\delta^2 S$ is negative, but it could become chaotic with positive values, the greater of which would dampen the fluctuations. Additionally, Lesne and Laguës (2012) maintained that the coherence length ξ is "the range of correlations of the order parameter in the system," (p. 37) and that it is "the smallest distance over which the order parameter could change" (p. 65). The coherence length converges near the critical point. For a three-dimensional vortex near the critical point , Lesne and Laguës (2012, pp. 68, 98) estimated the coherence length to be:

$$\xi \sim \exp\left(1.5t^{-0.5}|\right) \tag{6.3}$$

$$\xi(t) = \xi_0 t^{-\upsilon} \tag{6.4}$$

where υ is a scaling parameter equivalent to (p. 180):

$$\upsilon = \log b / \log \lambda_1 \tag{6.5}$$

The parameter b refers to the number of dimensional sites in the system, and λ_1 is the Lyapunov exponent for $\delta^2 S$. Coherence length and, therefore, the Lyapunov exponent are temperature dependent. In his Catastrophe Theory model , Thom (1972, p. 48) emphasized that the "formal temperature of the system is $T = (\delta S/\delta x)^{-1}$; geometrically, the temperature is the reciprocal of the average over the energy hypersurfaces of the mean curvature of the hypersurface." If we imagine the system as a curved surface , the temperature is the reciprocal of the entropy and, hence, involves the increase of the

coherence lengths and decrease of Lyapunov variables in the vicinity of the critical point for the irreversible phase change.

Finally, Prigogine (2002, p. 299) summarized the relations involved in irreversible phase shifts as involving the following system dynamic characteristics:

1. Coupling of systems leads to interactions, resonances , or correlations between units;

2. Resonances and correlations prevent integrability;

3. Non-integrability leads to "irreversibility and to a probabilistic description" of the system;

4. Non-integrability ends stasis.

Relating this situation to path coefficients and trajectories, Hiley (2012) argues the directional intersection of the past and future as "process" or "becoming." Specifically, he invokes physical and biological arguments from Feynman (1948), who described a moment as a wave function sum of multiple pathways containing information from the past that intersects with a conjugate wave function of multiple pathways containing information from the future, and Kauffman's (2000) emphasis on current potentialities translating into the future based upon constrained past events that actually occurred. This latter point was illustrated in Fig. 5.2. Hiley's (2012) perspective has the appearance of bidirectional, reversible time, but his emphasis is on the quantum level, not macroscopic events that emerge from the microscopic in a directional sense of becoming.

For health systems and trajectory analysis , we therefore are interested in the intersection of previous biological and behavioral events, constrained by events/pathways of the past that reached the present moment, and future potentialities based upon the decisions, knowledge, imagination, and technologies that we have in the present. How well that we implement decisions and knowledge depends upon the health data that we collect, the comprehensiveness and validity of this information for specific individuals, conditions, and environments, the subsequent molding of policy and likely effective interventions, the application of specific treatments and follow-up programs to positively change conditions for improved individual health outcomes, and the continuous monitoring plus feedback evaluation of each of these processes during the treatment and follow-up. Therefore, the healthcare process itself is a trajectory that has multiple potential pathways, the sum of which, if carefully planned, can lead to desired results for the trajectory of health outcomes in the recipients. Additionally, many

interventions require careful, continuous applications for months or years, depending upon the unique genetic, epigenetic , environmental, and social characteristics of each healthcare recipient.

Hiley's directional intersection of past and future becoming model applies to all trajectories: individuals (e.g., patients, family members, clinicians, researchers, policymakers), environments, molecular and cellular events, etc. It is impossible to even begin to measure all of these interactions. Consequently, our models will be crude at best. Clinical epidemiology can provide us with strong cause-and-effect treatment programs that yield generalized positive outcomes, but negative results can ensue for some individuals due to many extraneous factors. Behavioral models have been weaker, given the looser predictability of individual and group behaviors resulting from human interactions and the trillions of synaptic connections within the human brain alone, leave alone the remainder of the nervous system.

6.4 Human Development

Models of child, adolescent, and adult psychosocial development generally describe human behavioral "stages" (Erikson, 1968; Feshbach & Feshbach, 1969; Hoffman, 1976; Kagan, 1984; Miller, 1993; Newman & Newman, 1991; Vygotsky, 1978). Such models estimate rough patterns of psychological and mental capacity change that correlate with significant changes in neurocognitive development. In most psychosocial models, the change falls onto six cognitive dimensions: competencies, self-encoding, expectancies, values, goals and plans, and self-control strategies (Newman & Newman, 1991, p. 112). These latent factors often take other names, including self-concept and motivation.

Directional psychosocial development is lifespan oriented. It involves innate behaviors , classical conditioning, operant conditioning, social learning, and cognitive behaviorism (Newman & Newman, 1991, p. 114). Whereas innate and other behaviors can be redirected along different pathways through the stimulus-control training of threshold responses (Skinner, 1935) and pharmacological interventions, most behaviors are much more complicated through many years of interfering positive and negative experiences that confound an individual's neurocognitive and emotional development, further coupled with genetic uniqueness. As has already been discussed, these are unidirectional, irreversible interventions if the recipient appropriately follows the treatment regimen. Behavior is altered to a different pathway, not reversed.

For most infants and children, cognitive and emotional development occur in tandem, with smiling, delight, laughter, and joy occurring within the first 6 months, and positive self-evaluation and exploration occurring by 2 years (Newman & Newman, 1991, p. 215). Nevertheless, negative parenting and other negative environmental experiences can lock early development into long-term aberrant behaviors that may be

difficult to overcome even with extreme interventions. Such behaviors might be characterized by extremes of anger, fear, and shame.

Subsequent behavioral development stages are arranged by approximate age ranges, although children and adolescents develop at different rates. Erikson (1980) proposed eight stages, including trust, autonomy, identity and intimacy stages, and integrity (see also Miller, 1993). Similarly, Heath (1977) proposed successive stages beginning with symbolism, recognizing others, developing interpersonal relationships, becoming mentally/emotionally stable, and becoming autonomous; these developmental stages are evaluated across domains of intellect, values, self-concept, and interpersonal relationships. Kohlberg (1976) proposed six stages of moral judgment in child and adolescent development that proceeds through levels of increasing responsibility in society: reward versus punishment, social approval, laws, contracts, and ethics.

Nevertheless, Hiley's (2008) quantum model of process cited Piaget and Inhelder's (1967) study of children who mapped their neighborhood. The study found that the child's mind conceptually maps distances to locations based upon individual context and perception of priority, not on physical distance. Hiley's (2008) argument is that thought is a process that emerges from the quantum regime, just as Heisenberg's Uncertainty Principle demonstrates that observation influences outcomes. The Piagetian, Eriksonian, Kohlberg, and other prominent human development theories are primarily social and context-oriented, although not in a sense that can be evaluated from a probabilistic perspective. Even with behavioral and information processing approaches to individual and group behavior changes, little has been done to map complex genetic, epigenetic , and intricate social support and environmental factors impacting specific and global behaviors.

Take aggressive behaviors , for instance. Violence represents a serious threat to global health, according to the World Report on Violence and Health (World Health Organization, 2002). We can approach both subtle, psychological violence and overt physical violence from multiple perspectives: the human capacity for evil as rebellion against God; an evolutionary adaptation for survival in hostile environments; and neurological imbalances, etc. Nobel Literature laureate Aleksandr Solzhenitsyn (1973, p. 147) observed, "Power is a poison well known for thousands of years…. For those, however, who are unaware of any higher sphere, it is a deadly poison. For them there is no antidote." Continuing, "But the line dividing good and evil cuts through the heart of every human being" (p. 168). Assuming seven hundred million years of metazoan evolution, it is doubtful that an expanding one hundred years of higher education could begin to reverse the hard-wired survival nature of aggression in human and other animal nervous systems (Lorenz, 1966).

Furthermore, the capacity to allow aggression to occur is very strong, as Milgram (1965) established with his provocative but illuminating obedience to authority simulated electroshock experiments. Likewise, empathy seems to be a unique attribute

for humans and higher primates, yet its actual practice appears to be contextual depending upon social situations and pressures (Hollar, 2016). The moderation of aggression, except for defense, is a phenomenon that must be re-taught and ingrained for every generation within social and cultural institutions. There are no simple solutions, and variations in aggressive neurocognitive tendencies obviously exist, as the World Health Organization (2002) documents.

Therefore, multiple necessary and sufficient factors must be evaluated for controlling aggression and other behaviors that harm one's own health and that of others. Again, irreversible processes are involved and should be addressed by effective mechanisms that shift the behaviors . These approaches require the increase of directionally shifting undesirable behaviors by increasing the entropy or Lyapunov trajectory variable between the person's initial undesirable behavior and alternative behaviors, including targeted desirable behaviors. Simultaneously, this involves increasing coherence, or similar patterns (i.e., increased coherence lengths) between the person's behavior and desired behaviors. Therefore:

$$\lambda = \delta^2 S \sim \xi^{-1} \tag{6.6}$$

If the behavior is desirable, then λ must be minimized to avoid a drastic trajectory change. Similarly, the coherence length ξ must be maximized to match the desired behavior with its continuation. For biochemical reactions, this is achieved with appropriate reactants, energy supply, catalysts, and support matrix. Likewise, for behavioral interventions, appropriate long-term support mechanisms must occur, not a temporary or brief intervention and no follow-up. For most behavioral interventions, support and monitoring must be continuous for long periods in order to maintain the coherence and to minimize the λ deviation from trajectory. Rarely is this done due to staffing issues, time, money, resources, keeping track of patients, willingness of patients, family, and peers to adhere to the intervention, and overwhelming obligations to other patients.

If the behavior is undesirable, then λ must be manipulated to direct a trajectory change to an improved condition. Correspondingly, the coherence length ξ should be reduced to match the desired behavior with the change. In physiological systems, this approach is accomplished via phase shifting (see Chaps. 11 and 13), usually involving energy -driven shocks to specific systems (e.g., the myocardium) or by targeted pharmaceuticals (e.g., antidepressants). Such shocks might be temporary or long-term, the former more so for behavioral conditions, so continued follow-up monitoring and interventions often are required.

One approach to behavioral change is the introduction of decision-making heuristics (Kahneman, 2003; Swets, Dawes, & Monahan, 2000) that require System II Reasoning (see Chap. 2). Prisoner's Dilemma and Nash equilibrium scenarios seemingly promote cooperation between individuals (Nash, 1950; von Neumann & Morgenstern, 1953).

However, Press and Dyson (2012) demonstrated that for previous move, memory-based iterative Prisoner's Dilemma scenarios, one player with a specific strategy can set the other player's scores within a range of values, regardless of that player's awareness or evolutionary strategy. The implication from this finding is that decision makers can establish an "unfair" advantage with respect to their own versus other's outcomes in social cooperation situations, even in so-called fair games. Consequently, in periods of limited resources, it will be a natural tendency for decision makers to "stack the deck" against others and in favor of their own whims, a phenomenon that has been well established in human and animal behavior research (Hemelrijk, 2002; Lorenz, 1966). Even in our best decision-making scenarios, personal biases can produce bad decisions and outcomes (Swets et al., 2000; Table 2.1).

Adler and Posner (2006) offered an alternative perspective on changing individual behaviors . They advocated the economic approach of Pareto Analysis, where one can map individual utility preference curves between two alternative behaviors. The essence of their argument is that if Alternative A is enforced as a social good, then individuals supporting Alternative B will lose. The solution is to determine the differential profit advantage over the status quo for winning supporters of Alternative A and then use this differential to offer compensation to the losers, thereby encouraging losers to convert to Alternative A. Whether or not this approach consistently works in practice is debatable, but it supports the concept of offering long-term supports and incentives for individuals to change unhealthy behaviors. Punishing individuals likely will be unsuccessful, despite experiments by Tversky and Kahneman (1974) on Prospect Theory risk aversion tendencies by most decision-makers.

Pareto Analysis mirrors the Lotka-Volterra two species competition model, which assesses population growth and resource parameters. Rate of population increase generally determines which population wins. However, the two species can coexist with a balance if each species self-regulates (Smith & Smith, 1998, pp. 179–181). In this regard, individuals who receive the resources and treatments to control their conditions or behaviors are more likely to achieve a balance between preferred conditions over less desirable conditions, here using conditions in place of species.

Elliot Aronson's social psychology team (Stone, Aronson, Crain, Winslow, & Fried, 1994) used an induced hypocrisy approach to significantly improve the numbers of college students who used protective devices against sexually transmitted diseases, basically signing a contract that psychology "bound" them to follow through with a commitment. Such approaches have been expanded into other public health and social training efforts. Again, directional but not reversible change can be used to manipulate trajectories for positive thought and decision-making as applied to improved behaviors . Whereas much of behavior may be "hard-wired" into our species or strongly influenced by negative early life experiences, such strategies, coupled with longitudinal supports, can help many, but not necessarily all people with some of their behavioral

problems or with changes that would be beneficial to them and to society at large. As a further example, Mischel et al. (2011) described how one's childhood capacity for self-regulation with respect to delayed rewards tends to strongly positively correlate with stability and success in adulthood. We cannot reverse or reset people back to these early stages to make corrections. Instead, our goal is to redirect their behavior trajectories close to an improved direction moving forward in time.

The above description only superficially touches the vast literature on neurocognitive and developmental psychology, but the obvious fact is that each human is unique, genetically and/or epigenetically. Even at the physiological or biochemical modification level, the outcomes of treatments/interventions will be probabilistic in nature. This is the reason why we utilize the quantum approach, disputable, but advocated by many (Hiley, 2008; Wheeler, 1962, 1989; Zurek, 1998).

6.5 Summary

Whereas the coherence length and its inverse dominant Lyapunov exponent , ξ and λ, originally were defined within the context of quantum systems, Zurek (1998) maintained that λ, following Ruelle (1989), is also a measure of entropy . Furthermore, he separates the coherence length ξ into critical point and system size components, such that a macroscopic system such as the solar system can behave in a quantum fashion. The wavefunction for the system's existence emerges past the critical ξ and grows, squeezing in certain regions to reduce the largest Lyapunov exponent (and entropy) λ. For systems that have very large ratios of size to the critical coherence length, the coherence time will be very large such that stability will be maintained as entropy continues to be created but at far-from-equilibrium conditions, consistent with Prigogine's observations.

As we move forward with later chapters, these two variables will figure prominently in the mapping of trajectories for behavioral and physiological phase shift experiments. Furthermore, they are consistent with the method of path coefficients as currently utilized in multivariate regression and structural equation model analyses (see Chap. 4). Health and medical interventions serve as modulators to set the boundaries for trajectory change, hence maintaining λ within reasonable limits and the irreversible arrow of time . Furthermore, per Prigogine and Thom's mathematical models of order generated at far-from-equilibrium conditions and critical points , there is emergence of behaviors/processes (Hiley, 2012) that decohere, or lose coherence, from the quantum realm, as processes become unique and evolve along trajectories with large coherence lengths and times. This represents a new way of thinking for healthcare analysis, but it is consistent with a probabilistic description of current interventions and Wheeler's (1989) admonition for researchers to think along quantum lines, similarly along Kahneman's (2003) System II Reasoning and Wilson's (1998) Consilience applied

across all disciplines of knowledge.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_7

7. Energy Levels and Potentials

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Abbreviations

ATP Adenosine triphosphate

DNA Deoxyribonucleic acid

MRSA Methicillin resistant *Staphylococcus aureus*

RNA Ribonucleic acid

Many of us can relate to the school science example of potential energy with the river held back by a massive dam. In that example, gravity serves as a force for the conversion of the potential energy to kinetic energy , whereas the dam serves as the counter or negative force. As a result, we have the standard potential and kinetic energy equations:

$$E_p = mgh \tag{7.1}$$

$$E_k = 0.5\ mv^2 \tag{7.2}$$

where m represents mass in kilograms, g is the acceleration due to gravity (9.81 ms^{-2} at sea level), h is the height of the mass above the ground state (e.g., sea level or the bottom of the dam, depending on one's perspective), and v is velocity in ms^{-1}. The structural materials and curvature design of the dam must provide enormous strength against the staggering weight of the river, along with release points to relieve accumulated water.

7.1 Energy Is Central to Life Processes , Health, and Change

All living processes involve the conversion of energy for work at the physiological and molecular levels. We could define health as optimal functioning driven by efficient

transfers of energy. It is clear that disease taps the body's energy and resources. Viruses disrupt cellular metabolism specifically to replicate more viruses. Similarly, pathogenic bacteria release toxins that damage tissues, and the body must commit substantial energy for an immune response. Certain genetic or metabolic conditions alter the efficient functioning of biochemical pathways or mitochondrial energy production. Lack of exercise and poor nutrition leads to weakened body systems. Biochemical instabilities in regions of the central nervous system can produce inefficient or aberrant neurotransmission across trillions of synapses as well as neuroendocrine imbalances characteristic of varied mental conditions.

Public health and medical care have overlapped their services to some extent for the past 100 years, although public health has focused on prevention and monitoring, whereas medicine has focused specifically on treatments for conditions. Consequently, health and epidemiology have focused on the behavioral , social, and environmental "macroscopic " aspects of health. Medicine has focused on the physiological, biochemical, and cellular/molecular aspects of health. An understanding and integration of both are necessary for healthcare professionals from both disciplines to advance care and improved Healthy People outcomes. Therefore, when health policy experts discuss better health outcomes, they need to address functioning, level of performance, and the molecular/biochemical/bioenergetics aspects of health at a serious and not haphazard level.

Besides potential and kinetic energy at the macroscopic and microscopic scales, we can add one unique quantum perspective, Albert Einstein's mass energy equation describing the staggering energy that can be released by the transformation of a mass under nuclear temperatures:

$$E_{\mathrm{m}} = mc^2 \tag{7.3}$$

where c represents the velocity of light (approximately 3×10^8 ms^{-1}).

Einstein's relation is of little, if any, relevance to the bioenergetics of living systems or the potential relationships between body systems, health behaviors , individuals, and environments. Potential and kinetic energy relationships do relate at both the macroscopic classical level that we encounter in our daily lives and most physiological processes as well as at the microscopic quantum world at super subatomic distances smaller than the Planck length, $l_{\mathrm{h}} = 1.62 \times 10^{-35}$ m (or Planck energy $E_{\mathrm{h}} = 1.22 \times 10^{19}$ GeV; Levy-Leblond & Balibar, 1990).

7.2 Quantum Metabolism and Health

Still, Davies, Demetrius, and Tuszynski (2011, 2012) theorized that cancer and mitochondrial abnormalities may operate at the quantum level or at least in a quantum fashion, following from Hayflick's (2007) emphasis on molecular and genomic

instability as hallmarks of the aging process. Davies et al. (2012) emphasized that 1.9×10^{14} atoms/cell and approximately 1×10^{3} mitochondria per cell yields 1.9×10^{11} atoms energized per mitochondria, remarkably close to their estimated biological Planck's constant for the production of adenosine triphosphate (ATP) for energy in the approximately 3×10^{13} cells of the human body (see also Hollar, 2016). The mitochondrion is central to most cellular processes. It reproduces independently of the surrounding cell, having its own genome as well as having transferred a significant portion of its genome to the cell nuclear chromosomes, and it generates via electron transport carriers and hydrogen cation pumping a bioenergetics potential well of $\delta p \approx 220$ mV (i.e., the protonmotive force) that recycles the cellular energy molecule adenosine triphosphate (ATP; Nicholls & Budd, 2000; Picard, Shirihai, Gentil, & Burelle, 2013). Following a quantum approach, Hiley (2012) argued the importance of process in physical systems from which phenomena emerge, an approach that is increasingly being explored for ecological systems (Benincà, Ballantine, Ellner, & Huisman, 2015; Grimm & Railsback, 2005), and he suggested that quantum phenomena might be applicable for macroscale classical systems if the value of Newton's gravitational constant ($G = 6.673889 \times 10^{-11}$ Nm^2 kg^{-2}) fluctuates, which does vary with earth 's rotation rate over a 5.9 year cycle, or one-half of an 11-year solar cycle (Anderson, Schubert, Trimble, & Feldman, 2015; Bracewell, 1988).

Whereas the mitochondrion is a complex energy organelle that we cannot reliably measure in living organisms, its centrality to life demands our attention. Good health depends upon its functioning to enhance cellular, tissue, and overall individual fitness. Relegating it to the "difficult" scientific disciplines does little to advance our appreciation or innovative applications of scientific knowledge to health care. Energy potentials define all interactions for life, so the shifting energy conditions within the body reflect levels of health over the trajectory of the lifespan.

As we are describing path coefficients and a novel perspective on energy and surfaces in human relations, we tie these concepts together from three biophysical viewpoints:

1. Thermodynamics , the study of energy, its transformations, and "the relations among heat, work, and the properties of systems which are in equilibrium " (Lay, 1963, p. 1);

2. Topology, the study of the properties of objects that endure continuous transformations (Henle, 1979, p. 1);

3. Biotribology, the study of friction, lubrication, wear, and structural design between contacting biological surfaces (Dowson, 2012, p. 9);

4. Ecology , “the study of the interactions that determine the distribution and abundance of organisms” (Krebs, 1978, p. 4);

5. Catastrophe Theory , the study of underlying phenomena that are the basis of regional fluctuations occurring around physical transition points (Thom, 1972, p. 42).

We use thermodynamics to measure changes in energy within living systems, both from a pure kinetic/potential dichotomy and from the information content of living systems.

7.3 Systems Topology and Ecology

Topology is relevant because all living processes involve and occur on surfaces , whether the surface is a lipid bilayer cell membrane, a coastal estuary, or a building. Indeed, even psychological processes and thought may be mapped upon theoretical manifolds (Hiley, 2012). Related to Topology is Biotribology since cells, tissues, behaviors , and human interactions occur between surfaces in contact. Lightning in most instances occurs due to buildup in the potential difference between a negative region of cloud (one surface) and positive ground (a second surface), in the process creating energetic reactions between atmospheric nitrogen and oxygen to produce nitric-based molecules important for life (Uman & Krider, 1989). Similar processes occur across the inner mitochondrial membrane.

Ecology examines interactions between organisms that determine their distribution and can be applied to inter- and intra-cellular cooperation and competition between cells, organelles, and viruses , even molecules just as it can describe the systems dynamics of a grassland, estuary, or rainforest. Finally, catastrophe theory links all of these disciplines together into the actual emergence of phenomena from system interactions and the underlying mathematical as well as physical properties leading to system behaviors . Whereas traditional public health and medicine examine the physical presentations of given health conditions via the traditional disciplines (e.g., epidemiology , microbiology, endocrinology, cardiology , urology, etc.), our approach involves the complementary, underlying systems approaches to unraveling the trajectories of necessary and sufficient factors leading to health conditions as well as to health outcomes. Therefore, we primarily are interested in problems of ultimate, not proximate, causation.

All life and all physical events in the universe are predicated on energetic potentials and driving forces to maintain these potentials. The earth is not a closed system, nor is the solar system despite the staggeringly vast interstellar distances and near complete

vacuum conditions between even nearby stars. For our solar system, the sun overwhelmingly is the driving energetic force, releasing 2.4×10^{39} MeV s^{-1} of energy and 1.8×10^{38} neutrinos s^{-1} isotropically (i.e., all directions; see the discussion by Rolfs & Rodney, 1988, p. 491). About 64×10^{9} neutrinos cm^{-2} pass through the earth 's surface each second, although it is the dissipated energy that drives all life on earth . Furthermore, the sun , its planets, a trillion comets, and other orbiting objects orbit over 250×10^{6} years at 2.5×10^{17} km distance the central black hole singularity of the Milky Way galaxy at a relative velocity of 16.5 km s^{-1} and oscillating above and below the galactic plane at a periodicity of 66×10^{6} years (Bash, 1986; Frisch, 1993), the latter no doubt affected by some unknown external driving force from the galaxy's past.

Some of the tiny but relatively substantial percentage of energy that reaches the earth 's surface is absorbed by the thylakoid membranes of photosynthetic bacteria and algal/plant chloroplasts, with the natural semiconductor chlorophylls, carotenoids, and xanthophyll's triggering a series of coupled oxidation/reduction reactions along quinone and cytochrome molecules that are highly conserved in structure and that ultimately reduce nicotinamide-based cofactors for further coupling to water, carbon dioxide/oxygen, glucose, and other metabolic cycling reactions in cells. Without thylakoids to capture solar energy, animals, protozoans, and fungi steal glucose and metabolites from plants and from each other to further couple metabolic activities and the reverse cellular respiration activities (oxidation/reduction potentials again between quinones and cytochromes) that drive the recycling of the energy molecule adenosine triphosphate (ATP) and ultimate energy release in eukaryotic mitochondria or bacterial cell membranes. In both processes, quinones and cytochromes transfer electrons from high to low potential, in the end creating a hydrogen cation gradient across the inner mitochondrial membrane of eukaryotic cells that serves as the proton-motive force that drives the recycling of ATP by the complex protein F1 ATPase. Therefore, living systems cycle energy along potential gradients and coupled, cycling systems in order to survive (Eigen & Schuster, 1979), thereby driving each other, with the predominantly ultimate driver being the sun .

In humans and within other organisms, this coupling continues with the endless biochemical pathways that are responsible for cellular and tissue function, muscular activity, synthesis of blood, bone, cartilage matrix etc., differentiation of tissues, neuroendocrine activity, etc. that ultimately manifest themselves in physiological functions and neurological activities that define health and healthy behaviors . These immense systems represent marvels of creation and the development of life on earth . Nevertheless, we must deal with energetic relationships, particularly the interactions of these systems, friction, wear-and-tear, system breakdown, and entropy (i.e., the Second Law of Thermodynamics) and the enormous task of counteracting the negative outcomes of these processes for optimum health.

7.4 Catastrophes

Thom (1972, p. 42) defined "an ordinary catastrophe point" as a point y on a four-dimensional space **B** × **T**, "if the intersection of the catastrophe set K and the ball $b_r(y)$ of center y and sufficiently small radius r has, as model, a nonempty embedded semianalytic polyhedron without interior point, and also the restrictions of the processes to the open balls $b_r(y)$ are all isomorphic for sufficiently small r." What this means is that a small region of a sphere describing all possible processes (Fig. 7.1; see also Fig. 5.2 in Chap. 5) is unstable and creates system collapse for any other regions of relative stability within the sphere of all possible processes at that moment in time. The three dimensions of **B** represent a surface, or manifold (see Chap. 11), that changes over time **T**.

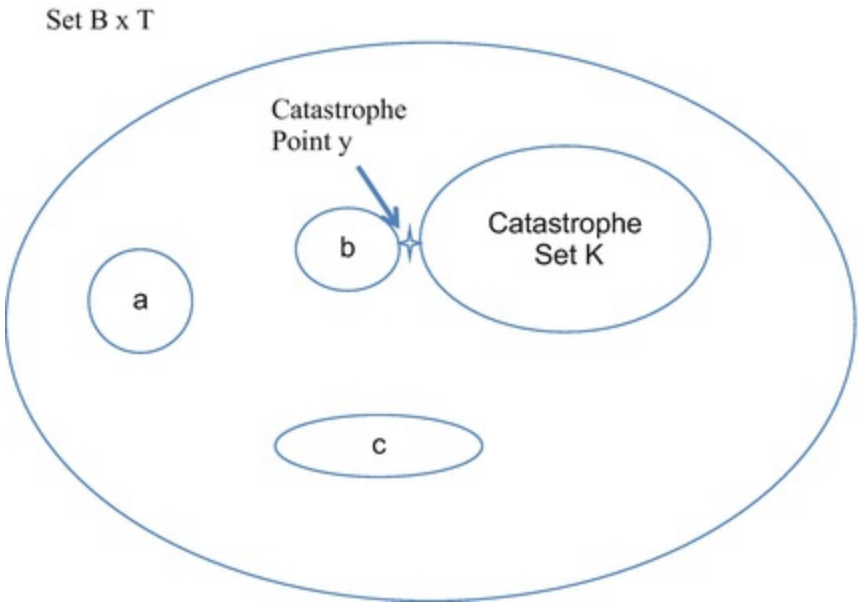

Fig. 7.1 Illustration of Thom's (1972, p. 42) description for Interacting Regions of Stability (i.e., "*b*") and Instability (i.e., "*K*")

Thom (1972) proceeded to classify seven elementary catastrophe types on manifolds M within regular spacetime $\mathbf{R}^4$ coordinates (i.e., **B** × **T**). Particular focus was on the parabolic and hyperbolic umbilics, which resemble wave behaviors , in both of which regional fluctuations about catastrophe points lead to bifurcations or cusps that collapse the system to a different state at a lower, stable energy potential.

As stated above, the purpose of Catastrophe Theory is to understand the regional fluctuations within the neighborhoods of catastrophe or critical transition points (i.e., the explicate, macroscopic reality that we see) in order to model the underlying, hidden phenomena of the catastrophe point itself (i.e., the implicate, quantum reality) (Hiley, 2012; Thom, 1972). Thom (1972) described competition between catastrophe regions

(see Fig. 2.5 in Chap. 2) to collapse multiple, interacting systems down to lower, more stable potential energy states. He went on to attempt a predictive model for the development of morphogenetic patterns in embryogenesis (Thom, 1972, pp. 161–199), an approach that ultimately failed in describing a constructive process. Nevertheless, Catastrophe Theory still may have applications for improved understanding of physiological processes, particularly cyclic processes in physiological rhythms (e.g., bone remodeling) and age-related catastrophic declines in cardiovascular vessel stability /elasticity and hemodynamics as well as immune system collapse in the surveillance of cancer and opportunistic pathogens.

To further outline the notion of catastrophe points , Thom (1972, p. 18) made the important distinction between continuous and discontinuous processes, the latter occurring in catastrophe events when a mathematical function describing change in a point of the set $\mathbf{B} \times \mathbf{T}$, or one of the function's derivatives, experiences a discontinuity. That is, the process experiences a drastic shift or change from one level to another. Invariably, processes involve the exchange of energy, so the discontinuity generally involves a catastrophic collapse to a lower, stable energy level with the release of energy, per the second law of thermodynamics . Alternatively, the input of energy to a process at a specific threshold point can drastically "jump" the process to a higher stable energy level. For example, the vaporization of water from the liquid to gaseous states involves a strong input of energy at the critical temperature, 100 °C, with structural changes in physical properties and processes at the critical temperature, a phenomenon termed critical opalescence.

Such structural changes are poorly understood but reflect the importance of trajectory analysis in health care. Physiological systems must be maintained within narrow limits for optimal functioning. Maintaining good health, both physiologically and behaviorally , involves the prevention of catastrophic changes involving collapses or jumps. Preventing aberrant behaviors and physiological anomalies will involve phase shifting these processes to a different, stable level, as will be discussed in Chap. 11. Such prevention might involve the input of energy, but it also will involve coupling interventions that maintain the physiological and behavioral processes at the revised stable level over long periods, thus forcing coherence or resonance of the desired processes or behaviors .

7.5 Energetic Jumps and Interventions

As discussed in Chap. 2, most behavioral interventions to reduce substance use/abuse, obesity, etc. have poor long-term outcomes for a variety of reasons. Most notably, failure to maintain the intervention, the resonant/coherent force, leads to rapid recidivism or return to the original bad behaviors. This is not necessarily the case for physiological jump interventions, which generally respond well to the input of a sudden

re-stimulus (as with treatments for arrhythmias) and definitely for longitudinal , continuous stimuli (e.g., cardiac pacemakers). Behavioral interventions are considerably more difficult due to individual decision-making, environmental influences, levels of education and knowledge related to conditions, goal-setting, and the complexities of neuroendocrine physiology and its influence on individual drives and behaviors. Most behavioral interventions are educational or pharmaceutical in nature. Behavioral interventions usually require long-term family, peer, and other social supports that may or may not be consistent. Furthermore, educational interventions may lack specificity or validity (see Chap. 5) to the actual underlying condition. Pharmaceutical interventions may target specific neurotransmitters and/or genetic targets with success; however, they may trigger a cascade of unpredictable secondary events due to the complexities of cellular biochemical pathways across multiple body tissues.

To illustrate the energetic principle of jumps, the electronic orbits of atoms are quantized at specific energy levels. As with lightning, the Bohr model of the atom is a system where electrons orbit the nucleus at speeds approaching that of light itself. The ground state at energy level 1 is the most stable point, a zero point of zero potential energy , which all systems (e.g., water behind a dam) attempt to reach. This is the second law of thermodynamics, the Law of Entropy, in which an isolated system tends to move from organization to randomness or equilibrium , the latter representing lack of structure and random equal distribution of information. With the input of energy, information can be organized into structures near self-organizing, seemingly chaotic, critical points that are far from equilibrium (Petrosky & Prigogine, 1993).

The two electrons with the lowest energy level are at the ground state, with potential energy at zero. The electron orbits (1s) are relatively spherical in this state. The second energy level can accommodate up to eight additional electrons (2s2p2p2p), each of whose momentum maintain their orbits at a higher energy level. One second-energy level with two electrons (2s) is spherical at a greater distance from the nucleus, whereas the remaining six electrons (2p's) orbit with elliptical patterns (Sommerfeld, 1916). Similarly, the third energy level accommodates 18 electrons (3s3p3p3p3d3d3d3d3d) with a circular and progressively more elliptical (and energetic orbits).

For an electron to move from a ground state to a higher, more elliptical energy level, the electron must gain energy from an external source, perhaps a collision with a photon. For an electron to transition to a lower energy level, energy must be released. Atoms have characteristic emission spectra based upon the release of electromagnetic energy from these electronic transitions, which are continuously, dynamically occurring. Spectrometric observation and recording of heating a pure element yields these spectra. For example, electrons transitioning from any of the outer energy levels to the ground state energy level 1 release electromagnetic energy at various wavelengths within the

ultraviolet spectral range. The ultraviolet electromagnetic energy spectral wavelengths (i.e., Lyman ultraviolet atomic spectrum) can be calculated using the following Diophantine equation (Coughlan & Dodd, 1991):

$$1/\lambda = R\left[\left(1/k^2\right) - \left(1/n^2\right)\right] \quad (7.4)$$

where λ represents wavelength (not Lyapunov exponent as will be used elsewhere in this book), R is the Rydberg constant (1.0973732×10^7 m^{-1}), k represents the target energy level ($k = 1$ for the Lyman spectral series), and n represents all other energy levels ($n = 2, 3, 4$, etc. if applicable for the Lyman spectral series).

If the target energy level for electronic transitions is the second energy level (above ground state), the emitted energy will be visible light (i.e., Balmer spectral series). Equation 6.4 will apply for the calculation of the series wavelengths, except $k = 2$ and the outer energy levels now will be $n = 3, 4, 5$, etc. if applicable. The same holds for the Paschen infrared spectral series ($k = 3$ and $n = 4, 5, 6$, etc. if applicable).

The general pattern of these transitions is that the shorter the electron transitions from outer energy levels to higher energy levels as staggered "ground" or "lower" energy states, the longer the spectral wavelengths and, therefore, the lower the energy. Returning to elliptical orbits, Ruelle (1989, p. 72) used elliptical models to describe the increased deviation or entropy in trajectory paths from an initial, equilibrium point. Ruelle's model (Fig. 2.6) could apply to zero ground states with maximum entropy or to far-from-equilibrium points, in either case with the eccentricity of the ellipse estimating the degree of discrepancy with the initial state. It also aligns with the phase shift transitions of electron resonant states in the microscopic environment of the atom as well as in the phase shift transitions that we desire to achieve in improved health, or the maintenance of stable, desirable physiological systems.

Ruelle's (1989) model applies to Poincare return maps (Fig. 2.2) for the trajectory analysis of a behavior or process that cycles and returns to a previous point or nearby over time. Physiologically, this can describe a Circadian rhythm , a heartbeat, daily glucose/insulin cycles with meals, neurological disturbances , or basic repetitive patterns of human decision-making and daily routines. Ellipses map deviation from the initial trajectory . With electrons in the Bohr atomic model, ellipses illustrate deviations based upon stable energy patterns.

Ruelle (1989) proceeded to quantify the deviations in maps to the λ Lyapunov exponents of the mathematical functions that describe trajectories . The Lyapunov exponents are the real parts of the eigenvalues, the solutions to the zeroes of the mathematical functions. Ruelle (1987) also demonstrated that the Lyapunov exponents are equivalent to the fractal dimension of the system and the Kolmogorov entropy . Therefore, the Lyapunov exponent serves as the measure of change in dynamical systems. This includes stable systems far-from-equilibrium as well as phase shifts that convert the systems to other energy states. It further maps the critical points for

catastrophe events in far-from-equilibrium systems.

Electrons, lightning, mitochondria, etc. illustrate the universality of underlying physical processes that drive regular processes at all levels, both living and nonliving. Hayflick (2007) even lists aging as a process in both nonliving and living matter among his six criteria for aging, including molecular instability as a critical event in these six criteria, genomic in origin for living organisms. Thus, thermodynamics is central to these events. Topology and biotribology introduce the boundary conditions of surfaces , such as the outer and inner mitochondrial membranes for bioenergetic events. Ecology introduces system relationships between different entities specific for living systems. Catastrophe theory provides the mathematical basis for all underlying behaviors across these complementary systems approaches.

Returning to the atomic example and the sun , Eigen and Schuster's (1979) hypercycle model of coupled energetic events is further illustrated by the Triple-Alpha Process that is essential for the generation of carbon, an essential element for living organisms and their biomolecules. This process involves stellar temperatures in the tens of thousands of degrees to fuse two alpha particles (i.e., Helium nuclei stripped of their two electrons), thus forming an unstable Beryllium nucleus that would decay on its own if not for the teeming froth of Helium nuclei in the stellar atmosphere. A second collision forms a triple alpha complex that has the exact resonance frequency (7.65 MeV) of an excited but stable state of Carbon. This is the mechanism by which Carbon forms (Rolfs & Rodney, 1988, pp. 386–389). Just as with electron energy levels, atomic nuclei of elements can have various potential energy excitation states that are resonance levels for smooth inter-conversion with other elements.

The situation with Carbon formation in the Triple-Alpha process is unique. If the 7.65 MeV Carbon resonance had been slightly lower, or the Oxygen 7.12 MeV resonance had been slightly higher, the two would have coincided, and all Carbon formed from the Triple-Alpha process would have subsequently converted to Oxygen, and life would not exist. The lower Oxygen resonance level does allow for some Carbon-Oxygen conversion, but this level is unstable such that many Oxygen complexes decay back to Carbon so that there is a balance between these elements when they are scattered through space from novae and supernovae (Hoyle, 1981; McGrath, 2009; Rolfs & Rodney, 1988).

This resonance process in electron orbitals and atomic nuclei excitation states further demonstrates the role of potential energies at the quantum level. Resonance in these processes also is equivalent to the coherence of quantum as well as correlating macroscopic processes that were described in Chap. 5. It is the process of decoherence between processes and their environments that leads to trajectory changes as the size of macroscopic processes beyond the critical coherence length that expand and have squeezed regions that can correlate with specific states/conditions, all involving energy and entropy changes (Zurek, 1998).

7.6 Stability and Instability in Health

The stability and instability of physiological processes and behaviors related to health measurements and outcomes relates to the coherence of states in far-from-equilibrium events (Petrosky & Prigogine, 1993). Deviations from coherence represent entropy , or the largest Lyapunov exponent , as body systems become aberrant. Treatments attempt to restore stable energy levels by resonating or cohering processes and behaviors with an external driving force (e.g., pacemaker, pharmaceuticals, peer supports).

For macroscopic physical processes, these principles apply in the compartmentalization of information and energy across the membranes and matrices of cellular organelles, tissues, entire organisms, and systems of organisms. Conditions such as diabetes, cancer , and even aging result from disruptions of temporal trajectories for bodily processes as well as physical/temporal disruptions of the surfaces /structures that support these processes (Davies et al., 2011, 2012; Hayflick, 2007; Picard et al., 2013; Thom, 1972). The disruptions serve as external driving forces that shift processes and structures to different resonance patterns that cumulatively contribute to physiological decline over time. As described in Chap. 6, these processes are not reversible (i.e., the Arrow of Time; Petrosky & Prigogine, 1993; Prigogine, 1977, 2002), but medical and physiological interventions can contain, to varying degrees, the altered trajectories associated with deleterious conditions and diseases. Interventions can establish boundaries to altered trajectories that contain progression of disease.

Nevertheless, immune compromise and/or age, lack of exercise , poor nutrition , and epigenetic /environmental insults, etc. can make these boundaries tenuous, such that a mild infection could become severe and life-threatening, resulting in sepsis. With good health, the robustness of body systems' bioenergetics at all levels will result in high thresholds that must be exceeded with low probability for acute or chronic illness to ensue. With age, severe injury, and physical decline, the thresholds are relaxed, increasing the probability that opportunistic infections could be deadly, secondary conditions to capitalize on these events, and the body to have fewer immune, neuroendocrine, and energy reserves to respond. The fragility of processes and structures such as pH balance, lymphocyte regeneration, capillary and arterial wall integrity, etc. can catastrophically collapse within days for the stage-four cancer patient, the older individual, or even a young individual with an aggressive MRSA (i.e., multiple-drug resistant *Staphylococcus aureus*) infection.

An ecological systems perspective maintains that these energetic interactions for health and disease must involve the consideration of every reasonable necessary and sufficient condition (Benincà et al., 2015). As described above, the 3×10^{13} cells of the human body contain approximately 3×10^{16} mitochondria, and these cells have

differentiated into specific tissue structures and functions based upon programmed epigenetic differential development. Additionally, the human body interacts with at least these many bacterial cells on body surfaces , and some intracellularly. Continuous exposures to environmental bacteria , fungi, protozoa, helminths, microscopic arthropods, etc. combined with nutrition , wear-and-tear on the body through motion and exposure to electromagnetic radiation and environmental chemicals make for staggering complexity in the regulation of body systems. Most bacteria on body surfaces are harmless, but some (e.g., *E. coli*) can become opportunistic infections given compromises to health. At the non-cellular level, viruses reproduce by destroying cells or by inserting into cellular DNA and potentially disrupting gene regulation.

Consequently, our bodies represent complex, multi-species ecosystems, with competition between species as well as cooperation/competition between cells/tissues of the body. Even within cells, the interactions between gene, RNA, and proteins are intricate, even coupled with mobile genetic elements and endogenous retroviruses (potentially over 20% of the genome) are at least as complicated as the extracellular competition (Claus & Liebert, 2014; Löwer, Löwer, & Kurth, 1996).

The public health response to prevention and treatment is global in nature. The vast complexity of inter- and intracellular body systems is impossible to regulate for even remotely fine detail. Most pharmaceuticals have various side effects, some severe for individuals with specific genetic/epigenetic backgrounds, given the extensive networking of molecular interactions within and between cells. Given this complexity and the thermodynamic fact of entropy (stochastic noise in systems), our health policy and interventions can never be perfect. Nevertheless, we can optimize approaches to medical and health care by using interdisciplinary systems thinking to improve the trajectory of health for individuals.

Therefore, epidemiological assessments are at best approximations, likewise for any other measurement tools that we attempt to develop. Hence, the decision matrix and ROC curves (Table 2.1 and Fig. 2.2) are useful tools to triangulate across multiple measurement devices to predict outcomes (Swets, Dawes, and Monahan, 2000; see Chap. 2). Longitudinal analyses on multiple factors across genetic , behavioral, and environmental domains per individual are important for improving health. Furthermore, this improved monitoring must be performed ethically with individual consent so that maximum, quality health, bioenergetics , and longevity can be achieved per individual wishes.

Path coefficient trajectories move forward these interdisciplinary principles so that proper assessments of individual and population health are comprehensive and realistic. As we argued in Chap. 5, these trajectories are directional. Paths lead to limited outcomes that are dependent upon the previous factors and events on a temporal line. Theoretically, all existence is interaction and the exchange of energy fields, per Nobel physicist Richard Feynman's famous quotation (Gleick, 1992, pp. 5, 283), and these

bioenergetic interactions represent the intersection of the past and the future (Hiley, 2012; Prigogine, 1977, 2002). As we will see in Chap. 8, even non-events potentially can have consequences in these events.

The challenge to public health researchers and epidemiologists is to adopt interdisciplinary systems perspectives for greater impact on health studies and interventions promoting improved outcomes. Research must go far beyond the standard demographics and basic self-report interviews or routine examination measures. Everything cannot be measured, but genomics and measures such as allostatic load and American Heart Association risk factor assessments (Hollar, 2013; Hollar & Lewis, 2015) can be a start for continuous, ethical monitoring of health, patient empowerment, and objective health improvements.

7.7 Summary

All processes require energy at all levels. Living systems and health are defined by far-from-equilibrium stability that is maintained by the synergy of systems, organized information and energy, and resilience to return to stability following disturbances . When health is compromised, suitable interventions involve energetic jumps, where the system is moved from one less energetic phase to a higher energetic phase. Health improvement requires the maintenance of the energy, whether or not it is actual energy or support resources, devices, and medicines to maintain the "jump" phase.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_8

8. On Negative Probabilities and Path Integrals

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Abbreviations

ATP Adenosine triphosphate

pCO_2 Percentage carbon dioxide

pO_2 Percentage oxygen

A quotation with no clear written citation but with enormous relevance to the human condition came from the famous theologian Dietrich Bonhoeffer : “Silence in the face of evil is itself evil. God will not hold us guiltless. Not to speak is to speak. Not to act is to act.” Consistent with Bonhoeffer’s faith (Bonhoeffer, 1933 [1995]), action and inaction both can produce outcomes that impact the human condition. For trajectories and path coefficients (Chap. 5), Bonhoeffer ’s statement applies to every aspect of human decision-making beyond its charge for us to pursue justice. It demonstrates that a negative action (i.e., inaction) can produce positive or negative effects just as much as a positive action, given that either precludes the occurrence of alternative pathways (see Fig. 5.2). Even on the macroscale of human interactions, this phenomenon mirrors the quantum microscale theories of process for interacting pathways and their probabilities (Bohm, 1987; Feynman, 1948; Feynman & Hibbs, 1965; Hiley, 2012).

8.1 Healthcare Analysis and Medical Errors

Health care involves myriad processes and procedures that vary widely in their scientific grounding, ranging from specific biochemical and diagnostic tests to less clear behavioral procedures. Decision-making and safety precautions abound, although the efficacies and degrees of success for the various processes and procedures continue to be the subject of evaluation. The Institute of Medicine (Kohn, Corrigan, & Donalson,

1999) estimated that possibly up to 100,000 Americans needlessly die each year due to medical errors . The study specifically identified major sources of these errors, including diagnostic errors, systemic process inefficiencies, lack of teamwork, lack of communication, failure to perform follow-up checks with patients, etc. Kohn, Corrigan, and Donaldson (Kohn et al., 1999, p. 3) argued, "The goal of this report is to break this cycle of *inaction*."

Many medical errors might be attributable to false diagnoses related to individual heuristic biases in decision-making processes , a psychological issue outlined by Kahneman (2002) in his Nobel lecture (see Chap. 2). Croskerry (2003) and Redelmeier (2005) identified specific "shortcuts" in reasoning and fallacious thinking that lead to misdiagnoses and errors; they also suggested cognitive strategies and colleague verification as corrective measures for biased heuristics in clinical care, per Kahneman 's (2002) arguments.

The Institute of Medicine report (Kohn et al., 1999) spawned many patient safety initiatives across the United States (e.g., TeamSTEPPS®; Hollar & Rowland, 2015). Safety and efficiency initiatives across every aspect of hospital and clinic facilities management and clinical procedures have been considered to address every conceivable aspect of correct diagnoses and procedures to minimizing infection transmission. Nevertheless, Makary and Daniel (2016) estimated that approximately 251,000 Americans needlessly died each year from 1999 to 2013 due to medical errors .

If Makary and Daniel (2016) are correct, the many efforts to improve the patient safety may have failed. Regardless, health care faces an even more daunting task to address processes of action and inaction to provide beneficent, nonmaleficient (i.e., "do not harm") care. Greater attention needs to be placed on the contextual and environmental factors impacting each person's care, given the complex social, epigenetic , and other environmental factors that can influence short- and long-term health outcomes (see Fig. 3.4). Consequently, errors of omission can be just as serious as errors of commission.

8.2 Population Health Distributions

Population health measures often assume a Gaussian (i.e., normal distribution), as shown in Fig. 8.1. For simplicity, let us say that the condition is body temperature, where the human population mean is 98.6 °F (i.e., 37.0 °C, 310.15 K). Approximately 68% of the healthy human population will have a normal body temperature +/− one standard deviation (i.e., a few tenths of a degree) from this mean. Approximately 96% of the healthy human population will have a normal body temperature +/− two standard deviation (i.e., an additional few tenths of a degree) from this mean. Furthermore, for any individual, these conditions can vary on a daily basis, by age, and by other factors,

with body systems (e.g., inspiration/expiration, sweat) compensating to maintain physiological balance. Therefore, any individual could fall across a spread of temperatures at a given measurement time. The cumulative distribution of all humans would form a Gaussian distribution for this particular variable (Fig. 8.1).

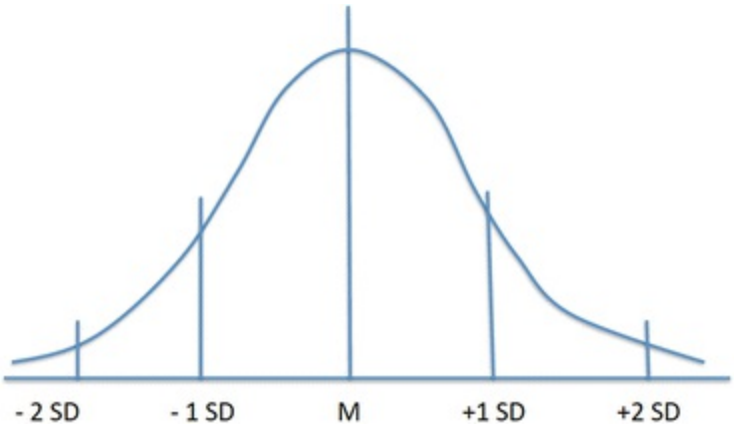

Fig. 8.1 The Gaussian, or normal, distribution (M = mean for the sample of individuals or events; SD = standard deviation). The rise and fall of the curve represents increasing and decreasing individuals/events, respectively

The same situation would hold for other variables such as blood pH, renal creatinine clearance, HDL cholesterol, etc. If we examined certain physiological states (e.g., heavy exercise) or genetic inheritance, we might encounter subpopulation s whose mean values are skewed high or low (Fig. 8.2) from the "normal" Gaussian human distribution for that particular variable. When various human subpopulations are superimposed (Fig. 8.3), a Gaussian normalized distribution generally emerges.

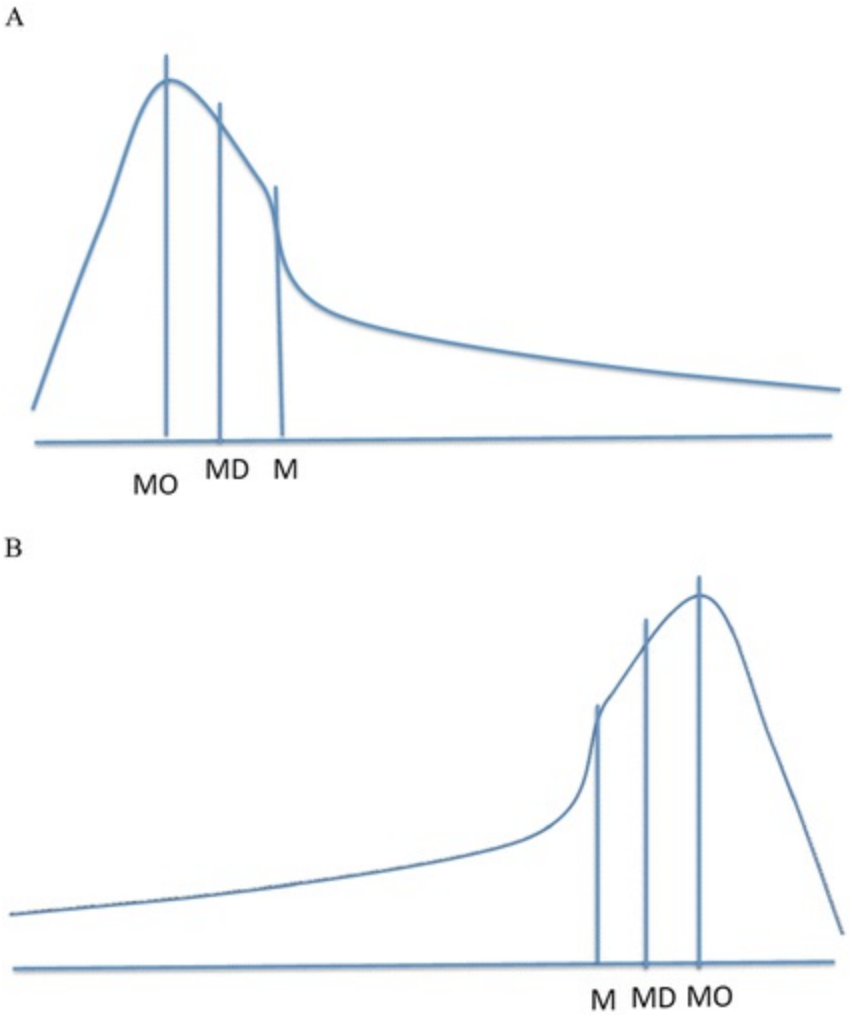

Fig. 8.2 Skewness of distributions. (**a**) Positive skew (mean > median > mode). (**b**) Negative skew (mean < median < mode)

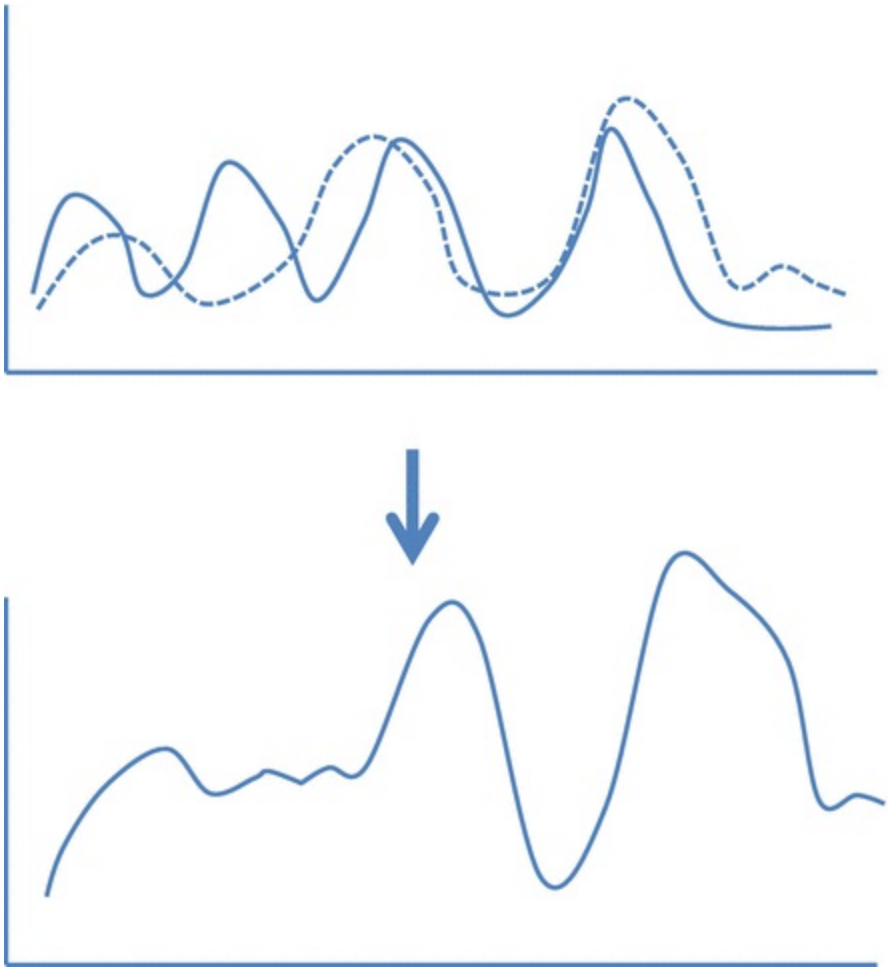

Fig. 8.3 Superposition of interacting, correlating, and/or coupled distributions

8.3 Superposition of Wave Phases (States) and Negative Probability

This principle of superposition is basic to wave behaviors and the analysis of harmonic systems (e.g., ocean waves). For individuals, measured behaviors may provide specific values at given times, but cumulatively, all individuals fall on a normalized distribution of values. Feynman and Hibbs (1965) observed that measurements can be more precise with large classical systems, including multiplicative probabilities of occurrence for multiple variables, but measurements are less predictable and rely more on superposition of probabilities as we approach ultramicroscopic and quantum levels. There are some researchers (Davies, Demetrius, & Tuszynski, 2012) who argue that certain biological processes (e.g., mitochondrial bioenergetics , cancer) may operate along these quantum probabilistic rules.

With any distribution of individual values for a given health condition, we can predict what the individual value might be based upon various additional health factors. Based upon statistics and epidemiology , the probability of a given value or outcome

should fall between 0 and 100% (i.e., 0–1). Nevertheless, at least for quantum microscale events, Dirac (1942), negative probabilities can occur (e.g., −100% to 0, or −1 to 0).

The idea of negative probability is not necessarily nonsensical. Feynman (1987) described the use of negative probabilities as a practical heuristic, much in line with Kahneman 's (2002) System II reasoning (see Chap. 2), and as an accounting approach to intermediate events leading to an observable/measurable reality. An immediate example comes from cash or checking transactions. If a person has $500 but makes a purchase by writing a check for $850 (i.e., leaving them −$350) while anticipating being paid $2000 the next day when the $850 would actually be cashed (i.e., resulting in $1650), the final result of this "floated check" scenario is positive. The same situation certainly applies to credit card transactions. The negative event is a temporary transition between successive observed events.

Lay (1963, pp. 291–292) provided a similar scenario with respect to entropy . Using Boltzmann's entropy equation, he calculated the probability of a one-pound mass falling from a given height to the ground at a specific temperature:

$$S = k \ln\left(\frac{W_2}{W_1}\right) \tag{8.1}$$

where S is entropy , k is Boltzmann's constant, ln is the natural logarithm, W_2 is the probability of the mass (system) having a macrostate on the ground at the end of the process , and W_1 is the probability of the mass having a macrostate in the air at a given starting height. Obviously, when the object is dropped (in the presence of gravity), the probability of the object reaching the ground is a certainty (i.e., $p = W_2/W_1 = 1.0$). Given the number of molecules in the object, Lay (1963, p. 292) calculated $W_2/W_1 = 3.77 \times 10^{18}$, virtually a certainty. Now, the probability of the object reversing its trajectory is the inverse, $W_1/W_2 = 2.65 \times 10^{-17}$, virtually zero.

In a real system , there would be counteracting forces to affect the rising or falling of this object. Of course, gravity is a central driving force downward. However, we could provide the object with energy to go upward against gravity. Balancing these two forces, we have the following equation:

$$F = \mathrm{ma} = \mathrm{kmv}^2 \tag{8.2}$$

where the left-hand force expression represents Newtonian gravity and the right-hand force expression represents a restoring force constant with kinetic energy . If the vectors for these forces are directly opposite each other, then we have zero motion, perfectly balanced. Increasing one force over the other causes the object to either rise or fall. As such, the probability of rising could be expressed as a positive probability (between 0 and 1) based upon the increasingly greater strength of the kinetic energy applied to the object, whereas the probability of falling would be expressed as a

negative probability (between 0 and −1). The converse situation could be described for increasing gravity and falling. Consequently, positive and negative probabilities represent relational descriptions between polar opposites, and they are directly applicable to the linear continuum of health conditions and behaviors that we assess, treat, and follow up on a daily basis.

Feynman (1987) challenged researchers to think beyond the conventional use of positive probabilities. This approach has not been used in statistics or epidemiology . Nevertheless, it has immediate implications to applied research interventions with positive and negative health conditions and behaviors. Figure 8.4 shows a continuum of outcomes for a given health condition, in this case a behavioral disorder. The severity of the disorder can extend from none to maximum, with the mean symptoms for the general population located somewhere in between the extremes of the behavioral continuum. No two individuals will be alike, even for the same diagnosed condition, even with identical genetic alleles affected. The objective of the behaviorist is to minimize the disorder, or at least to keep the symptoms at or below the population mean. These efforts might involve counseling, psychological or educational interventions, or prescription medications, along with the cooperation of the patient and social/environmental supports for these efforts.

Fig. 8.4 Continuum of behavioral or physical conditions. The mean is shown with a skewed 95% confidence interval

8.4 Applications of Negative Probabilities

From a population mean perspective, we can view the behavioral disorder (Fig. 8.4) bidirectionally toward two polar opposites, absence versus maximum conditions. With this approach, negative probabilities apply in one direction, positive probabilities for the other. Statistically, this situation is exactly what we find for standardized distributions, where the z-score means are set to zero.

Bartlett (1945) argued that the use of negative probabilities is consistent with the description of physical processes as long as negative events are coupled with positive events, with all events summing to 100% or 1.0. Feynman (1987) reiterated these arguments while distinguishing the summative nature of macroscopic classical probabilities compared to the superpositioning of probabilities at the super-microscopic quantum level.

Feynman ’s (1987) approach can be illustrated by the scenario presented in Table 8.1. Given two mutually exclusive conditions A and B, both totaling 1.0, condition A

includes one result that has probability −0.8, or an 80% probability of not occurring, much like Lay's self-levitating object in the absence of an energy source. Counterbalancing this result is result 3 under condition A with probability 1.5, or 150%, which also is permissible in excess of 100%. Result 3 at 1.5 is a negative probability of not occurring, algebraically a positive probability. Of the four results under condition A, result 2 at −0.8 is the least likely. Result 3 is the most likely to occur. Nevertheless, the four all-encompassing situations couple to yield a total probability of 1.0 for all events together, a requirement consistent with the laws of thermodynamics (Bartlett, 1945; Feynman, 1987). Condition B yields a standard set of positive or zero results, equally acceptable with all results summing to 1.0.

Table 8.1 Negative probability coupled with positive probabilities. See Feynman (1987) for further discussion and examples

Result	Condition	
	A	B
1	0.2	0.3
2	−0.8	0.5
3	1.5	0.0
4	0.1	0.2
Total	1.0	1.0

In living systems, the principle of negative probabilities can be illustrated in enzyme catalysis. An enzyme increases the likelihood that an energy -requiring chemical reaction will occur by lowering the activation energy required for a set of reactants to interact and to produce specific molecular products. Physically, this is accomplished by the genetically encoded shape of the enzyme protein, a specific set of tens to hundreds of amino acids which hydrogen bond and fold to a functional structure at body temperature. The three-dimensional protein structure of an enzyme is shaped to physically match or to conform to the shape of the chemical reactants. Therefore, by shape, the enzyme combines with and brings the reactants into close proximity, something that would be extremely unlikely to occur with the reactants randomly floating in a liquid, gas, plasma, or other types of substrates. Less energy is required because the enzyme brings the reactants together. The high negative probability of the reaction never occurring is controlled, and the likelihood of the reaction increases, often a millionfold or more increased probability in the presence of the enzyme.

Once again, enzymatic catalysis illustrates the coupling phenomena that enables negative probabilities to temporarily occur within an overall process . Eigen and Schuster appropriately modeled these coupling patterns in living systems through their Hypercycle Model, which applies to every level of molecular, cell, tissue, and organismal systems interactions. The interdependency of multiple systems, and systems

within systems, represents the resiliency of life itself, both for processes that insure proper functioning and survival, per Tinbergen's (1963) four principles (see Chap. 2), but they also serve as the reason why aberrant processes can be so difficult to modify for improved health.

For example, cardiac arrhythmias emerge when aberrant myocardial tissue regions begin stimulating muscular contractions that are incoherent with the normal sinoatrial stimuli that initiate successive filling and contractions of the atria and ventricles for efficient forcing of blood to the lungs and body. The task of the neuro-cardiologist is to bypass or to eliminate these ectopic foci. Similarly, aberrant synthesis and release of neurotransmitters in various regions of the brain can lead to aperiodic acute or prolonged mood disorders, depression, anxiety, paranoia, etc. that are incoherent and must be controlled to enable the person to psychologically and physically function. In both situations, the resiliency of coupled systems represents a strong positive probability of occurrence, but re-coupling of systems can restore order when negative probabilities , the probability of the event never occurring, are overcome.

8.5 Cancer

Similarly, cancer occurs when mutations or changes in gene regulatory pathways transform an affected cell to an immortalized state that rapidly proliferates. Every animal contains cells that become cancerous on a daily basis. Fortunately, an effective immune system usually identifies these aberrant cells and destroys them. Unfortunately, some cancer cells can mask themselves against the immune system's self-versus-nonself cellular monitoring, begin proliferating over a long latent period during which growth and metastasis occur before manifesting systems are identified. In cancer , negative and positive probabilities are applicable given the weakness of our diagnostic tools to reduce the latency period for detection and prompt treatment.

This fact was most keenly demonstrated by Stevens (1960) and then by Mintz and Illmensee (1975), who showed that teratocarcinoma cells that are injected into early-stage mouse embryos can differentiate into normal structures and into complete, normal mice, respectively. Without positional information, cancer cells proliferate and contribute to disease/death. Coupled with the positional information of developing embryonic cells, their molecular machinery is redirected from an immortalized, dedifferentiated phenotype to a normal, body position-specific phenotype. Without the molecular communication from neighboring, developing cells, the cancer cells continue with positive probability for spread. With the coupling of neighboring developmental intercellular molecules, the probability not only is reduced to zero, it becomes negative as the former cancerous cells develop normally.

This is an astounding finding given that the internal molecular machinery of cancer cells is chaotic, including abnormal chromosome numbers, shifting of bioenergetics to

an anaerobic, glycolytic pathway, and substantial epigenetic acetylation of histones and chromosome regions, thereby substantially altering gene expression and development. The reversal of these events in the embryonic environment illustrates negative entropy as well as the concept of molecular instability in cancer and aging (Hayflick, 2007).

8.6 Balancing Health and Probabilities

Returning to Lay's (1963) falling or rising mass probability example, objects fall due to the gravitational attraction of much larger bodies, namely the earth . Lay (1963, p. 291) states that the object could defy gravity and rise only by "…conserving energy and cooling off during the process ." If we consider the earth-moon system, there are multiple balancing, or LaGrange points (e.g., L1, L2, L3, L4, L5), where an object would perfectly balance between the counterbalanced gravitational forces of the earth, moon , and sun. From this multiple-body perspective, the probability of an object falling to earth or to the other bodies would be zero at one of the Lagrange points. The probability would exponentially approach positive one or greater (for earth) and simultaneously negative one or greater (for moon and sun) if the body was slightly closer to the earth from the respective Lagrange point and started accelerating toward the earth.

Therefore, for health conditions, we can achieve a balancing point where a condition can go in either direction. Probabilities range from positive to negative due to one's perspective/orientation on the continuum of the condition. The principles of stability and instability determine the maintenance of the condition at this balancing point or its trajectory deviation to various extremes. Sometimes stability lies within a narrow range, such as blood pH in the 7.35–7.45 logarithmic range. For other conditions, it lies above a specific threshold, such as synaptic firing rates for cognitive functioning, or below a specific threshold , such as carotid body monitoring of blood oxygen levels (activated for high pCO_2, simultaneous low pO_2 levels).

8.7 The Wave Function

Every classical or quantum process can be described by a wavefunction Ψ that acts across our conventional four-dimensional or alternative n-dimensional spaces. For example, the electrochemical proton gradient produced by the pumping of hydrogen cations by the F-1 ATPase across the inner mitochondrial membrane within our cells is $\Delta\Psi \approx 160$ mV. Incorporating a -1 pH differential across the membrane, the total proton motive force that sustains human and all eukaryotic life is $\Delta\mu_{H+} \approx 220$ mV (Nicholls, 1982). Similarly, electrocardiograms , electroencephalograms , Circadian rhythms , bone remodeling units, cardiac and cerebrospinal pulses represent wave behaviors at

the tissue level.

Waves are sinusoidal functions that permeate the universe at all levels for both living and nonliving matter and for energy itself. Every wave has an amplitude, including positive crests and negative troughs from baseline "calm," and each wave endures for a finite period of time, depending upon external contributing as well as damping forces (Fig. 8.5). The standard one-dimensional wave equation (plus time) for an oscillating spring or vibrating string is (Loy, 2007, p. 306):

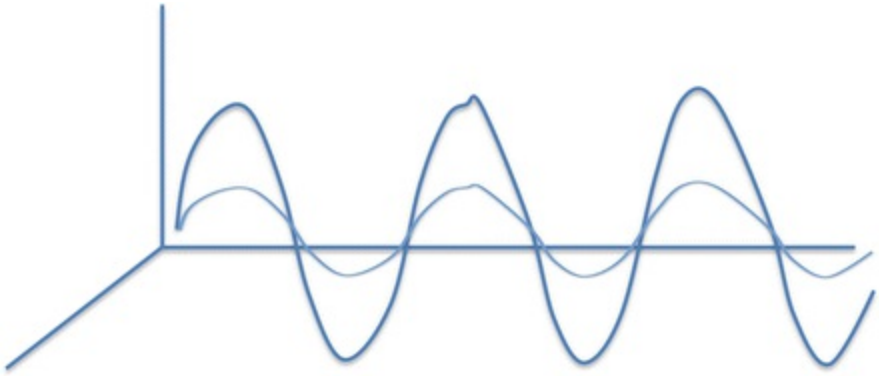

Fig. 8.5 A standing wave

$$\frac{\delta^2 u}{\delta t^2} = \left(\frac{\rho}{T}\right)\left(\frac{\delta^2 u}{\delta x^2}\right) \tag{8.3}$$

where x represents the distance from one end of the string or medium, u represents the vertical displacement of the string or medium from equilibrium , ρ is the mass density of the string/medium, and T is the tension (i.e., pressure) in the string/medium. The driving force that created and/or sustained the wave plus the inertial motion of the wave contribute to its motion, whereas friction with surrounding contact media, the tension in the wave, and other dissipative forces work against the continuation of the wave (Bracewell, 1965; Loy, 2007).

Equation 8.3 describes the wave as a function of displacement (e.g., Amplitude) over time. In describing the heating of solids, Joseph Fourier developed a remarkable transform that converts the wave equation into a function of amplitude and frequency (Bracewell, 1965, 1989). As an example, a light wave appears white and travels omni-directionally over time. A prism breaks a light beam into its component frequencies and amplitudes (Bracewell, 1989). Similarly, a musical note can be transformed into multiple fundamental, second, third, etc. harmonic waves (Loy, 2007). The Fourier transform equation is (Bracewell, 1965, p. 178; Bracewell, 1989, p. 94):

$$F(f) = \int_{-\infty}^{+\infty} f(t)\, e^{-i\omega t} \mathrm{dt} \tag{8.4}$$

or

$$F(f) = \int_{-\infty}^{+\infty} f(t)\ (cos\omega t - i\ sin\omega t)\,dt \tag{8.5}$$

where ω is the angular frequency ($\omega = 2\pi f$ or 2π/period), also called pulsation, the rate of change of the phase of the wave. We can adjust Eq. 8.4 to illustrate waves overlapping with different phases:

$$F(f) = \int_{-\infty}^{+\infty} f(t)\, e^{-i(\omega t+\phi)}dt \tag{8.6}$$

where the phase:

$$\phi = \frac{\delta}{T_0} \tag{8.7}$$

is the spatial relationship of a wave with respect to another "standard" wave having period T_0 (Fig. 8.6). The phase ϕ depends on the difference positive or negative δ from T_0. We will explore the applications of this phase difference to the computation of the Lyapunov exponent (previously introduced with coherence length) in Chaps. 11–13. The phase difference in health conditions is what we seek to adjust for returning a periodic condition to a "normal" range of functioning.

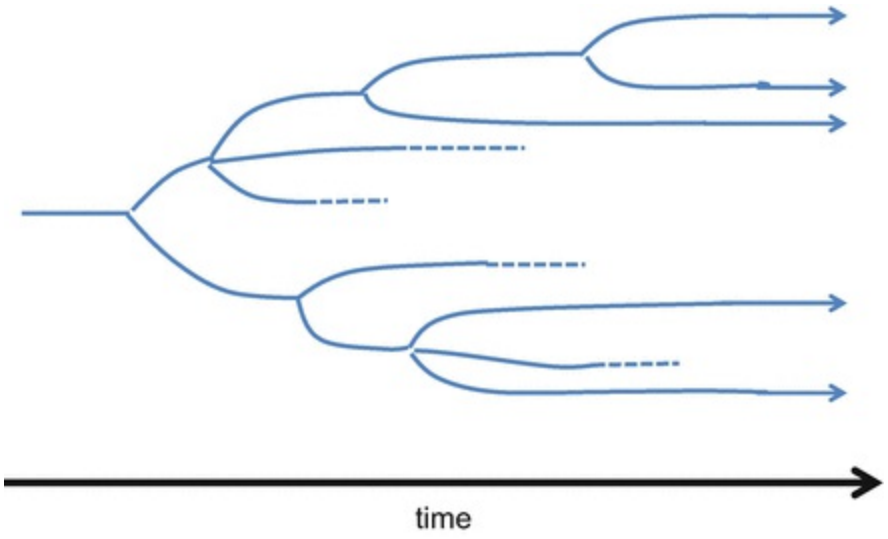

Fig. 8.6 Paths, and alternate pathways/trajectories that never happened

8.8 Feynman 's Path Integrals and Wright 's Path Coefficients

Wave functions can be applied to cellular biochemistry, physiological rhythms, music, seismology, and planetary science, any phenomenon where systems interact, especially at resonant frequencies. Wallerstein and Elgar (1992) evaluated wave functions and velocities for ocean waves breaking with the friction of the sloping beach, deriving Eq. 8.3 with the ratio of pressure change to density change (dP/dρ) replacing ρ/T. Most

notably, they found that the wave function behavior of ocean breakers was similar to the pulsation of RR Lyrae and Type II Cepheid variable stars.

At the quantum level, Feynman and Hibbs (1965, p. 58) described the wavefunction for a single particle as:

$$\frac{\delta\Psi}{\delta t} = \left(\frac{-i}{\hbar}\right)\left[\left(\frac{\hbar^2}{2m}\right)\left(\frac{\delta^2\Psi}{\delta x^2}\right)\right] \tag{8.8}$$

where $\hbar$ is Planck's adjusted quantum constant (1.05×10^{-34} J s) and m is the mass of the particle. The probability of a particle being at a certain location is the square of the wavefunction, $[\Psi]^2$. From the quantum perspective, the probabilities of interacting systems are not additive as with classical systems. Instead, the probabilities of interacting wavefunctions must address interference between the wavefunctions:

$$p_{AuBuC} = [\Psi_A + \Psi_B + \Psi_C]^2 = p_A + p_B + p_C + \left(\Psi_A\Psi_B^* + \Psi_A^*\Psi_B + \Psi_B\Psi_C^* + \Psi_B^*\Psi_C + \Psi_A\Psi_C^* + \Psi_A^*\Psi_C \right. \tag{8.9}$$

where the latter starred components in parentheses denote the interference terms. This reality of quantum systems allows for the expression of negative probabilities as well as complementary positive probabilities greater than 1.0 (Feynman, 1987).

From a health perspective , negative probabilities and the quantum wavefunction model may apply to molecular events in the cell and in neurocognition, consistent with Hiley's (2012) process theory. The quantum wavefunction may also apply to instabilities in aging (Hayflick, 2007) and in cancer (Davies et al., 2012). Feynman (1948) and Feynman and Hibbs (1965) further stress that quantum wavefunctions are the sum of all possible pathways (positive and negative) over which a particle could possibly have traveled en route from one spatiotemporal point to another. Their kernel equation for all possible paths of classical action from point a to point b (in three dimensions plus time) is (Feynman & Hibbs, 1965, p. 65);

$$K_{ba} = \int_a^b \exp\left\{\frac{i}{\hbar}\int_{t_a}^{t_b}\frac{m}{2}\left[x'^2(t) + y'^2(t) + z'^2(t)\right]\mathrm{dt}\right\} Dx(t)Dy(t)Dz(t) \tag{8.10}$$

where x, y, and z are directional components (i.e., quaternions) for the various paths, m represents mass, $\hbar$ represents Planck's constant, and the derivatives of time, x, y, and z dimensions are shown.

For a given health condition , there are many pathways or trajectorie s to follow, although some trajectories have much greater probabilities than others. When a cell follows a cancer ous pathway, it can be difficult to redirect the pathway, especially if the genetic or epigenetic change is locked into other cells as well. Similarly, addiction tendencies can be locked into specific pathways. Nevertheless, Mintz and Illmensee (1975) demonstrated that positional information could redirect the differentiation of a cancerous tumor. Therefore, our goal is to redirect high probability unhealthy pathways

to lower probability healthy trajectories that can be maintained. Again, the phase shift mechanism will be emphasized in Chaps. 11–13.

8.9 Coupling, Accounting, and Superposition

The energetic and positive/ negative probability information sharing/transfer between biochemical systems was well established by Eigen and Schuster (1979) and in countless biochemical pathways beyond the central cyclic /coupled pathways of cellular respiration and photosynthesis. Nicholls (1982, p. 3) specifically emphasizes the coupling of ATP synthesis, essential for all endothermic, bioenergetic chemical reactions, to eukaryotic mitochondrial and photosynthetic membranes and bacterial membranes. The central element that enables this coupling is "a proton electrochemical potential."

Living organisms are characterized by compartmentalization of chemical activities, especially so for eukaryotes, such that entropy is reduced and even exported from the cell (i.e., negative entropy). Toxic byproducts of metabolism and even highly acidic or basic chemicals that are essential for metabolism are contained within specialized vesicles, lysosomes, and other membrane-bound organelles. Margulis (1998), McMenamin and McMenamin (1990), and Thomas, Shearman, and Stewart (2000) noted that calcium is a necessary but toxic chemical within the cellular cytoplasm, yet excess calcium is exported outside of the cell, sometimes completely excreted from the organism, but often coupled with other necessary organismal activities, notably the construction of skeletons and exoskeletons. With respect to this extracellular calcium role in organisms, it represents a critical focal point for health and aging because infection and dysfunctional physiological processes lead to the abnormal calcification of blood vessels, cartilage, the kidneys, and other tissues, processes that are intricately associated with major human pathologies: heart disease, cancer , arthritis, dementia, and atherosclerosis (Carson, 1998; Hashimoto et al., 1998).

The coupling of negative and positive probability systems also figures prominently in the study of coupled physiological oscillators. Granada, Hennig, Ronacher, Kramer, and Herzel (2009) mathematically modeled positive and negative feedback responses for heart physiology , neural networks , and Circadian rhythms . Central to these processes is the maintenance of phase response curves (PRCs) that are influenced by neurotransmitters, melatonin, environmental factors such as light and temperature, and molecules such as the Nuclear Factor Kappa B-lymphocyte (NF-κB) family of transcription factors, the latter implicated in cancer initiation and progression (Hoesel & Schmid, 2013).

Bartlett (1945) and Feynman (1987) described negative probability as necessary accounting techniques for processes in which there is coupling between systems and where such negative events and counteracting hyperpositive events are realistic but not

recorded at the endpoints of the process. Such a perspective especially is relevant in micro- and nano-second quantum events and the superposition (Fig. 8.4) of interacting wavefunctions that describe the spatiotemporal realities of processes, at both the quantum and classical levels. Such events are relevant to health at the molecular as well as complex systems level, as Hiley (2012) has emphasized with his process (i.e., "becoming") model of events. They also may pertain to molecular instabilities in cancer and aging .

8.10 Conclusion: Nonaction as Action in Paths

For trajectories and path coefficients, Bonhoeffer 's admonition that nonaction is action is pertinent for health care. Action s not taken have the negative probability of contributing to both positive as well as negative outcomes, for there always will be error such that we cannot predict the future. Our current history from human events to individual physiological events to an incredible array of millions of molecular events per cell per second is entirely dependent upon direct and indirect effects of immediate and remote past events at all of these levels. Furthermore, events that did not happen yielded our current situation at all levels. The future will be the same. The one caveat is that we can imagine the alternative pathways that never occurred due to zero or negative probabilities. In some instances, we can phase shift or jump a given situation or condition to an alternative, estimated desirable pathway, albeit with unpredictable side effects (Fig. 8.6). Phase shifting already is practiced in several biomedical fields, as will be discussed in Chaps. 12–14.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_9

9. Chaos Theory and Sensitive Dependence on Initial Conditions

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Abbreviations

Λ	Lyapunov exponent
ξ	Coherence length
LDL	Low density lipoprotein cholesterol
S	Entropy

Henri Poincare identified the sensitive dependence on initial conditions that contributes to chaos in his study of dynamical systems, most notably the 3-body or *n*-body problem of interacting objects/systems (Gleick 1987). One of the paradoxes of such systems is that increasing the number of interacting objects to immense numbers makes the prediction of systems behaviors more achievable, based upon statistical mechanics and fluid dynamics. Poincare introduced the study of the topology of dynamical systems and chaos.

Chaos represents one level of outcomes that results from turbulence in the nonlinear, dynamical evolution of a system (Ruelle 1989, p. 3):

$$dx(t)/dt = f(x(t)) + \lambda(t) \quad (9.1)$$

where $dx(t)/dt$ reflects the change in the trajectory of a point x, the change being a function of the position $x(t)$ and any disturbance to the trajectory, $\lambda(t)$, the first and largest Lyapunov exponent or eigenvalue solution to the trajectory equations. If there is no turbulence or change, $\lambda(t) = 0$, or if it is minimal such that the system is resilient and adjusts, then the trajectory will maintain itself over time, repeating itself with little deviation as $f(x(t))$.

Nevertheless, in reality, systems are not isolated, being impacted by external factors

(i.e., the environment) as well as by aberrant internal factors (e.g., mutation, dysregulation of processes). From a topological perspective, a system operates on a surface of interaction with these factors, as illustrated in Fig. 5.2, with trajectories of events that do or do not occur. As discussed in Chaps. 7 and 8, energy loss corresponds to increasing entropy , and vice-versa, from positive and negative probability perspectives for the system interactions.

9.1 Sensitive Dependence on Initial Conditions

In his analysis of turbulence, Poincare developed our idea of chaos as "sensitive dependence on initial conditions" (Gleick, 1987; Ruelle, 1989). What this means is that the slightest disturbances to a system may or may not have dramatic effects that alter the system over time. Even the presence of stochastic noise within a system (Gammaitoni, Hänggi, Jung, & Marchesoni 1998) can disrupt a predictable, periodic process such that its trajectory alters its periodicity , becomes aperiodic , or chaotic. The Poincare return map (Fig. 3.2) illustrates a periodic system that gradually becomes altered over time. In Fig. 3.2, the gaps between successive return trajectories can be measured as the Lyapunov λ exponents.

Along the same lines, Ruelle (1989) described the divergence of original and disturbed trajectories as divergent functions (Fig. 2.4) and as deformation of topological structures (Fig. 2.6). The elliptical analogy is most instructive, as the physical principle of birefringence involves the spherical, or isotropic, transmission of light through a transparent medium, whereas the distorted light pattern through a crystal exhibits elliptical diffraction. As outlined in Eq. 6.6, Ruelle (1989) related the Lyapunov exponent as a measure of chaos, at the same time representing change in entropy $\delta^2 S$, the inverse of coherence length ξ^{-1}, as well as Kolmogorov entropy and fractal dimension:

$$\lambda = \delta^2 S \sim \xi^{-1} \tag{9.2}$$

9.2 The Lorenz Attractor and Chaos

Whereas much of Poincare's initial observations was ignored for 80 years, Edward Lorenz (1963) revived his observation of sensitive dependence in his study of disturbances to periodic weather patterns. As we know, weather prediction is difficult, even over a few days, due to the dynamic changes in the Jet Stream and multiple air currents, frontal systems, solar forcing on the ionosphere and stratosphere, tropical heating of oceans, internal crust heating, and the earth's rotation, among other factors . Lorenz (1963) introduced the ellipsoid analogy and developed the first differential convection equations, borrowing from Saltzman (1962), to model nonlinear changes in

weather patterns:

$$dx/dt = -\sigma x + \sigma y$$

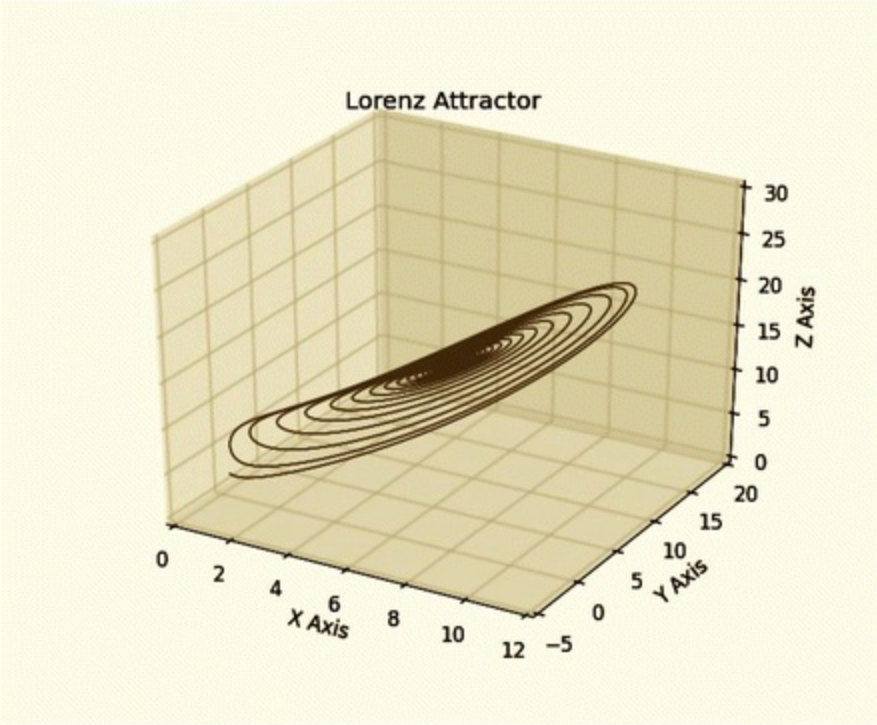
$$dy/dt = -xz + rx - y$$

$$dz/dt = xy - bz \quad (9.3)$$

where σ is the Prandtl number, the ratio of momentum diffusivity to thermal diffusivity, r is the ratio of the fluid Rayleigh number to its critical value, and the b term is a parameter related to the coefficient of thermal expansion. Lorenz (1963) modeled disturbances to x, y, and z over time and solved for the real roots (i.e., eigenvalues or Lyapunov exponents) for the characteristic equation. He discovered that small disturbances to these parameters could plunge the system from a regular periodic wave to a doubling periodic process with alternative centers, or chaos with no apparent periodicity .

We can replicate Lorenz' (1963) findings with a simple Python program (Fig. 9.1). Fig. 9.1a shows a spiraling attractor (i.e., single point) with the parameters $\sigma = 4$, $r = 16$, and $b = 2.667$. Figure 9.1b shows relative stability with the system oscillating unpredictably between two attractors, where $\sigma = 8$, $r = 16$, and $b = 1.667$. Lorenz found three complex roots or eigenvalues from his calculations, and he concluded (p. 136) that "if unstable steady convection is disturbed, the motion will oscillate in intensity." He also concluded that long-term prediction of atmospheric conditions is "impossible" given its nonperiodic nature. Whereas the atmosphere is roughly predictable year after year from Fig. 9.1b, micro-variations will occur, but even the overall stability of the atmosphere over thousands of years might be uncertain.

A. Spiral attractor



B. Quasi-Periodic Cycle leading to Chaos

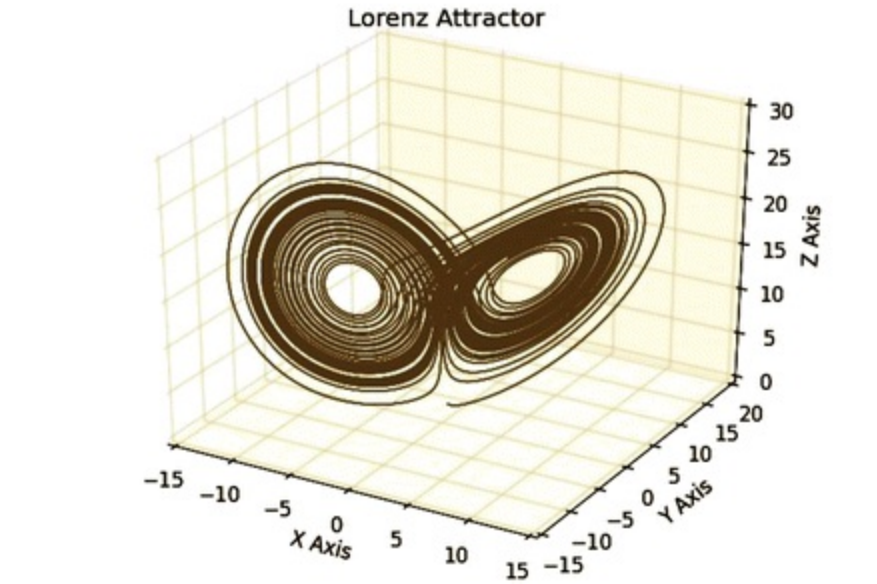


Fig. 9.1 Modifications of parameters with respect to Lorenz' (1963) equations and periodic attractor/chaos, using Enthought Canopy Python. (**a**) Spiral attractor, (**b**) Quasi-Periodic Cycle leading to Chaos

Considering Fig. 2.3, systems may attract or follow periodic cycles via circular or toroidal trajectories (Figs. 2.3a and 2.3d). Instability occurs when the system repels or is chaotic (Figs. 2.3b and 2.3e), as with the Lorenz attractor (Fig. 9.1). Generally, stability is achieved with attractor systems (Fig. 2.3a) which have Lyapunov

characteristic exponents $\lambda < 0$, whereas a saddle (Fig. 2.3c) attracting and repelling has $\lambda \sim 0$. Periodicity generally occurs near $\lambda \sim 0$, but doubling and quadrupling of periodicities generally occurs with less stability and greater positive λ. Lyapunov exponents $\lambda > 3$ generally are chaotic (Li & Yorke, 1975; Ruelle, 1989). Topologically , Ruelle (1989, p. 72) as well as Glass and Mackey (1988, p. 54) described this pattern as the stretching of a sphere into an ellipsoid (see Fig. 2.6).

Two-dimensionally, this pattern can be compared to the eccentricity ε of a circular object:

$$y^2 = 2x - \left(1 - \varepsilon^2\right) x^2 \tag{9.4}$$

Eccentricity ε represents the ratio of the distance from a fixed point on the object to its focal point with respect to the distance of the fixed point from the directrix of the object. In other words, eccentricity is a measure of stretching from uniformity. When $\varepsilon = 0$, we have the equation for a circle ($y^2 = 2x - x^2$). When $0.7 \leq \varepsilon < 1$, the object is an ellipse. When $1.0 \leq \varepsilon < 1.3$, the object is a parabola. When $\varepsilon \geq 1.3$, the object is a hyperbola. Just as with Lyapunov exponents, the greater positive values indicate greater deviation from the original trajectory or pathway form. Therefore, we can conclude that:

$$\lambda = \delta^2 S \sim \xi^{-1} \sim \varepsilon \tag{9.5}$$

Glass and Mackey (1988, p. 54) calculated the Lyapunov exponent to be:

$$\lambda = \lim (t \to \infty)\ 1/t\ \left[\log_2 (r(t)/r(0)\right] \tag{9.6}$$

where r is the length of the ellipse principal axis at time t compared to time 0.

An offshoot of Lorenz' (1963) work, including the refocusing on chaos and the study of nonlinear dynamics in living and physical systems, was the "Butterfly Effect" analogy (Gleick, 1987; Hollar, 1992). This illustration suggested that minor air currents generated by a butterfly flapping its wings in Asia could alter weather patterns halfway around the world. The emphasis is on "sensitive dependence on initial conditions." Whereas such a scenario probably does not happen in reality, the concept should be merged with our overall understanding that multiple factors contribute together to produce overall system outcomes. Some researchers take the Butterfly Effect analogy too seriously such that any small disturbance can drastically alter trajectories, whereas reality shows us that many factors interact and superimpose to regulate a system, with only blunt impacts pushing the system beyond a critical threshold . Many systems are highly resilient such that a unique combination of factors at specific threshold levels is necessary to shift a system from one state to another.

9.3 Phase Space

Lorenz (1963) emphasized the phase space of the atmospheric system and its quasi-periodicity . Glass and Mackey (1988, p. 51) described the phase space as a

topological region of all possible states for a system, some neutral, others stable or unstable. Points within a phase space may be influenced by local regions of high or low potential energy such that a point will tend to move toward a local minimum unless it is influenced by external forces (van de Walle, Hong, Kadkhodaei, & Sun, 2014). Consequently, over time, the trajectory of a point will stay consistent within a stable local region (e.g., steady orbit) or a region where forces are balanced. Alternatively, the point will drift toward its local minimum of potential energy, unless it is forced/energized to a higher energy level (e.g., Fig. 3.5). This perspective is analogous to Thom's (1972) description of catastrophes resulting from the competition from competing, interacting systems, resulting in collapse to a lower energy potential or minimum (Fig. 3.5). Thom (1972) discussed the negative relationship of temperature and entropy , with temperature being the inverse of the mean hyperspace curvature of the mean system entropy.

As a result, systems may exhibit periodic (i.e., repeating) behaviors with little deviation. These systems can include both normal and arrhythmic electrocardiograms where the sinoatrial node or ectopic foci, respectively, contribute to the local minimum of the phase space. In either case, the system is periodic within its local phase minimum for a spatiotemporal period. Nevertheless, the arrhythmias represent a significant deviation from normal with a chaotic Lyapunov exponent $\lambda > 3$ along with serious pathological effects for the heart and blood delivery to tissues . Consequently, we seek to identify forces that can be manipulated to reset the phase state of the affected cardiac system to a near-normal phase state.

The same condition holds for other physiological rhythms or dysrhythmias covering a wide range of processes from the molecular and cellular to the tissue and organismal levels, further compounded by the dependence of macroscale events (e.g., disease, organ functioning) on diverse interconnected molecular pathways within cells. The interconnectedness of so many processes becomes vulnerable to chaos during aging and the corresponding loss of immune system cells to destroy diseased tissue as well as with compromised body systems during specific pathological conditions (e.g., pneumonia, botulism, cholera).

Behavioral disorders and conditions likewise can be susceptible to chaotic events from the more uncontrollable molecular and neurotransmitter abnormalities at the cellular level to socioenvironmental conditions that lead individuals to make bad decisions. The former events usually cannot be overcome by psychological interventions; pharmacological agents that target molecular targets on cell membranes are necessary to drive biochemical pathways toward stability from chaos. The latter events involve both psychological counseling, education, and changed environments to help individuals and groups to make conscious decisions to move their lives to stability.

9.4 The Systems Perspective

The systems perspective in the trajectory analysis of health systems involves the following steps:

1. The normal trajectory pathway.

2. A model of the pathway with all detectable contributing (and barrier) forces.

3. Mapping of the pathway under conditions of changing forces.

4. Measurement of deviations from the normal pathway using differential equations and the solution of real root eigenvalues (i.e., Lyapunov exponents) and the coherence lengths of systems around critical points .

5. Identification of factors for applied interventions.

6. Testing interventions for safety and ethical conditions.

The modeling of relevant factors in maintaining or changing trajectory paths can be difficult. Even with the identification of major factors, small unidentified factors might provide sensitive dependence that could yield chaotic conditions if not properly addressed. Currently, we are at the model stage for most treatments, with few applied interventions.

Epidemiologically , the coefficient of determination (i.e., R^2) is the standard measure of the contributions of many independent variables to the variation in a dependent variable during multiple regression. The coefficient can be evaluated for cumulative independent variables as well as for individual variables in forward and backwards stepwise procedures. Nevertheless, even the best study generally provides a cumulative $R^2 = 0.60–0.70$, leaving $1 - R^2 = 0.30–0.40$, or 30–40% of the variation in outcomes measurement that cannot be explained by the independent variables. Poincare , Lorenz, and many others have demonstrated that it can be the tiny 1% variable that triggers dramatic change in the dependent, or outcomes variable over time.

Consequently, the case is clear for longitudinal analyses of continuous, or at least frequent, data points for the evaluation of the development and progression of conditions, further reinforced by the measurement of periodicity and deviation from trajectories. If a trajectory changes, what current or new variables/events might have contributed to the trajectory change? The measurements and analyses will not be much

different from standard epidemiology , only the approach and long-term vision for a complex, nonlinear systems perspective .

9.5 Ecological Systems and Health

In recent years, much attention has been paid to the interface between the ecological environment and public health. Ecological research has utilized a systems model for many decades. Public health has been slow to embrace the even broader, multiscale approach of ecological effects on the individual from the macroscale to even more complicated molecular ecology on the microscale .

Chaos rarely has been observed at the global ecological macroscale. Species interactions have been modeled and simulated through extensive scenarios. Many of these models expand upon the famous Lotka-Volterra predator–prey cycles or incorporate aspects of game theory such as the Prisoner's dilemma or the Nash equilibrium . Nevertheless, actual ecological systems remain relatively stable and resilient, even with the onslaught of human activities. Still, various researchers warn of tipping points in climate or habitat loss that would plunge the planet or major geographic regions into irreversible and even chaotic change.

We have examples of physiological thresholds beyond which pathological changes occur (e.g., body temperature , pH, insulin/glucose balance, LDL cholesterol levels, at-risk cancer genetic profiles), although even these thresholds can vary from person to person due to individual uniquenesses. For example, Dawes (1988, p. 73) evaluated published data on Wolfe's mammographic classification and later occurrence of breast cancer , noting that 92 percent of cancers occurred in the high risk group, although considering the entire sample of participants from a Bayesian analysis, those individuals in the high risk group had a breast cancer risk of only 12%. Still, mammographic screenings are advisable with increasing age, despite this statistic and some debate in the medical community. Improved diagnostic techniques have modified these interpretations, but the situation illustrates the epidemiological concept of necessary and sufficient conditions, the multiplicity of variables that together contribute to health outcomes. Furthermore, Swets, Dawes , and Monahan (2000) demonstrated that the triangulation of multiple diagnostics adds to the predictability of these assessments (see also Hastie & Dawes, 2009). It also should be mentioned that the many necessary and sufficient variables that lead to a given health outcome are not necessarily incrementally additive from a standard epidemiological and classical point of view. Instead, variables correlate to varying degrees and overlap in their effects, thereby indicating the need for superposition of variable states to decipher more complex effects, a quantum approach previously argued in Chaps. 6 and 7.

Returning to the ecological systems approach, the introduction of invasive species has altered the dynamics of ecosystems, often by eliminating the diversity of native

species, but such systems have remained balanced, albeit at an altered composition. Studies of biological diversity on islands (MacArthur & Wilson, 1963) showed that species diversity was maintained given critical distances between islands. For shorter distances, species could migrate and alter the ecology of neighboring islands, with distances varying for different species' migratory capabilities. For greater distances, migratory colonization was less likely. This phenomenon has been referred to as percolation (Feder, 1988), and it relates strongly to the coherence length ξ that is inversely related to the Lyapunov exponent and chaos. Simberloff and Wilson (1969) further demonstrated the island biogeography model by fumigating small mangrove islands and observing the subsequent arthropod repopulation and species compositions over time.

Percolation physically involves the movement of one substance over a medium (Davis, Trapman, Leirs, Begon, & Heesterbeek, 2008; Feder, 1988). Consequently, properties of the medium such as shape, extent, porosity, temperature, etc. define the trajectory of the substance and its ultimate distribution over the surface of the medium. Most importantly, Feder (1988) identified a *percolation threshold* that limits the spread of the substance. By Feder's (1988) definition of the percolation threshold, failure to exceed the threshold limits the spread to a localized region, and he compares this situation to a high coherence length. Therefore, the coherence length ξ is the inverse of the percolation threshold, which makes the threshold directly proportional to the Lyapunov exponent λ. Therefore, the lower the threshold (low λ but high ξ), the more confined the trajectory of a moving substance (i.e., less change). Conversely, the higher the threshold (high λ but low ξ), the more expansive the trajectory spreads for a moving substance (i.e., more change).

Whereas percolation originally was studied from a physical chemistry perspective, biologists have started applying the concept to the study of population dynamics and disease spread. For example, Davis et al. (2008) determined that Bubonic plague (bacterium *Yersinia pestis*) spread via flea vectors among great gerbils (*Rhombomys opimus*) becomes epidemic when more than 33% of the extensive gerbil tunnel systems are occupied. This finding makes sense given that closer proximity should increase the probability of flea transmission. The tunnel occupation is influenced by "movement" factors such as gerbil reproduction. Davis et al. (2008) appropriately concluded that percolation represented a strong model for measuring disease spread and epidemics involving viruses and bacteria.

Eigen (2002) applied similar reasoning with his antiviral strategy to overwhelm rapid viral replication within cells by introducing mutations to a threshold collapse point that halts the viral spread. Dobson (2000) noted that a localized Southern U.S. rabies strain in raccoons became a continuing, widespread epidemic when unknown infected raccoons were geographically transplanted to the mid-Atlantic U.S. Real et al. (2005) demonstrated the geographic divergence and spread of two rabies strains in

Ontario. Charles Darwin (1859, 1907) cited geographic isolation as one of the primary mechanisms of evolutionary change.

John Christian and colleagues (Christian & Davis, 1956, 1964; Christian, Flyger, and Davis (1960) examined the physiological effects of overcrowding and stress on experimental laboratory rats and field studies of deer (see also Hall, 1969). This work built upon Hans Selye's (1950) General Adaptation Syndrome of stress. Most notably, Christian , Flyger, and Davis (1960) conducted autopsies on hundreds of Sika deer that died from overpopulation stress on James Island, Maryland in 1958. What was astonishing from this event was the capability for the deer to migrate and the absence of any physiological conditions except one: adrenal hypertrophy. This model is pertinent to physiological chaos (high λ) due to the class proximity (low ξ), and the resulting stressful interactions leading to divergence from normal physiology .

This inverse relationship between λ and ξ seems to be counterintuitive. However, from the topological viewpoint of the trajectory, λ is the differential "distance" between successive orbits, whereas coherence "length" ξ refers more to correlation between successive orbits, that they are more alike when λ is small and less alike when λ is high.

Benincà, Ballantine, Ellner, and Huisman (2015) modeled the seasonal chaotic dynamics of species fluctuations in intertidal zones on the North Island of New Zealand. They particularly focused on three dominant species: the barnacle *Chamaesipho columna*, the alga *Ralfsia* cf. *confusa*, and the mussel *Xenostrobus pulex*. Over several years, they found that the species' abundances followed relatively periodic cycles with slight variations around $\lambda \sim 0$ with occasional instabilities when λ was slightly positive. They concluded that seasonal habitat, climatic, and other environmental variables were responsible for variations in the forcing of each species' abundance and distribution patterns. Their findings are fairly characteristic of ecosystem dynamics, which tend to be resilient even with substantial environmental changes, albeit often with changes in the levels of ecosystem species complexity . As MacArthur and Wilson (1963) and Simberloff and Wilson (1969) demonstrated, distance is critical to the population stability and spread of species.

Ecological and bodily systems can undergo dramatic change given specific events. An Eastern North America deciduous forest that experiences wildfire is "reset" to an original state, then progresses through the stages of old field succession , beginning with a vast diversity of grass and herb species whose seeds benefited from the fire that ended the lives of the dominant hardwood trees. The grasses and herbs modify the environment such that the environment then favors pine and cedar trees, which also germinated from the fire, but which inhibit the grasses and herbs. The pines and cedars have a finite lifespan and are eventually replaced by the hardwood oak and hickory trees that can dominate the field/forest for hundreds of years until the next wildfire. The local and long-term periodicities in old field succession are evident, along with the intermittent disaster that triggers chaos. Nevertheless, the percolation of neighboring species and

species that benefit from the chaos "reset" the periodicity of the system.

Similarly for physiological systems , the body may encounter acute or chronic chaos via infections or aberrant chemical imbalances. With respect to infection, even from opportunistic bacteria of the body's microbiome that become displaced into weakened body regions, the body mounts an immune response involving pro-inflammatory, T-helper lymphocyte 1 (Th1) responses as well as anti-inflammatory, T-helper lymphocyte 2 (Th2) responses. An imbalance between these immune responses can lead to establishment of the infection, failure of immune response to antigens in cancer , and hyper-inflammatory responses that can contribute to disease. Sepsis is a major killer of older adults, and it typically involves uncontrollable infection spread to vital organs with a hyperinflammatory response that damages major organ systems (e.g., heart, kidneys). Inflammatory disorders are pervasive in a variety of major health conditions (e.g., cancer, heart disease, diabetes, stroke, neurodegeneration), and their chaotic dynamics are intricately linked to the disruption of metabolic regulation (Hotamisligil 2006).

Reproductive behaviors and pregnancy play a central role in these metabolic processes and the control of disease. Peak human performance and the beginning of aging occurs at adolescence, although emotional and cognitive brain development leads to risk behaviors during adolescence and early adulthood that coincide with the largest increase in the probability of dying throughout the human lifespan (ages 14–24) for both males and females, regardless of race or culture, as measured by Gompertz curves (Ricklefs & Finch, 1995). Immune defenses are intricately involved with the maintenance of body systems and the elimination of infections until reproductive capability and protection of offspring can be achieved. Higher immunity via specific Major Histocompatibility Locus (i.e., Human Leukocyte Antigen) phenotypes can be detected across multiple behaviors and serve as a gauge for reproductive preference, although the act of reproduction often comes with the tradeoff of reduced immunity and risk exposure to pathogens (Hollar, 2009; Lee, 2006; Tregenza, Simmons, Wedell, & Zuk, 2006).

The Monarch butterfly *Danaus plexippus* follows an equally extraordinary annual periodic cycle of birth, migration, reproduction, and reliable return to the place of its birth, all occurring over approximately four generations of varying lengths (Flockhart et al. 2013). The Monarch cycle begins with overwintering adults on coniferous trees located in an approximately 50 square mile area of freezing Mexican mountainsides, then northern migration during the Spring , with successive migratory generations reproducing and feeding off milkweed plants. The fourth generation, born in Canada, makes the entire return journey during Autumn to the same 50 square mile area in Mexico (Oberhauser & Solensky, 2004). The mechanism by which this migration occurs and how a fourth generation can map a return to the birthplace of the first generation are unknown. The periodicity of this migration for survival is consistent, even with

migratory disruptions and population declines caused by pesticides, predators, and hurricanes.

Even pregnancy represents a profound shift from normal physiological functions. The placenta represents an extraordinary mutualistic adaptation between mammalian cell physiology and endogenous retroviruses incorporated over the course of millions of years. The viral syncytins lead to fusion of cells and placentogenesis (Lavialle et al. 2013), which provides mutualistic benefits from mother to developing infant, and vice-versa. It even functions as a barrier to prevent infection (Robbins, Skrzypczynska, Zeldovich, Kapidzic, & Bakardjiev, 2010), although like any tissue it can become cancerous under metabolic instability .

9.6 Complexity and Stability

From these brief examples, we see that the complexity of living systems involves a careful balance between periodic trajectories that maintain stability and disturbances that can positively shift the trajectory to a new trajectory (e.g., pregnancy) for a biological purpose, but many disturbances can create instabilities that ultimately compromise health for the short-term (e.g., disease, injury) or long-term (aging). Biological systems at multiple levels maintain stability for health, whereas deviations from stability represent chaos. The task of the health epidemiologist is to measure chaos and the variables contributing to chaos. The task of the health policy maker is to introduce programs and protocols for controlling these variables. The task of the clinician is to restore the body to stability.

Each system has its own unique features for its level of biological hierarchy, whether the system involves biochemical pathways on a cell membrane, the methylation and acetylation of gene control regions on chromosomes , cell-to-cell communications, or large structural interactions between body systems. There are no consistent, universal models to explain all of these systems. However, we are proposing the use of the Lyapunov exponent as a measure of trajectory divergence in these systems when they are evaluated over time. Similarly, the coherence length, or correlation, measures the consistency between successive iterations of a system when it returns to a similar point on a periodic cycle. Just as the earth follows an elliptical orbit that is at perihelion (nearest the sun's focus of the ellipse) around June 20 and that is at aphelion (furthest from the sun's focus of the ellipse) around December 21, we can reliably plot the earth's position on the ellipse from year to year (ignoring overall solar motion), such that its $\lambda \sim 0$. The solar system has been remarkably stable over millions of years, although long-term resonances between planets potentially could plunge this system into chaos, perhaps with further forcing actions as the solar system oscillates along the galactic plane.

Human physiology and earth ecosystems are much more finite in their duration. Our

bodies have positive and negative feedback processes that maintain overall system stability . Nevertheless, perturbations to system trajectories can alter the periodicities of trajectories over time and even plunge some systems into chaos. Chaotic events might be short term, in the case of epileptic seizures or occasional arrhythmias, or they might be chronic and debilitating. The longitudinal collection of multiple variable data at many time points can establish patterns of system behaviors and the events that lead to their deviation (i.e., disruptors or barriers) as well as events that restore the stability of these systems (i.e., facilitators). As stated in previous chapters, the current statistical and epidemiological practice is to collect snapshots of data for individuals when the variables associated with these data might vary on an hourly, daily, or weekly cycle . A given snapshot of data collection might occur at a cyclic high or low point, or within the window of a cycle that is normal, when a subsequent cycle might be aberrant. For proper analysis of trajectories for dependent variables and their explanatory independent variables, multiple data collections must occur to better establish the shape or topology of event trajectories that more comprehensively explain the many interacting aspects of a complex system.

For the maintenance of stable systems, we recommend the maintenance of positive regulatory forces. This involves the introduction of resonances for the system with identified facilitator variables. The goal is to superimpose these forcing variables on the system so that the system variables resonate with the forcing variables, and their systems superimpose. From a measurement perspective, the variables correlate, or have a high coherence length, such that $\lambda \sim 0$ or is negative . Furthermore, we should increase physical distances of individuals or body systems from disruptors, thereby preventing percolation. We know that environments can shape systems, so environmental controls are important for systems stability.

To disrupt an undesirable system, we have to jump the system aberrant cycle or chaotic dynamics to an alternative cycle that is relatively periodic to normal. Doing this might require bioenergetic interventions, as is often used for electrophysiological processes. For behavioral interventions involving educational programs or counseling, changing the individual's environment could be productive. Environmental changes might involve lighting, diet, or exercise as long as the interventions are consistent and maintained with individual follow-up supports. Alternative behavioral periodicity changes might involve confrontation with one's own behaviors or moving them into a different environment. In considering treatment for a bullied adolescent who had contemplated suicide, Solhkhah, Olds, and Englund (Solhkhah, Olds, & Englund, 1999) asked whether we should treat the patient psychologically or change their environment, or both. By chaos theory, the environment shapes the behaviors. Therefore, changing the environment is a critical component because it represents the surface on which the system events and variables percolate, thus changing the trajectory of the system.

Thus, we are dealing with λ as trajectory change, the coherence between recurrent

systems over time, and the environmental forces that maintain or alter the systems. Longitudinal trajectory analysis involves these measurements to detect stability in periodicity , or altered systems that have altered periods or are chaotic. As many variables must be considered, since any variable can be a forcing contributor to change, beginning imperceptibly via initial conditions.

9.7 Summary

Henri Poincare introduced us to sensitive dependence on initial conditions. Edward Lorenz mapped trajectory changes for atmospheric systems to demonstrate these ubiquitous effects. As a result, long-term patterns can be roughly predicted, but never exactly. The Lyapunov exponent λ represents a measure of chaos, at the same time representing change in entropy $\delta^2 S$, the inverse of coherence length ξ^{-1}, as well as Kolmogorov entropy and fractal dimension:

$$\lambda = \delta^2 S \sim \xi^{-1} \tag{9.2}$$

Therefore, we have a valuable tool for measuring trajectory change in systems, which operate very similarly for behavioral , physiological, ecological, meteorological, and planetary systems.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_10

10. Poincare Return Maps

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Abbreviations

PQRST Electrocardiogram peaks and troughs for heart wavelike contractions

PTSD Post traumatic stress disorder

In regression analysis , we attempt to fit a curve to a set of points that relate the dependent variable to one or several independent variables. The best fit for the curve uses the least squares distances between the independent variables and their respective means to construct this curve. Nevertheless, Thom (1972) argued that a curve similar in form to the pattern of points best models the behavior, even if it does not have the best correlation of points compared to the least squares or best fit criterion.

10.1 Periodicity and Trajectories

Poincare identified the importance of pattern of form with his return map (Figs. 3.2 and 10.1). A process begins at point A and follows a changing trajectory over time until it returns close to or exactly at its original starting point, say point b, sometime later, a time quantity that we will refer to as the process period T. The process can continue and return some time later at point C, and so on with time. We know that the distance from points A to B and from points B to C is the Lyapunov exponent λ , which will have the value zero if the points coincide. Nevertheless, if λ varies positively or negatively, the process trajectory is either moving toward an attracting point or is diverging, potentially toward chaotic behavior with large differences from the initial or previous trajectory paths to our imaginary starting point. Changes in system variables and/or disturbances /perturbations to the process ultimately create the trajectory deviations as measured by λ.

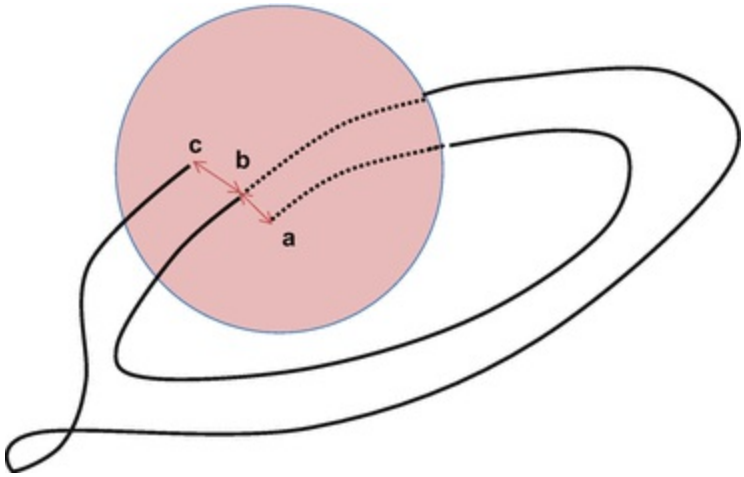

Fig. 10.1 Poincare Return Map, starting at point a on a manifold, then cycling over time back to later equivalent point b, then a second "orbit" back to later equivalent point c, etc.

Comet Halley and billions of other comets follow orbits of varying eccentricity and distance around the sun , with Halley following a rather short period $t \sim 76$ years. Comets with greater eccentricity are likely to extend their orbits to the far reaches of the solar system, being more likely to be perturbed by interstellar objects and dust as well as being energetically more likely to escape the gravitational attraction of the sun. Therefore, comets with shorter eccentricity ε will be more likely to return to similar points in their orbits , with little if any perturbation from the outer planets, and to have a λ close to zero.

Your pulse is the arterial response to repeated periodic contractions and relaxations of your heart, roughly a period $t \sim 1$ s. The myocardium rhythmically contracts and expands (relaxes), returning to an identical position in its "orbit" with the forcing of blood through the arteries being detected as the pulse during this repeating trajectory, approximately 86,000 times per day. Certainly, the contraction/relaxation trajectory varies over the course of minutes in response to exercise , standing/sitting, emotional arousal, or medications, etc. The heart's trajectory through time and space can more precisely be measured using an electrocardiogram . Specific electrical stimuli and atrial/ventricular contractions can be seen as PQRST waves . The electrocardiogram can be changed in periodicity and form by the same physiological and pharmacological stimulators, but it also can be altered by heart anomalies and heart damage, creating altered PQRST waves . Therefore, we can measure altered λ for normal and abnormal cardiac processes.

Human behaviors can be even more dramatic and difficult to measure as a result. The behavioral realm is so difficult because the psychological developmental theories, the educational interventions, the neuroscience , and the genetic/epigenetic regulation , etc. have not advanced and converged to the point that we can establish strong cause-and-effect epidemiological explanations (i.e., necessary and sufficient contributing

variables) for given behaviors . Both Feynman (1988) and Dyson (2004) argued the importance for clearly defined and measurable models that yield valid predictions. Feynman (1988, p. 81) stated, “In order to calculate the probability of an event, one must be very careful to define the complete event clearly.” Similarly, Dyson (2004, p. 297) argued that to evaluate problems, one must either have a clear, working model or a precise mathematical methodology , furthermore being willing to abandon a model that does not work.

10.2 The Return Map

The Poincare return map is a model for measuring changes in trajectories and for evaluating the effects of forces that facilitate or present barriers to the pathways. It is important to measure the stability of a trajectory or its deviation. With either situation, one seeks to understand the variables that maintain stability or that create the deviation. Then, we can experiment with manipulation of the variables to return a deviated pathway to stability or to jump an aberrant stable pathway to an altered stable trajectory that is closer to better health . Furthermore, such considerations must incorporate direct and indirect effects over spatiotemporal, longitudinal scales, per Wright’s (1934, 1960) method of path coefficients . Health events rarely occur spontaneously, in isolation, with full manifestation.

We can envision the Poincare return map as a periodic process such as a pendulum or spring , the classic model of simple harmonic motion (Fig. 10.2). As we have described previously, all processes are pulsations over space and time, starting and eventually returning to a roughly equivalent point or measured value after a period of time. As with the earlier examples, the earth elliptically orbits the sun in approximately 365.25 days, the moon and earth orbit a gravitational focus beneath the earth’s surface every $t \sim 28$ days, consistent but slightly variable over hundreds of millions of years due to changes in the properties of the sun, earth, moon, other planets, comets, and interstellar objects that interact at great distances over time. Of course, the earth does not return to the exact same location in space after $t \sim 365.25$ days, only it does so relative to the sun, which pulls the entire solar system in its $t \sim 250 \times 10^6$ year orbit around a supermassive black hole singularity at the center of the Milky Way galaxy, moving at a velocity if $v \sim 16.5$ km s^{-1} and oscillating above and below the galactic plane at a periodicity of $t \sim 66 \times 10^6$ years (Bash 1986; Frisch 1993, p. 198; Rolfs & Rodney 1988). Even the sun’s atmosphere pulsates from stellar nucleosynthesis, and the earth’s crust and oceans pulsate with the gravitational pull of the moon . Everything pulsates, or oscillates, returning to a previous position.

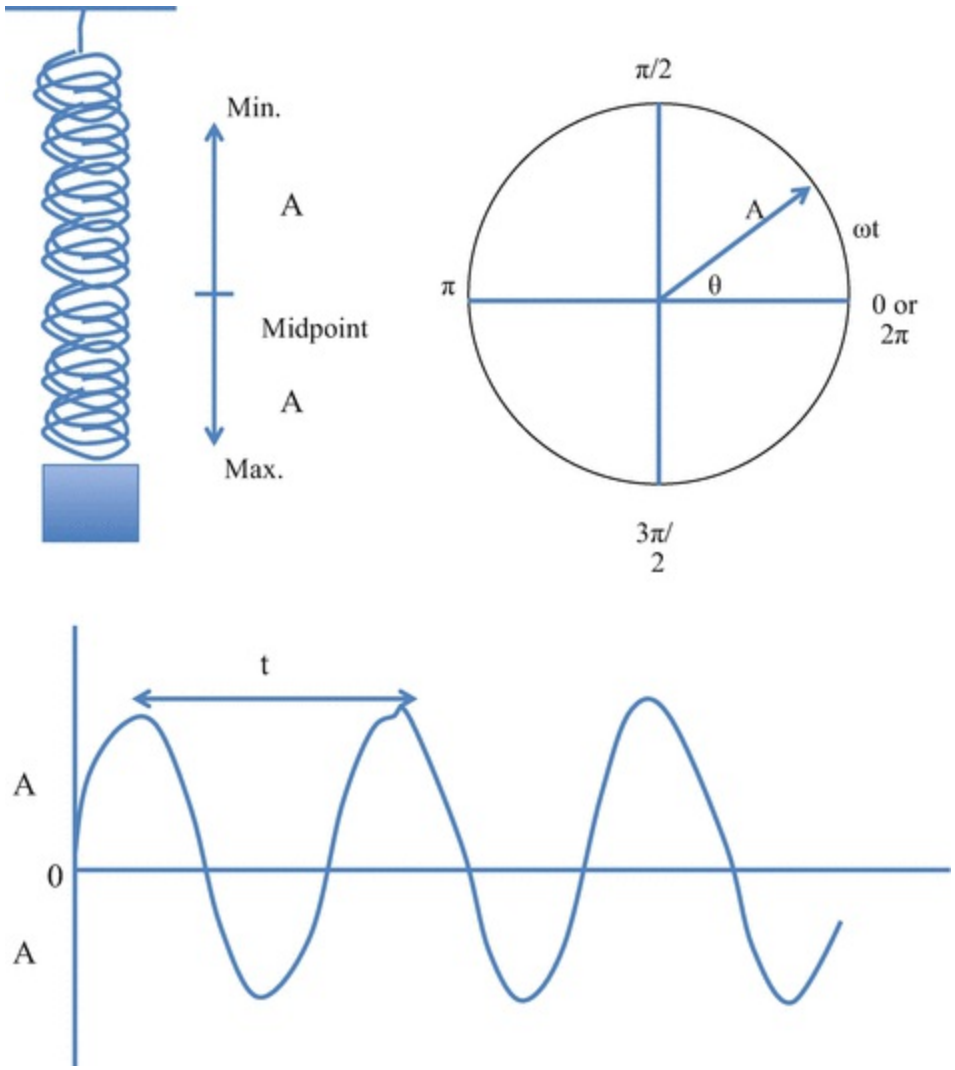

Fig. 10.2 Periodic motion with a spring and its trajectory mapped as a sine wave on the unit circle

Returning to our pulse example, the heart beats approximately once per second, returning to its previous point, whether or not you measure this point at peak contraction, relaxation, or somewhere in between. Similarly, people have routine behaviors , including sleep-wake cycles that are strongly influenced molecularly by day-night cycles based upon the earth's tilt and rotation, as well as appetites for certain foods or substances set in motion by initial or prolonged contact with these entities. A calm demeanor can be disrupted by contact with an aggressive individual, an unpleasant sight, or the sudden memory of an unhappy past experience. Indeed, posttraumatic stress syndrome (PTSD) , depression, anxiety, and social deviancy can result from brain neurological connections that were established from learned negative experiences, literally etched on people's brains, and that trigger a cascade of hopelessness and further behaviors that are counterproductive to individual and group health and welfare. Furthermore, it is unfortunate that aggressive individuals in all walks of society rely on unethically and maliciously forcing these negative experiences on others to control and

to psychologically limit their potential. Poverty, violence , and other stressful environments psychologically can create aberrant, yet stable, neurobehavioral cycles that are difficult to modify. People also vary considerably in their resiliency against such negative forces. Likewise, societies and cultures vary widely in their tolerances for negative behaviors and the sociocultural forces that drive these behaviors .

For the spring example of simple harmonic motion (Fig. 10.2), the driving forces for the spring include its inertia of motion and the weight/gravitation as well as damping forces that work against the driving forces. Together, they create an oscillation or pulsation, wavelike behavior that goes up (peaks), reaches a neutral balancing point, then to a lowest point (trough), then back up to the neutral point and the peak again, etc. Consistent driving forces that counteract the damping forces maintain the oscillation, which represents a sinusoidal format.

The spring reaches a maximum displacement, or amplitude A, in either the positive or the negative direction as it oscillates back and forth, peaking and troughing. The wave also can be represented by a circle, merely a translation of the wave, with the oscillation position being expressed by an angle $\theta = \omega t$ showing position in its cycle and the amplitude A being the radius of the spring. The horizontal displacement of the spring is expressed by the following equation:

$$x = A \cos \theta = A \cos \omega t \tag{10.1}$$

whereas the vertical displacement is expressed by the equation:

$$y = A \sin \theta = A \sin \omega t \tag{10.2}$$

Here, ω represents the angular frequency or pulsation and is equivalent to 2πf, or the frequency multiplied/adjusted by one complete cycle, 2π radians or 360°, and 4π, 6π, and 8π radian multiples thereof. It is the position in a given cycle at a specific time for a given phenomenon or behavior .

Combining Eqs. 10.1 and 10.2, we have the standard equation for the real and imaginary parts of simple harmonic motion, also consistent with the wavelike properties of electromagnetic radiation:

$$z = A (\cos \omega t - i \sin \omega t) \tag{10.3}$$

where i represents the imaginary number (i.e., square root of −1). Equation 10.3 is relevant for sinusoidal motion, which generally fits most types of physiological rhythms to varying degrees and certainly to electromagnetic radiation and large-scale planetary /universal motions. As discussed in Chapter Seven, the Fourier transform of a signal event or behavior converts the amplitude of the signal from a function of time to a function of frequency, as broken down into its harmonic frequencies (Bracewell 1965, 1989; Loy 2007):

$$F(f) = \int_{-\infty}^{+\infty} f(t) e^{-i\omega t} dt = \int_{-\infty}^{+\infty} A (\cos \omega t - i \sin \omega t)\, dt \tag{10.4}$$

Figure 10.4 illustrates the transform of a periodic signal to its sinusoidal, harmonic

frequency breakdown. The same can be done for any signal and for the superposition of correlating or interacting signals. Furthermore, the first and second derivatives of the fundamental sinusoidal wave in Fig. 10.3 represent exact 90° (i.e., π/2 radian) shifts in the sinusoid. Musical spectra/notes can be broken down into fundamental and secondary harmonics via Fourier analysis (Loy 2007). Even the Fourier harmonics of solar activity have been recorded in tree rings and geological sediments (Bracewell 1988).

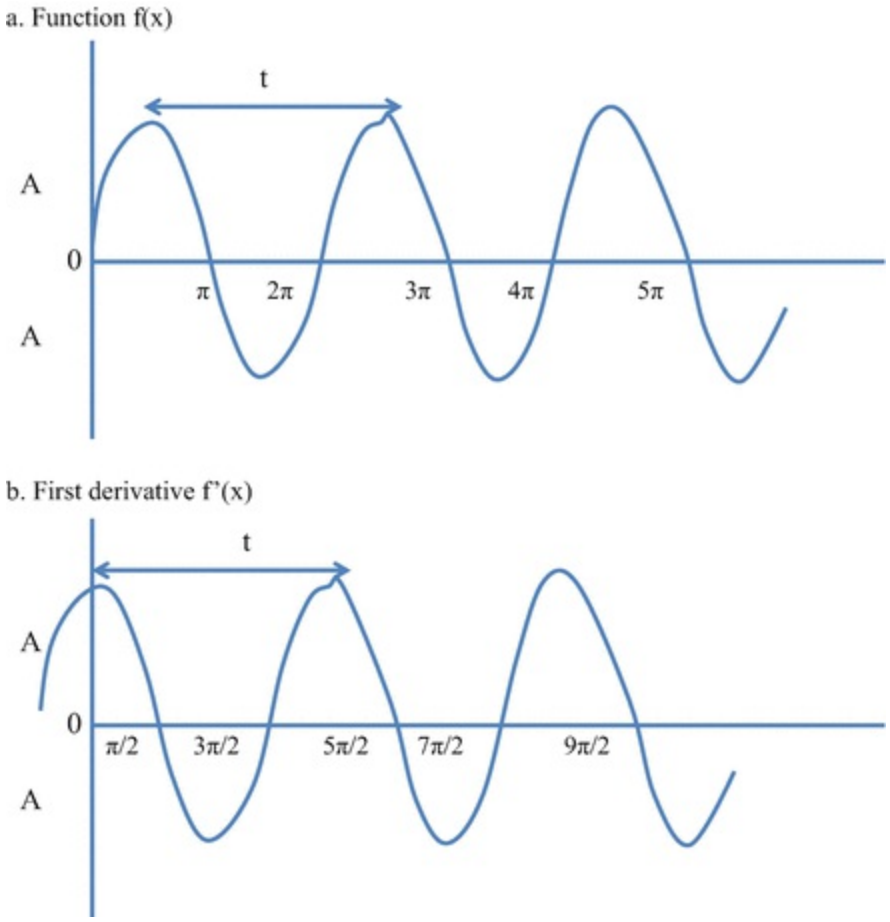

Fig. 10.3 Each successive derivative represents a phase shift of π/2 radians (i.e., 90°) for the sine (or cosine) curve. (**a**) Function $f(x)$, (**b**) First derivative $f'(x)$

10.3 Superposition of Harmonics

The superposition of driving forces alters the pure sinusoid shown in Figs. 10.2, 10.3 and 10.4, giving us the varied physiological patterns that approximate sinusoidal cycles in living systems. In terms of trajectory analysis and Poincare periodic return maps, the use of sinusoids such as Circadian rhythms , electroencephalograms , longitudinal repeating behaviors , etc. adds to our arsenal of tools to analyze change. A variation in the sinusoid alters the Poincare return map so that there is a difference when the system returns to any equivalent point at a later time. The Lyapunov exponent and coherence

lengths measure this difference in periodic/aperiodic motion or change in the system.

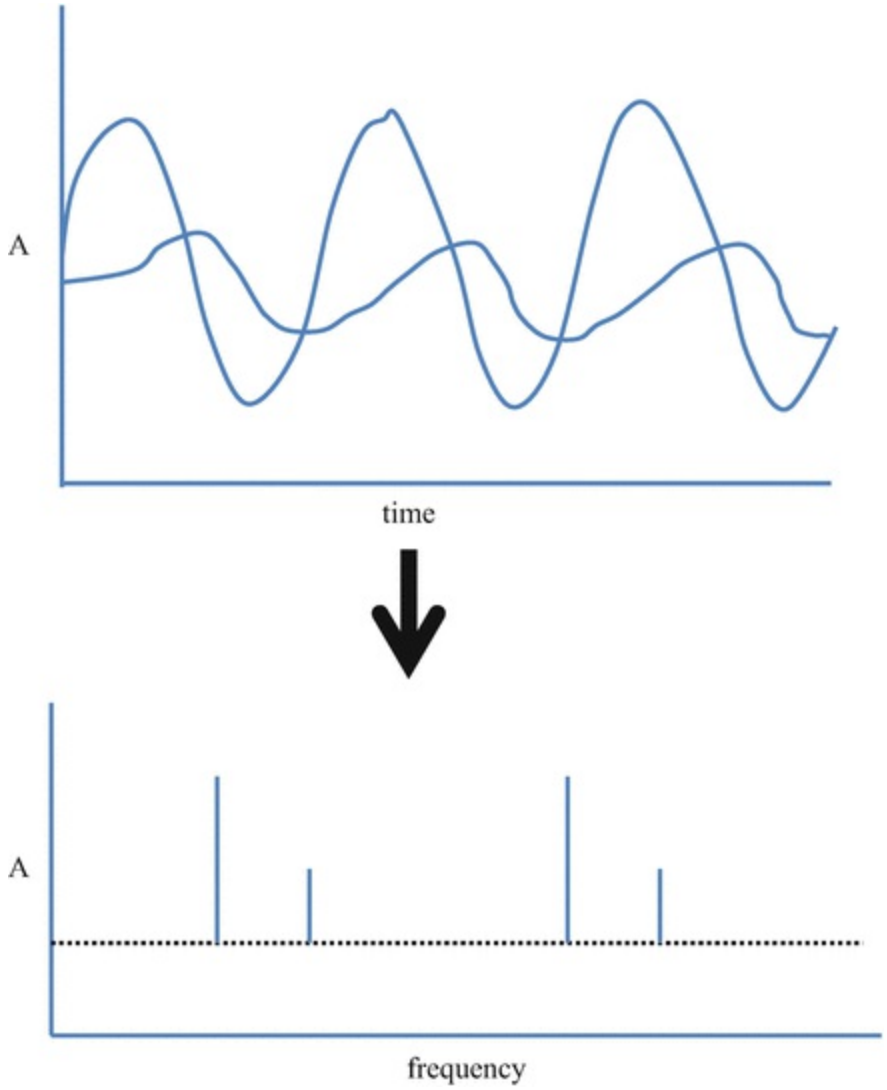

Fig. 10.4 The Fourier transform converts a spectrum of Amplitude (A) across time to Amplitude by frequency

The superposition of harmonics comes from the correlations/interactions of contributing driving forces, also termed independent variables. The traditional R^2 coefficient of determination merely estimates the individual and combined contributions of these variables. The $1 - R^2$ residual leaves us with a sizeable unknown combination of variables, positive and negative, actions and inactions, that also contribute in some way to the behavior of the system and any deviations over time. These deviations also include the observations of the experimenter, per Schrodinger's uncertainty principle , that can interfere with the trajectory of the system with even the most carefully controlled experiments. On this note, the failure to control for, or even to consider, past and present historical events as a threat to the validity of experiments is widespread in research, further demonstrating the need for the longitudinal analysis of trajectories.

Named longitudinal studies of various population groups all include the historical

and other threats to validity (see Chapter Four). Most such studies follow a population that declines in participation over time and that is "photographed" at particular time points. Certainly, we cannot reduce the interval between time points to zero for continuous monitoring, and such studies are highly useful. Nevertheless, the overall conclusions from these studies drive public policy, usually positively, although we wonder at the patterns that are missed based upon the choice of interval periods between data collection points.

Healthy People 2010 and 2020 goals for U.S. Health are evaluated in a summative fashion at 10-year intervals (National Center for Health Statistics 2012) as well as a 2-year intervals via cross-sectional studies such as the National Health and Nutrition Examination Survey (Hollar 2013; Hollar, 2016; Hollar & Lewis 2015). Geographic national variation in the United States is provided annually since 2010 by the University of Wisconsin Population Health Institute/Robert Wood Johnson Foundation County Health Rankings (www.countyhealthrankings.org; Hollar 2015), although these data are aggregate in nature, based upon national longitudinal studies as well as local health department reporting, the latter subject to bias due to reporting errors as well as a skewed demographic service population .

The Lancet (2016) annually assesses epidemiological factors that contribute to mortality , disability, and health risks by nation and global region. Within this study, GBD 2015 Mortality and Causes of Death Collaborators (2016) mapped new HIV cases and persons living with HIV/AIDS (p. 1471), a sinusoidal curve that initiated and started log phase growth by 1990, peaking around 1998, then decreasing, then increasing at the heightened 1998 plateau around 2015. Similarly, they showed (p. 1494) aperiodic and chaotic cycles of deaths due to war, natural disasters, and other causes from 1970 to 2015. Whereas these data are annual "snapshots," they are a genuine attempt to measure national and global trajectories for large-scale independent variables as they affect mortality .

These curves mirror sinusoidal exponential growth curves for populations that have unlimited resources and minimal predation (Fig. 10.5). However, we know that in reality, resources eventually become limited and disease/predation occurs, such that the differential between births and deaths slows the population growth. Excessive growth could be followed by rapid collapse in the face of famine, disease, and/or excessive predation, much like the Christian , Flyger, and Davis (Christian, Flyger, & Davis 1960) study of Sika deer collapse from overpopulation stress . If the population achieves stability , it will cycle sinusoidally up and down around the population's carrying capacity with respect to the environment, the environment's support capability in terms of numbers for the population. In this situation, the population will grow and slightly exceed the carrying capacity, then decline below the carrying capacity threshold due to mild famine or the action of predators . Then it will rise again and cycle accordingly.

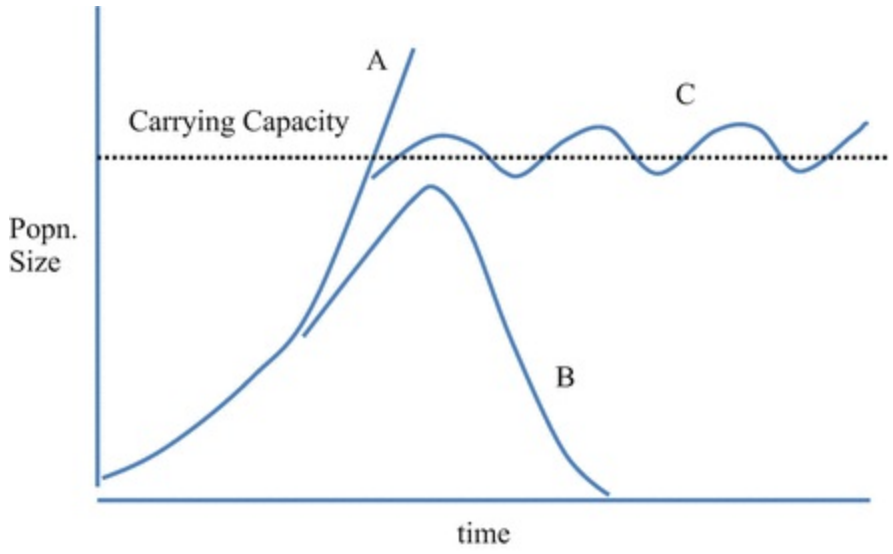

Fig. 10.5 Population Growth Curves with rapid logistic growth (*A*), collapse (*B*), or stabilization (*C*). See Beck, Liem, and Simpson (1991, pp. 1219–1223); Curtis and Barnes (1994, pp. 776–778); Krebs (1978, pp. 180–188); Lotka (1956, pp. 80–85, 130–136); and Smith and Smith (1998, pp. 160–162) for more descriptions and examples

Consequently, population cycles for any organism or cell, predator or prey, are molded by driving forces from the environment, the manifold or surface surrounding the living system in question. In the case of the Causes of Death Collaborators' (2016) persons living with HIV/AIDS, it is numbers for a specific human population of individuals who are striving to survive a serious disease. Forces that drive the spread of the disease increase the number of cases, and improved prevention programs as well as unfortunate deaths decrease the number of cases over time.

Within all of these situations, the Poincare return map is at play. We are not looking at statistical significances between variables. Instead, we are mapping patterns and changes in patterns, the topology of systems and processes that can be relatively stable or that can wildly swing into chaos . As we have reiterated throughout the earlier chapters, we wish to maintain healthy stability by manipulating the positive environmental driving forces (e.g., behaviors , exercise , nutrition , epigenetic regulation , social supports) that contribute to such stability, whereas we seek to manipulate unhealthy stability and chaos by introducing driving forces that jump the system to a different trajectory and level of stability.

10.4 Phases and Periodicity

Poincare's return map also can be viewed within the phase of successive 2π cycles. Per the angular frequency or pulsation $\omega = 2\pi f = 2\pi/t$ (Fig. 10.2), the frequency f is the number of cycles per second, whereas the period t is the time required to complete one cycle from phase 1 to 2 of 360° or 2π radians. Frequency and period are the inverse of each other, whereas angular frequency ω is the 2π standardization of the frequency f, and

the angular frequency ω measures the rate of change of phase of the system (i.e., the pulsation). We can evaluate each phase φ and the change in phase Δφ of a system by the following equation (Lévy-LeBlond and Balibar, 1990, pp. 182–183):

$$\Delta\varphi = \omega\Delta t - \mathbf{k}\Delta\mathbf{r} \tag{10.5}$$

where **k** is a vector of rates of spatial progression and Δ**r** is the distance for a wave phase from point 1 to point 2, regardless of the direct or convoluted length of each possible path that the system takes from point 1 to 2. Lévy-LeBlond and Balibar (1990, p. 183) also note that each possible path from points 1 to 2, per Feynman's (1948) multiple pathway's quantum approach, has its own partial amplitude and phase (p. 183):

$$\varphi_n = -\int \mathbf{k}d\mathbf{r} \tag{10.6}$$

Setting the change in phase Δφ to zero, we can substitute eq. 9.5 into 9.6, yielding

$$\varphi_n = -\int \omega\Delta t \tag{10.7}$$

Therefore, a system in phase n that is consistent over time (i.e., $\lambda \sim 0$) can be evaluated for all possible pathways (i.e., trajectories) of the system under the integral of possible pathways, using Eq. 10.7. This finding allows us to consider consistency of system phase status or deviancy over successive return maps. If a system deviates (i.e., $\lambda < 0$ or $\lambda > 0$), the new phase can be evaluated compared to the former phase, along with driving forces contributing to each phase as well as to the change. This finding also translates into Thom's (1972) definition of stable and catastrophe sets, and the catastrophic collapse of a system when a point (e.g., phase) intersects the catastrophe set or region.

For a molecule, biochemical pathway, mitochondrion , cell, organ, organ system, or individual organism, there are many pathways or trajectories that can occur over time. All of them occur partially independently but partially dependently upon driving forces in the immediate cell or organismal environment. The dependence, or correlation, of these varied possible events and non-events, positive and negative, at multiple levels further compounds the number of possible microscale and macroscale events, seemingly to infinity. Therefore, the narrowing of the time length between successive events enables us to make better models for prediction and interventions. Still, the limitations of our resources and time for collecting numerous, accurate data at physiological and behavioral levels for many individuals, while not invading their privacy, result in current epidemiological analysis at gaps of months or even years, if at all, beyond pretest , intervention, and posttest .

Iovane, Laserra, and Tortoriello (2003) called attention to the universality of continuous, wavelike processes, even with occasional catastrophic discontinuities , across living and nonliving phenomena across the universe. They examined the allometric scaling of mass, radius, and number of nuclear particles for various systems,

finding a fractal scaling constant of 1.38 for Carbon, ~1.5 for eukaryotic cells and organisms, ~1.4 for the sun and each of the planets, and ~1.5 for galaxies and galactic clusters. Such scaling estimates have been used to make loose arguments for the primacy of processes around magic numbers such as the fine structure constant and Fibonacci numbers. Such allometric scaling laws have been applied to aging across humans and various species, with a scaling factor around 0.75 based upon body mass and metabolic rate, although criticisms of such scaling approaches include the possibility that the relationships might be curvilinear (Agutter & Tuszynski 2011; Hollar 2017).

Regardless of these scaling arguments, it is clear that sinusoidal periodicity characterizes all physical processes, further translating into mental and behavioral processes that can further affect the physical processes, etc. The quantum nature of physiological events , based upon molecular interactions within cells that are influenced by environment and behaviors , may be applicable at organismal and other macroscale levels because of their basis in these molecular interactions, not limited to the Planck length of $l_h = 1.62 \times 10^{-33}$ cm (Davies, Demetrius, & Tuszynski 2012).

Liu, Slotine, and Barabási (Liu, Slotine, & Barabási 2011) provided mathematical models that complex, dense, and relatively homogeneous networks (i.e., roughly equal spread between network nodes) can be controlled by manipulating a few, identified driving forces at the critical points , or nodes, of the network. They found that nodes with high connectivity in networks could lead to greater system regulation . For example, gene regulatory networks in yeast have higher, less centralized nodes and are more difficult to regulate, whereas metabolic pathways, neural pathways, the World Wide Web, and intra-organizational communications have fewer, more critical nodes upon which regulatory focus can be applied. If correct and applicable across diverse types of systems and processes, this observation may provide strongly applicable yet simultaneous sobering ethical implications on where and when we manipulate systems in a positive, responsible manner.

Furthermore, the applications of interventions to periodic and aperiodic phenomena in neuroscience , physiology , and health must be carefully evaluated for the potential introduction of chaotic effects, however small, to system trajectories. An epidemiological assessment of necessary and sufficient conditions while leaving open the potentiality of additional, unmeasured forces having an impact must be part of effective model development, testing, policy, and interventions.

As stated earlier, our primary approaches to manipulating periodic or aperiodic trajectories will involve energetic jumps with specific driving forces or the superposition of correlating driving forces with the resonance of their wavefunctions . This returns us to the spring example, where a careful balance of inertial and driving forces is maintained by dissipative forces. From an astronomical perspective, Hitzl (1975) argued that even periodic cycles can contain quasi-periodic components that achieve stability at specific resonance frequencies or energy levels . Such processes

probably are responsible for the long-term (i.e., tens of millions of years) stability of the planetary rotations . However, specific superpositions of correlating forces can yield instabilities at specific resonances, as has been shown for the Saturnian moon Hyperion, various near-Jupiter orbiting asteroids, Neptune-Pluto, even Jupiter and Mercury, as well as turbulence in the solar atmosphere (Malhotra 1998; Perdang 1983; Wisdom & Peale 1984). Walker and Ford (1969) specifically demonstrated that the superposition of 2:2 and 2:3 resonances produced a merged region of instability that disrupted typical phase spaces into chaotic trajectories (see also Weisstein 2016). Even the solar system has no permanent guarantee of permanent stability , even neglecting potential outside driving forces in the galaxy.

Interestingly, phenomena as diverse as solar atmospheric oscillations, earthquakes, voltage fluctuations across neurons , and classical music display a $[1/f]^{\beta}$ power law or rhythmicity, with $1 < \beta$ contributing to more periodic, stable patterns compared to $\beta < 0.5$ chaos and instability (Levitin, Chordia, & Menon 2012; Perdang 1983; Verveen & Derksen 1968). The similarity between the contribution of β to periodicity is similar to the coherence length ξ that is inversely proportional to the Lyapunov exponent λ .

10.5 Physiological Periodicity

Physiological events can be stable over minutes, days, months, and even years. Nevertheless, such systems are much more susceptible to acute changes. Even the act of standing or sitting immediately changes heart rate, for instance. Kumar et al. (2004) mathematically modeled factors involved in the development and progression of sepsis, one of the leading, pathogen-based causes of death for older adults as well as for infants. Consistent with epidemiological studies of sepsis, they found that the level of immune response to sepsis represents a tradeoff in terms of the eradication or chronic nature of the condition. Too often, the immune response is hyper-elevated with elimination of the pathogen, however, with continued chronic inflammation and subsequent damage to body tissues. They considered several models, all dependent on various immune-related parameters and initial conditions, such that even relatively health conditions could be maintained through a reasonable long-term, cyclic immune response with a low-grade infection. They further showed the correspondence between system stability and $\lambda \sim 0$, with any $\lambda > 0$ leading to instability and chaos . Most importantly, Kumar et al. (2004, p. 152) stated that “any therapy for persistent non-infectious inflammation must target the slow pro-inflammatory mediators.” Despite their findings, it is not clear if this model or other similar models have been demonstrated in clinical treatment, as sepsis continues to be a significant problem for vulnerable individuals, especially when they have experienced traumatic health events and/or chronic severe illnesses.

With the phase patterns of Poincare return maps and shifts of phase described

earlier in this chapter, Granada et al. (2009, p. 12–13) identified a four-stage approach to testing disturbances to phased systems: (a) Describe the oscillating system; (b) Describe the disturbance; (c) Measure phase changes for disturbances at different cycle points; and (d) Plot the Phase Response Curve (Δφ versus φ; Fig. 10.6) to study the regions of stability versus instability . We will explore the generation of these curves, topological maps of disturbed change versus stability in Chaps. 10 and 11. To these four points maintained by Granada et al. (2009), we add one additional point: (e) Identify regions of stability based upon the Phase Response Curve Δφ versus φ to provide the appropriate intervention stimulus to return the system to normal (i.e., initial conditions) or to move an undesirable phase to a different stable phase (Fig. 10.6).

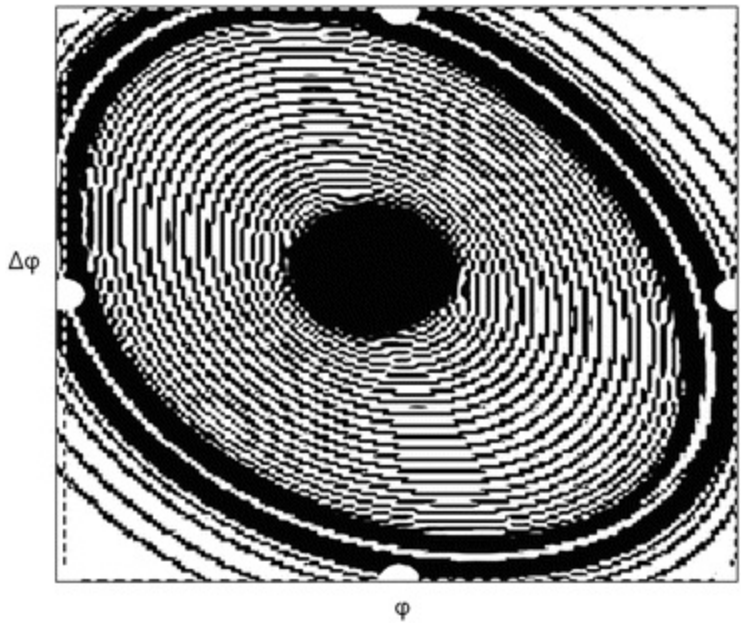

Fig. 10.6 A Phase Response Curve mapping the change in phase versus phase. Regions of attraction are solid, periodic regions are circular, and chaotic regions follow the irregular gradients around the plot edges for this particular example generated with an Enthought Canopy Python program

Therefore, we have the capacity to epidemiologically map the time series evolution of any biological system, including physiological and molecular pathways and their relationships with behavioral patterns impacted by these pathways and the environment. Model development must be specific with realistic contributions of independent variables to the extent of our measuring capability, the clarification of normal and aberrant phases in the phase space of the Poincare return map for that particular system. A further realization is the fact that many systems overlap, correlate, and/or contribute to each other, so many models will be overlapping, further illustrating the complexity of living systems and the need for our epidemiological models to much better address the reality of comprehensive systems perspectives .

The quantum metabolism model applies in these studies because all biological and

other physical systems are fractal in nature, following power laws across multiple levels of hierarchy for the universe, from below the Planck length to galactic clusters, maintaining remarkable periodicities and patterns that we still have not grasped even to a tiny degree. Furthermore, all biological events are intrinsically quantum from a molecular systems perspective . Systems cycle and return to specific reference points in their cycles so that we can measure the consistency of their phases/cycles for good or bad. These are the points where a rigorous research program identifies the central variables and how to best manipulate these variables for improved health. Even with sensitive dependence on initial conditions , we must be careful, for even the best models for good purposes might have unintended results. We must be vigilant in the research and its practical applications.

10.6 Summary

Physiological systems are periodic and follow return maps. They may vary somewhat due to stress and other environmental events, but the systems generally return to their regular patterns. Healthy behaviors and physiologies are consistent over time, but so are unhealthy behaviors and morbidities, which in some instances will be chaotic. Unhealthy conditions either can be energetically jumped to altered phases or may be superimposed with reinforcing supports, medicines, and other resources to a healthier phase state.

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11. Health Conditions and Behaviors as Surfaces

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Abbreviations

PRC Phase response curve

PTC Phase transition curve

PTSD Post traumatic stress disorder

Life happens at surfaces . All life on earth , the biosphere, represents a thin film, a living bubble, that covers a few thousand meters of solid, liquid, and gaseous surfaces representing the tenuous outer boundary of the planet (mean radius = 6371.0 km; www.nasa.gov). Life exists on these boundary substrates to such limited heights and depths in order to maximize access to nutrients and energy (see Chap. 7) for growth and reproduction. Complex interactions of photosynthetic, mutualistic, and predatory organisms exist across a large forest or grassland and even on the surface of a leaf.

Similarly, the human body consists of approximately 5×10^{13} cells descended and differentiated from the initial zygote at conception, and these cells are arranged in various tissues, all of which secrete an extracellular matrix (e.g., collagen matrix, keratin, cartilage, bone, blood plasma) that is a solid or liquid surface for support, protection, and nutrient acquisition. Even within the eukaryotic cell , cytoplasmic membrane components organize protein, carbohydrate, and nutrient transport, with the most prominent cellular organelle being the energetic mitochondria , constantly morphing and merging/splitting into different forms and numbering between 200 and 3000 per cell, over 7000 per cardiac myocyte (Hollar, 2016; Picard, Shirihai, Gentil, & Burelle, 2013). Each mitochondrion generates a continuous proton motive force of approximately 220 millivolts that drives the recycling of adenosine triphosphate for

energy-coupled chemical reactions throughout the cell and body that are essential for life.

Therefore, energy transitions on and across membrane surfaces are essential to life and occur at every level of life. These processes are central to body systems and functioning as well as to social and environmental surfaces. We will even take the position that behaviors, thoughts, and actions that can be recorded also occur on surfaces. Trajectories of conditions and behaviors occur on surfaces, thereby leading us to a topology of health .

11.1 Topology, Surfaces, and Manifolds

Whereas the field of geometry deals with objects that can withstand rigid motions, topology studies objects that can withstand "reversible continuous transformations" (Henle, 1982, p. 1; Tufillaro, Abbott, & Reilly, 1992, p. 12). Topologically, any "smooth geometric space (line, surface, solid)" without sharp edges is termed a manifold (Tufillaro et al. 1992, p. 10). Manifolds are critically important in trajectory analysis because we seek to analyze as much as possible relatively continuous changes in conditions and behaviors. Consequently, we must address the differential equations describing these changes, and differential equations describe vector fields operating on manifolds. Smoothness means that rectangles and sharp-pointed cones are not manifolds.

Therefore surfaces with boundaries represent manifolds, and forces acting on points located on surfaces can be studied. Spheres, cylinders, and tori represent recognizable surfaces that are manifolds. A mitochondrion approximates a torus, and the different shell coiling mechanisms of varied snail species approximate tori, spheres, and cylinders (Pappas & Miller 2013). For practical purposes here, we will use the sphere as a sample space (e.g., Fig. 5.2). Given behaviors or conditions operate on a surface universe of possible behaviors and conditions. Forces (e.g., variables, latent factors; see Chap. 5) act on these phenomena, affecting point trajectories and potentially distorting the surface, hence the topological relevance.

Rene Thom (1972) applied topology to describe reversible catastrophic events that produce morphological changes in organismal development. His approach was only partially successful, but merging nonlinear dynamics with Thom's elementary catastrophes offers potential applications for public health research and specifically primary interventions to improve health. Cvitanovic et al. (2004, p. 38) defined a differentiable dynamic system as follows:

$$f^t : \mathbf{M}_1 \rightarrow \mathbf{M}_2 \tag{11.1}$$

where f represents a flow or function acting and being acted upon over a period of time t, and $\mathbf{M}$ represents its surface or manifold at initial condition 1 and final condition

2. Manifold shape can take on many different forms. Furthermore, the manifold surface can be irregular, leading to alternative pathways that require different energetics from time 1 to time 2, consistent with the method of path coefficients , energetic potentials and probabilities, and return maps described in previous chapters. Pappas and Miller (2013) described simple algebraic rules for the evolution of a sphere to a toroid :

$$x = \cos v \cos u \rightarrow (2 + \cos\ v)\ \cos u$$

$$y = \cos v \sin u \rightarrow (2 + \cos\ v)\ \sin u$$

$$z = \sin v \tag{11.2}$$

where u represents a 0–2π angle that is equivalent to longitude on the sphere or transformed toroid , and v represents the latitude on the sphere or 0–2π angle on the curvature of the tubular toroid. A further slight modification can yield a cylinder (Fig. 11.1). Pappas and Miller (2013) demonstrated the small mathematical variations by which the varied genetic encoding of gastropods and mussel species generate secreted shell phenotypes of varied whorl and aperture.

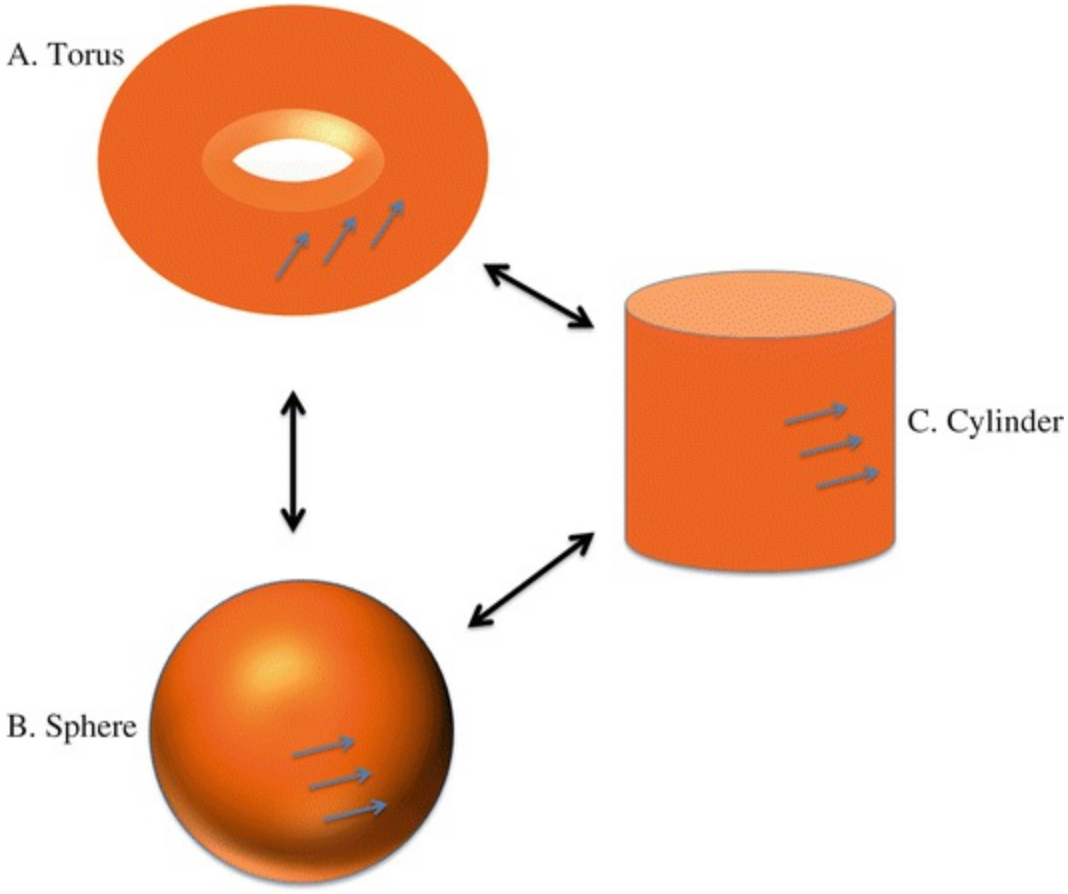

Fig. 11.1 Examples of Manifolds and their transformations. Note the directional vectors (*arrows*) showing curvature changes in trajectories over the surfaces/manifolds

The toroid pattern (Fig. 11.1) is central to the function of the energetic

mitochondrion , although truly the mitochondrion is a toroid-like structure within another toroid: a homeoid. The dynamical changes in the structure of mitochondria and fused mitochondria play a central role in healthy, energetic tissue (Picard et al. 2013). The molecular pathways that recycle ATP and energy for the cell ride the topological changes on the inner mitochondrial membrane, as described in Chap. 7. The quantum activities of these molecular pathways exhibit wavelike, periodic trajectories that occur on the manifold or surface of the curving, wavelike inner mitochondrial membrane. Thus, all phenomena are dependent on their surfaces, environments, and previous history and can be modeled for interventions and guidance.

As outlined in previous chapters, health events and behaviors are exclusively periodic events that are dependent upon layers of multiple other phenomena and environments. Here, we add the additional perspective of environmental surface or manifold. Manifolds will never be as smooth as the spheres or toroids shown in Fig. 11.1. Instead, they will more closely resemble the geological terrain of a mountain valley. Even now, scientists are beginning to study the skin, digestive tract, and other body surfaces as dynamical surfaces on which a complex ecology of thousands of bacterial species representing the metabolome reside. The altered blood flow around an atherosclerotic plaque or bulging aneurysm represents aberrant physiological events that involve flows over surfaces with dire health consequences.

Similarly, the outward psychological behaviors of individuals can be modeled on the surfaces of their environments, which are both physical and cognitive in nature. The living conditions, health environment conditions, work conditions, access to adequate nutrition , clean water, and safety from violence represent very real quantities that can be measured in space and time, as even these processes vary from moment to moment, positively and negatively impacting the conscious state of the individual or in hidden ways subcognitively or even at the molecular level, creating stabilities and/or instabilities at various levels. We know that cancers have unknown latent periods of varied lengths, depending upon the nature of action of the single or multiple triggering events over time. Likewise, psychological trauma can be mapped neurocognitively, genetically , and conceptually to relevant contributing social and other environmental events. The last component is far more difficult to achieve due to its general occurrence in the past. Nevertheless, the reliving of recorded memories, both accurate and distorted, plays a major role in event recurrence for PTSD , depression, suicide, and substance abuse.

Structurally, we are not at the point of modeling the surfaces of environments, so our focus will continue to be the trajectory of processes and the driving forces that impact those processes. The study of manifolds is a primary focus of mathematical topology, and its applied aspects lie within the realm of astrometry and geometrology. There are many potential innovative applications of the latter with physiological systems , an area that has seen promising progress with bone histomorphometry (Eriksen, Axelrod, &

Melsen, 1994). Gradients on a manifold can be expressed by the following equation:

$$\text{Grad } \mathbf{M} = \mathbf{i}\,(\partial \text{m}/\partial \text{x}) + \mathbf{j}\,(\partial \text{m}/\partial \text{y}) + \mathbf{k}\,(\partial \text{m}/\partial \text{z}) \tag{11.3}$$

where **M** represents the manifold and vectors **i**, **j**, and **k** represent directional force vectors across the x, y, and z dimensions, respectively. Spatiotemporally, the **i**, **j**, and **k** vectors enable the introduction of Clifford algebras and quaternions, which can be used in rotational studies of objects and surfaces at both classical and quantum levels (Fauser, 2002; Hiley, 2012; Kuipers, 1999). Hiley (2012) maintained that Clifford algebras such as Eq. 11.3 describe phase space and the process of "becoming" for both classical and quantum trajectories.

The application of the partial derivative across each of the *x*, *y*, and *z* dimensions, using Cartesian coordinates, is a further component of standard advanced calculus courses. Topologically, we can examine area, volume, and other dimensions for uniform or heterogenous three-dimensional objects using spherical coordinate systems, where we transform the Cartesian *x*, *y*, and *z* coordinates to (Boas, 1983; Zeilik & Smith, 1987):

$$\begin{aligned} x &= r \sin\theta \cos\phi \\ y &= r \sin\theta \sin\phi \\ z &= r \cos\theta \end{aligned} \tag{11.4}$$

where *r* represents the radius or distance of a point from the origin (0,0,0), equivalent to the amplitude in our spring example from Chap. 10. The angle θ represents the angle of *r* from the *z* axis (i.e., North using the right-hand rule), and the angle ϕ represents the position of *r* with respect to the *xy* plane and rotating about the *z* axis (i.e., East–West). Think of a spinning gyroscope: the activity, action , or process of spinning is maintained, like a spring , by inertial and driving forces (e.g., input of energy to maintain the spin) that are opposed by dissipative forces (e.g., friction of the flat planar surface as well as air resistance, a gaseous surface). The volume of a sphere or spheroidal-type structure can be determined using triple integration across each dimension (Boas, 1983):

$$\text{Volume} = \int\int\int f(r,\theta,\phi) = r^2 \sin\theta \;\; \text{d}r \;\; \text{d}\theta \;\; \text{d}\phi \tag{11.5}$$

Likewise, distorted manifold surfaces similar to spheroids can be studied using intersections of other functions with the standard spheroid shape and function.

Behaviors and physiology can be modeled three-dimensionally, with consistent periodic flow representing a sphere or ellipsoid, then λ trajectory deviations being equivalent to eccentricity ε as the spinning gyroscope model becomes unstable and aperiodic along parabolic, hyperbolic, and chaotic pathways (Fig. 11.2) and the relation (Eq. 8.5):

$$\lambda = \delta^2 S \sim \xi^{-1} \sim \varepsilon \tag{11.6}$$

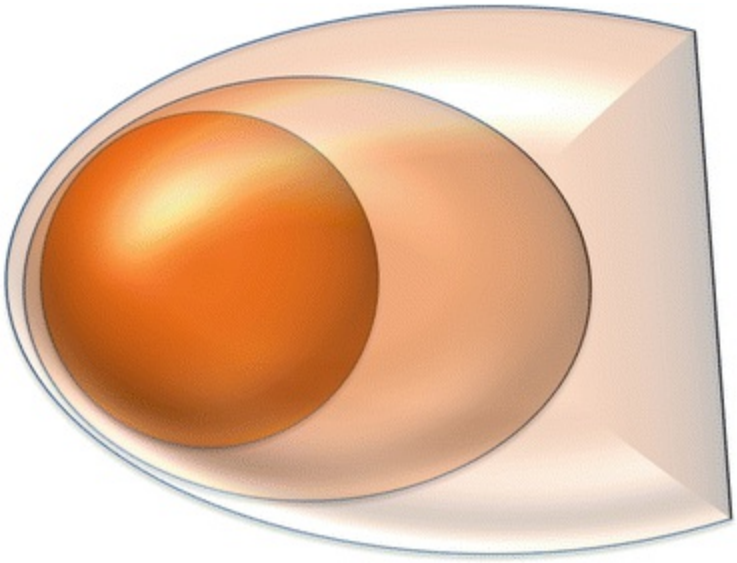

Fig. 11.2 More spheroids, this time bending their trajectories by deforming their typologies. Generally, forces acting on systems change the system, but the environment itself can change, either physically or symbolically based upon these forces. A sphere is topologically deformed to an ellipsoid, then to a paraboloid, etc., with increasing eccentricity ε that is proportional to Lyapunov exponent λ

The eccentricity ε of parabolic forms, where $\varepsilon = 0$ for a circle/sphere but increases with stretching of the manifold, was mapped directly to aperiodicity and chaos by Eigen and Schuster (1979) while evaluating information complexity in biochemical reactions.

Note the direct relationship of Eq. 11.4 to the Pappas and Miller (2013) manifold manipulation of spheres and tori to closely model snail and mollusk shells, an approach that equally is applicable to the modeling of animal bodies, their organs, and cellular components. The spherical coordinates, along with their close cylindrical, elliptical, and polar coordinate systems, further illustrate the importance of surface shape and energy potential flows across these surfaces, varying curvature defining the direction of trajectories and the influence of driving forces in the surface environment. The curvature and sinusoidal patterns are connected as well to the Fourier transform that has so many scientific applications (e.g., signal analysis) and that was briefly discussed in Chap. 10. All of these central mathematical concepts stem from Euler's famous identity for the exponential (Loy, 2007, p. 67):

$$e^{i2\pi n} = \cos(2\pi n) + i \sin(2\pi n) = 1 + 0i \tag{11.7}$$

where e represents the exponential (i.e., e = 2.71828) related to the logarithms, i is the square root of −1, and n represents any angle in cyclic periodicity . Moreover, the angular frequency ω is connected via these relationships.

11.2 Driving and Dissipative Forces on Trajectories

The driving forces that maintain a trajectory and the dissipative forces that cause a trajectory to deviate either continuously act on the trajectory or act at specific points, respectively. The dissipative forces might be a sudden jolt to the system or the merging of correlating, superposed external systems on a continuous basis. Figure 11.3 illustrates the example of a jolt or slight nudge to the system. A cyclic , sinusoidal wave phenomenon with period t_0 proceeds without interruption. However, an alternative, equivalent wavefront is disrupted by a force that extends the width of the third wave by δt so that the period initially is shifted to length t_1, coupled with disruptions of subsequent waves in the wavefront, waves that might be shorter or longer in periodicity. Overall, the frequency $f = 1/t$ and the angular frequency $\omega = 2\pi f$ or $\omega = 2\pi/t$ are altered as well. Some systems have multiple maintenance forces and are resilient, such as an elevated heartbeat that returns to normal following exercise and sudden stress . Another physiological process would be the return to homeostasis of blood glucose levels a few hours following a meal, a phenomenon dependent on insulin production, a system in its own right that depends on other systems: insulin signaling and cell-surface receptors, hormone stimuli from the hypothalamus, etc.

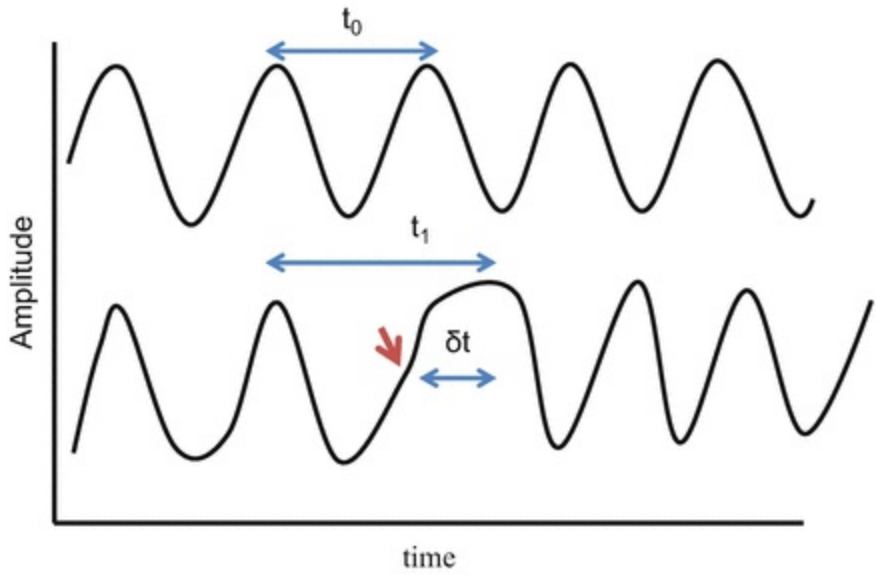

Fig. 11.3 Initial wavefunction with period t_0 that is interrupted (*below*) by a disturbance in the third wave by a time differential δt to produce a trajectory change to period t_1. Note that the two wavefunctions are now out-of-phase, consistent with Lyapunov exponent λ and Poincare Return Maps (Chap. 10). See (Glass & Mackey, 1988, pp. 102–106) for further elaboration on their mathematical analysis of phase shifts

Behaviorally, resiliency in this model could include a minor injury from which recovery is swift, or an individual's bad decision that is immediately followed by their correction to reverse the decision and thereby remedy the situation. As we have

discussed earlier, multiple facilitating forces increase the likelihood of resiliency. What often is difficult to determine are the parameters defining the amplitude of these forces and their proper cyclic timing to maintain stability .

The downside of Fig. 11.3 includes events where the dissipative forces are strong, overcoming resiliency, and resulting in a maintained, aberrant δt and t_1. Physiologically, such events might be acute or chronic. Acute examples would include cardiac arrhythmias or other dysrhythmias, neurocognitive seizures, etc. that might be restored after a certain time period but could reoccur due to repeated exposures to the disturbing forces. Chronic examples would include conditions such as diabetes or other metabolic disorders that have a sudden driving disruptor during the lifespan or that are genetically encoded from birth.

Behavioral events can be acute or chronic as well. Acute events could be major negative life events that produce profound behavioral changes from which individuals might not be able to recover without social supports. Powerful emotions such as sudden anger, depression, hopelessness, etc. might overwhelm normal cognitive functioning, and affected individuals could engage in very poor decision making that yields even more negative consequences. As noted in Chap. 6, aggression and other forms of psychological violence are major threats to public health (World Health Organization, 2002) and are a very real component of human behaviors. Chronic behavioral events follow similar patterns , although these behaviors can be more entrenched and equally unpredictable based upon neurocognitive imprinting and later triggering events.

Therefore, the time scale of events figures prominently, but it is even more elusive when we attempt to move a two- or three-dimensional forces model through the fourth dimension of time. Many conditions enjoy a latency period before they are fully manifested, so mapping forces/variables from the past and establishing a causal connection is difficult. Furthermore, the thresholds that trigger a recurrence of a physiological or behavioral event might be periodic, aperiodic , or chaotic, probably more to the latter situations for behavioral events. Different human cultures structure their environments in varied formats such that different factors or forces drive the incidence and prevalence of certain behavioral traits. Nevertheless, human patterns are remarkably similar across ethnicities and cultures, including aging curves, although lack of clean water, nutrition , and health care causes the death curves to be steeper at earlier ages for populations living in poverty. Circadian cycles resonate with many physiological processes so that these processes are similar. Individual genetic and epigenetic factors, even between monozygotic twins, can yield different health outcomes. Environmental exposures over time yield differing health results per individual, depending upon varied critical events that have short- or long-term effects. We can never come close to measuring every factor at every critical time point, but our epidemiological methods must collect more repeatable measurements for complex genetic , biochemical, social, and environmental factors/forces at as many time points as

possible to more realistically track the occurrence of health conditions. Even then, we can only intervene to affect divergences in trajectories to some degree for health improvement. The second law of thermodynamics (i.e., the law of entropy) dictates that all systems will tend to move to the ground state. Change is inevitable despite all of our efforts. Nevertheless, it is the work of public health to maintain the trajectories of good health as much as possible.

11.3 Examples

Glass and Mackey (1988, pp. 22–25) provided a mathematical description of a Glass, Guevara, Bélair, and Shrier (1984) study involving electrochemical disturbances to spontaneously beating, cultured chick ventricular myocytes . Their description mirrors the example illustrated in Fig. 11.3. A disturbance shifts the original wavefunction or wave train phase from its initial period t_0 to a new period t_1 that is δt longer (or shorter) than t_0. Whereas this system is strongly resilient and returns to the t_0 periodic pattern relatively quickly, not all such systems do so at the same rates, if they return at all. Glass and Mackey (1988) covered numerous examples of resilient and chaotic systems in their seminal book, which was the first work to provide direct applications to biomedical research and applied health interventions.

As a follow-up to their chick heart example and the parameters in a phase shift disturbance such as that shown in Fig. 11.3, Glass and Mackey (1988, p. 105) defined the initial system state or phase as $\theta_0 = 0$, whereas shifted phases following a disturbance would be defined as $\theta_n = t_n / t_0$. Consequently, they defined (p. 106) the change of phase:

$$\Delta\theta = (t_n - t_0)\,/t_0 \tag{11.8}$$

Most importantly, Glass and Mackey (1988, p. 107) used the unit circle phase change (Fig. 9.2) to illustrate a convenient geometric tool for measuring the disturbance effect (proportional to λ). In Fig. 11.4, we show the initial phase $\theta_0 = \omega t$ and the altered phase $\theta_n = \omega t_n$. Glass and Mackey (1988, pp. 106–107) provided a trigonometric calculation for the new phase space , simplified to

$$\theta_n = 1 + \theta_0 - t_n/t_0 \tag{11.9}$$

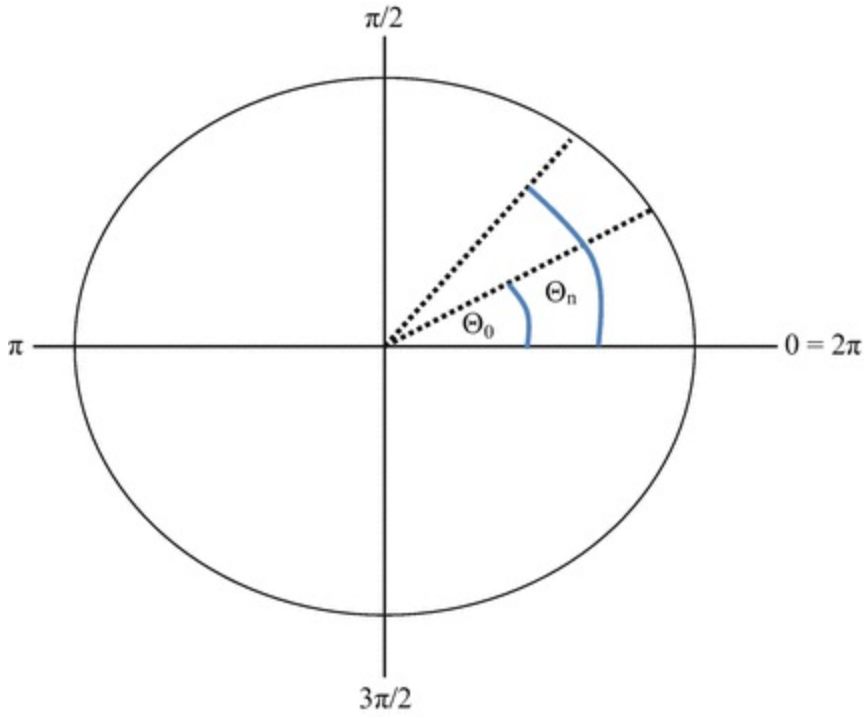

Fig. 11.4 Phase Angle changes with respect to phase shifts and the unit circle (Chap. 10 and Fig. 11.3 above). See (Glass & Mackey 1988, pp. 104–110) for a more extensive discussion on the mathematical development of the Lyapunov exponent for this phase angle shift

This equation enables the determination of a Phase Transition Curve (PTC) , also termed a Phase Response Curve (PRC) that was introduced in Chap. 10. Glass and Mackey's PTC and simplified equations couple with the Lyapunov exponents to provide a straightforward, structured approach to mapping trajectories for any type of longitudinal data that exhibit linear cyclic or nonlinear, chaotic properties.

The equivalence to the Poincare return map to the PTC or PRC lies in the shifting of system phase states over time due to consistencies and/or deviations in trajectories. Endless reiterations of cycles and varied cycles can be mapped so that phase/change regions of stability , periodicity , and instability can be evaluated. The further advantage is the visual aspect of the topological analysis, as the system or phenomenon can be viewed even if it is a non-physical (e.g., psychological-behavioral) process. The mathematics are not complicated, and the methodologies are complementary to inferential statistical and epidemiological approaches to data analysis.

11.4 Phase Space Resetting and Health

Phase response curves for health conditions are straightforward. For a given condition, a strong (positive) health condition should be the ideal base state for the biochemical pathway, cell, tissue, and the entire individual. Phase changes $\Delta\theta$ will occur in a cyclic fashion based upon environmental noise, slight disturbances that provide minor impacts

on the system, which promptly recovers and continues cycling within short time frames. Dramatic impacts on health systems will prolong or even substantially alter the trajectories of normal health for a given body function or structure, yielding nonlinear, potentially unstable phases. Even with the small changes that may seem minor, one perspective on aging is error accumulation over time to a threshold point where system collapse occurs. In humans, aging generally begins at adolescence and progresses gradually, with major declines beginning around age 60. Actuarial estimates place a doubling time on the probability of dying roughly every 7 years. The epigenetic evidence on changes in gene regulation between monozygotic twins and between young and older individuals bears out the accumulated small changes that add up over time, consistent with Poincare's sensitive dependence on initial conditions.

Our emphasis on the conceptual mapping of physical and psychological processes in phase spaces represents a dramatic shift from standard statistical and epidemiological practice. Nevertheless, it offers the possibility of improving our understanding of the complex interplay of independent and dependent health variables as a continuous, dynamic flow, as life truly exists, albeit with the breaks, the discontinuities that represent health limitations, disease, and aging . Furthermore, we see this approach as a unifying principle across all disciplines, particularly given the substantial contribution that nonlinear methods have made in applied mathematics and the physical sciences. Challenges in health research involve obtaining enough buy-in to see the benefits of these methods as well as the increased demands on obtaining multiple data points, telemetry wherever possible to visualize individual health as progressive manifolds of interacting biological, physical, social, and environmental variables across each three-dimensional surface and moving forward through the fourth dimension of time. This approach also continues the scientific approach of the last century for providing realistic models of the forces within and around us that clearly exist but that too often are unseen or unnoticed.

Glass and Mackey (1988) were highly successful at moving this approach to applied physiological interventions , as we will see numerous examples in Chap. 13. Returning to their phase model, we introduce the topological concept of the winding number. The winding number is the number of negative counterclockwise or positive clockwise revolutions of a nonzero vector or vector field over a bounded surface or manifold , with each revolution returning the vector to its equivalent starting position on the curve (Henle, 1982, pp. 48–52). Similarly, Glass and Mackey (1988, pp. 107–109) used the winding number concept to illustrate the phase shift Poincare return map of a trajectory following a periodic cycle (Fig. 11.4).

Specifically, they emphasize that for a periodic, cycling process, a displaced wave can only crossover its original wave once (i.e., one cycle). Therefore, there are two possible winding numbers for periodic phenomena: 0 and 1. We will ignore the counterclockwise −1 as it is merely a reflection of the positive 1. Simultaneously, they

argue that there are two types of phase resetting curves: Type 1 and Type 0. A Type 1 phase resetting curve involves a negligible displacement or disturbance m (see the parameters above) such that $0 < m < 1$, and the system recovers to its original state. Alternatively, a Type 0 phase resetting curve occurs when the disturbance $m > 1$ is substantial, and the $\Delta\theta$ phase shift of the wave is substantial such that a new wavefunction or wave train is established. In his analysis of the Hénon attractor (similar to the Lorenz attractor described in Chap. 9) and its fractal reiteration at multiple scales, Ruelle (1989, p. 18) described the contraction factor m at $0 < m < 1$ being reversible for the cycling of the attracting trajectories, whereas $m > 1$ tended to be chaotic; he further related this disturbance parameter to the Jacobian and the central Lyapunov exponents , as we will discuss their derivation in Chap. 12.

If we map each subsequent phase to its previous phase for many iterations , a Type 1 phase reset back to its original phase (i.e., small disturbance $0 < m < 1$) will show the continuous periodic curve along the diagonal shown in Fig. 11.5. Alternatively, a large disturbance (i.e., $m > 1$) for a Type 0 reset to a new phase will show disjoint, separate curves (Fig. 11.6) when each subsequent phase is mapped to its previous phase for many iterations.

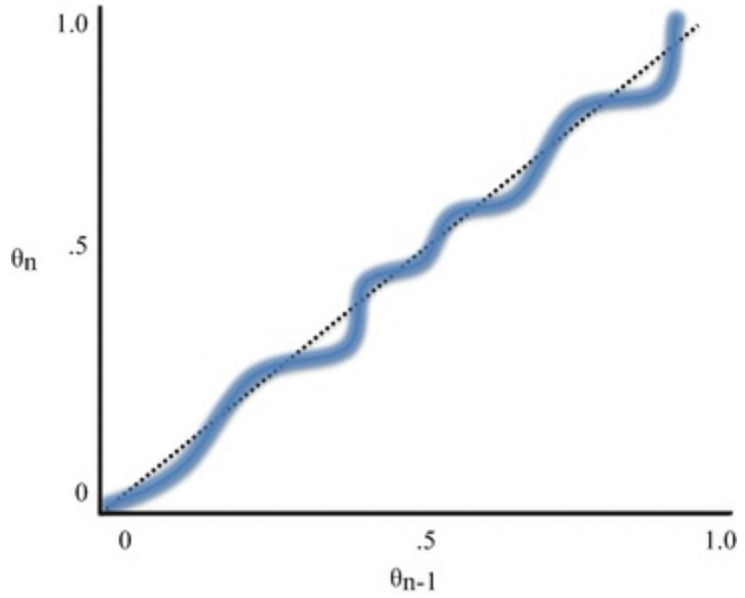

Fig. 11.5 Type 1 Phase Shift

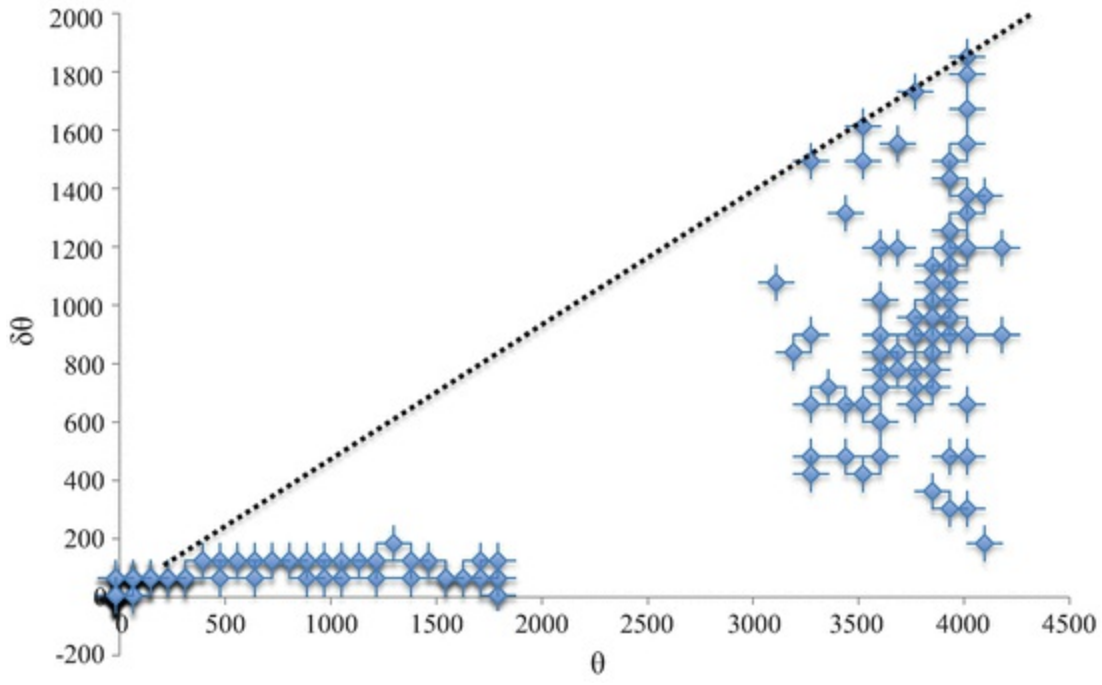

Fig. 11.6 Type 0 Phase Shift. Notice to the bifurcation divergence of clustered points compared to the Type 1 Phase Shift shown in Fig. 11.5

The meaning of these two graphs (Figs. 11.5 and 11.6) is that the relative coherence between a slightly disturbed rhythm and the original wavefunction is maintained, so that the two waves are out of phase, they eventually precess and "smooth out" due to the action of the counterbalanced driving and dissipative forces; the resulting relationship between reiterative θ_n and θ_{n-1} phases is periodic itself (Fig. 11.5)! Hence, there is no permanent, detectable change in resilient systems that return to normal. A physiological example would be the immune system as it responds to and eradicates a cold virus over the course of a few weeks. Behaviorally, a person might start an exercise program, thereby breaking a sedentary cycle; yet, the pressures of work, family, and other obligations might distract them over time, thus forcing their health behavior back to the more negative sedentary cycle.

A true jump, or discontinuity , from one phase to another maintained phase is reflected by Fig. 11.6, where there is little coherence between reiterative θ_n and θ_{n-1} phases; the graphs curve away from a central periodicity . Here, a physiological example would be the decline in myostatin during early adulthood such that new muscle growth is greatly reduced or stopped. Conversely, Professor Se-Jin Lee (2007), the discoverer of myostatin, has successfully developed molecular interventions in myostatin receptor and transforming growth factor beta (TGF-β) signaling biochemical pathways in mice so that muscle mass is quadrupled, even in older mice. Behaviorally, an individual committed to starting and maintaining an exercise program, altered diet, or abstinence from alcohol and tobacco could make such a phase shift in their cycle of

behaviors if appropriate support mechanisms (i.e., energy , social and environmental resources, replacement activities) are provided and maintained for the individual.

Thus, Glass and Mackey (1988) provided a research program for nonlinear analysis that can be incorporated into our epidemiological perspective. Their approach already has been applied to cardiology , neuroscience , and other physiological disciplines. Ecologists have extended this work to the analysis of species interactions and environmental factors that influence the distribution of organisms in biomes and ecosystems. The systems perspective has been loosely promoted in public health through biopsychosocial models, but the longitudinal mapping of complex interactions is the next step in the development of health research and epidemiology .

Both Ruelle (1989) and Glass and Mackey (1988) calculated the Lyapunov exponent λ . As described earlier, Ruelle (1989) described λ as being equivalent to a system's fractal (i.e., reiterative) dimension, Poincare return map differentials, as well as to the information entropy of a system. We later illustrated its inverse relationship to coherence length and to Glass and Mackey's (1988) disturbance parameter m in the calculation of phase shifts. For a transitioning manifold , Ruelle's (1989, p. 42) equation for λ is as follows:

$$\lambda = \int \log\left(|df/dx|\right)\ \rho(dx) \tag{11.10}$$

where df is the change in the flow of the process on the manifold per change in point x on the manifold, while ρ is a probability measure of the change in x (i.e., dx). Think of an expanding balloon, starting with two adjacent points that separate with the expansion of the manifold (i.e., balloon's surface), akin to Ruelle's eccentricity ε of a stretched circle. Furthermore, in solving for the dynamical equations of an evolving trajectory, numerous characteristic exponents (i.e., λ's) may be generated as solutions of the system Jacobian matrix (see Chap. 12). The primary (i.e., largest) λ is proportional to the dynamic transformation of the system from a disturbance . Negative λ's are attractive, $\lambda = 0$ is stable and circular, and $\lambda > 0$ are bifurcating periodic until $\lambda >$ ~3 is chaotic (Li & Yorke, 1975). As we will see in Chap. 11, the absolute value of the determinant of the Jacobian matrix is the sum of the λ's. This sum is equivalent to the disturbance measure m cited by Glass and Mackey (1988) and in Fig. 11.4, equivalent to the change in trajectory for the system in the Poincare return map .

Glass and Mackey's (1988, p. 54) equation for λ is

$$\lambda_i = \lim\left(t \to \infty\right)\ 1/t \log_2\left[r_i(t_n)/r_i(t_{n-1})\right] \tag{11.11}$$

where t is the time point and r is the principal axis of the changing ellipsoid (i.e., manifold) during the return Poincare trajectory of the system. Therefore, for Eq. 10.10, we are comparing each reiterative comparison of r at time t_n to its previous value at the next earlier time period t_{n-1}. As a result, we have a quantitative measure on the phase shifts (Type 1 and Type 0) described in Figs. 11.5 and 11.6.

Thus, Glass and Mackey (1988) established a program for the mathematical techniques to be used in trajectory analysis . They state explicitly these applications in cardiology and neuroscience , although we emphasize their applicability in all aspects of health analysis, given the availability of longitudinal data for many time points. Currently, such data is substantially limited with the exception of stored telemetry on patients receiving specialized medical treatment. Rarely is such data analyzed retrospectively, even then with limitations of available variables to specify and measure a relatively complete systems model. The situation is much worse with social/behavioral research, which relies mostly on respondent self-reporting of limited data and attrition during the course of the study, major barriers to research validity (Chap. 4). Prospectively, epidemiologists and other health/medical researchers should consider the planning of studies that comprehensively gather such data, with patient consent and proper research ethics guidelines. Furthermore, a new generation of health information analysts will be needed to properly gather and decipher the complex relationships in longitudinal genetic, epigenetic , physiological , behavioral, social, and environmental variables that impact health.

11.5 Summary

All evolving systems are dynamical and undergo phase changes at multiple levels, microscopic to macroscopic . In modeling realistic, comprehensive health outcomes on systems of health independent variables, it is important that we carefully specify these models based upon the available data, their collinearity with each other, and their interactions across multiple systems and levels of hierarchy (e.g., molecule to cell to organ systems). The advent of reliable data storage and ethical sharing of data on mobile smartphone applications represents a promising disruptive technology for improving our data capture to enable the analysis of phase changes across multiple physiological and behavioral changes for individuals and social networking groups/populations. Phase mapping of health systems at cellular, organ, and individual levels gives us the opportunity for higher level understanding of health conditions and interventions to improve health.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_12

12. Jacobian Matrices and Lyapunov Exponents

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Abbreviations

Det Determinant

HLA Human leukocyte antigen

MHC Major histocompatibility complex

PRC Phase response curve

TNF Tumor necrosis factor

TRAIL TNF apoptosis inducing ligand

Following the model change of a system as a sphere being stretched into an ellipsoid, Cvitanovic et al. (2004, p. 133) described the flow of a dynamical system as the following process:

$$f^t(x(t_0)) : x(t_0) + \delta x \rightarrow x(t_1) + \mathbf{J}\delta x \tag{12.1}$$

where f represents the flow, x represents a point or region on a manifold and its trajectory over a Poincare return map from time 0 to the end of its period time 1. The change in x, δx, is compounded by the Jacobian matrix **J**, the matrix of tangent equations for the trajectory of the flow. Cvitanovic et al. (2004, pp. 132–134) further equated the shear and stability of the trajectory to **J** and specifically the Lyapunov exponents λ, the positive diagonal elements of **J** that are the "mean rate of separation of trajectories of the system" (p. 132) and that can be calculated as (p. 134):

$$\lambda = (1/t)\ \ln\ (|\delta x(t_1)|/|\delta x(t_0)|) \tag{12.2}$$

which matches closely the Glass and Mackey ((1988), p. 54) derivation of λ (Eq. 11.10). For our examples, we will use Eq. 12.2 due to its use of base 10 natural logarithms

consistent with the Ruelle (1989) and Cvitanovic et al. (2004) emphases on λ as the exponent of the exponential function for $\delta x(t)$.

Therefore, we have an objective measure for the rate of change of trajectories for any dynamical system. This methodology was developed by the Russian mathematician/physicist Aleksandr Lyapunov (1857–1918) in his 1892 doctoral dissertation on the stability of moving fluids. The Lyapunov exponents provide a mean rate of change for each possible trajectory or path of the system during its cyclic behavior , and the Jacobian matrix that contains the Lyapunov exponents provides the overall stretching or contraction of the system on its manifold/surface . This mathematical formalism solidifies trajectory analysis as a different approach to science that is most applicable to physiological and behavioral health analysis. It further illustrates the applications of topology to health problems, both physical and conceptual in nature.

Cvitanovic et al. (2004) provided a novel, applied approach to the study of nonlinear dynamics in physical systems that clearly explains the mathematics and supported their examples with Python syntax. Furthermore, they offered a free, online MOOC (i.e., Massive Open Online Course) from the Georgia Institute of Technology beginning in 2014.

12.1 The Jacobian Matrix

The Jacobian matrix relates the topological change on a given system trajectory. To compute a Jacobian matrix, we start with a flow with multiple component functions across several dimensions. For example, suppose we have a flow with three functions for the x, y, and z dimensions:

$$f(x, y, z) = \left(2x + 24y + 8, 5x + 3, 3x + y^2 + 12z\right) \tag{12.3}$$

then the three component functions have the following partial differential equation solutions:

$$\begin{aligned} \partial f/\partial x &= (2, 5, 3) \\ \partial f/\partial y &= (24, 0, 2y) \\ \partial f/\partial z &= (0, 0, 12) \end{aligned} \tag{12.4}$$

For instance, the three $\partial f/\partial x$ solutions in Eq. 12.4 were computed using the derivative of x in each of the three function component equations for Eq. 12.3. Likewise, the $\partial f/\partial y$ and $\partial f/\partial z$ solutions were computed using the derivatives of y and z, respectively.

The solutions to Eq. 12.4 relate directly to the Jacobian matrix , which has the following structure for a three-component/dimension function:

$$\mathbf{J} = \begin{vmatrix} \partial f_1/\partial x_1 & \partial f_1/\partial y_1 & \partial f_1/\partial z_1 \\ \partial f_2/\partial x_2 & \partial f_2/\partial y_2 & \partial f_2/\partial z_2 \\ \partial f_3/\partial x_3 & \partial f_3/\partial y_3 & \partial f_3/\partial z_3 \end{vmatrix} \tag{12.5}$$

Therefore, the solutions for Eq. 12.4 can be substituted into Eq. 12.5, with consecutive x values for the three component functions filling the first column, the consecutive y values filling the second column, and the z values filling the third column of the matrix.

From a trajectory perspective for this example function, we can see three different pathways f_1, f_2, and f_3 that form the outline of the flow section as the flow deviates on its Poincare return pathway. Each pathway f has three-dimensional x, y, and z components in phase space at any given moment. Therefore, we also can express the Jacobian within the perspective of time just as we can project to polar or spherical coordinates, as we will follow below. Whereas the epidemiologist need not calculate the Jacobian matrix for a mapped trajectory of health behaviors , we provide this derivation to demonstrate its topological relevance but, most importantly, its relevance to Lyapunov exponents .

Continuing, we substitute the solutions from Eq. 11.4 into Eq. 11.5 to obtain

$$\mathbf{J} = \begin{vmatrix} 2 & 24 & 0 \\ 5 & 0 & 0 \\ 3 & 2y & 12 \end{vmatrix} \tag{12.6}$$

The next step is to compute the characteristic exponents of the Jacobian matrix , here termed the Lyapunov exponents. Because this particular example is a third-order matrix with nine elements, we will subtract λ from each of the diagonal elements to begin the computation of the Lyapunov exponents:

$$\mathbf{J} = \begin{vmatrix} 2-\lambda & 24 & 0 \\ 5 & 0-\lambda & 0 \\ 3 & 2y & 12-\lambda \end{vmatrix} \tag{12.7}$$

Typically, the determinant is calculated as a cross-product subtraction of the diagonal elements for a 2 × 2 matrix. In the case of higher-order matrices such as Eq. 12.7, we must solve the determinant of the matrix, and hence the Lyapunov exponents , via blocks of 2 × 2 matrix sections. Using Thomas'(1969, pp. 716–718) permutation method involving row 1 element multiplication for each of the corresponding row 2/3 minor 2 × 2 matrix sections, we obtain the following:

$$\text{Det} = (2-\lambda)\begin{vmatrix} -\lambda & 0 \\ 2y & 12-\lambda \end{vmatrix} - 24\begin{vmatrix} 5 & 0 \\ 3 & 12-\lambda \end{vmatrix} + 0\begin{vmatrix} 5 & -\lambda \\ 3 & 2y \end{vmatrix} \tag{12.8}$$

which equals

$$\text{Det} = (2-\lambda)\left[(-\lambda)(12-\lambda) - 2y(0)\right] - 24\left[5(12-\lambda) - 3(0)\right] + 0\left[5(2y) - 3(-\lambda)\right] = (2-\lambda)\left(\lambda^2 - 12\lambda\right) - 24(60-5\lambda)$$

(12.9)

Using the Khayyam-del Ferro-Tartaglia-Cardano solutions for cubic formulas (Weisstein 2016), one solution of $\lambda \sim 10$. Both Boas (1983) and Pedhazur (1982) provide thorough descriptions of matrix algebra, Jacobian matrices, determinants, and characteristic equations with applications in the physical sciences as well as in behavioral research, respectively. Tufillaro, Abbott, and Reilly (1992) and Wolfram (2002) provided further elaborations and computer examples for the relationship of positive Lyapunov exponents to Poincare's sensitive dependence on initial conditions.

The epidemiologist is not concerned with the calculation of the Jacobian matrix or of λ via the Jacobian matrix to perform trajectory analysis for physiological or behavioral longitudinal health data. While the Jacobian provides a topological perspective on the stretching parameter m from Chap. 11, proportional to the eccentricity ε, we know that these parameters are directly proportional to λ. Therefore, we will utilize the Cvitanovic et al. (2004) Eq. 12.2 above. The Lyapunov exponent λ measures expansion or contraction of a trajectory from its previous cycle.

12.2 Transition Points

Lyapunov exponents (λ's) can be linked to transition points between single period and period doubling events in bifurcation diagrams as a system changes its periodicity ; such behavior ultimately leads to the transition points for chaotic behavior. Such transition points involve de-coherence (Zurek 2002) from the system's prior state: a phase transition as described in Chap. 10. At high coherence, we have a Type 1 phase shift (see Fig. 11.5) where λ is small and system stability is maintained when the original and disturbed phase states precess and superimpose, returning the system to normal behavior. For physiological and behavioral systems, this is what we observe for healthy conditions and behaviors as well as for long-term unhealthy behaviors. A Type 0 phase shift (Fig. 11.6) leads to de-coherence, or reduced coherence (i.e., high λ) as the original and altered periodic systems diverge during a genuine transition. The Type 0 shift is what we observe when a healthy condition changes to a less healthy or unhealthy condition that, nevertheless, is stable over time. A Type 0 shift also is what we attempt to achieve when we try to alter an unhealthy condition to a stable, more healthy situation. Chaos ensues (i.e., typically $\lambda > 3$) when there are dramatic shifts from one state to another, with no consistency in states over time, such that there is no periodicity and the measured behaviors/conditions can vary across wide extremes.

For practical purposes , we will focus on two-dimensional examples that are more representative of the types of data that are collected in health/medical research. Previously, we have utilized several three-dimensional models as examples; these approaches are gaining greater applications in research with three-dimensional imaging of organ systems (e.g., Positron Emission Tomography (PET)), three-dimensional data

analysis (e.g., Geographic Information Systems), and three-dimensional simulation, prototype, and production of health devices, even on the nanoscale (e.g., 3D Printing/Additive Manufacturing).

Boas (1983, pp. 220–223) demonstrated the applicability of Jacobian matrices to the analysis of three-dimensional change, specifically calculating volume and moment of inertia calculations using the Jacobian. The Cartesian to spherical coordinate conversion is:

$$\begin{aligned} x &= r \sin\theta \cos\phi \\ y &= r \sin\theta \sin\phi \\ z &= r \cos\theta \end{aligned} \tag{12.10}$$

The parameters r, θ, and ϕ are described in Chap. 10 and are illustrated in Fig. 12.1. We can convert the Jacobian for Eq. 11.5 to convert spherical coordinates:

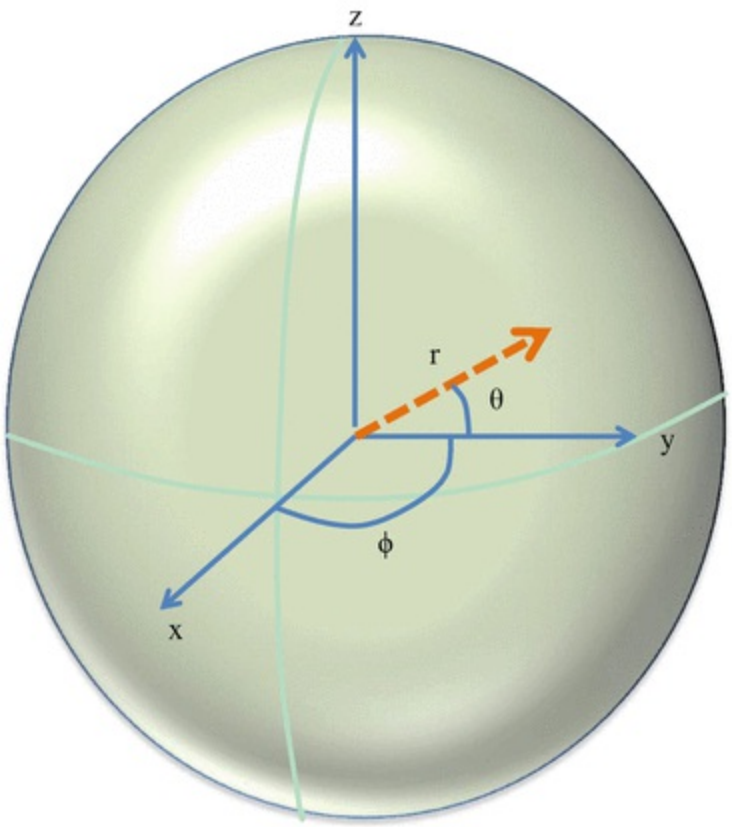


Fig. 12.1 Spherical coordinate system

$$\mathbf{J} = \begin{vmatrix} \partial x/\partial r & \partial y/\partial r & \partial z/\partial r \\ \partial x/\partial\theta & \partial y/\partial\theta & \partial z/\partial\theta \\ \partial x/\partial\phi & \partial y/\partial\phi & \partial z/\partial\phi \end{vmatrix}$$

The matrix format is a convenient approach to making these conversions and to generating change of function equations such as change in volume of the manifold, computing topological changes in the manifold, and mapping the velocities of points on

a changing manifold. Calculating the Lyapunov exponent λ would be much more complicated for spherical, polar, and other coordinate systems. Fortunately, we have computer programs (e.g., Python) that enable rapid computation with as few as a dozen lines of syntax for three-dimensional phase change models. For the epidemiologist, direct comparisons of two-dimensional data can utilize Eq. 12.2.

12.3 Examples

Examples of phase change studies and stability analysis using λ in the field include analyses of human walking patterns and the electroencephalography of normal versus epileptic brainwave patterns. Bruijn, Bregman, Meijer, Beek, & van Dieën (2011, 2012) and Bruijn, Meijer, Beek, & van Dieën (2013) explored the use of maximal Lyapunov exponents in the assessment of the effects of small perturbations on varied foot parameters, gait functioning, and the probability of falling. Specifically, they studied short-term λ estimates for fewer strides (0–1) versus long-term λ estimates for more strides (4–10). They found that discrepancies in the correlations between stability and λ, recommending short-term λ as a stronger predictor of stability . Reynard, Vuadens, Deriaz, and Terrier (2014) studied short strides for healthy and unhealthy patients, finding that patients had significantly higher λ (less gait stability) than healthy controls. In this study, $\lambda < 1$ but was consistently higher for patients measured for both step frequency and measures of trunk acceleration from various positions/dimensions. The results from these two sets of studies demonstrate the applicability of physical and/or behavioral processes that follow periodic patterns (e.g., stepping) and therefore are amenable to trajectory analysis using nonlinear estimates such as λ. At the same time, the studies can be enhanced with the assessments of individual step parameters and their effects upon λ instead of global movements. These studies are moving in this direction, illustrating the complexity of any behavior in these types of analyses. Furthermore, health conditions such as gait stability can vary for a variety of conditions, both healthy and unhealthy. For example, engaging in certain work activities (e.g., heavy lifting) and even certain exercises (e.g., running on an uneven road surface , walking a large, energetic dog) might expose an individual to unexpected environmental disturbances beyond merely one's level of body structural capacity and functional level. Consequently, assessments of stability using λ should incorporate comprehensive biopsychosocial models that truly are relevant to the given health situation.

Southwell, Hills, McLean, and Graham (2016) examined spine stability and neuromuscular control among 13 healthy individuals before and following exercise. They used surface electromyography to measure back muscle activation (i.e., change) due to the effects of exercise and quantified the phase difference of the muscle using λ. Whereas the sample size was very small and there was no significant difference in λ for muscle activation stability from pre-exercise to post-exercise, muscle activation did

increase. Despite no change in muscle stability, they argued that λ represents a useful estimate for change in the dynamical activity of muscle, as measured by cyclic, stimulus-based instrumentation. They concluded that a specific abdominal drawing-in exercise activity did not improve muscle activation stabilization and that stability training should be individualized (Southwell et al. 2016). Consequently, the study showed the epidemiological fact that small sample sizes weaken statistical power and the meaningful utility of measures such as λ. At the same time, this type of study and the author's conclusions illustrate the relevance of individual measures as compared to the group, and λ may be useful for mapping both individual and group trajectories in exercise, health, and behavior .

From a neuroscience perspective , Lehnertz (2008) provided a thorough review of nonlinear dynamics methodologies, including λ, for evaluating electroencephalograms of normal brainwave patterns versus epileptic seizure patterns. Coupled with neuro-imaging, nonlinear analysis can localize affected brain regions as well as map time series trends of aberrations in EEG patterns during both asymptomatic periods and seizure events. Lyapunov exponents can estimate the complexity of factors that contribute to the onset of seizures. Lehnertz (2008) emphasized the necessary next step, prediction, that is missing from studies of nonlinear dynamics as applied to the study of seizures and brain functioning. Likewise, Kuhlmann, Grayden, Wendling, and Schiff (2015) argued this weakness in applications of nonlinear dynamics to the study of epileptic seizures.

Whereas Glass and Mackey (1988) primarily focused on animal models of electrical and stimulation of the heart, producing and restoring dynamical activity, work that has been extended to applied cardiology applications (see Chap. 12), comparable models for electrical and chemical stimulation of the brain have been researched less, as Lehnertz (2008) and Kuhlmann et al. (2015) have emphasized. The science of nonlinear dynamics has been developed from mathematical and physical science disciplines over the past 150 years. Nevertheless, the development of applied models in animal and human studies has progressed more slowly, particularly given that the study of nonlinear dynamics in medicine did not begin until the late 1970s and the 1980s. They have seen almost no applications in health research. Sketchy models have been developed, but there is a clear need for basic and applied research to bring this approach to health and an expanded role of medicine, particularly given its substantial success in the physical sciences (Wolfram 2002).

From a molecular medicine perspective , Aldridge, Gaudet, Lauffenburger, and Sorger (2011) examined the effects of various intracellular pro-apoptotic (i.e., cell death) caspase proteins in relationship to extracellular pro-apoptotic proteins such as Tumor Necrosis Factor (TNF)-related Apoptosis Inducing Ligand (i.e., TRAIL). They used phase space analyses of the ratios of TRAIL/caspase levels to study whether or not the potentially apoptotic cell follows a Type 1 or Type 2 pathway. They found that slight

variations in the protein levels led to a higher ratio for Type 2 and a lower ratio for Type 1, based upon λ measurements of the divergent trajectories for the in vitro tested cells. The comparison works very much like the statistical regression measurement of an outcome variable (e.g., type of cell death) based upon varying levels of two independent variables, with λ being the trajectory divergent measure away from the diagonal even balance between the effects of the competing independent variables. The Aldridge et al. (2011) study and many others like it offer the opportunity to examine discrete molecular effects on a given outcome from an overall systems phase perspective, an approach that requires only slight modifications from the linear analyses of cell and biochemical processes in the research literature for many decades. Still, many of these studies are in vitro, potentially affected by the manifold environment of the test tube or cell culture surface , and thus may not accurately represent how the molecules and cells will behave in vivo, within the physiological environment. Glass and Mackey (1988) discussed these limitations, although the applications thereof have translated into applied medicine (Chap. 14). Molecular Cell Biology can move forward with this approach, and health research must begin to follow this approach as well with the combination of realistic genomic , physiological, and behavioral systems studies.

Ecology has traditionally used a systems perspective . Falck, Bjørnstad, and Stenseth (1995a) computer modeled latitudinal gradients of abundance for eight Holarctic rodent species from data collected by Turchin (1993). Except for the Point Barrow site (71°N) the more northerly species had slightly negative dominant (primary) Lyapunov exponents from 71 to 68°N. Rodent species living between 68 and 64°N had positive λ's < 1, whereas more southerly species (56–38°N) had exclusively negative λ's, with three species sites exhibiting $\lambda < -1$. Falck et al. (1995a)) concluded that the Holartic gradient of rodent species abundance is not chaotic ($\lambda < 3$), but nonlinear differences do exist between the southerly and northerly populations . For human health, geospatial analyses of human populations located in gradients of various environments (e.g., urban, rural), socioeconomic status, proximity to healthy food, schools, etc., violent crime statistics, etc. are amenable to this type of nonlinear analysis using straightforward, computed Lyapunov exponents. From a genetic perspective, Cavalli-Sforza, Menozzi, and Piazza (1994) mapped the distribution of humans worldwide based upon data from a bank of measured genotypes, particularly the Human Leukocyte Antigen (HLA)/Major Histocompatibility Complex (MHC) alleles for the highly polymorphic region on chromosome six, for specific populations. They found that these gene markers can map population migrations and admixture between populations, phenomena that have been very dynamic over the many thousands of years of human history. Fortunately, such inferences can be derived from the genetic data, particularly for HLA/MHC. Alas, it is the way that we structure our datasets and data collection procedures that limit us from having time series data with repeated measures. Even geographic information systems that are widely available could be of great value to the

analysis of complex human health conditions that are impacted by environments.

In response to a second research study providing more detailed studies of these Holarctic species distributions and maintaining chaotic fluctuations for the more northerly species, Falck, Bjørnstad, and Stenseth (1995b) examined bias estimates of Lyapunov exponents , still concluding that the northerly and southerly distributions are different but not chaotic. The stability of species distributions and movements of populations within specific biomes/environments (i.e., flow) is very relevant for ecological research, and the comparative approach for real data coupled with computer simulations used by Falck et al. (1995a), 1995b) as well as by other researchers (e.g., scrub jay behavior studied and modeled by van der Vaart, Verbrugge, & Hemelrijk 2012) represents a robust approach to validating models. Hemelrijk and Kunz (2004) and Reid, Hildenbrandt, Padding, and Hemelrijk (2012) applied nonlinear fluid dynamics, three-dimensional mapping, and basic behavioral and physical principles to model the movements of fish schools.

Besides these novel analyses of group motions to fluid flow, the application of nonlinear dynamics to species distributions is the major application to ecology . As described in Chap. 9, Benincà, Ballantine, Ellner, and Huisman (2015) modeled the seasonal dynamics of intertidal species, finding approximately 2-year periodic cycles with slight variations around $\lambda \sim 0$ with occasional instabilities when λ was slightly positive. Whereas this analysis focused on competing species within a dynamically changing ocean environment, we can also see the applications of the species population size over time, a fluid flow across that fourth dimension. Dakos et al. (2009) noted that plankton species cycle in abundance based upon regular seasons each year, but the types of species succession are irregular from 1 year to the next. Furthermore, external environmental effects on this irregular succession appeared to be minimal. The authors termed the irregularity "chaotic," based upon a positive λ, although we know that period doublings and other bifurcation tend to produce altered periodicities that do not truly qualify as being chaotic until $\lambda > 3$. The seasonal variations in species abundances are not surprising, and the irregular succession from year to year might result from changes in population dynamics and competition between species, which Dakos et al. (2009) consider as possible explanations. Other unmeasured factors certainly might be involved as well.

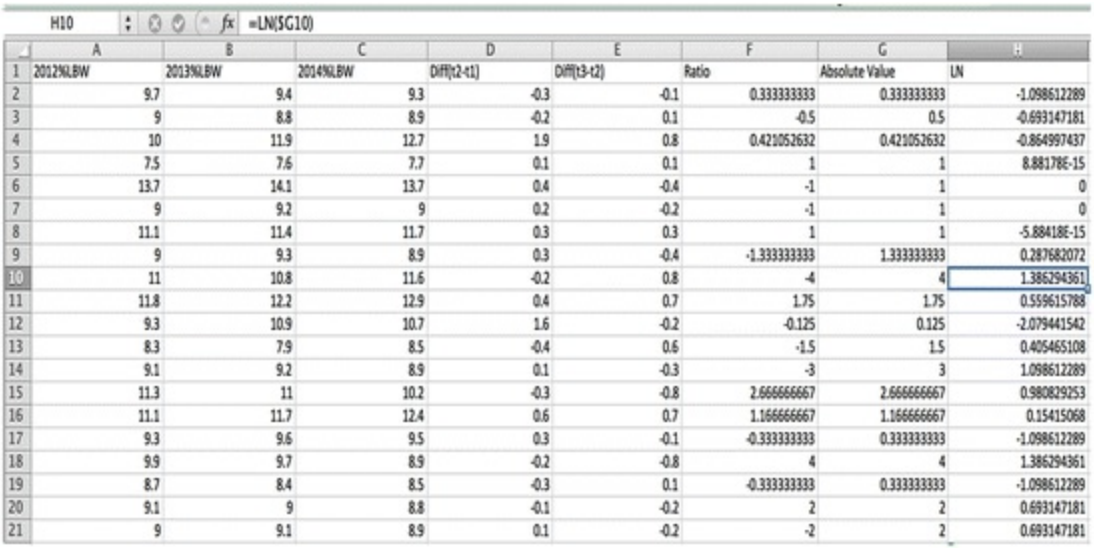
12.4 An Applied Health Research Example

Low birth weight represents a significant public health problem that is associated with many sociobehavioral variables, including younger maternal age, lower socioeconomic status, lower education, and substance use/abuse. We used a combined nonlinear Lyapunov exponent calculation and geospatial analysis for county level percentages of low birth weight babies using the County Health Rankings (University of Wisconsin

Population Health Institute and Robert Wood Johnson Foundation; www.countyhealthrankings.org). The County Health Rankings represent a compilation of data collected from county health departments, the U.S. Census Bureau, Centers for Disease Control and Prevention (CDC) National Center for Health Statistics, the National Center for Chronic Disease Prevention, the Centers for Medicaid Services (CMS), the National Center for Education Statistics, and the Dartmouth Atlas of Health Care (see Hollar 2015).

Annual data is available from 2010 to 2017 ongoing for a variety of health variables along with algorithmic constructions of county rankings within each U.S. state for a total of 3221 U.S. counties. Data can be downloaded in Excel format for states or for the entire United States. Therefore, for this example, the unit of analysis is U.S. county (i.e., aggregate data), not individual, and the variable being studied is raw data computed by county births for each year to generate the raw Percentage of Low Birth Weight Babies. Whereas the County Health Rankings are limited with respect to a potentially biased sample with respect to data reporting from county health departments, which generally serve poorer segments of the population despite overall missions to improve the health for all citizens, the birth data are from the U.S. Census. Furthermore, the birthweight is a reliable measure from Newborn Screening and Birth Certificate data sources, contrary to the less reliable gestational age estimate for preterm births (Wilcox 2001).

Figure 12.2 shows a screenshot of a Microsoft Excel spreadsheet that shows 20 out of $n = 3135$ U.S. county units that had complete data for Percentage Low Birthweight Babies during 2012, 2013, and 2014. The first three columns (Columns A–C: 2012%LBW, 2013%LBW, and 2014%LBW) show the county percentages for each of these 3 years. The next step is to solve, per Eq. 12.2, the Lyapunov exponent λ for each county's change in Percentage Low Birth Weight Babies. To start with, calculate for each county the differential Percentage Low Birth Weight between 2012 and 2013 (Column D: Diff($t_2 - t_1$) and the equivalent differential between 2013 and 2014 (Column E: Diff$t_3 - t_2$) by merely subtracting Column A from B and Column B from C, respectively. Then, divide Column E by Column D to obtain the ratio of the time 2 differential to the time 1 differential (Column F), per Eq. 12.2. Column G is the absolute value of the t_2/t_1 ratio value shown in Column F. This computation is necessary in order to compute the natural logarithm of Column F, thereby yielding the Lyapunov exponent λ in Column H. We will ignore the scaling factor $1/t$ for the computation, as this parameter does not greatly affect λ and is dependent upon the time scale used, in this situation 1 year, yielding $1/1 = 1$. Additionally, some Column F values will not compute if t_1 in the denominator is zero. As a result, only $n = 2229$ of the $n = 3221$ counties produced λ estimates using this Excel spreadsheet approach.



H10 =LN(SG10)

	A	B	C	D	E	F	G	H
1	2012%LBW	2013%LBW	2014%LBW	Diff(t2-t1)	Diff(t3-t2)	Ratio	Absolute Value	LN
2	9.7	9.4	9.3	-0.3	-0.1	0.333333333	0.333333333	-1.098612289
3	9	8.8	8.9	-0.2	0.1	-0.5	0.5	-0.693147181
4	10	11.9	12.7	1.9	0.8	0.421052632	0.421052632	-0.864997437
5	7.5	7.6	7.7	0.1	0.1	1	1	8.88178E-15
6	13.7	14.1	13.7	0.4	-0.4	-1	1	0
7	9	9.2	9	0.2	-0.2	-1	1	0
8	11.1	11.4	11.7	0.3	0.3	1	1	-5.88418E-15
9	9	9.3	8.9	0.3	-0.4	-1.333333333	1.333333333	0.287682072
10	11	10.8	11.6	-0.2	0.8	-4	4	1.386294361
11	11.8	12.2	12.9	0.4	0.7	1.75	1.75	0.559615788
12	9.3	10.9	10.7	1.6	-0.2	-0.125	0.125	-2.079441542
13	8.3	7.9	8.5	-0.4	0.6	-1.5	1.5	0.405465108
14	9.1	9.2	8.9	0.1	-0.3	-3	3	1.098612289
15	11.3	11	10.2	-0.3	-0.8	2.666666667	2.666666667	0.980829253
16	11.1	11.7	12.4	0.6	0.7	1.166666667	1.166666667	0.15415068
17	9.3	9.6	9.5	0.3	-0.1	-0.333333333	0.333333333	-1.098612289
18	9.9	9.7	8.9	-0.2	-0.8	4	4	1.386294361
19	8.7	8.4	8.5	-0.3	0.1	-0.333333333	0.333333333	-1.098612289
20	9.1	9	8.8	-0.1	-0.2	2	2	0.693147181
21	9	9.1	8.9	0.1	-0.2	-2	2	0.693147181

Fig. 12.2 Snapshot of Excel spreadsheet that calculates Lyapunov exponent λ for the variable Percentage Low Birth Weight (LBW) Babies (δt_{n-1}: t_1 = 2012 to t_2 = 2013; δt_n : t_2 = 2013 to t_3 = 2014) for each of 3141 United States county units (20 counties shown). The last column (LN) is the estimate, minus 1/t in Eq. 11.2. Data obtained from the County Health Rankings (2012–2014)

Software programs that generate Poincare return maps or phase response curves generate more precise estimates of λ, and they address the zero denominator issue due to the fact that they solve for the Jacobian matrix characteristic exponents, also called eigenvalues. For the epidemiologist exploring λ comparisons in data such as provided in this example, the Excel approach provides approximate estimates that are easy to compute with a spreadsheet.

Interpreting Fig. 12.2, note that negative or positive Lyapunov exponents λ do not necessarily correspond to improvements in the health condition being analyzed. Remember that we are considering $\lambda < 0$ to be attractor phenomena toward a central point, whereas $\lambda \sim 0$ represents stability with relative periodicity of cyclic behaviors, $\lambda > 0$ represents bifurcations into period doubling or quadrupling, etc. with alternating period cycles, and $\lambda > 3$ generally implies unpredictability in cyclic behaviors (i.e., chaos).

First, we need to consider whether or not the measured behavior is desirable or undesirable. Obviously, Low Birth Weight is undesirable for infant health. For instance, the second county in row 3 of Fig. 12.2 had a negative differential of −0.2 from 2012 to 2013 (Column D), which is a desirable decrease. However, the same county had a positive differential of 0.1 from 2013 to 2014 (Column E), which is an undesirable increase in Low Birth Weight following the previous year's decrease. Taking the absolute value to compute λ for Eq. 12.2 (Fig. 11.2, Columns F–H) eliminates the effect of the decrease or increase. For this county, $\lambda = -0.693$, which means that this county appears to be spiraling toward an attractive point in the Low Birth Weight phase space , something that health policy experts for this county would want to address to try to

restore stability ($\lambda \sim 0$). Therefore, the health researcher and health policy maker must consider differential change over time (positive or negative) as a trend, and then simultaneously examine the stability of the change.

Looking at county 8 in row 9, there was a positive differential of 0.3 from 2012 to 2013 (Fig. 12.2 Column D), which is an undesirable increase in Low Birth Weight. However, the same county had a negative differential of −0.4 from 2013 to 2014 (Column E), which is a very desirable increase in Low Birth Weight following the previous year's decrease. However, $\lambda = 0.288$, indicating a repulsion from stability for a potential period doubling bifurcation for Low Birth Weight. The county clearly experienced a substantial shift from 2012 to 2014, definitely a positive improvement, but unstable, nonetheless. From a nonlinear perspective, extreme shifts can be troublesome if they shift abruptly again in an unpredictable fashion. The goal for all of these counties, consistent with Healthy People 2020 objectives, is to continue decreasing Low Birth Weight percentages consistently, so that when we compare subsequent time differentials, $\lambda \sim 0$, which indicates consistency.

At the same time, we can have worsening Low Birth Weights that are consistent over time with $\lambda \sim 0$. County 7 in row 8 is consistent with an increase in percentage of 0.3 at each time point, generating $\lambda \sim 0$–15 decimal places. County 10 in row 11 is increasing Low Birth Weight with $\lambda = 0.560$. Obviously, we need more differentials at later times t_3 (2014–2013), t_4 (2015–2014), etc. to obtain a better feel for the overall trend, and to examine any interventions or events that might have contributed to the increase or decrease in the variable being measured. Therefore, we need two statistics: λ and the differential direction of change for each time point. Furthermore, we need to think topologically across dimensions and time to evaluate the system, whether it be Low Birth Weight percentages, percentages of obese adults, teen birth rates, child mortality , percentage of smokers, etc.

Figure 12.3 shows a histogram of the distribution of Lyapunov exponents across $n = 2229$ counties where λ could be computed. The distribution is approximately Gaussian (i.e., normal), with a mode of 0. The mean of all exponents is $\lambda = -0.2628 +/- 1.017$ with a maximum of 3.570 and a minimum of −4.060. The middle 50% of all exponents fell between −1.064 < $\lambda < 0.405$. Overwhelmingly, counties are close to relative stability with respect to Low Birth Weight. Clearly, this is a major public health issue that merits vigilant monitoring and attention.

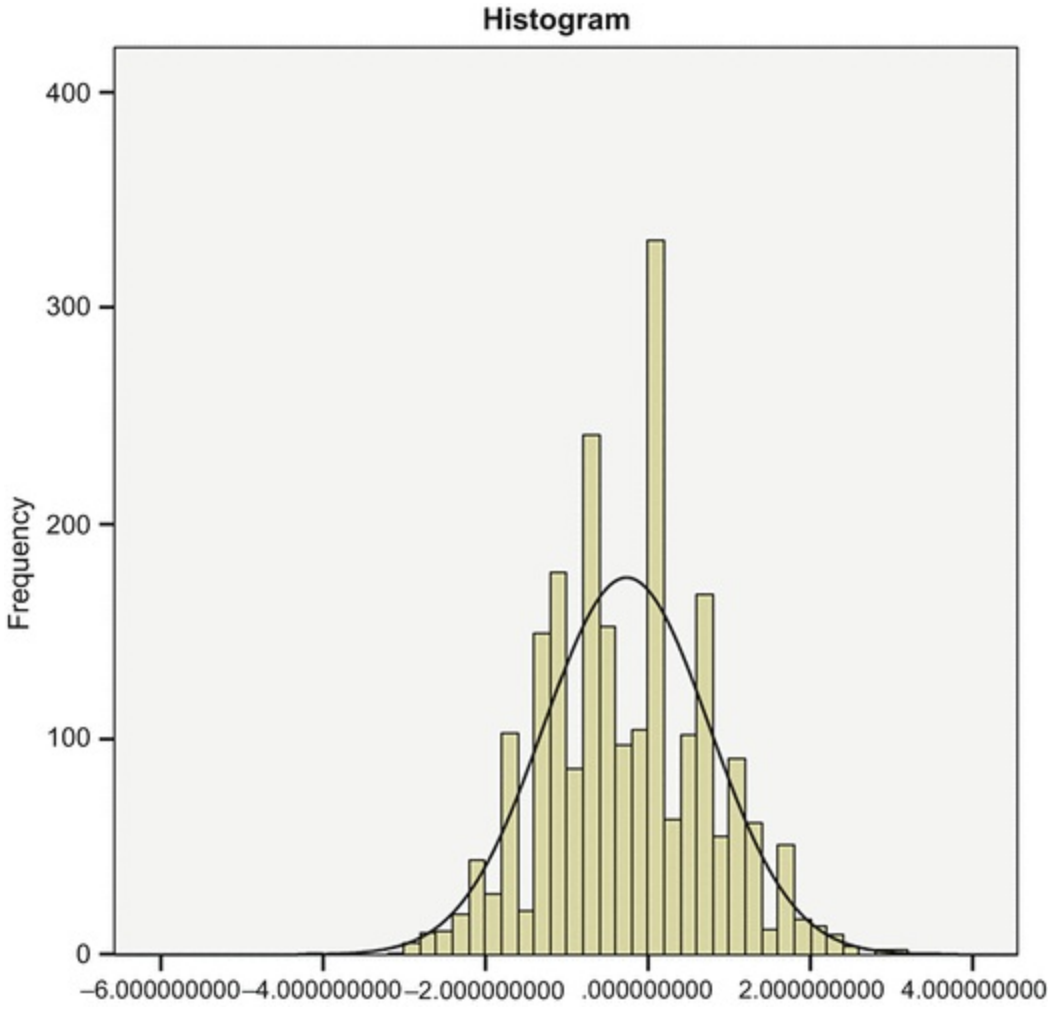


Fig. 12.3 Histogram of $n = 2229$ out of $n = 3141$ county Lyapunov exponents that were computable from Fig. 11.2. The mean $\lambda = -0.2628$ +/− 1.017 with a maximum of 3.570 and a minimum of −4.060. The distribution approaches normality (Gaussian) with a median at approximately $\lambda \sim -0.288$. Note the slight negative skew

From a geospatial perspective , we mapped the $n = 2229$ county Low Birth Weight λ's for 2012–2014 in Fig. 12.4 and compared the geographic pattern to the raw values of Percentage Low Birth Weight in 2015 (Fig. 12.5). The counties mapped in Fig. 12.4 show no overall pattern, as the counties with high positive λ's (shown in burgundy) are scattered and generally not contiguous. This finding reflects the stability measure of change for the counties, a parameter that appears to be independent of geography. However, actual statistics on Low Birth Weight (Fig. 12.5) clearly shows a geographic clustering of high Low Birth Weight percentages (burgundy shaded, no relation to Fig. 12.4) in the Southeastern United States, especially along the Mississippi River, rural Appalachia, and the Atlantic coastal plain, all areas impacted by socioeconomic disparities that are closely associated with less access to adequate maternal, child, and other health care contributing to more negative birth outcomes.

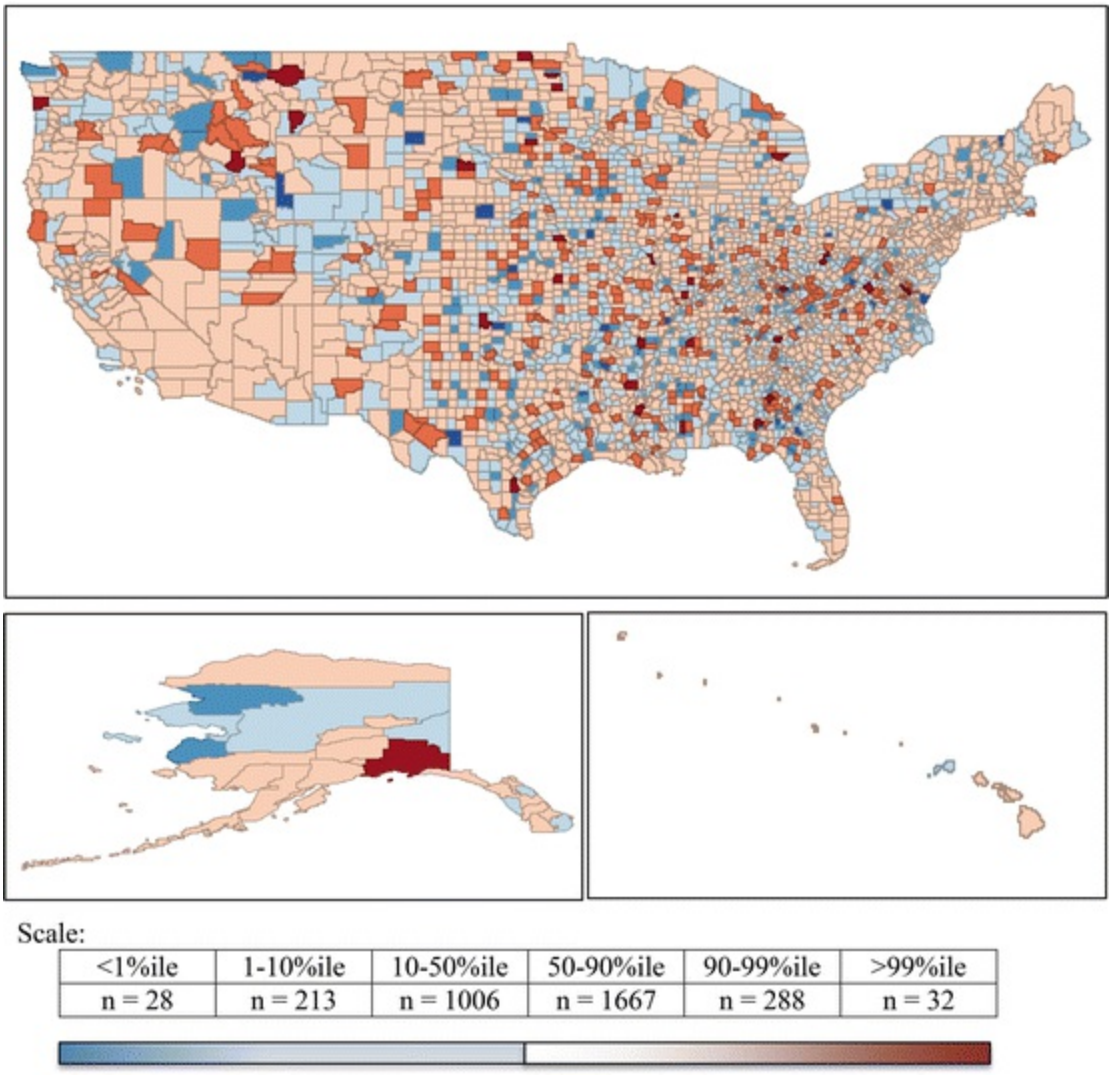


Fig. 12.4 Geospatial distribution High positive (*burgundy*) versus Low negative (*dark blue*) Low Birth Weight Lyapunov exponents (2012–2014) for $n = 2229$ of $n = 3141$ U.S. counties that had complete data. Data obtained from the County Health Rankings and mapped using the freeware GeoDa (available from https://spatial.uchicago.edu/software)

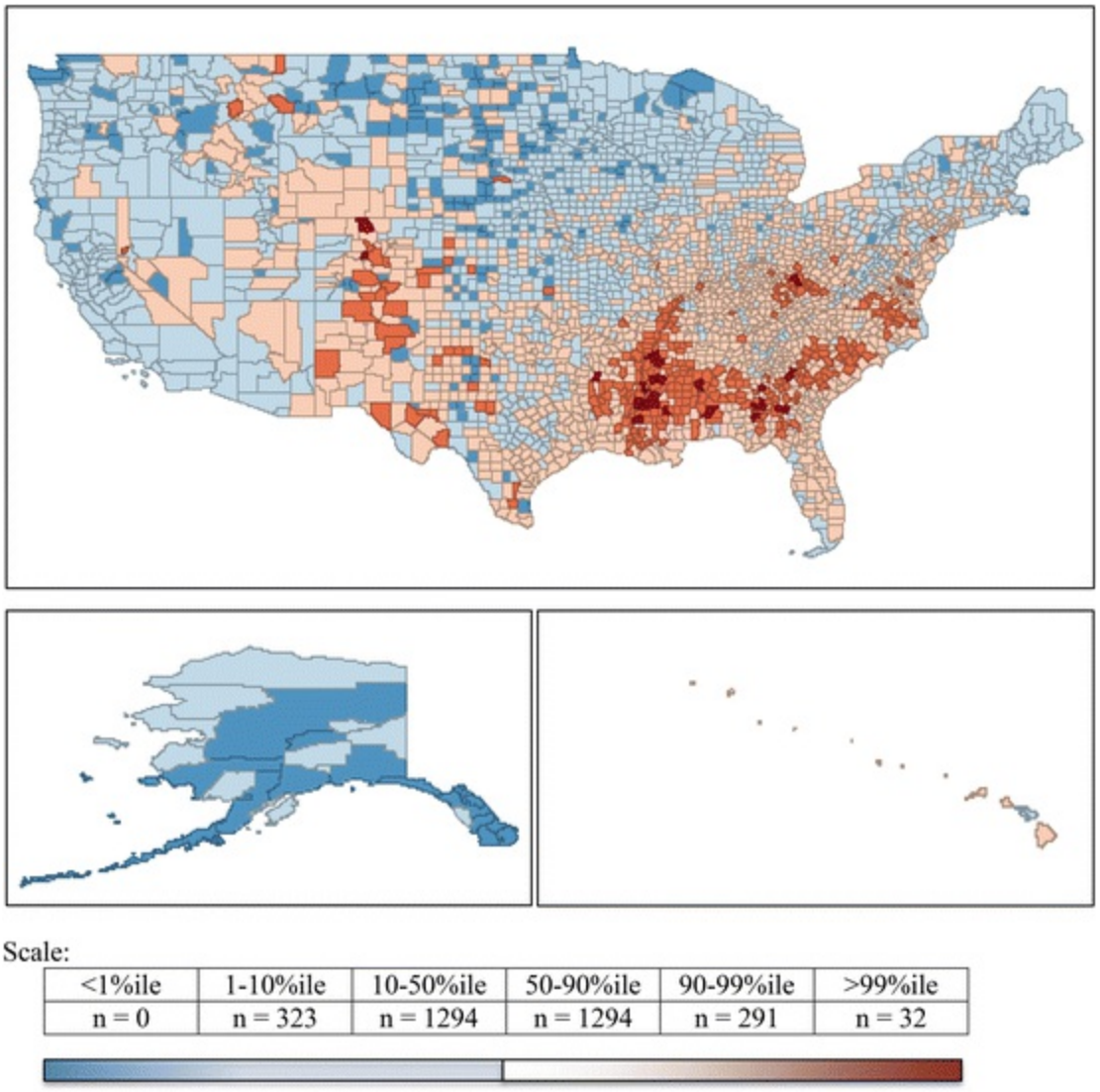


Fig. 12.5 Geospatial distribution of High (*burgundy*) versus Low (*dark blue*) Low Birth Weight Percentages per continental U.S. county in 2015, as compared to the 2012–2014 Lyapunov exponents in Fig. 11.4. Data obtained from the County Health Rankings and mapped using the freeware GeoDa (available from https://spatial.uchicago.edu/software)

12.5 Summary

The Lyapunov exponent λ represents a measure of stable or unstable change in the nonlinear behavior of systems. The Cvitanovic et al. (2004) book, course (ChaosBook.org), and Eq. 12.2 represent a starting point for novice epidemiologists. Glass and Mackey (1988) provided relevant applications in health and medicine. Zurek (2002) described this process as the stretching and squeezing of a dynamical system, simultaneous with the decoherence and regained coherence, respectively, of a wavefunction . In the next chapters, we will examine applied approaches to maintain stability of desired physiologies and behaviors, plus mechanisms of jumping a stable, undesirable system to a different phase state. The Lyapunov exponent λ must be

considered in conjunction with time trends on consistent increases or decreases in the measured behavior, that is, the periodic cycling of the measured phenomenon/system.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_13

13. Jump Conditions

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Abbreviations

NaCl Sodium chloride

PV=nRT Ideal Gas Law Equation for Pressure, Volume, and Temperature relations

R-H Rankine-Hugoniot

Every moment in time represents a phase transition of one's life, usually minor but nevertheless involving some sensitive dependence on a condition that triggers a change somewhere within the body, and usually little changes in many different places. Of course, there are cyclic phenomena (e.g., chemical and cellular reactions, daily routines) that generally return to previous states with precision or with seemingly insignificant alterations. But some moments might involve dramatic changes that permanently alter the trajectory of one's life, behavior, health, functionality of a body part or organ, etc. Sometimes, we impose these changes on ourselves with varying degrees of success. Other times, changes are due to random events or due to the actions of others, well- or ill-intended. Changes can be gradual or rapid.

13.1 Rapid Change

The shape shifting dinoflagellate Pfisteria can metamorphose from its relatively sessile dormant cyst to grow several hundred-fold in size within minutes. Similarly, this author has witnessed the occurrence and rapid growth of an integumentary mole within minutes. A sparse research literature exists that indicates that substantial morphological changes can occur within human and other mammalian organs under conditions of health and disease. All of these changes involve the triggering of rapid change via a phase shift across a critical threshold , an event driven by various causative factors that vary

depending upon the type of event.

Sharkey et al. (2010) and Sharkey, Lesser, and Maron (2011) described Takotsubo cardiomyopathy, an acute illness that predominantly affects women older than 50 years, that mimics a heart attack, and that is driven primarily by stress . In this condition, the heart becomes malformed and appears similar to a Japanese takotsubo, a ceramic container used to capture octopi, although the condition appears to be controllable. Research is examining the extent of any cardiac damage that might occur due to this condition, particularly for older adults. This condition adds credence to Selye's (1950) pioneering work on stress and the role of the endocrine system , Christian's (1950, 1961) demonstration of adrenal steroid hormones and stress in overpopulated mammals, Seeman, McEwen, Rowe, and Singer (2001, 2002) development of allostatic load (i.e., physiological stress) indicators that included adrenal , renal, and cardiovascular variables, and Hollar and Lewis' (2015) demonstration of negative heart age differentials among people with mobility limitations. The neuroendocrine connection between the kidney and the heart is further illustrated by the Huang et al. (2014) study that showed that removal of sympathetic nerves from the kidney stabilized ventricular rhythms in dogs and reduced the occurrence of arrhythmias.

Therefore, the manipulation of specific variables can change the phases of normal and abnormal behaviors in either direction across specific threshold or critical points. Our approach so far has been to balance examples between physiological and behavioral interventions that represent the overwhelming majority of health conditions, from biopsychosocial perspectives with biophysics applications. Granted, research studies have more strongly supported physiological interventions. Nevertheless, there is a rich ethological/ecological literature that can drive future interventions in the nonlinear analysis of the more varied and elusive behavioral health conditions. Obviously, there is overlap with neurological research and interventions, but the complex socioeconomic and environmental impacts provide a level of complexity that can be studied and manipulated.

13.2 Thresholds

Female goats will reject a newborn kid if she does not make physical contact with it during a 1 hour sensitive period following birth (Klopfer, Adams, & Klopfer, 1964). Skin-to-skin mother-newborn infant contact has been advocated, as research has shown significant short-term physiological benefits for the infant, although long-term effects are less clear (Bramson, Lee, Moore, Montgomery, & Neish, 2010). Similar sensitive period and other threshold effects have been demonstrated with the famous bird chick imprinting experiments (Lorenz, 1937), bird song learning, and other forms of animal communications (Konishi, Emlen, Ricklefs, & Wingfield, 1989; Partan, 2013).

The research on threshold critical periods and sensitive conditions has been

established in human and animal behavior , and much additional work remains to uncover new stages of sensitivity across the lifespan. Major effects appear to occur during early infancy and then during adolescence. We now move to the analysis of these critical points in the behavioral physiology of humans and other animals, and how they transition or jump across these bifurcations or discontinuities , usually an irreversible process .

13.3 Phase Transitions at the Biological Systems Level

One of the simplest physical phase transitions that we witness is the change of state of a substance from solid to liquid to gas/vapor with increasing temperature, or the reverse process with decreasing temperature. We take this process for granted, even though the physical principles behind this phenomenon are complex. We think of this process primarily with respect to water, yet it occurs with every physical substance. The unique properties of H_2O stem from the covalent bonding angles of its three atoms, its capacity for ionization in interaction with other molecules, and its unusual hydrogen bonding pattern with other water molecules such that it is most dense slightly above the freezing point (0 °C or 273.15 K), very unusual for most molecules. Water freezes as the temperature drops through 0 °C, and it melts as temperature moves above this point. Water boils/vaporizes as the temperature rises through 100 °C, and it liquefies as the temperature falls below this point.

There are millions of molecules, some as simple as molecular hydrogen (H_2), others more complicated such as octane (C_8H_{18}), others extremely complicated such as chlorophyll a, or a complex protein containing hundreds of amino acids. Structural variations of these molecules exist. The properties of the ringed benzene (C_6H_6) are dramatically different from those of cyclohexane (C_6H_{12}) or of the relatively linear hexane (C_6H_{14}). A few hydrogen differences make for different structures and conformations.

Protein structures are highly complex , often depending upon a few critical amino acids at specific locations along the linear sequence in order to fold into a three-dimensional, functional entity with active sites to correctly bind a substrate, perform an enzymatic activity on the substrate to drive a chemical reaction, and thus lower the activation energy required for a previously improbable process (see Chap. 7). A single mutation that alters just one amino acid can drastically alter the three-dimensional manifold structure needed for proper functionality of the protein. This is what happens in so many genetic and metabolic conditions (e.g., sickle cell hemoglobin, phenylketonuria, etc.), sometimes resulting in severe disability and/or drastically reduced lifespan. Others can be controlled. Still, for human health, one can see the multitude of situations where something can go wrong, which ultimately happens with

aging when a resilient physiology simply cannot keep up with the accumulated pathway alterations and associated damage. All humans are homozygous for a lethal mutation of the gene encoding the enzyme L-gulonolactone oxidase; however, there is no effect if we consume fruits and green leafy vegetables to obtain the Vitamin C that we cannot produce (Hollar, 2012; Nishikimi et al., 1994). It is estimated (Eckhardt, 2001; Williams, 1956) that the probability of having zero abnormal alleles out of 100 genes is less than 1%, and humans have approximately 25,000–30,000 functional genes per genome! The potentiality of such minute effects does not even include the even more influential psychological and environmental stressors that trigger methylation and acetylation gene control changes in 1×10^{15} cells across the human body with unpredictable, but cumulative effects across the lifespan (Hollar, 2017).

As an extension of his quasispecies model for molecular change and evolution , Eigen (2002) discussed phase transitions with respect to viral replication within cells. Eigen argued that natural selection operates on the process of replication of thousands of virions within cells, with mutation introducing variants such that density fluctuations similar to what happens during liquid/vapor transitions could produce transitions (i.e., critical opalescence) to successful bursts of viruses from the destroyed cell, or collapse of the viral replication cycle due to being hyper-competition of deficient mutant viruses. As a result of these observations, he suggested that the introduction of mutations could be an effective medical strategy for battling viral infections. Most importantly, Eigen (2002, p. 13374) described the quasispecies as the information population of "condensed mutant distribution that results from the phase transition representing natural selection" and that it is "determined by one (namely the largest) eigenvalue of its system of dynamical equations." In other words, a replicating system of varied viruses, cells, animals, information, etc. reproduces exponentially to a phase transition point , measurable via the Lyapunov exponent (eigenvalue), where the system transits to survival of specific mutant types.

Similarly, Kozak and Benham (1974) had modeled the denaturation of a protein to a Riemann-Hugoniot catastrophe, with the disruptive effects of temperature, pressure, and/or other environmental agents (e.g., radiation, other molecules) affecting the hydrogen bonding of the functional three-dimensional protein so that it falls apart and is no longer functional. The disruptive agents cause the phase shift at a critical point , similar to a bifurcation point and marked by the Lyapunov exponent. Their model borrows heavily from Thom's (1972) work on catastrophe theory and falls neatly into the scope of Eigen's (2002) arguments that he had built from the earlier Eigen and Schuster (1979) quasispecies Hypercycle model of biochemical evolution. We will return to Kozak and Benham's model when we examine "jump conditions" below.

Even physiological processes such as bone remodeling (Eriksen, Axelrod, & Melsen, 1994) are continuous dynamic processes. In the mammalian skeleton, complementary sets of bone destroying osteoclast cells and bone producing (calcium

phosphate) matrix-secreting osteoblast cells cut and rebuild a bone remodeling unit that recycles ~40 mm of bone per day. This represents a substantial amount of tissue replacement. Many variables contribute to the predominance of bone destruction or bone building, including the activities of the antagonistic thyroid/parathyroid hormones calcitonin and parathormone, respectively. Additionally, nutrition in the form of fat-soluble vitamins A, D, E, and K as well as calcium and phosphorus minerals is essential, coupled with exercise as well as natural sunlight exposure for integumentary production of vitamin D. Other hormones are involved as well, including control of blood cell production within the marrow of flat bones. Disease, genetic conditions, and poor absorption of nutrients with age ultimately lead to bone remodeling collapse and the increased likelihood of fractures, sclerosis, and other structural declines.

Thus, we have systems impacting systems, and variables impacting variables within these systems at all levels of biological complexity . Phase transitions occur on a continuous basis, usually resulting in stability , but becoming unstable with aging and disease. The accumulated damage to tissues, particularly post-mitotic adult tissues, was noted by Brunk and Terman (2002) as a distinguishing feature of the aging process. Eigen's (2002) information-based quasispecies model directly relates to the exponential growth and collapse of healthy physiologies and behaviors due to thermodynamic entropy (Lyapunov exponents) as well as to Thom's (1972) catastrophe theory . In line with Eigen's (2002) comparison of these processes to critical opalescence phase transitions, Lesne and Laguës (2012) cited Nobel laureate Pierre Curie's doctoral dissertation demonstration that magnetic field dynamic properties correspond in their physical behaviors to the density and pressure of moving fluids.

13.4 The Phase Transition

Returning to our water example, the phase transition between solid and liquid occurs at 0 °C, and the phase transition between liquid and vapor occurs at 100 °C. Based upon the ideal gas law, PV = nRT, pressure *P*, temperature *T*, and volume *V* contribute to the phase transition points of substances. Figure 13.1 shows a Pressure-Temperature variogram for water, with the three phases delineated along boundaries of interaction between temperature and pressure. Following each boundary curve, increasing pressure can drive the transition of liquid to solid to lower temperatures while mitigating the increase in temperature curve that is associated with gas to liquid condensation or gas to solid sublimation. The triple point, where all three phases co-exist, is 0.01 °C at a pressure of 4.56 mmHg for water. At this point, an increase, decrease, or some combination for both temperature and pressure will drive water into one of its three states. Note that at the triple point, the three phases exist together. However, the critical point of water is the temperature and pressure at which the phases disappear, a crushing pressure of 165,680 mmHg (i.e., 218 atmospheres with 1 atm = 760 mmHg at sea level)

and 374 °C. At the critical point, critical opalescence occurs with an inflection point that in the van der Waals isotherms as the pressure and volume increase for the now supercritical fluid that is neither liquid nor gas but can become one or the other without a phase transition.

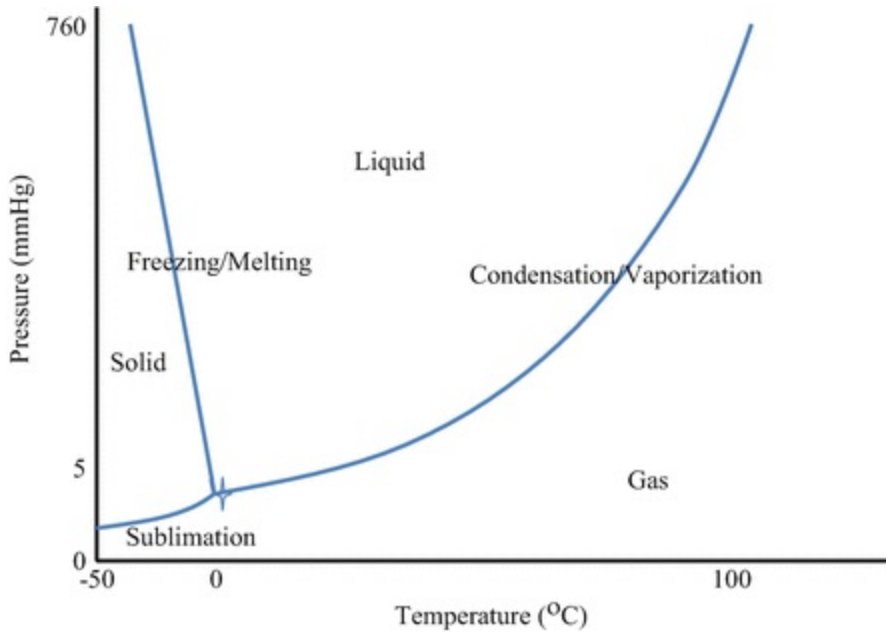

Fig. 13.1 The standard triple-point phase transition variogram for water . The triple point for this unique substance, where all three phases coexist, is $T = 0.01$ °C at $P = 4.56$ mmHg. See Masterton and Slowinski (1977, pp. 270–278) and Spencer, Bodner, and Rickard (2008, pp. 320–327) for comparable discussions and examples

As with the triple point, freezing, and boiling points , the properties of each molecule determine the temperature and pressure where these phase transitions occur. Furthermore, we can adjust the pressure to change these transition points as well as by adjusting the purity of the substance with contamination by another substance, as the addition of NaCl to water decreases the freezing/melting point and increases the boiling point. Whereas the triple point for water is 0.01 °C at a pressure of 4.56 mmHg, the triple point for carbon alone is 4491.85 °C at a pressure of 76,015 mmHg. Whereas the critical point for water is 165,680 mmHg and 374 °C, the critical point for benzene is 36,480 mmHg and 289 °C. For mercury, it is 1476.9 °C and 1,307,200 mmHg (or 1720 atm). For helium, it is −267.96oC and 1702.4 mmHg (or 2.24 atm). At the critical point, the liquid phase cannot exist despite further increasing pressures. Additionally, Fig. 13.1 for water shows that the freezing/melting point decreases with pressure because liquid water is more dense than ice water. For most substances, this relationship is the reverse.

Therefore, the transitions of conditions depend upon the effects of the substance properties in conjunction with the environmental variables. Such is the case with health, as we will continue with the water phase transition comparison. Figure 13.2 shows the

heat energy required to force water from one phase to the next. Below the freezing point, the specific heat required to increase the molecular motion of water molecules (increased temperature) is 0.49 calories/g °C. Between the freezing and boiling points, the heat requirement increases to 1.00 calories/g °C, and above boiling, the heat requirement returns to 0.44 calories/g °C. However, what is most striking are the two transition points at freezing and boiling. For each gram of water at the freezing point, it takes 80 calories to move water from the solid to the liquid state, far more than the energy required to warm water between the phase transition points. Even more heat is required for each gram of water at the boiling point, 540 calories, to move liquid water to a vapor phase. Yet at these phase transition points, the temperature remains constant until enough heat energy is applied to completely convert all molecules to the next state. Likewise, when the temperature drops, it remains constant as the molecules release the equivalent heat energy until they all convert to the lower phase.

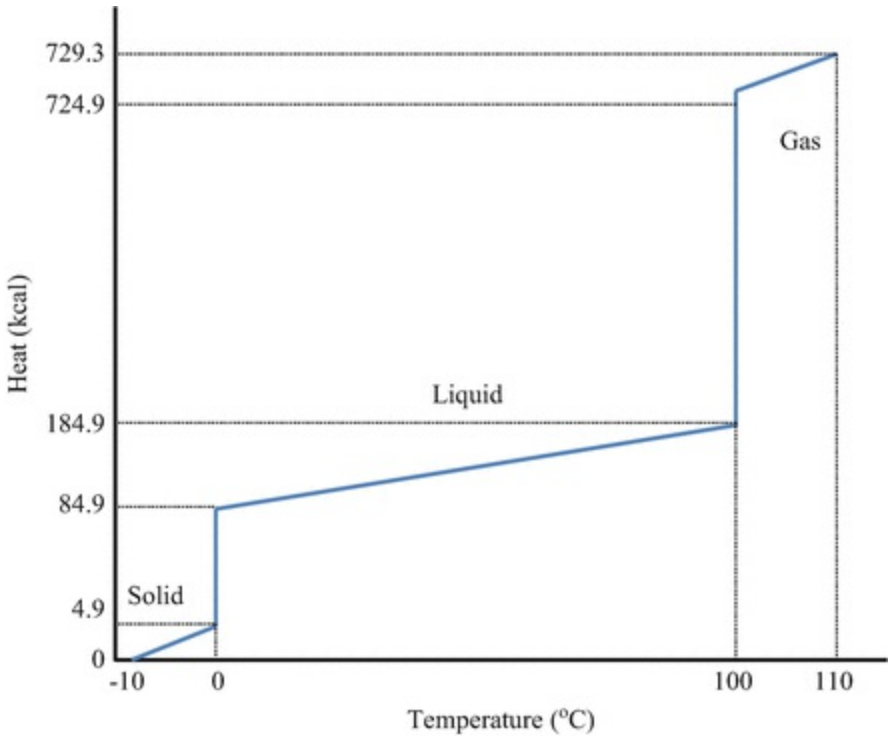

Fig. 13.2 Heat (i.e., Enthalpy) requirements to change 1 gram of water from solid ice to liquid to gaseous phases, or conversely, the amount of heat released during cooling from gas to liquid to solid ice. Note that at the freezing and boiling points, a substantial amount of heat energy is required to convert water to the next, more energetic phase, with no increase in temperature. In between the phase transitions , less energy is required

Dirac (1958) noted that at transition points , the amount of energy or information exponentiates, which relates to the tremendous enthalpy (heat) change that occurs at constant temperature during the phase transition , with the exponential curvature occurring on both sides of the transition point (Fig. 13.3). The simple equation for this discontinuity between two phase states is:

$$\delta(x) = +\infty, \quad x = 0$$
$$0, \quad x \neq 0 \tag{13.1}$$

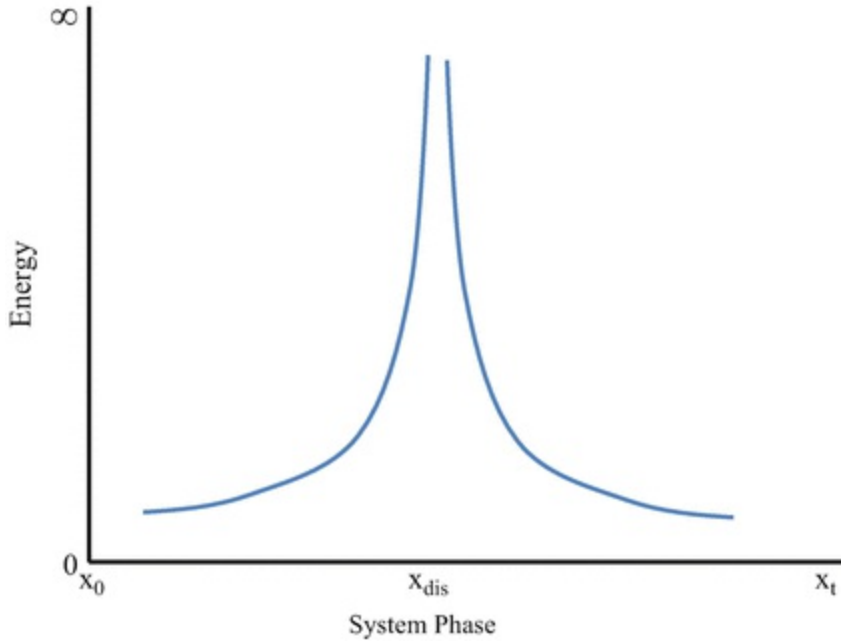

Fig. 13.3 The Dirac delta function for quantum systems

This phenomenon relates directly to all transitions as the energy/information component of these systems rises dramatically at the transition point . Nicolis and Prigogine (1981) noted its importance in their studies of reversibility/irreversibility and the creation of structure near critical points located far from equilibrium . Thom (1972) observed this phenomenon in his models of elementary catastrophes. The phenomenon also occurs at shock boundaries when one fluid flow collides with an opposite flow or immovable object, such as the bow of a ship moving through the water, the bow shock of the Voyager 2 spacecraft reaching the energy barrier at the edge of the solar system solar wind, an aircraft crossing the sound barrier at Mach 1, the meeting of the downward negative and upward positive leaders of a single lightning bolt, any explosive wave, waves crashing on a beach, the pulsation of RR Lyrae type variable stars, and the Prandtl-Glauert singularity observed when a jet or spacecraft on launch breaks the sound barrier through the atmosphere (Fig. 13.4 for Mach angle) (Oertel, 2010; Richardson, Kasper, Wang, Belcher, & Lazarus, 2008; Uman & Krider, 1989; Wallerstein & Elgar, 1992). Eigen and Schuster (1979) also noted the hyperbolicity of such transitions that are evident in the approach to sound barriers (Fig. 13.4). Oertel (2010) notably related the shock singularity phase transition during ventricular contraction fluid dynamics to wind flow and eddies around a jet wing airfoil.

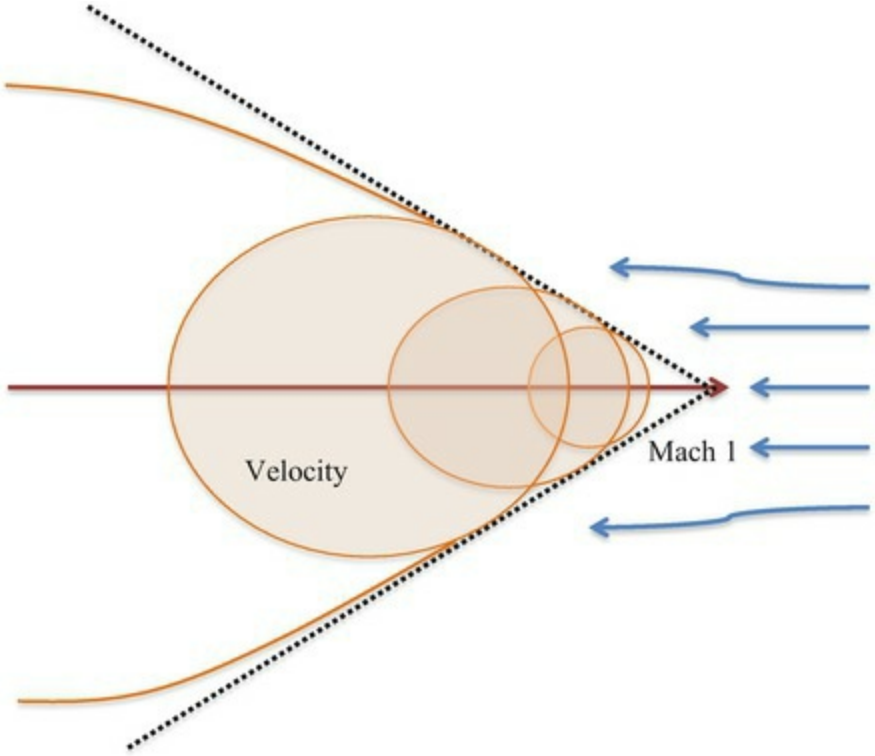

Fig.e 13.4 Jet approaching the Mach 1 transition critical point against air flow with compression of the wing pressure topology. Compare to Figs. 2.6 and 11.2

Figure 13.4 reminds us of the stretching of the ellipsoid that is characteristic of trajectory change and positive Lyapunov exponents (Figs. 2.6, and 11.2), albeit in reverse. As an air/spacecraft moves faster toward the critical point at which the air explodes around the force of the accelerating jet or rocket, the flow around the craft is initially hyperbolic, then parabolic, then elliptical, then smaller and smaller circles toward the critical point and accompanying sonic boom. From our discussion of the Lyapunov exponent λ (Chap. 12), the coherence length increases as the flow converges on the critical point, and the Lyapunov exponent decreases as the trajectory path difference approaches 0 at the critical point , with the Dirac delta function spike (Fig. 13.3). The Mach shock also can be described as an advancing standard shock wave (Fig. 13.5) in which an advancing disturbance wavefront with pressure P_2, density ρ_2, and temperature T_2 intersects the pre-shock, undisturbed region with pressure P_1, density ρ_1, and temperature T_1. The phase shift occurs at the intersection of these two regions.

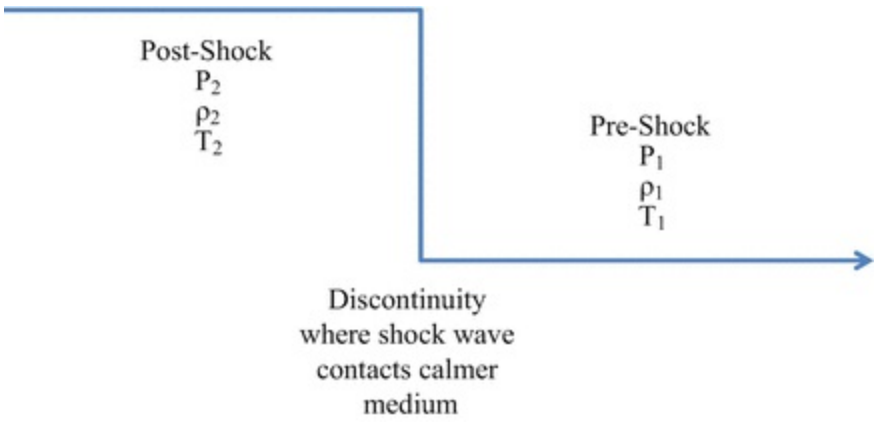

Fig. 13.5 Discontinuity phase transition of a moving shock wave as it continuously encounters a pre-shock "calmer" medium. Compare to Fig. 13.4

As mentioned earlier, Kozak and Benham (1974) described the denaturation of a protein as a Riemann-Hugoniot catastrophe (Fig. 13.6), which basically represents two alternate phases of a system in contact but not overlapping. A jump condition between the two phases (high energy versus low energy) is very much like a phase transition for water or benzene. The collapse from the higher energy state to the lower energy state represents a catastrophe (e.g., population collapse, electron move to lower energy levels of an atom) with the release of energy. Alternatively, energy or information can be provided to a lower energy phase to drive and maintain the system at the higher stable, perhaps at a stable resonance state with its surroundings, much like a laser boosts electrons to higher energy levels. This latter situation represents a jump condition. The jump across the Dirac delta function discontinuity represents a symmetry break across an energy barrier . When this break happens, coherence declines and the Lyapunov exponents λ increase, and there is one Lyapunov exponent λ associated with each transition point jump or bifurcation between one phase and another. Prigogine (2002) explained that the presence of resonances or correlations (i.e., interactions) between systems prevents integrability for the mathematical description of such events, and he specifically stated (p. 299) that "non-integrability arises from the limit of large volumes," which is exactly what happens at the transition point and Dirac delta function. Prigogine goes on to state that integrable systems that do not correlate are static, whereas interactions/resonances lead to dynamic behaviors and the creation of ordered structures. Thus, we see that it is in the vicinity of the critical point for phase transitions and where $\lambda \sim 0$ but not absolutely 0 at the Dirac limit where novel structures and processes form.

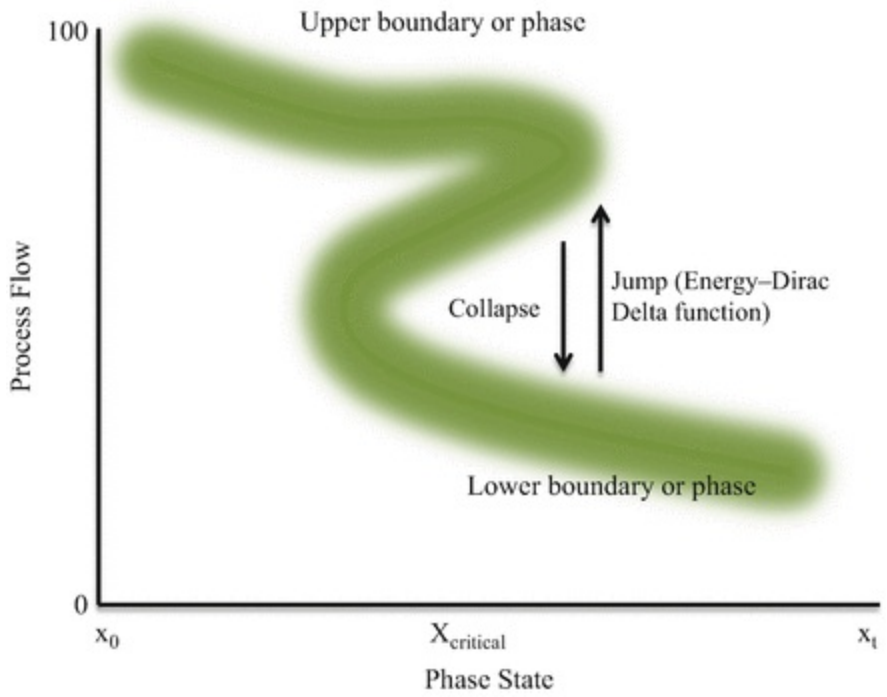

Fig. 13.6 The Riemann-Hugoniot Catastrophe, coupled with the Dirac delta function. The energy required to jump at the transition is represented by the vertical arrows

From a health trajectory perspective , we are seriously interested in the jump conditions for the alteration to normality of an aberrant physiological or behavioral phase state. From the discussion above, jumps are standard medical interventions (e.g., electrical, pharmaceutical) when they are carefully studied and implemented given the varied conditions of the patient. The remainder of this chapter examines the jump conditions to shift a health condition from one phase state to another. The previous discussion is heavily physical chemistry oriented from a public health perspective, although it is fairly basic to the fundamental principles of physical science. Nevertheless, we illustrated the universality of the phase transition process across multiple domains of physical and behavioral science, the fact that all change involves such jumps or transitions across a Dirac barrier . The events occur at both classical and quantum levels, as Hiley (2012) emphasized in his concept of becoming in quantum and classical systems, as one wave front from the past encounters another wave front from the future. The next step in epidemiological analysis is the identification of the relationships between variables and outcomes in phase space so that the sensitive effects of each contribution contribute to a desired shift in phased health conditions.

13.5 The Rankine-Hugoniot Jump

The standard model of fluid and even solid shock dynamics is the Rankine-Hugoniot Jump or R-H Jump conditions, which were derived by physicists William John

Macquorn Rankine and Pierre Henri Hugoniot during the late 1800s (see Rankine, 1870; Hugoniot, 1887). The jump condition is the critical point at the phase interface between two systems by which the advancing wavefront displaces another wavefront (Fig. 12.5). It also represents the energy gap between the maximum and minimum phases in the Riemann-Hugoniot catastrophe (Fig. 12.6; Kozak & Benham, 1974). For the advancing shock wave u_2 and the recipient pre-shock wave conditions u_1, there exists an infinitesimally small condition u_j (Field, Walley, Proud, Goldrein, & Siviour, 2004; Kerley, 2006; Salas, 2007):

$$u_1 dx_j/dt - u_2 dx_j/dt + \int_{x_1}^{x_j} u_j dx + \int_{x_j}^{x_2} u_j dx = -f(u)_{x_1}\Big]^{x_2} \tag{13.2}$$

which shows the transition through u_j. Interestingly, this equation corresponds to Feynman's kernel integral K from states a to b over all possible paths (Feynman & Hibbs, 1965, p. 38):

$$K(b,a) = \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} K(b,c)\,K(c,a)\; dx_c dx_a \tag{13.3}$$

where c is the intermediate state at a given transition and spatiotemporal distance between a and b. Furthermore, $K(c,a)$ represents a kernel of all possible pathways between a and intermediate c, and $K(b,c)$ represents the subsequent sum of all possible pathways between intermediate c and the final state b. Returning to our shock wave advance with post-shock and pre-shock phase transition intersection (Fig. 13.5), the pressure/density P/ρ Shock Hugoniot is derived as (De Nittis & Moro, 2012):

$$[\gamma/(\gamma-1)]\;(P_2/\rho_2 - P_1/\rho_1) = 0.5\,(P_2 - P_1)\,(1/\rho_1 + 1/\rho_2) \tag{13.4}$$

where γ represents the specific heat ratio for the gas. The Shock Hugoniot describes the pressure and density relationships at the phase transition critical point with constant temperature, as with the transition points in Fig. 13.2. Our next step, now that we have defined measures for the transition point as the Lyapunov exponent , is to describe how to create a jump condition in the transition of healthcare conditions.

13.6 Critical Opalescence

Prigogine (2002) maintained that the breaking of symmetry in systems is necessary for the existence of far-from-equilibrium structures such as molecules, cells, tissues, and organisms. As described above, symmetry breaking involves shifting the system from one phase to another, especially with fluctuations in the vicinity of the critical point between the phases. Albert Einstein (1905) and Marian Smoluchowski (1906) described these fluctuations in their seminal work on Brownian motion; they demonstrated that fluctuations occur near the critical phase transition points under pressure and temperature, the phenomenon of critical opalescence (see Gopal, 2000).

The phase transition is given this additional property because the light scattering through the substance becomes so large that all frequencies are present, giving the substance a whitish appearance. Cummins and Swinney (1966) examined the energy requirements of phase fluctuations in the vicinity of the critical point, emphasizing that the differential light scattering phenomenon approaches infinity, as with the Dirac delta function, when the system approaches the critical point .

Einstein (1907) and Debye (1912) would extend this work on critical point fluctuations with their quantum theory of harmonic vibrations in crystalline solids. More recently, Davies, Demetrius, and Tuszynski (2012) used one of Einstein's (1907) equations to argue the relationship of metabolic energy E_n in oscillating molecular interactions as molecular instability that might explain cancer and aging . Specifically, they calculated that the numbers of energetic molecules that are associated with all of the mitochondria (approximately 3000 per cell on average) in a typical human (about 1×10^{15} cells) indicated that metabolism could be considered to be a quantum process. The possible ramifications from this chain of induction would be the occurrence of phase transitions at the molecular level that lead to biochemical changes in human health and disease, especially conditions such as cancer (see Hollar, 2016).

Critical opalescence in the random motion of molecules and the scattering of light energy represents just one more illustration of the universality of phase transition processes at both quantum and classical levels for both nonliving and living systems. The mathematical description of this process returns us to the Lyapunov exponents , phase response curves , and coherence lengths between systems, the concepts that were built into our description of trajectory analysis during previous chapters. Prigogine and colleagues developed a substantial description of these system changes, most notably illustrating their irreversibility . Nevertheless, we know that the divergence of trajectories and the shifting of phases can be measured and adjusted. We do not have accurate information to make such modifications for all systems, but the new applications of the science of nonlinear dynamics to health can greatly improve the delivery of health and medicine. In previous chapters, we have argued that the central approaches to the improvement of behavioral and physiological health plus levels of functioning are (a) jumping the system (Phase 0 instead of Phase 1 transitions; see Chap. 11) or (b) overlapping driving forces with the designated process to reinforce a system's trajectory. In all instances, energy and longitudinal maintenance are often necessary. Rarely do we encounter the "quick fix," for which our health system too often relies despite overwhelming evidence on its efficacy in many situations.

13.7 Jumps in Health Trajectories

Kastner (2007) further emphasized the conundrum of the Dirac delta function at the transition point . Moreover, he specifically states that "a topology change is a necessary

condition for a phase transition to take place." As mentioned earlier in this chapter, explosions/detonations are examples of phase transitions, as a disturbance transmits itself through a medium (Fig. 13.5), with a continuous driving wavefront displacing a calmer medium with a moving critical point of transition between them as the wave expands.

Of particular relevance to the detonation wave analogy is the hydraulic jump. To visualize such a jump, imagine water pouring from a faucet onto the flat surface (not the drain) of a sink. Depending upon the velocity and volume of water flow (i.e., force), the water strikes the flat surface and forms a circular, heightened wave crest at some distance r_j from the initial impact point. The value r_j is the jump radius. Kasimov (2008) explained the mathematical approaches to calculating r_j, since it has important roles in the statistical estimates of fluid mechanics in reservoirs, dams, and rivers but also in biological systems such as arterial blood flow. We will consider the latter conditions in Chap. 14. The power of the phase transition at the hydraulic jump wave crest depends upon several factors, including fluid velocity, pressure, and density, just as with the shock wave in Fig. 13.5.

Kasimov (2008) noted that research shows the phase transition is weaker if the fluid is viscous; that is, higher viscosity for a fluid correlates with resistance to flow. Kasimov (2008, p. 195) noted that Bush, Aristoff, and Hosol (2006) discovered that the addition of a surfactant chemical (e.g., detergent) stabilizes the system and its transition across the jump from a flat wave to an elevated wave crest. From a health perspective, the most obvious example is the pulmonary lung surfactant, whose lipids and proteins produce a hydrophobic/hydrophilic layer that reduces surface tension in the alveolar cells , which can then more efficiently engage in the phase transitions of absorbing atmospheric oxygen and nitrogen while expelling carbon dioxide from the cells of the body. The decline in pulmonary surfactant production with age and with specific conditions (e.g., emphysema) leads to instability and declining function for gas exchange that continuously is needed for survival as well as disruptions that promote the growth of opportunistic lung bacteria to infect parts of the body and produce the potentially deadly sepsis, a major killer for older adults as well as for infants with certain health conditions.

This direct physiological benefit of pulmonary surfactant for hydraulic jump phase transition gas exchanges is obvious. It further gives us a glimpse into the physical principles that universally are necessary for stability of systems and their trajectory changes. A disturbance can be smooth or chaotic. Therefore, the provision of health interventions must include factors that are both necessary and that create stability during the transition process. Such smoothing processes can enable a Type 0 Phase Shift with a large wavefront crest that can be maintained with little resistance from the internal driving forces as well as from the environment. In Fig. 13.6, the jump typically will be from a lower boundary to a more energetic upper boundary. An undesirable system

collapse with loss of energy would occur otherwise. Therefore, the health intervention factors must provide the resources and energy for the individual and/or condition to make the change and be maintained. Think of an effective pharmaceutical dosage. Too low of a dosage does not phase shift the condition or behavior to the desired scenario. Likewise, too high of a dose could be ineffective as well due to dosage effects on genes and/or enzymes that are targeted within cells, along with unintended effects on other biochemically connected molecules and enzymes that are not affected at lower doses. The focus is on getting the right dosage for a given patient with unique genetic , epigenetic, physiological, behavioral, social, and environmental circumstances.

Thus, an effective Type 0 Phase Shift must cross the critical transition point smoothly with factors that facilitate a large jump to the next condition, with little perturbations of the system during each transition. We can measure the transition point or points, which is/are the Lyapunov exponents of the Jacobian matrix for the flow equations that describe the system. A large coherence length ξ or jump radius r_j means stability and smooth flow for the transition, which is equivalent to a low Lyapunov exponent or characteristic function λ. Variables that positively contribute to smooth transitions will have these properties. We next apply these nonlinear measurement principles to applied cardiologic interventions.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_14

14. Applications to Cardiology and Neuroscience

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Abbreviations

AMP Adenosine monophosphate
ATP Adenosine triphosphate
CPR Cardiopulmonary resuscitation
CVA Cerebrovascular accident (stroke)
ECG Electrocardiogram (also EKG)
EEG Electroencephalogram
HRV Heart rate variation
LVEF Left ventricular ejection fraction
PER2 Circadian rhythm enzyme
RNA Ribonucleic acid
ROS Reactive oxygen species
SCN Suprachiasmatic nucleus
VF Ventricular fibrillation
WSS Wall shear stress

The applications of trajectory analysis to health and medicine have been most pronounced in the disciplines of experimental cardiology and neuroscience. The cardiology work over several decades has involved the modeling/simulation of cardiac disturbances , most notably fibrillation and arrhythmias, and the attempted restoration of normal cycles as applied to in vitro studies of beating, cultured myocytes. Similarly,

neurological studies of nerve activity have involved in vitro studies of cultured axons , beginning with Hodgkin and Huxley's (1952) famous study of squid axon, to electrical monitoring of muscle contractions in animal and human studies. Analses of multiple organ systems have been conducted, including extensive work on normal and abnormal insulin responses to glucose elevation following meals as well as monitoring of muscular excitation involved in respiration, urination, uterine contractions during birth, and sexual activity. Most importantly, Glass and Mackey (1988) presented the bold, relevant concept of dynamical diseases that result from disruptions of normal electrophysiological and hormonal activities in cells, tissues, and across the entire organism, perhaps even between individuals as we witness with chemical communications between social insects and even between individuals of highly sociable mammalian and avian species (Wilson 1975).

14.1 History of Nonlinear Dynamics in Physiology

Glass and Mackey (1988) provided numerous animal studies of manipulated cardiac function and electrocardiograms to illustrate sensitive dependence on initial conditions and the phase shift from one patterned set of cycles to an altered pattern. The central features of this model included a normal periodicity that is interrupted by a disturbance that shifts the periodicity (Fig. 11.3). They quantified the phase shift of electrocardiograms and calculated the phase angle of the shift from normality (Eqs. 11.7, 11.8 and Fig. 11.4). They focused on the development of phase response curves (Figs. 11.5 and 11.6) that show the following:

(a) The mapping of each subsequent phase angle onto its previous phase angle in an iterative cycle (Figs. 11.5 and 11.6 for Type 1 and Type 0 phase shifts, respectively).

(b) A subsequent mapping of the differential phase change for each successive pair of phase angles versus each phase angle (Fig. 10.6). This is the true phase response curve.

From these two mappings , the researcher as well as the practitioner can evaluate the extent of change in a system from continuous, telemetric or longitudinal , multiple data point scans of patient measurements. The information from A above gives us the methodology for calculating the Lyapunov exponent for the system, thereby providing us with an assessment of the attractive or repulsive instability , stability , or chaotic uncertainty tendencies in the behavior of the system. The information from B above enables the researcher to identify combinations of variables that produce small or large differential changes, regions of stability versus chaos , and the likely targets for

adjusting the system to maintain stability.

From this early work, Glass, Nagai, Hall, Talajic, and Nattel (2002) mapped the entrainment of aberrant cardiac electrocardiograms in cardiac arrhythmias. Glass et al. (2002) noted that cardiologists treat arrhythmias by inserting several cardiac catheters through veins into the heart and then either delivering brief electrical stimuli to reset the abnormal rhythm or killing specific tissue regions with an electromagnetic pulse that is set of specific frequencies. For the latter method, the torus-like topological manifold for the arrhythmic wave is disrupted. For the former method, the phase reset stimulus must be placed near the affected site of the "re-entrant" arrhythmia to prevent its recurrence. Glass et al. (2002) modeled the phase signaling reset stimulus and found that the greater the distance between the reset stimulus and re-entrant arrhythmia site, the more likely that noise interference in the electrical signaling of the heart muscle can interfere and allow the reentry of the aberrant stimulus. They also discussed the importance of moving from one-dimensional to two- and three-dimensional models in the simulation and prediction research involving such physiological interventions, especially given the widespread availability of computer programs that can provide these process visualizations.

Much of this work started with Winfree's (1972) studies of the aperiodic and chaotic nonlinear dynamics involved with the Belousov-Zhabotinsky reactions, where a petri dish mixture of several substances (e.g., potassium bromate, cerium(IV) sulfate, sulfuric acid) with a redox indicator changes color over time as the reaction cycles back and forth. Winfree noted that slight shifts in the angle of the plate as well as defects in the plate surface create wave foci that mimic pacemakers. Winfree published many papers related to this phenomenon, and Winfree (1983) applied these results to the phase response curve mapping and the use of high stimulus/low stimulus Type 0/Type 1 phase resetting of abnormal cardiac rhythms. This work, coupled with that of many other researchers, has established the mathematical methodology for mapping the complex dynamics of electrochemical reactions in living tissue and potential interventions to restore disturbed rhythms.

Glass' research group has worked on the mathematical modeling of nonlinear, cardiac arrhythmias for decades. Krogh-Madsen, Butera, Ermentrout, and Glass (2012) built upon the Glass et al. (2002) observations to cite several problems of such theoretical models when they are applied in experimental research :

(a) Often, it is difficult to measure the correct phase of the rhythmic oscillation, especially when it is applied to individual cells.

(b) Cyclic systems in organisms (i.e., nerves, cardiac, and other muscles) involve ion-exchange processes across cell membranes, which can be complex with many

potential environmental disturbances that can be difficult to model and that have not been extensively modeled from a nonlinear perspective.

(c) Substantial differences exist with the developed nonlinear models and the results of in vitro experimental models involving cells, such that little work has been done to even consider the in vivo interactions between networks of cells, leave alone the effects within entire organisms.

Despite these limitations, Krogh-Madsen et al. (2012) argued that phase resetting models based upon weak coupling could be translated into experimental applications, especially if noise interference from other stimuli can be controlled. Furthermore, the Type 0/1 phase resetting distinction can be applied, more so for the Type 1 phase reset .

Despite these limitations , Gray, Chattipakorn, and Swinney (2005) studied the defibrillation of fibrillating, isolated pig hearts. Ventricular fibrillation (VF) is the leading cause of death in many parts of the world. VF is caused by chaotic electrical-muscular stimulation by the occurrence of ectopic foci, aberrant myocyte groups that experience changes in trans-membrane ionization and trigger spiral waves across the myocardium. The spiral waves interfere with the normal sinoatrial node stimulation of the ventricular contractions that force blood out of the heart to the lungs and body. Usually, there are multiple ectopic foci, and while they do interfere with each other as well as with the normal sinoatrial node, they do not cancel each other. The result is a quivering myocardium (i.e., heart attack) with permanent myocardial damage, failure to deliver oxygenated blood to the body tissues, and death within minutes. The use of cardiopulmonary resuscitation (CPR) and cardiac defibrillators, especially the latter, are needed to restore the normal or near-normal heartbeat.

14.2 Phase Resetting

Gray et al. (2005) demonstrated that the induced pig heart fibrillation and phase resetting restoration could be mapped with phase response curves . Specifically, they tested low stimulus Type 1 resetting versus high stimulus Type 0 resetting (Glass & Mackey 1988; Figs. 10.5 and 10.6) during defibrillation, finding that Type 0 phase resetting was more effective at restoring a relatively normal beating pattern. As with Krogh-Madsen et al. (2012), Gray et al. (2005), p. 4677 stated the basic principle of phase resetting for VF is to stop “reentrant spiral waves” by interfering with “the continuous change in phase around the singularity.” Here, the singularity refers to the origin or critical point of discontinuity (see the critical points in Chap. 12) at the ectopic foci. They concluded that only a strong defibrillation stimulus (i.e., Type 0 phase reset) can stop the extopic foci and the recurrence of reentrant, aberrant waves in the heart muscle. Nevertheless, they stress that the analysis of VF is difficult due to the

spontaneity of the ectopic foci and their disruptive spiral waves, which may be different for varying patients. Still, they clearly established the effectiveness of Type 0 phase resetting.

The Gray et al. (2005) study represented a clear demonstration of the applications of trajectory nonlinear analysis in applied physiology. We still have the limitation of not having applied these approaches extensively with human physiology and health, although Krogh-Madsen et al. (2012) have demonstrated cardiological interventions along this line with cardiac catheter electrical stimulation of the heart or radiofrequency ablation of myocytes to Type 0 reset heart arrhythmias. Thus, the applications of nonlinear dynamics are beginning to be used for the improvement of serious human health conditions.

The same principles of heavy stimulus (Type 0) versus weak/low stimulus (Type 1) phase resetting represent the central approach to restoring normal trajectories in physiological rhythms. Clearly, there are applications where this approach can be used across multiple physiological and even behavioral systems, not necessarily involving electrical stimuli but instead involving high bursts of hormones or specific pharmaceuticals. Such approaches need to be carefully studied and tested via clinical trials in order to determine the optimal stimuli for each given condition, minimization of side effects, consideration of genetic, epigenetic , and other physiological differences between individuals, and a priority of patient safety. The electronic, implantable cardiac pacemaker was developed in the 1960s by the Medtronic, a company founded by Earl Bakken and Palmer Hermundslie. This device provides electrical stimuli to the heart muscle to maintain its normal beating pattern. Our goal is to develop pacemakers, electronic, chemical, or behavioral, that provide energy for phase shifts to improve health.

Umapathy, Nair, Masse, Krishnan, and Rogers (2010) provided a thorough overview of phase mapping cardiac fibrillation that parallels our discussion in Chap. 11. They show that human VF is chaotic, very similar to the Lorenz chaotic attractor (Fig. 9.1). Among the observations that they noted from cardiac fibrillation research included substantial differences between epicardial and endocardial phase maps during VF and the existence of both 3D scroll waves continuously moving through the myocardium as well as a limited number of large wave fronts that are up to 8 cm long.

The phase stability of myocytes in the myocardium lies not only at the level of ion-exchange contractility across the myocyte membrane under the electrical stimulation/depolarization contractility effects of the approximately 1 s sinoatrial node , or from the occurrence of ectopic foci singularities that provide aberrant electrical stimulations. Myocytes have the highest level of mitochondria of any cell, approximately 7000 or more, compared to a few hundred up to 3000 for other cell types. Each mitochondrion pumps hydrogen ions across its inner membrane to recycle adenosine diphosphate (ADP) to the energy molecule adenosine triphosphate (ATP) via

oxidative phosphorylation. The mitochondria cumulatively function most efficiently when they fuse together into long chains that span across the cellular cytoplasm, with decreased membrane permeability, increased oxidative capacity, and less damaging free radical production (Chen & Chan 2004; Hollar 2016; Huang, Galloway, & Yoon 2011; Picard, Shirihai, Gentil, & Burelle 2013).

However, Aon et al. (2009) used a metabolic sink/block model to argue that when the body and its cells are subjected to physiological and oxidative stress , there is an accumulation of Reactive Oxygen Species (ROS) or free radicals such as superoxide. Normally, mitochondria exhibit an oscillating transmembrane electrochemical potential (i.e., proton-motive force) of approximately 220 millivolts due to the hydrogen ion pumping and trans-inner membrane pH gradient described above. The accumulation of ROS disrupts the transmembrane proton-motive force into chaotic oscillations accompanied by loss of ATP and activation of potassium channels in the sarcolemma of the connected myocytes . Additionally, the malfunctioning mitochondria will tend to cluster in chains across the cytoplasm, not fused as with their optimal functioning. This chain reaction of energy disruption across connected myocytes extends across the myocardium and may be the primary explanation of arrhythmias (Aon et al. 2009).

If this is the case, then the disruption of stable heart rhythms fractally extends from the organ down to the molecular level, consistent with aging and cancer models of quantum molecular instability and nonlinear dynamics (Davies, Demetrius, & Tuszynski 2012; Hayflick 2007; Hollar 2016). Aon et al. (2009) also based their model on a Complex Systems Approach of chaos that Sornette (2000) maintains is universal across all stressed systems, behavioral and physiological at all levels, including organizations. For the cardiologist, Aon et al. (2009) derived a membrane ion-channel based “safety factor” for estimating successful cardiac electrical conduction for normal rhythms.

Sabelli and Lawandow (2010) measured electrocardiograms from newborns, adults, and older adults and computer modeled R-to-R amplitude peaks and distances. They used specific software programs to generate measures of complexity , novelty, diversity, and causality for Heart Rate Variation (HRV), including Lyapunov and other exponents. They defined novelty (p. 387) as “the ratio of the recurrence rate of the original data with the recurrence rate of a randomized copy of the data.” Sabelli and Lawandow (2010) found that HRV is a predictor of cardiac health across age groups, as a decline in HRV complexity correlates with declining cardiac health. Most importantly, they argued that HRV novelty as measured by a low data/randomized data recurrence ratio indicates health, whereas heart rate stability with consistent, longitudinal R-to-R amplitudes is a measure of “imminent death” (p. 404).

If correct, the Sabelli and Lawandow (2010) study would indicate that dynamical change in heart conditions, within reasonable boundaries, might be a desirable goal for healthy exercise . The roles of the sympathetic and parasympathetic nervous systems come into play with respect to stress and regulation, such that the heart and other

systems may be cyclic and need occasional challenges to reset and maintain resiliency. In other words, no or little change (i.e., relative stasis) could be detrimental to health. Such a perspective would be consistent with lifelong activity and renewal in personalized health programs, breaking bad routines, and mixing up the body's growth and positive development.

Sabelli and Lawandow's (2010) findings do not address the multilevel system roles of mitochondria and specific electrochemical events in myocytes and across the myocardium that Aon et al. (2009) evaluated, so we must consider these perspectives as well. Petrie and Zhao (2012) studied cardiac alternans, a serious condition that involves instabilities of cardiac rhythm that are associated with slower transmembrane ionic repolarization of the myocardium and that is a major contributor to ventricular fibrillation. During each normal heartbeat, the stimulus from the sinoatrial node triggers a 1:1 depolarization response from the myocardium, whereas in alternans, the elevation of voltage during the depolarization oscillates between short and long values, creating an aberrant 2:2 resonance pattern (Petrie & Zhao 2012, p. 3653). They concluded that the electrical stimulation of the heart can be statistically modeled to predict cardiac alternans, including use of Lyapunov exponents with values of $\lambda \sim -1$ or lower.

These studies provide us with varying levels of prediction for applied cardiological interventions and for early diagnosis. More research needs to be done to establish the predictive validity of these measures. Furthermore, the theory and models need to be moved into applied practice.

14.3 Neuroscience Models

Neuroscience models have followed the same pattern of theory and model development followed by animal models. Whereas nonlinear cardiology research has provided some promising predictive measures at the organ level, as described above, the neuroscience models have mostly remained at the cellular level. Hodgkin and Huxley's (1952) squid axon has proven to be the standard that has been followed in nonlinear neuroscience research.

Schultheiss, Edgerton, and Jaeger (2010); Schultheiss, Prinz, and Butera (2012) identified the infinitesimal phase response curve to measure the resonance of associated neurons. Goldberg, Atherton, and Surmeier (2013) noted the difficulties involved in modeling the effects of small disturbances on neuronal firing. They developed an analytical model that spectrally analyzes the phase response curve for normal and delayed neuronal activity. Smeal, Ermentrout, and White (2010) support the use of such phase response curves to model neuronal synchrony. Furthermore, there is substantial evidence to support their use in the modeling of small neural networks (Goel & Ermentrout 2002; Smeal et al. 2010).

Just as with cardiology, the trajectory analysis or nonlinear analysis of biological

systems predominantly remains with theory and experiment. Obviously, the measurement of finite, small disturbances in electrical activity and synchronization between cultured cells can be complicated, compounded when the numbers of cells are increased. Even with large, classical systems such as organizational communications or social networking between individuals, the analyses of network systems have been qualitative at best. Some dynamic network models have been developed for the upregulation and downregulation of gene activities (i.e., messenger RNA production) in microarray analyses of condition-specific genes (see Petrusz, Jeyaraj, & Grossman 2005 for a network analysis of 381 genes regulated by androgen hormones in testicular tissue). Our cellular nonlinear models have only been applied to small clusters of cells in vitro when neurons can extend for many centimeters and even meters in some instances, with potential branch axon and dendritic connections with many other neurons, especially so with hundreds of millions of central nervous system brain and spinal cord nerves. The human brain contains over 100 billion neurons with tens of trillions of connections with each other.

Therefore, neurological models with clusters or small networks of cells probably do not fully measure the intricacies and myriad effects of cross-stimulation and other environmental effects upon neurons . The issue is complexity , a phenomenon closely related to nonlinear dynamics that itself is an emergent science. We can take neurology to the mitochondrial and molecular network level within each neuron as well, making the complex interactions even more staggering. Whereas the immensity of nervous systems represents one level of complexity, this fact by no means implies that the heart is less simple. The entire cardiovascular system includes hundreds of thousands of miles of vessels, each with smooth muscular layers and innervation by neurons . At some point, however, we have to take the jump from in vitro models and experiments to the applications in vivo with living organisms such as with the cardiac catheterized stimulus or ablation of arrhythmic myocytes .

One of the most promising areas where such physiological interventions could be made involves the manipulation of the circadian clock. Studies of these systems involve light, specific brain regions, and biochemical/molecular pathways within the immediate cells and other cells stimulated in synchrony with the initial receptor cells. The Suprachiasmatic Nucleus (SCN) is a bundle of several thousand synchronized neurons located in the hypothalamus above the optic chiasma where the two optic nerves cross in the midbrain. Light enters the eye and strikes the thousands of retinal nerve endings, which transmit the converted light electrical signal through the optic chiasma onto the visual region of hundreds of thousands of neurons in the occipital brain lobe for image processing. Light signaling in the optic chiasma is transmitted along a different nerve pathway to the SCN. The SCN receptor cells are stimulated by retinal ganglionic cells that produce melanopsin, and these receptors in turn secrete neurotransmitter proteins extracellularly to stimulate the synchronized SCN circadian cells via cyclic AMP

biochemical pathways within these cells (Pulivarthy et al. 2007). One of the most critical enzymes in this pathway is PER2, which is not activated during daylight but is accompanied by normal circadian rhythms. Light bursts at critical periods during the night lead to production and expression of PER2 coupled with damping of circadian rhythms (Pulivarthy et al. 2007). Therefore, this cell/molecular process maintains bodily rhythms based upon light stimulation. Most importantly, the SCN synchronously oscillating cells are autonomous. Each of them is capable of maintaining the rhythm and secreting the necessary neurotransmitters and hormones to affect other neurons and tissues. The synchronization of these SCN oscillating neurons is central to many nonlinear analyses of physiological systems given that the SCN with the hypothalamus regulate so many physiological processes. Repeated light bursts can induce aberrant or altered circadian rhythms , with subsequent broad physiological effects, and the manipulation of the SCN presents one area of promising interventions for improving health and behavior by phase shifting circadian rhythms . The paired, synchronous cell studies previously described are primarily aimed at this central physiological system.

Brager, Stowie, Prosser, and Glass (2013) studied cocaine and light effects on the activity and circadian modulation by PER2 using wild-type and per2 mutant mice. This was to test the biochemical effects of cocaine, given the fact that cocaine targets the SCN and disrupts circadian rhythms . They found that light appropriately phase delays circadian rhythms in both types of mice, especially the mutants, but they also found that cocaine phase advances the rhythms even in the presence of light. Therefore, Brager et al. (2013) provided clear evidence that cocaine acts on the SCN and circadian rhythm phase disruption via the PER2 protein. In an earlier study, Brager, Ruby, Prosser, and Glass (2011) demonstrated that acute ethanol exposure also disrupted and phase shifted circadian rhythms by targeting the SCN.

Like the electrocardiogram , neurological dynamics research has utilized measures of electrical brain activity via electroencephalograms and event-related potentials. Glass and Mackey (1988) covered examples of EEG phase disruptions for seizures. Paul, Sinha, and Patnaik (2015) examined EEG patterns in normal and stroke rat models, where they were able to demonstrate that Lyapunov exponents for normal brain waves tended to be negative toward attraction or slight stability near zero, whereas the exponents were positive for animals with induced cerebral ischemia. They also demonstrated inverse coherence lengths as measures of phase state disruptions for stroke. From a less invasive approach with human subjects, Funato et al. (2016) modeled phase shifts in stance and walking factors as modified by various disturbances . The analysis of nonlinear physiological trajectories can be mapped from molecular to cellular to organismal functioning levels.

14.4 Hydrodynamics

Given that much of our understanding of nonlinear trajectory dynamics comes from the study of fluid motion, a promising but overlooked area of potential study lies within the scope of blood fluid dynamics and the mechanical properties, particularly elasticity, of blood vessels. Besides cardiac failure or central nervous system disruption, the structural collapse of blood vessels or inefficient blood fluid dynamics represent an additional physiological decline in aging and disease. Except for the thin-walled, gas exchange capillaries, arteries and veins contain a smooth muscle layer that rhythmically contracts and forces the flow of blood, a phenomenon that can be detected with the diastolic blood pressure in between heart beats. Each blood vessel layer also contains elastic-like connective tissue that is flexible for maintaining vessel integrity while moving blood. With aging , the smooth muscle weakens, and the connective tissue becomes less flexible. The rapid, sometimes turbulent flow of blood through specific vessels can deform vessels such that they rupture and/or accumulate atherosclerotic plaques that further compromise vessel integrity and function. Blood vessel ruptures (i.e., aneurysms) can occur in any vessel, but they are far more serious when they involve ruptures in the brain or coronary arteries, thereby starving downstream cells and causing irreversible cellular death and tissue damage. Aortic aneurysms are invariably fatal due to the massive blood loss.

Consequently, the phase structural stability of vessel walls and the accompanying blood fluid dynamics represent important areas of trajectory analysis for these tissues in health and disease. One of the seminal studies on fluid dynamics that has been extensively studied in vitro and that has substantial applications to hemodynamics as well as to other cellular and physiological functions is Rayleigh-Bénard Convection. This phenomenon involves the smooth as well as turbulent flow of fluid between two rotating cylinders, accompanied by the convection of heat energy across the system due to the phased flow. As with other studies, Scheel, Emran, and Schumacher (2013) developed mathematical models of optimal fluid flow and heat dissipation based upon the Prandtl number, a ratio of fluid motion viscosity to heat energy diffusivity. Slight disturbances to fluid flow can drastically alter trajectories, such that the Prandtl number represents one of several measures of linearity/nonlinearity in fluid flow and thermal convection with these systems. We can relate Rayleigh-Bénard convection to vapor or fluid flow between two moving surfaces , whether we are considering molecular and bioenergetic events between the inner and outer mitochondrial membranes or atmospheric currents between the earth's crust and stratosphere.

Considerable interest has been placed on fluid motion in blood vessels and in heart function. Sforza, Putman, and Cebral (2009) studied cerebral aneurysms that result in cerebral ischemia or cerebral vascular accidents (CVA). Over time, blood velocity can force stress and strain on the vascular endothelium, particularly impacting Wall Shear Stress (WSS) with the loss of endothelial cells and damage to the elastic connective tissues in the inner and middle layers of the vessel wall. Of particular focus in the brain

is the Circle of Willis vasculature, where "deviations from normal anatomy result in a redistribution of wall pressures and increased WSS at branch points" (p. 96). The Circle of Willis is particularly vulnerable to cerebral aneurysms with increasing age, with pressure increases from stringent physical activities (even from a sudden rise from rest upon waking) that can rupture the weakened vessels.

Sforza et al. (2009), p. 102 stressed that "high-flow hemodynamic forces" and weakened vessel walls (WSS) contribute to cerebral aneurysms, coupled with the increased production of nitric oxide that triggers endothelial cells to die (i.e., apoptosis) as part of the dynamic remodeling of vessels over a person's life (just as with bone and skin remodeling, etc.). Surrounding organs and skeletal structures might abrade vessels as well. Most importantly, they stressed the importance of three-dimensional imaging to develop "patient-specific" models for diagnosis and treatment.

Gharib, Rambod, Kheradvar, Sahn, and Dabiri (2006) examined heart health not from electrochemical stimuli but from efficient blood flow during ventricular contractions. The most widespread assessment of heart output for healthy and cardiac patients is the Left Ventricular Ejection Fraction (LVEF) or volume. Gharib et al. (2006) argued that the LVEF is a linear flow model, whereas the actual blood flow through and out of the ventricles during ventricular contraction (systole) is a three-dimensional vortex with high fluid dynamics and pressure. They developed and validated an alternative measure, the vortex formation time that accurately predicts normal and abnormal ventricular function. The vortex formation time considers the nonlinear dynamics of vortex formation and trajectory change between and during contractions; it is a function of the left ventricular ejection fraction (LVEF) plus left ventricular end-diastolic volume, mitral valve diameter, and the percentage of left ventricular stroke volume that comes from ventricular filling from left atrial contraction.

These studies demonstrate the importance of fluid flow and its proper assessment in the hemodynamics of stroke and heart disease, which combined kill more people each year than cancer and most other causes of death combined. Patient-specific models of genomics for cancer and other condition predictions have been advocated with genetic technology. Therefore, we should provide more comprehensive diagnostic imaging of the cerebral vasculature and fluid flow in the heart, even extending such approaches to the pulmonary circuit, kidney nephronic function, etc. Trajectory deviation measures are available for accurate prediction to enhance diagnosis and appropriate patient-specific treatments.

These applications can be applied to other medical interventions as well. Chen, Kreider, Brayman, Bailey, and Matula (2011) demonstrated via microphotography that certain procedures such as ultrasound require the introduction of air bubbles, which subsequently can trigger jetting of blood and deformations in vessel walls, potentially contributing to rupture (i.e., aneurysm). Tosun, Montoya, and McFetridge (2011) found that tissue grafting and the introduction of artificial structures into the body can

introduce phase remodeling of the vasculature. The implications are clear: medical treatments can improve health but may trigger unexpected physiological disturbances in their own right. This is where secondary conditions emerge in health care, along with some unexpected sentinel events. This certainly is true with pharmacological agents, which target one or a few molecules but their action on that molecule may trigger a cascade of unexpected effects on other molecules. Hence, medications have side effects, all due to sensitive dependencies on initial conditions.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_15

15. Understanding the Evolutionary Historical Background Behind the Trajectories in Human Health and Disease

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Abbreviations

ACTH Adrenocorticotropic hormone
Alu/SINE Retrotransposable elements of DNA across the genome
CRF Corticotropin releasing factor
DNA Deoxyribonucleic acid
HIV Human immunodeficiency virus
HLA Human leukocyte antigen
HPG Hypothalamic-pituitary-gonal hormone axis
HPT Hypothalamic-pituitary-thyroid hormone axis
IFN Interferon
IL Interleukin
LTR Long terminal repeat
MHC Major histocompatibility locus
OR Olfactory receptor
ROS Reactive oxygen species
TNF Tumor necrosis factor
VNO Vomeronasal organ

As we have emphasized across previous chapters, multiple scientific disciplines such as systems ecology (Brenchley & Harper, 1998; Krebs, 1978), molecular medicine and development (Wolpert et al., 1998), aging theory (Hayflick, 1994; Ricklefs & Finch, 1995), and quantum biological information systems theory (Eigen, 2002; Eigen & Schuster, 1979; Kitano, 2004; Smith & Szathmary, 1999) infer an intricately complex, multi-layered order to life, health , and the universe with stepwise, fractal evolutionary processes occurring at each of these levels throughout the history of life on earth . Therefore, we argue a consilience (Wilson, 1998), a synthesis of interconnecting immune, endocrinologic, and sociologic mechanisms to explain aspects of behavior and disease, with a key emphasis upon allorecognition and inter-individual immune rejection (i.e., quite literal self versus non-self) antagonistic relations.

15.1 The Relevance of Hierarchy

Whereas entire genomes, including the human genome, have been sequenced, the overwhelming majority of those species' DNA sequences have not been elucidated with respect to their intricate regulatory mechanisms (i.e., epigenetics), both within and between "genes," let alone the extensive polymorphisms and somatic modifications at many loci, thereby generating wide haplotype and epigenetic variations for each locus within and across species (McKusick, Valle, Francomano, Antonarakis, & Hurko, 1997; Waterston, Lander, & Sulston, 2002). The varying genomes across species and the interspecific variations at thousands of shared genetic loci represent an immense historical record, much of it so far indecipherable, of 3.8 billion years of molecular evolution, including molecular competition and cooperation, at multiple hierarchical levels of physical molecular structure composing living organisms within a presumed biologically closed biosphere covering the thin, earth's surface (Margulis, 1998; Smith & Szathmary, 1999).

As systems of cooperating and competing molecules, cellular life exhibited evolutionary molecular change internally while remodeling the external physical and chemical environment (Carroll, 2001; McMenamin & McMenamin, 1990; Vernadsky, 1997). This process involved variation in individual characteristics due to mutations at the pre-cell molecular life level of the primordial soup and at the cellular, subcellular, and molecular levels as these living processes became sequentially subsumed and modified into hierarchical structures of life (Eigen & Schuster, 1979; Smith & Szathmary, 1999). For the first two billion years of life, the maximum level of complexity was the single, non-organelle cell of the Prokaryotae, Cyanobacteria, and Archaea (Brenchley & Harper, 1998; Smith & Szathmary, 1999).

Nevertheless, environments and microenvironments exist at the cellular, subcellular, and molecular levels for all living organisms. Therefore, variation in single molecules,

parts of cells, or the intricately complex molecular systems comprising even a prokaryotic cell would be subject to selection. Nevertheless, the molecules composing living cells “compete” and “cooperate” within hierarchical layers of living and environment-molded structures, particularly closely related pseudogenes, retrotransposons, endogenous retroviruses , and exogenous retroviruses, which differ merely by the presumed extent that they can deliver “offspring” copies outside of their “host” cell (Lower, Lower, & Kurth, 1996). The result is a hypercycle (Eigen & Schuster, 1979; Fig. 15.1) of interacting molecular systems competing for resources and substrates while being hierarchically arranged within cooperating structures to support system survival. Key features of such hypercycles include (Eigen, 2002; Eigen & Schuster, 1979; Smith & Szathmary, 1999):

1. A finite set of connected replicators.

2. Replication rate dependency on the concentration of the previous, linked cycle replicator.

3. Ecological stability in the absence of disruptions.

4. Esets of disrupted cycles at a different functional level.

5. Critical error thresholds above which there is an accumulation of mutated messages leading to collapse.

6. Multiply redundant hypercycles to maintain system stability (i.e., allostasis and homeostasis).

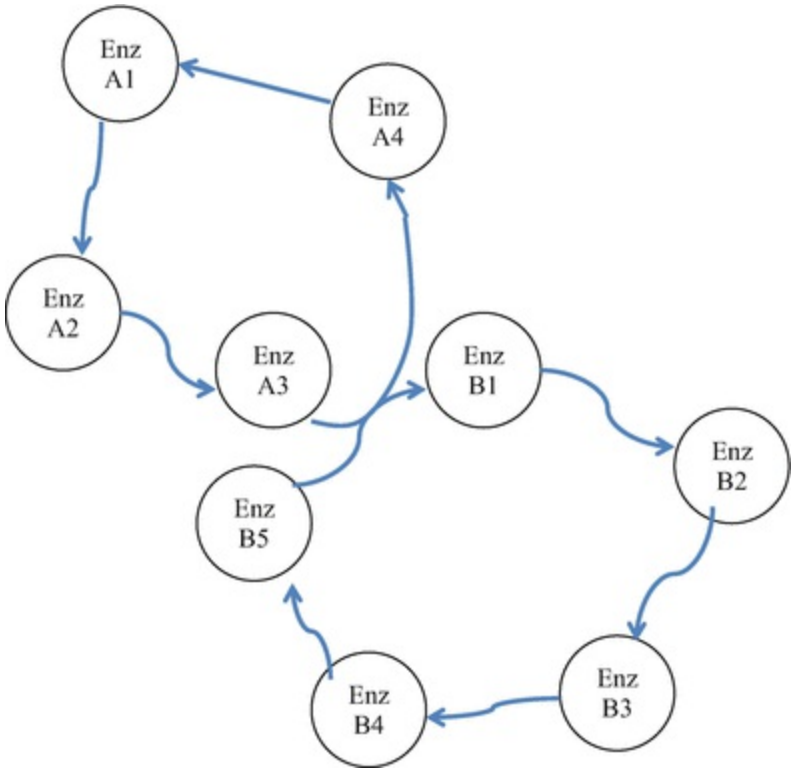

Fig. 15.1 A possible hypercycle, with cycles influencing other cycles. See Eigen and Schuster (1979)

This model strongly illustrates the role of trajectory dynamics from molecules to living organisms, particularly the role of disturbances and phase resetting plus the importance of redundancy within cells and tissues so that the organism is highly resilient to disease. This latter phenomenon is maintained as good health at least through the periods of reproduction and child-raising for mammals, including humans. One of the primary tenets of aging (Hayflick, 1994) is that senescence begins post-reproduction . Hayflick (2007) also argued that molecular instability was an additional tenet of aging processes in living and nonliving matter, and that human longevity has been extended by medicine such that we are confronted with a paradox where the evolution of genes had not prepared us for post-reproductive longevity.

15.2 Health, Systems, and the Development of Life on Earth

Disruptions to the health of any living system can occur on the micro- or macroscales . On the macroscale, one of the most significant disruptions of the life-environment hypercycle occurred approximately 1800–2000 million years ago, at which point the planetary cyanobacterial stromatolites had released substantial toxic oxygen quantities into the atmosphere. Reduced components of the atmosphere and seafloor were precipitated from solution (e.g., chert deposits) by living cells, and the atmosphere shifted from reducing to oxidizing . The resulting oxygen crisis no doubt led to the

extinction of many prokaryotic and Archaean species (Smith & Szathmary, 1999).

Natural selection for life to survive the oxygen crisis appears to have favored endosymbioses, by which purple bacteria penetrated large aerobes and evolved into present-day mitochondria as bioenergetic components of eukaryotic cells. The net results of the oxygen crisis, one of the few global selection events in the history of life on earth , included a shift from a reducing to an oxidizing atmosphere, selected for cellular metabolisms that could detoxify oxygen and free radicals, increasing competition among oxygen-mediated metabolic pathways and hypercycles , the sequestration of anaerobes (e.g., Archaea) to anoxic environments such as deep sea hydrothermal vents, later animal guts, sporal dormancy until habitation of a low oxygen cellular host, and permanent endosymbiotic eukaryotic cell protection against oxygen (Brenchley & Harper, 1998; Smith & Szathmary, 1999).

Consequently, there was redirection of prokaryotic evolution , favoring cyanobacteria and aerobic eubacteria and cooperation of cellular forms to create subcellular symbiotic relationships leading to subcellular organelle compartments, a new hierarchical level of life upon which natural selection could act. Most importantly, this global selection event "set" the genetic mold among crisis survivors and symbionts (an evolutionary bottleneck) for a limited range of possible biochemical and structural natural responses to oxidation stress , repercussions that are faced by every post-oxygen crisis species and species composite, especially Metazoa (e.g., senescence, cancer).

With these changes, the period from 2000 to 700 million years ago saw the evolution of complex unicellular and colonial eukaryotes as well as multicellular algae within the oxidizing atmosphere. From this point forward, compartmentalization of microenvironments to protect anaerobic symbionts and to manipulate aerobic purple bacteria (i.e., mitochondria) and phototrophs (chloroplasts) in new colonial and multicellular hierarchies would add more levels of selection, while at the same time, living processes were beginning to control planetary levels of atmospheric oxygen, methane, and carbon dioxide, the first two components being chemically incompatible.

Choanoflagellates originated 1000 million years ago, seafloor Ediacarans developed complex, motile forms between 573 and 543 million years ago, and an explosion of Cambrian life forms occurred approximately 543 million years ago (Brenchley & Harper, 1998; Carroll, 2001; McMenamin & McMenamin, 1990). The Cambrian "explosion" established all of the major animal taxa and body forms known today and represented a third, global selection event in the history of life on earth following the Oxygen Crisis. The Cambrian explosion coincided with a combination of environmental and molecular competitive events, the latter "setting" or "hard-wiring" the subsequent foundation of eukaryotic structural and functional attributes for the remainder of life history. This focused trajectory of life's trajectory excluded all other morphological forms and limited life to specific skeletal arrangement patterns as determined by surviving species that carried specific sets of genes (Erwin, Valentine, &

Jablonski, 1997; Thomas, Shearman, & Stewart, 2000).

What we are illustrating in this chapter is how disturbances , small and large, provided profound phase shifts to the direction of life on earth (see Fig. 5.2). Disturbances came from the environment as well as from the activity of life itself (e.g., Oxygen Crisis) on the environment. On a much smaller scale, think of how old field succession occurs on an abandoned field in temperate climates: it starts with grasses and wildflowers, which modify the soil to favor pines and other evergreen plants, which subsequently modify the soil with biochemicals to inhibit the grasses and wildflowers but ultimately favoring the subsequent growth of hardwood trees (Krebs, 1978). The Oxygen Crisis shifted the earth's atmosphere from reducing to oxidizing, set the course for the endosymbiosis of mitochondria in all eukaryotic life that emerged, including ourselves, and ironically led to the probable role of toxic oxygen and related free radicals/reactive oxygen species (ROS) in the aging process (Hayflick, 1994, 2007).

Consequently, catastrophic events (Thom, 1972) can lead to dramatic phase shifts in living systems, large and small. This is why we stress that the epidemiologist, the health policy maker, and the clinician should analytically think about health problems from a comprehensive systems perspective , seeing the proximate (i.e., immediate) causes of conditions as well as the ultimate causes. We must understand both the "how" as well as the "why."

Major environmental impacts around the Cambrian included oxygen/methane/CO_2 atmospheric fluctuations that may have created alternating Snowball and Hothouse Earth climates (Hoffman, Kaufman, Halverson, & Schrag, 1998). With the appearance of such extraordinary multicellular diversity, gene duplications and mobile genetic elements led to the development of novel biochemical systems for the regulation/diversification of body patterns (e.g., ancestral Hox gene clusters) and for control of bacteria and other pathogens (e.g., the Major Histocompatibility Complex) (Erwin et al., 1997; Robinson-Rechavi, Boussau, & Laudet, 2003; Thomas et al., 2000). The ancestral Hox genes established an animal skeletal morphospace of 182 design pairs, 80% of which have been used in skeletal formations during the past 500 million years (Gravallese, 2003; Kawasaki, Suzuki, & Weiss, 2004; Robinson-Rechavi et al., 2003; Thomas et al., 2000; Yu et al., 2005).

Therefore, the Oxygen Crisis and the Cambrian explosion represented global selective bottlenecks/catastrophes that set the direction of multicellular animal and plant development/physiology ; acted at multiple hierarchical levels: molecular, subcellular, cellular, and multicellular; developed complex systems for pattern development and immune response; and established three new levels of selective hierarchy, tissues, organs, and organ systems, within a fourth encompassing hierarchical level, individual multicellular organisms, as layered, recursive components of species, populations , and biomes.

With respect to the last point, an intricate interplay between atmospheric $O_2/CH_4/CO_2$ levels and the utilization of carbonaceous skeletons is implied as a putative "ultimate" selective factor (Thomas et al., 2000). Similarly, an accumulating body of evidence implicates the Major Histocompatibility Complex (MHC)/Immune System and cytokines in animal skeletal remodeling as well as other body pattern processing events throughout animal development (Gravallese, 2003; Kawasaki et al., 2004).

Besides these possible linkages between various genetic systems, their biochemical products, increasing levels of organismal hierarchy, and biogeochemical processes, the great Cambrian species diversity competed for resources and evolved with strong selection for gene duplications and subsequent divergent evolution to produce genetic /biochemical hypercycles (Eigen & Schuster, 1979) plus selection for transposable genetic elements, retrotransposons, endogenous retroviruses , and repetitive sequences throughout whole genomes, with extensive genetic modification events occurring in the duplicated, heavily polymorphic MHC and Hox clusters as well as their "pseudogene" derivatives (Anzai et al., 2003; de Groot et al., 2002; Horton et al., 2004; Mungall et al., 2003).

Over the past 700 million years, land plants, invertebrate, and vertebrate animals have evolved based upon the multiple hierarchical selection events, all of them molecular to some extent, that were set in place by the Cambrian bottleneck. Over this period, there have been six major extinctions, most notably the Permo-Triassic Crisis of 240 million years ago during which approximately 90% of all species perished with all taxa being impacted, including the resilient insects (Erwin, 1996; Jin et al., 2000). Despite these catastrophes and redistribution of taxon frequencies, the basic hierarchical body plans, and molecular processes set during the Cambrian Explosion and by the more distant Oxygen Crisis remain as signature events in the global patterning of life. Furthermore, bacteria remain the dominant life form on the planet, independently, symbiotically, autotrophically, and parasitically (McFall-Ngai, 2001, 2002). Consequently, the evolution of defense systems against oxygen-mediated senescence, pathogens (via the Major Histocompatibility Complex), and death is most likely linked at the molecular and hierarchical levels of organisms (Cohen, 2002).

Therefore, it is probable that biogeochemical events in earth 's history have strong indirect effects upon every living organism alive today, natural selection and changes in trajectory dynamics operate at multiple hierarchical levels of molecules, organisms, and populations through hypercycles of interactions (Fig. 15.1), and the highly polymorphic Major Histocompatibility Complex (MHC) represents a key region of intense molecular competition that may be manifested at the organismal and population levels. The Cambrian genetic body plans included six Hox gene clusters and the ancestral MHC (Andersson, Svensson, Setterblad, & Rask, 1998; Besedovsky & Del Rey, 1996). The MHC , or Human Leukocyte Antigen (HLA) complex, located on chromosome 6, has

the following functions and characteristics for natural immunity and medical applications:

1. Protection against pathogens via modifiable gene rearrangements that encode general and specific immunoglobulins.

2. Tissue compatibility/incompatibility in organ grafts and transplants.

3. Clustering and superclustering of seemingly non-immune related genes having common functions, including histones, transfer RNA , zinc finger proteins, olfactory receptors, tumor necrosis factor , and heat shock proteins.

4. The presence of 0.34 Alu/SINE elements (retroposons) per kilobase of the human MHC II region, two human endogenous retroviruses , and 13–15 transcriptionally active, IFN-gamma responsive Long Terminal Repeats (LTRs).

5. Associations between several of these elements and genetic loci for severe autoimmune diseases such as multiple sclerosis and Type I diabetes.

6. The underlying process of distinguishing and responding to “self versus non-self” antigens throughout these processes.

15.3 The Major Histocompatibility Complex (MHC) , Immunity , and Behavior

The extended human MHC, or Human Leukocyte Antigen (HLA) complex, is divided into three major regions through which these gene clusters, superclusters, and retroelements are dispersed: MHC I, II, and III. The human MHC/HLA covers 4.6 megabases on the short arm of chromosome 6 (6p21.3) with at least 224 gene loci, representing the largest multigene complex in the entire human genome, as well as being the most polymorphic (Hollar, 2009).

The MHC class I genes encode glycoproteins that present endogenous antigens to $CD8^+$ T lymphocytes . Human MHC class I includes the HLA-A, -B, -C, -D, -E, -F, and -G loci (Hollar, 2009; Evans et al., 1999; Knapp, Cadavid, & Watkins, 1998). Each locus is highly polymorphic: The HLA-A locus includes at least 29 different alleles at relatively high frequencies across native human populations worldwide. Similarly, the HLA-B locus includes at least 60 alleles. These MHC/HLA I glycoproteins are

positioned exteriorly from virtually all somatic cell membranes, they are expressed at high frequency (~5 × 10^5 molecules per cell), they are associated with a non-linked immunoglobulin-related membrane protein called beta-2 microglobulin, and they enable $CD8^+$ T lymphocytes to identify "self" (Horton et al., 2004).

The MHC class II genes encode glycoproteins that present exogenous antigens to $CD4^+$ T lymphocytes (Horton et al., 2004). Like MHC I, the MHC II genes are highly polymorphic, and they encode the HLA-II DPA1 (DPw3a1), DPB1 (SB), DQA1, DQB1 (IDDM1), DRA, DRB1/DRB3 (the latter with many pseudogenes) (Horton et al., 2004). The expressed MHC/HLA II gene products are transmembrane glycoproteins that can be glycosylated but are typically expressed only on B lymphocytes , some T lymphocytes, and antigen-presenting macrophages. It should be noted that the MHC II genes include DAXX, whose protein product enhances Fas-mediated apoptosis, and TATSF1, whose protein product is an HIV transcriptional elongation cofactor (Horton et al., 2004).

The MHC/HLA class III genes encode Complement proteins and inflammatory cytokines , both of which are associated with immune responses to infection. HLA III AIF-1 encodes a pro-inflammatory cytokine -responsive macrophage protein, while TNF encodes pro-inflammatory tumor necrosis factor and BAT-3 encodes a proline-rich protein of unknown function that has a ubiquitin-like domain. These three MHC regions are highly conserved in mammals (Evans et al., 1999; Knapp et al., 1998).

The specific role of the MHC/HLA proteins is to interact with immune cells (leukocytes) in order to identify and protect "self" cells while identifying and destroying "non-self" cells and/or antigens. This central "self versus non-self" paradigm of immunity was developed by Burnett (1959). The mechanisms of MHC/HLA expression are extremely intricate, involving hierarchical selection events, cellular differentiation, and chemical communication involving neuroendocrine, hormonal, chemokine, and cytokine intercellular and trans-organismal chemical communications.

Leukocytes differentiate from stem cells located in the red marrow of flat bones via the feedback of hormonal signaling mechanisms. Dendritic cells formed in bone marrow accumulate antigens and mature through the influence of exposed pathogens, T lymphocytes , and pro-inflammatory cytokines such as TNF-alpha, Interleukin-1-alpha, Interleukin 1-beta, Interleukin 8, and Interleukin 9. The dendritic cells migrate to lymphoid organs such as the spleen and lymph nodes where they complete maturation, a process that involves intracellular increases in intracellular MHC/HLA II glycoproteins and their movement to the cellular membrane surface , increased chemokines (i.e., CD54, CD58, CD80, CD86, Cd40, CD25, CD83, Interleukin 12, and p55), as well as decreased actin cables. Anti-inflammatory cytokines such as Interleukin 10 can delay the maturation of dendritic cells (Banchereau & Steinman, 1998; Sternberg, 1997).

Within the lymphoid tissues, dendritic cells, and other maturing leukocytes, including thymocytes in the Thymus, there is positive selection for thymocytes having

low affinity T cell receptors that do not strongly bind MHC I or II "self" peptides, thus not having the tendency to reject "self" somatic cells. Thymocytes with high affinity T cell receptors are likely to reject self MHC antigens, receive no survival signal, and undergo apoptosis (Werlen, Hausmann, Naeher, & Palmer, 2003). Surviving thymocytes, dendritic cells, macrophages, and other antigen-presenting cells present endogenous antigens to $CD8^+$ cytotoxic T cells or exogenous antigens to $CD4^+$ helper T cells, thereby triggering an immune cascade. Furthermore, Interleukin 12 stimulates T helper cells to develop into inflammatory Interferon-gamma-producing Th1 cells and then to activate Killer Cells (via Cell Mediated Immunity), whereas Interleukins 4, 10, and 13 (plus virally produced mimics of Interleukin 10) induce T Helper cells to stimulate Th2 (Humoral) antibody production and clonal selection of B lymphocytes directed at a specific antigen (Sternberg, 1997). Furthermore, glutathione, which typically stimulates the Th1 response pattern, is blocked by the Human Immunodeficiency Virus (HIV) and by cancer cells (Dustin & Chan, 2000; Peterson, Heizenberg, Vasquez, & Waltenbaugh, 1998).

Therefore, the functionality of the immune system represents a hypercycle (Fig. 15.1) of defensive reactions that occur at the molecular, cellular, tissue, and organ levels, reactions that are both homeostatic and allostatic in terms of the balancing and extremes of reactance that are needed for an individual organismal unit to deal with the continuous viral, bacterial , fungal, and other antigenic/immunogenic assaults. Bacteria remain the dominant life form on earth in terms of prevalence and mass, and they proliferate independently within and without more compartmentalized organisms. Bacteria may even influence the developmental patterns of multicellular life forms. Consequently, inter- and intra-cellular developmental and chemical competition /cooperation occurs within organisms, following Wilhelm Roux's conceptualization of tissues and organs competing for resources until a homeostatic environment is reached (e.g., stem cell differentiation), thereby warranting an ecosystem analysis of cell, tissue, and organ interactions (Powell, 2005).

Within animals, the intermolecular and intercellular competition /cooperation balance can be illustrated in systems such as the T cell-mediated programmed apoptosis of limb bud tissue to generate fingers and toes during primate embryonic development (Wolpert et al., 1998), dendritic and T cell modulation of osteoclast differentiation to regulate the lifelong modeling and remodeling of bone under nutritional fluctuations, stress , and other environmental/physiological changes (Arron & Choi, 2000; Gilbert, 2001), neuroendocrine control of thymic physiological processes via cytokines (Savino & Dardenne, 2000), and inflammatory responses to infection plus autoimmune responses to "self" antigens (Werlen et al., 2003). The intricacies of immune interactions with other body systems, self antigens, and viruses will be elaborated further below.

The tenuous relationship between the identification of self versus non-self is further

complicated by variations in responses to potential pathogens. Whereas all gram negative bacteria such as Pseudomonas are virulent due to a membrane lipopolysaccharide lipid A segment, this pathogenic characteristic along with the species' associated bacterial pheromonal quorum sensing ability are essential properties for the mycorrhizal gram negative bacterial symbionts of leguminous root nodules, which represents 90% of living plants! At the same time, both animal and plant cells utilize ubiquitin for microbial defense by triggering the proteosome to degrade proteins in self-compatible cells (e.g., pollen), while ubiquitin-labeled proteins simultaneously have been associated with retrovirus budding (Newbigin & Vierstra, 2003; Patnaik, Chan, & Wills, 2000).

Besedovsky and Del Rey (1996) illustrated the organ, tissue, cellular, and intracellular hierarchical relationships between the immune, nervous, and endocrine systems. Both endocrine glands and neurons release hormones/neurotransmitters that target lymphocyte/leukocyte function, including chemokine homing and trafficking, ubiquitimation and intracellular processes, cytokine -mediated inflammatory status and target cells, somatic cell metabolism, endocrine gland hormone production, and neural regulation of neuronal growth, neurotransmission, differentiation and repair, thermoregulation, food intake, sleep, and behavior at the cellular and organ levels (e.g., central nervous system). A modification of their three-level hypercycle for neuron-immuno-endocrine interactions is represented in Fig. 15.2.

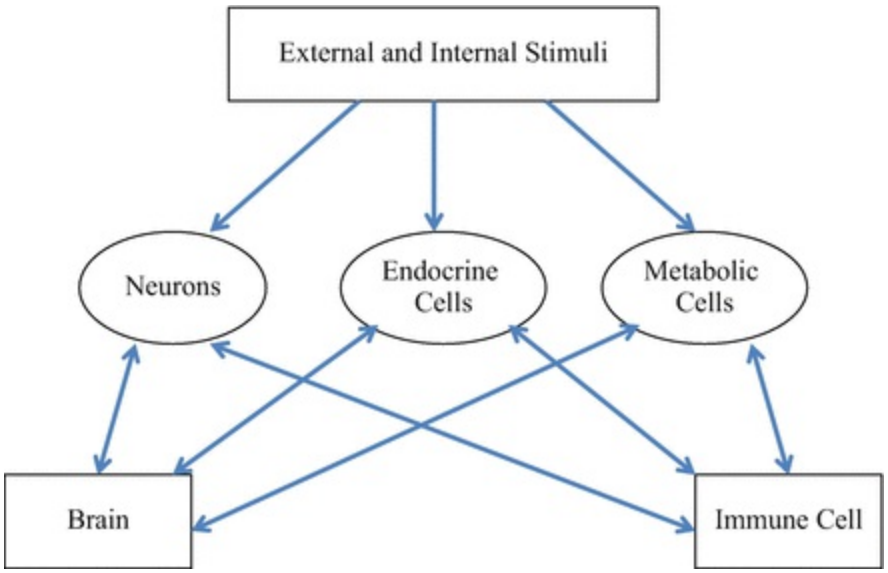

Fig. 15.2 A synopsis of the Besedovsky and Del Rey (1996, p. 67) psychoneuroimmunological model

The Besedovsky and Del Rey (1996) model incorporates the common molecular mechanisms that functionally connect the nervous, endocrine, and immune systems , which developmentally originate from common tissues and which can rapidly cause catastrophic pathology when they are homeostatically disrupted or allostatically

stressed. The unified hypercyclic model (Fig. 15.2) illustrates the continuity of living systems and their stressful environments at hierarchical levels, similar to Selye's (1950) General Adaptation Stress Model. The model also calls attention to the need for synthetic experiential analyses of hierarchical living systems and their components to address issues of ultimate causation in human behavior , including psychoneuroendocrinology, immunology, and evolutionary psychology/biology (Cohen & Herbert, 1996; Klein & Fedor-Freybergh, 2000; Wolpert & Evans, 2001). Damasio (2003) emphasized the fact that the neural communications to and from the body and brain are a continuous flow that defines the mental representations of the self and sensation that can be distinguished from others via the immune system .

15.4 The Brain–Body Connection

Besedovsky and Del Rey (1996) illustrated the connection between the brain, endocrine, and immune systems . More specifically, with physiological stress, brain neurons release pro-inflammatory Interleukin-1 (IL-1), which stimulates the production and release of Corticotropin Releasing Factor (CRF) by the hypothalamus, which in turn directs the pituitary gland to release Adrenocorticotropic Hormone (ACTH), which stimulates the adrenal glands to release glucocorticoids. Glucocorticoids, which provide negative feedback signals to the hypothalamus, complete the Hypothalamic-Pituitary-Adrenal (HPA) axis , the central endocrine-mediated physiological response to stress. Nevertheless, activation of immune system cells by pro-inflammatory cytokines TNF , IL-1, and IL-6 can reactivate and maintain the stressed HPA axis, even when the individual is located in a new environment (Pennisi, 1997). Prolonged HPA axis activation has deleterious effects upon the individual, including death, cancer , morbidities, autoimmune disease, and neurodegeneration (Allan & Rothwell, 2001; Christian & Davis, 1964; Selye, 1950, 1986; Turnbull & Rivier, 1999). With respect to neurodegeneration, the impact upon brain structures, behavior , and blunted immune responses in relationship to stressful events and physical trauma may involve numerous connected structures, including the hippocampus, amygdale, ventral tegmental area, nucleus accumbens, prefrontal cortex, orbitofrontal cortex, and the lateral olfactory tracts (Holden, 2001). Christian and Davis (1964) as well as Tausk (2001) applied these principles to the antagonistic interaction/balance between T_H1 (i.e., cellular immunity) and T_H2 (i.e., humoral inflammation immunity) in autoimmune morbidities/mortalities related to high social stress.

Cohen (2002) documented strong associations between the pro-inflammatory cytokines IL-1, IL-6, IL-12, IL-15, IL-18, TNF-α, TNF-B (lymphotoxin α), Interleukin-1 receptor antagonist (IF-1Ra), HMGB1, and M1F with sepsis, the leading cause of death for older adults and for infants. Additionally, the pro-inflammatory chemokines IL-8,

M1P-1α, M1P-1B, MCP-1, and MCP-3 also contribute to sepsis-associated inflammation and fibroproliferative diseases, especially with increasing age (Hayflick, 1994, 2007; Sandler, Mentink-Kane, Cheever, & Wynn, 2003). The pro-inflammatory cytokines IL-1, IL-6, and TNF- α activate T and B lymphocyte activities, fever, hypermetabolism, anorexia, liver acute phase protein synthesis, which with prostaglandins, Nitric Oxide Synthase (NOS), acute phase proteins, and IL-12, IL-15, IL-18, M1F, and HNGB1 create a physiological environment favorable to Staphylococcal or Streptococcal sepsis (Turnbull & Rivier, 1999). Furthermore, the chemokines IL-8, NAP-1, MIP-1a, and RANTES trigger phagocyte chemotaxis toward inflammatory sites, and the synthesis of nitric oxide by NOS inhibits mitochondrial respiratory pathways, further releasing damaging reactive oxygen species (ROS) (Nisoli et al., 2003).

Cumulatively, the prolonged activation of the HPA axis and corresponding suppressions of the Hypothalamic-Pituitary-Gonadal (HPG) and -Thyroidal (HPT) axes by stress-related immune cytokine /chemokine and endocrine/hormonal activities can severely disrupt organismal allostatic load. Allostatic load is associated with the following symptoms, including elevated serum and cellular coagulation factors, proinflammatory cytokines , stress hormones, ROS , cortisol, cholesterol/HDL ratio, and C-reactive protein, all of which are negatively associated with health (Franceschi et al., 2000; Hollar, 2013; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Ryff, Love, & Levy-Storms, 2002). Additionally, allostatic load is associated with decreased peak lung flow, decreased hippocampus size, increased adrenal and amygdala size, and increased systolic and diastolic blood pressures (Seeman et al., 2001, 2002). Of particular note are the high levels of allostatic load that are significantly associated with individuals having fewer than three friends (Cacioppo et al., 2002; Seeman et al., 2002).

With the Besedovsky and Del Rey (1996) model of neuro-immune-endocrine interactions (Fig. 15.2) and the Hypercylic model (Fig. 15.1) as core concepts, inter-individual behaviors might employ self- versus non-self principles. Evidence supporting this theory consists of the following research lines:

1. The neuro-immune-endocrine components of the HPA axis representing a molecular-to-organism, hierarchical system of competition and cooperation, with allostatic load occurring when the system collapses;

2. Inter-individual self-versus-nonself rejection and competition within human and other animal populations , thereby inducing allostatic load;

3. Correlations between stress , cytokines , allostatic load, interpersonal relations,

and HLA-related autoimmune diseases; and

4. Possible roles of retro-transposable elements, endogenous retroviruses , and stress -related epigenetic effects.

15.5 Stress and Behavior in Health Trajectories

In most animal societies , dominance hierarchies or “pecking orders” exist by which certain individuals exert more power over other individuals in accessing resources, mates, and quality territories. Documentation of such hierarchies has been well established among almost all mammalian and avian species, although a substantial body of empirical evidence demonstrates dominance relationships among invertebrate species as well, especially when species populations engage in any type of clustering, flocking, or other organized social behavior (Blount, Metcalfe, Birkhead, & Surai, 2003; Dugatkin & Godin, 1998; Eggert, Muller-Ruchholtz, and Ferstl, 1999; Jawor, Gray, Beall, & Breitwisch, 2004; Keeling et al., 2004; Lorenz, 1966; Maestripieri, 2002). All such hierarchies are dynamic, with frequent challenges and aperiodic hierarchy changes as coalitions of near dominants displace an alpha, as an alpha attacks perceived or imagined threats from subordinates, or as power relations change due to aging , death, disease, and environmental catastrophes. Furthermore, dominance rank may affect parental investment in the support of dominant offspring (Maestripieri, 2002).

The mechanisms by which dominance hierarchies are maintained include physical features of individuals, aggressive displays and vocalizations, and chemical communication via pheromones, therefore by sight, sound, and smell (Eggert & Muller-Ruchholtz, et al., 1999; Jawor et al., 2004; Keeling et al., 2004; Lorenz, 1966; Wedekind & Penn, 2000). Physical features include coloration. For instance, intense red plumage and a black neck/breast contrast tend to represent advertisements of domination, mating, and aggression in male cardinals, while a combination of red-orange bill and red underwing feathers correlates with reproductive success in female cardinals (Jawor et al., 2004).

Keeling et al. (2004) examined homozygous and heterozygous chicken offspring of a male red junglefowl and female white Leghorn intercross. They found that homozygous recessive pigmented offspring (black, black with white spots, grey, or barred) were significantly more likely to suffer feather-pecking damage than homozygous dominant and heterozygous individuals. This study demonstrated “spiteful behavior ” against individuals bearing a particular phenotype with no apparent benefit to the dominant perpetrator.

Furthermore, Blount et al. (2003) and Faivre, Gregoire, Preault, Cezilly, and Sorci

(2003), working separately with zebra finches and blackbirds , respectively, both demonstrated that physiologically high levels of anti-oxidant carotenoid pigments in males correlate positively with high immune function and sexual attractiveness. Therefore, depending upon the species, some combination of genetic , nutritional , and environmental effects impacts visual cues, most notably coloration or patterns thereof, visual-cue correlated immune status (i.e., resistance to disease), and correlated sexual attractiveness.

In humans, Gangestad and Thornhill (1997) found that males having less fluctuating asymmetry (i.e., high bilateral symmetry) in right-left physical features have significantly higher extra-pair copulations. In a subsequent study (Thornhill and Gangestad, 1999), they empirically demonstrated that ovulating women gave higher ratings of attractiveness to men who had high bilateral symmetry and desirable odors. Thornhill and Gangestad (1999) suggested that body odor pheromonal cues might arise from MHC antigens and/or androsterone in male sweat and urine.

Notwithstanding the visual and pheromonal/olfactory modes for detecting and reacting to dominance, the physiological consequences of dominance hierarchies are quite negative for more subordinate individuals (Christian & Davis, 1964; Lorenz, 1966) When stressed, subordinate individuals experience hyper-activated, continuous positive-feedback hypothalamic-pituitary-adrenal axes, chronic fight-or-flight endocrinologies, and eventual, cumulatively associated chronic pathologies resulting from physiological overload (Selye, 1986). In isolated, overcrowded populations , individuals are characterized by hyperadrenalopathy and elevated serum corticosteroids (i.e., glucocorticoids) that hasten massive die-offs (Christian & Davis, 1964). Chronically high corticosteroids promote rapid aging and death in stressed and reproducing semelparous animals (e.g., Pacific salmon) (Ricklefs & Finch, 1995). Subordinate status and chronic excessive HPA axis activation are well documented across a variety of species Brennan & Kendrick, 2006). The implications for victims of youth bullying and adult bullying/mobbing plus domestic violence (Craig, 1998; Cowie, Naylor, Rivers, Smith, & Periera, 2002) are sobering, although the psychoneuroimmunological impacts on these individuals have been studied only sporadically. Hollar (2009) provided evidence that people with certain HLA genotypes might be at heightened risk to be victims of violence , although there was no data on potential perpetrator HLA types, and very probably little such data exists that would enable even a pilot study of these possible associations.

15.6 Olfactory Pathways and the MHC

Whereas evidence indicates that possibly up to 70% of human olfactory receptor genes have become nonfunctional pseudogenes, there appear to be at least 339–388 intact, functional olfactory receptor (OR) genes and possibly 297–414 OR pseudogenes, with

many of these genes clustering on chromosome 11 although with wide genomic dispersion, including the chromosome 6 MHC supercomplex (Malnic, Godfrey, & Buck, 2004; Niimura & Nei, 2003). Despite wide assumptions that the human vomeronasal organ (VNO) is nonfunctional and that humans have four times the number of OR mutations compared to other primates (Gilad, Man, Paabo, & Lancet, 2003), additional experimental evidence indicates that the VNO OR receptors can respond to human pheromones (Monti-Bloch & Grosser, 1991; Monti-Bloch, Jennings-White, & Berliner, 1998). Furthermore, human VNO nerve fibers connect to a terminalis nerve, or cranial nerve zero rostral to cranial nerve I, that connects to the hypothalamus, limbic system, and HPA axis (Royet et al., 2000). The medial preoptic anterior hypothalamic continuum is a centralized limbic system structure that connects to the medial forebrain bundle, lower brain stem, hippocampus, cingulated cortex, septal area, amygdaloid complex, and olfactory structures, including the piriform cortex, olfactory tubercle, and olfactory lobes (Royet et al., 2000). Olfactory receptor neurons in the VNO mucosa utilize adenylate cyclase/cyclic AMP second messenger intercellular cascades, triggering electrical signals along olfactory nerves on the olfactory bulb protected by the cribriform bone to the cranial nerve I as well as the trigeminal nerve (Chen, Lane, Bock, Leinders-Zufall, & Zufall, 2000).

The functionality of the VNO and MHC selection among humans based upon smell indicates a chemical mechanism for interpersonal stress communication that could impact the HPA axis at the systems, organ, and cellular levels, demonstrating a hierarchical, hypercyclic psychoneuroendocrine model (Fig. 15.2). All animals release pheromones. The primary human odor glands involve the sebaceous glands, axillary apocrine glands, and genitalia/urinary region, with surface bacterial growth modifying these secretions and enhancing their volatility (Klein, 2000; Kohl, Atzmueller, Fink, & Grammer, 2001).

Wobst et al. (1999) first demonstrated that rats can distinguish between human urine samples of varying HLA A1 and B8 haplotypes. This observation was a confirmation of the Yamazaki et al. (1976) discovery that male mice prefer dissimilar MHC females. Human studies extend this finding. Not only can humans distinguish MHC/HLA odortypes, females and males both prefer individuals of the opposite gender who have dissimilar HLA types to themselves, while some studies indicate that human males prefer to have male peers of similar HLA odortype (Eggert & Luszyk et al., 1999; Eggert & Muller-Ruchholtz, et al., 1999; Wedekind & Furi, 1997).

Bakker and Zbinden (2001) suggested that individuals favor greater HLA differences and, therefore, heterozygosity for HLA haplotypes because MHC heterozygosity confers greater resistance to pathogens (see also Wedekind & Penn, 2000). They observed that female sticklebacks favor males with increasing numbers of diverse MHC alleles, despite the fact that too much MHC variation can lead to autoimmune disease. Furthermore, MHC heterozygosity also correlates with high body

symmetry, another indicator of disease resistance (Gangestad & Thornhill, 1997; Thornhill & Gangestad, 1999).

Therefore, humans engage in pheromonal communication at least to some degree. These findings should not be surprising, even on a limited basis, since pheromonal communication has been verified in all studied mammalian species. For example, elephants utilize a variety of hydrocarbons that are released in glandular secretions and in urine in response to various conditions such as stress, pregnancy, and male aggression (Rasmussen & Krishnamurthy, 2000). These volatile, chemosensory signals include MHC products released in urine that are detectable by the elephant VNO . Whereas Rasmussen and Krishnamurthy (2000) did not address MHC heterozygosity, such immune heterozygosity is established as a fitness parameter in mammals as diverse as mice and humans, in fish such as sticklebacks, and Atlantic salmon (Bakker & Zbinden, 2001; Landry, Garant, Duchesne, & Bernatchez, 2001; Rasmussen & Krishnamurthy, 2000). These observations are consistent with a theory of maximizing genetic fitness variation in mating (Landry et al., 2001).

Pheromonal communication, MHC and otherwise, is widespread in all animal species at multiple levels and hierarchies. It is useful in social spacing among humans, chickens, social insects, and social amoebae (Bonner, 1970), just to mention a few examples. The queen honeybee retinue pheromone can control the activities of an entire colony, including sexual suppression of sister workers (Keeling, Slessor, Higo, & Winston, 2003). Such gene-mediated chemical communication may also be associated with dramatically increased longevity for queens and the requirement of the queen's presence for worker survival (Corona, Estrada, & Zurita, 1999; Evans & Wheeler, 1999).

15.7 Summary

The development of life on earth provides us with a 3.8 billion year trajectory of major events, along with billions of undetected minor events, that shifted life into specific directions and explain much of the human condition today, especially the biological basis of our physiologies and health. As we approach health problems, we need to think comprehensively from a true systems perspective to consider both proximate and ultimate causation, the how and the why, of given conditions. So many unseen factors impact health, such as the MHC and our ability to detect differences between individuals and the evidence that such differences unconsciously can impact our biases toward each other. Trajectory analysis and sensitive dependence on initial conditions involves factors that are immediate and far into the past.

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David W. Hollar, Trajectory Analysis in Health Care, https://doi.org/10.1007/978-3-319-59626-6_16

16. Simulations, Applications, and the Challenge for Public Health

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Abbreviations

ABM Agent-Based Model

PRC Phase response curve

Even with the medical sciences, trajectory analysis remains an experimental tool that has not received widespread clinical applications. The advances in cardiology (see Chap. 14) have set the pace for other medical disciplines, and public health is the next step. The lack of telemetric and longitudinal data collection, or access thereof when extant, hinders our efforts to apply this methodology in conjunction with trend plus time series regression analyses of multiple variable data that is standard in epidemiology . Therefore, for this chapter, we are forced to utilize computer simulation, just as we have described for so many studies in previous chapters.

Thom (1977) argued that Catastrophe Theory attempts to describe phenomena and the underlying physical principles from which these phenomena emerge. He stated (p. 196), "If, in the interval of time (t_0,t_1), the system exhibited some morphology $(M_0{}^1)$, then one has to expect that in a further interval (t_1,t_2) it will exhibit some morphology $(M_1{}^2)$." This explicitly summarizes our previous chapter discussions of trajectory change, the nature of reality for any system as it evolves with internal and external disturbances from one time point to the next, the surface manifold encompassing the system changing morphology over time.

Additionally, Thom (1977, p. 196) cautioned researchers on the fact that, even with Catastrophe Theory , there remains (even 40 years later) no "complete qualitative classification of 'defects'" that is necessary to guide a quantitative analysis of

dynamical changes in systems. He proceeded to argue that "statistics is nothing but the interpretation of a cloud of points" (p. 197). Consequently, our epidemiological methods are limited, and applications of nonlinear trajectory analysis using Catastrophe Theory , chaos , and Lyapunov exponents are slowly moving from theory to applied practice in cardiology and neuroscience . Until we have more detailed, continuous data collections with many necessary and sufficient hypothesized contributing variables are needed to further experimental analyses and clinical/health applications. Major trajectory analysis journals such as *Chaos* and *Nonlinear Dynamics* still mostly focus on physical systems where data is easier to access, but the research published in these journals is moving toward human health applications. The universality of these systems illustrates common principles and the fact that the trajectories of living and nonliving systems map onto approximately equivalent manifolds (Thom, 1977).

16.1 Simulations

Along these lines, Grimm and Railsback (2005) provided a compelling case for the appropriate use of simulation and Agent-/Individual Based Models (ABM/IBM) in theory development and the modeling of actual ecological systems. Such simulations can work in parallel with the analysis of actual longitudinal data, further helping the researcher to more closely approximate reality. Simulation gains power as an analytical tool when models deal with complicated combinations of variables, each of which can be subtly manipulated to examine sensitive dependence on starting conditions. Thus, simulation currently has the advantage over actual field data analysis, even with comprehensive statistical programs such as structural equation and hierarchical linear modeling . However, it should be stressed that strong models parallel overall patterns of actual recorded behavior for physiological conditions and individual behaviors . Simulated Agent-Based Models also enable the detection of emergent behaviors that occur from the confluence of many variables, with unpredicted trajectories illustrating the complex interactions between many independent variables.

Both Grimm and Railsback (2005) and Gilbert and Troitzsch (2005) provided many simulation examples for Agent-Based and other two-/three-dimensional models, along with available software programs. Whereas Grimm and Railsback (2005) focused upon an extensive array of ecological and animal behavioral models that have dominated the research literature in those disciplines, Gilbert and Troitzsch examined simulation models across many fields, especially with social interaction models and cognitive/neural networking. Gilbert and Troitzsch also provided example computer code and output from several simulation software programs. Both the authors highlighted the freeware NetLogo (Wilensky, 1999), which provides a highly user-friendly desktop presentation and toolbar, including visual graphics of automatons (termed "turtles" although cows, trucks, and other icons can be used), graphing, and

syntax that can be manipulated. A large Models Library is available, and each program can be extensively modeled and changed to suit the researcher. Researchers may also create new programs from scratch, and any model can be tested using the Tools " Behavior Space" with numerical output to spreadsheets for statistical analysis.

Bonabeau (2002) advocated the use of Agent-Based Models for the analysis of human physiologies and behaviors . This work emphasized the simulation advantages of emergent properties and complex systems analysis. Frey and Goldstone (2013) demonstrated the use of simulation for cognitive science models of human cooperation and decision-making processes , approaches that are widely used by researchers. Grimm and Railsback (2005) maintained an experimental approach to all model development, including evidence-based theory development, proposing competing models, testing and refining models for retesting within reasonable limits. With respect to the latter point, any model can be repeatedly revised until it matches a given set of data, which is why the revision of experimental structural equation models with actual data is limited only to pre-analysis comparative models and post-analysis adjustments based upon high variable residuals. In contrast, the researcher can extensively revise and test Agent-Based Models because they rarely involve actual data. Instead, these simulation models are refined and ultimately compared to actual physical systems in nature.

16.2 An Example: Wilensky's Sheep–Wolf Predation

Ecological models have been strongly based on conflict/competition scenarios such as the Lotka-Volterra equations (Lotka, 1956) and Hawk-dove simulations (Gilbert & Troitzsch, 2005). Wilensky's (1999) NetLogo freeware platform provides numerous prepared models that can be modified, including biological, earth science, mathematical, social science, and system dynamics programs. These sample models are weak for physiological simulations, although the overall platform represents an opportunity for researchers who are interested in such simulations. The example presented here is the basic Wolf Sheep Predation model (Wilensky, 1997), which exists in several alternative formats, including a system dynamics model. Gilbert (2008) provided a concise applied description of Agent-Based Models, including NetLogo and other example models for beginning simulation researchers.

Wolf-Sheep predation (Fig. 16.1) has a display screen of turtles that are wolves and sheep on a green grass background. The researcher can specify a broad but limited array of turtle shapes in the Code toolbar, following the NetLogo User Guide. Command tabs are provided to the left of the display screen. The primary command tabs are "setup" and "go." Setup resets the display screen to the initial model system conditions that the researcher establishes with other command tabs, such that the initial numbers of wolves and sheep are provided on the display screen. Additional command tabs include

showing grass and energy changes on the population graph. The researcher can set a range of grass regrowth times with a sliding command bar/tab that is limited to 0–30 in Fig. 16.1. The researcher easily can modify these slide-bars to provide the option of other ranges by changing a single syntax line in the Code toolbar.

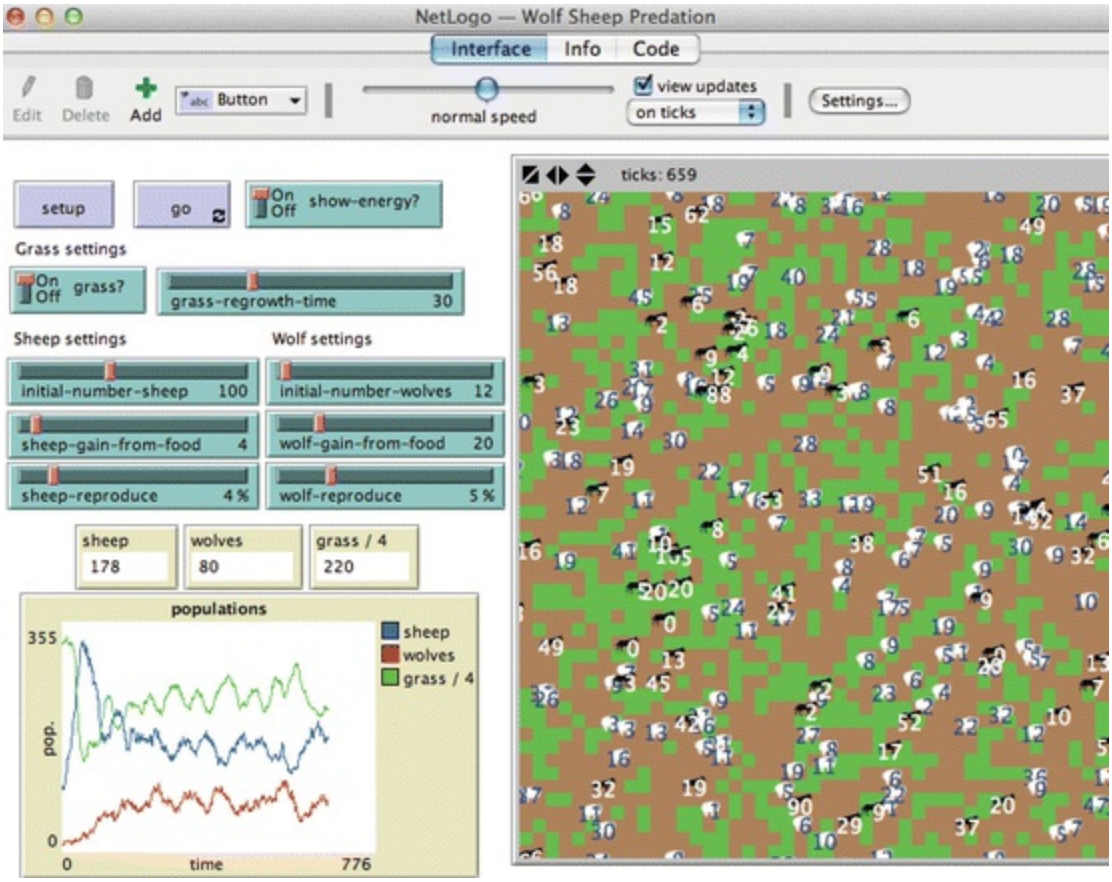

Fig. 16.1 Example output from the freeware NetLogo Sheep-Wolf Predation simulation. The software and Sheep-Wolf model were developed by Wilensky (1997, 1999).

Additional command tabs in Fig. 16.1 include "initial number of sheep," "initial number of wolves," "sheep gain from food," "wolf gain from food," "sheep reproduce" rate, and "wolf reproduce" rate. As with "grass regrowth time," the researcher can adjust the upper and lower limits on each of these slide-bars to establish the initial conditions for this three-species system. The sheep eat the grass and reproduce, thereby directly affecting their respective population numbers (remember the method of path coefficients , Chap. 5). Likewise, the wolves eat the sheep, which directly affects their respective numbers and indirectly affects the grass population via the sheep. All three species reproduce, further directly and indirectly affecting all species participants. There is an additional slide-bar to make the simulation go fast or slow.

This is a very simple model. Yet the variables that are provided can make the outcomes extremely varied, even more so if the researcher decides to introduce other variables and slide-bars to better approximate the natural world. Any slight adjustments

to one or several of these variables can drastically alter the cycles of grass, sheep, and wolves over time. Poincare's "sensitive dependence on initial conditions" definitely comes into play. As a result, a seemingly simple model such as Fig. 16.1 can become extremely complex when different types of forcing variables are considered. Many systems scientists have noted the paradox of the difficulty in describing a two- or three-body interacting system, whereas a complex aggregate of thousands of entities can be very precisely measured with minimal error.

For Wolf-Sheep Predation (plus grass), the equations of change can be described (Brown, 2007, p. 41; Smith & Smith, 1998, p. 193):

$$\begin{aligned} dS/dt &= rS - (1/G)S^2 - kSW \\ dW/dt &= mSW - rW^2 - eW \end{aligned} \tag{16.1}$$

where S represents numbers of sheep, dS is the change in numbers of sheep with respect to change in time dt, r is the rate of increase in sheep, G is the quantity of grass available, and k represents the death rate when sheep and wolves meet. Similarly, W represents numbers of wolves, dW is the change in numbers of wolves with respect to the change in time dt, m represents the rate of sheep-wolf encounters, n represents an overpopulation rate effect, and e represents environmental pressures on the wolves.

Sheep increase based upon their rate of reproduction r and if grass is plentiful. Note that sheep decrease if grass G is not plentiful (denominator), thereby increasing $-S^2$ for a logistic population decline. Sheep also decrease when they are killed by wolves ($-kSW$). Consider the similarity between this model and the driving versus dissipative forces in the cyclic motion of a spring (Fig. 10.2).

Likewise, wolves increase when they encounter sheep (mSW). However, they decrease when their rate of increase r becomes too great that they experience logistic decline ($-rW^2$). Wolves also decrease ($-eW$) due to environmental pressures such as disease, geographic barriers , etc. Again, there are driving and dissipative forces for the wolf population just as with the sheep population. Nevertheless, the two equations interact. We could easily introduce additional variables and rate parameters to better approximate reality. For example, human herding and protection of sheep, protection or killing of wolves, and periodic droughts, excessive rain, or other environmental events can affect this system. The predator-prey model has been used to examine economic competition (Bonabeau, 2002; Nasritdinov & Dalimov, 2010).

16.3 Running the Model

For one possible scenario of the model (Fig. 16.1), we have set the numbers of initial sheep and wolves at 100 and 12, respectively. The grass regrowth time is 30. The gain from food is 4 for sheep and 20 for wolves, given the different food sources (grass and sheep, respectively). Sheep reproduction is 4%, whereas wolf reproduction is 5%. The

graph of population cycling for all three species is shown in the graph through 776 time points, with 178 sheep, 80 wolves, and 220 grass patches at $t = 776$. The surface display shows numbered sheep and wolves, green grass patches, and barren brown patches. The model can be reset and run repeatedly with ever so slight variations in outcomes, although none major due to the consistent initial settings.

The numbers of sheep for the first 20 time points are shown in Fig. 16.2a and for wolves in Fig. 16.2b. In Fig. 16.2a, the same numbers are shown in columns A and D. With column A showing sheep population S at a specific time point t1, column B shows the sheep population S at the next time point $t2$. Column E shows the differential dS (i.e., dx) for each sheep population $t2 - t1$. Note that we could extend and compare the sheep population $t3 - t2$ and compute the Lyapunov exponent λ for the degree of trajectory change at each set of three time points throughout the simulation, thus combining λ with the phase shift diagrams that we will present below. Such a λ computation would follow the procedures described in Chap. 12 and Fig. 12.2.

A Sheep

	A	B	C	D	E
1	Sheep t1	Sheep t2		Sheep t1	Sheep dx/dt
2	100	102		100	2
3	102	111		102	9
4	111	114		111	3
5	114	124		114	10
6	124	132		124	8
7	132	141		132	9
8	141	150		141	9
9	150	158		150	8
10	158	171		158	13
11	171	182		171	11
12	182	196		182	14
13	196	214		196	18
14	214	236		214	22
15	236	264		236	28
16	264	297		264	33
17	297	321		297	24
18	321	340		321	19
19	340	371		340	31
20	371	391		371	20
21	391	429		391	38

B Wolves

G	H	I	J	K
Wolf t1	Wolf t2		Wolf t1	Wolf dx/dt
12	14		12	2
14	14		14	0
14	12		14	-2
12	11		12	-1
11	10		11	-1
10	10		10	0
10	9		10	-1
9	10		9	1
10	10		10	0
10	9		10	-1
9	9		9	0
9	9		9	0
9	10		9	1
10	9		10	-1
9	9		9	0
9	10		9	1
10	11		10	1
11	11		11	0
11	11		11	0
11	11		11	0

Fig. 16.2 Sheep (**a**) and Wolf (**b**) numbers from Fig. 16.1 simulation, with differentials

Likewise, the numbers of wolves for the first 20 time points, dependent upon the

sheep they eat and additional factors from Eq. 16.1, are shown in Fig. 16.2b. Columns G and J show the same wolf populations at these first 20 time points. Column H shows the wolf population S at the next time point $t2$. Column K shows the differential dW (i.e., dx) for each sheep population $t2 - t1$. We can also calculate the Lyapunov exponent for wolves at each time point comparison following the procedures outlined in Chap. 12 and Fig. 12.2.

Population cycling through $t = 300$ for sheep (blue) and wolves (red) using a NetLogo Behavior Space experiment is shown in Fig. 16.3. With a struggling early wolf population at times $t = 1–70$, the sheep experienced a rapid increase, then a precipitous decrease due to exhaustion of their grass food source. The sheep increased again with grass recovery, even as wolves continued to increase between times $t = 70–90$. There is an inflection point between the two populations at approximately $t = 91$, where sheep reach a second but lower peak population at $S = 380$ and wolves reach $W = 200$. With the overpopulated wolves from $t = 91–131$, the sheep declined almost to extinction with fewer than 40 individuals from $t = 131–161$. Consequently, the wolves collapse from $W = 400$ at $t = 131$ to a lower stable level of $W = 100$ at $t = 181$. The sheep increased and peaked at a lower level, never as high as their initial establishment peak, followed by a concomitant rise in the wolf population, etc.

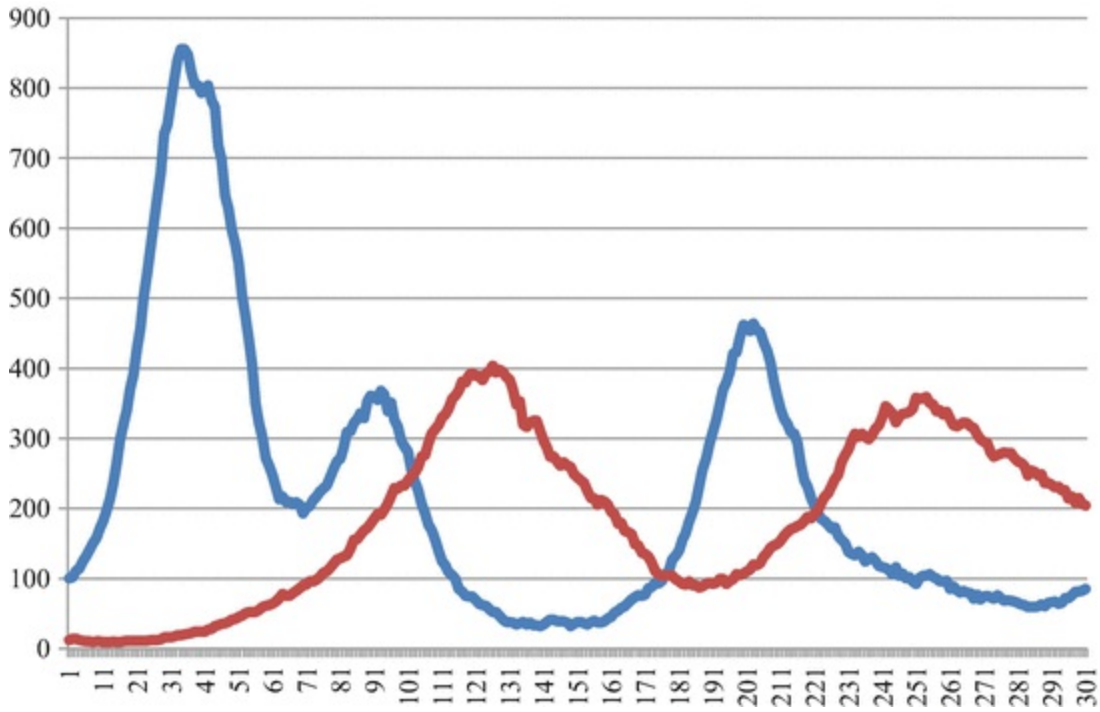

Fig. 16.3 Sheep (blue) versus Wolf (red) cycle plotted in Microsoft Excel

The two populations entered a relatively periodic cycle from $t = 131$ moving forward in time, with both populations oscillating up and down, appropriately slightly out of phase with each other due to their connectedness, like a spring around an

imaginary baseline of $W \sim S \sim 200$ individuals. The sheep peak and trough at populations higher and lower, respectively, than the wolves. Therefore, the wolf population overall change is more compact than the change in the sheep population. The sheep population initially was doubly periodic prior to stabilizing into a single cycle with the forcing wolf populations , grass source, and other environmental constraints. The stable carrying capacity was achieved, and the two, actually three with grass, populations stably cycled forward in time.

Figure 16.4 shows the Phase Response Curves (PRC) for changes in the sheep population . Figure 16.4a shows the mapping of each time population (ordinate) onto its immediate prior time (abscissa). The curve is intensively cyclic and expanding between population sizes $S = 40–380$ and includes larger, unstable loops for the larger populations, particularly the initial population increase to over $S = 800$ sheep. Fig. 16.4b shows a PRC comparing the change in population number dS/dt (ordinate) versus population size S (abscissa). This curve mirrors Fig. 16.4a with the cyclical pattern being more evident for the smaller population sizes. The wide variation loop for the initial population increase is evident. The cycles for the smaller population sizes are curiously repetitive at about $S = 150$, 200, 350, and 450. What is even more intriguing is the similarity in curvature and specific shapes between the $S = 800$ loop, the $S = 400$ loop, and the $S = 300$ loop, the last loop being somewhat difficult to distinguish from the repeated crossing paths. This repeating shape pattern is fractal in nature, indicating repetitive physical characteristics at different scales. The cyclicity of the sheep population is apparent from Fig. 16.4.

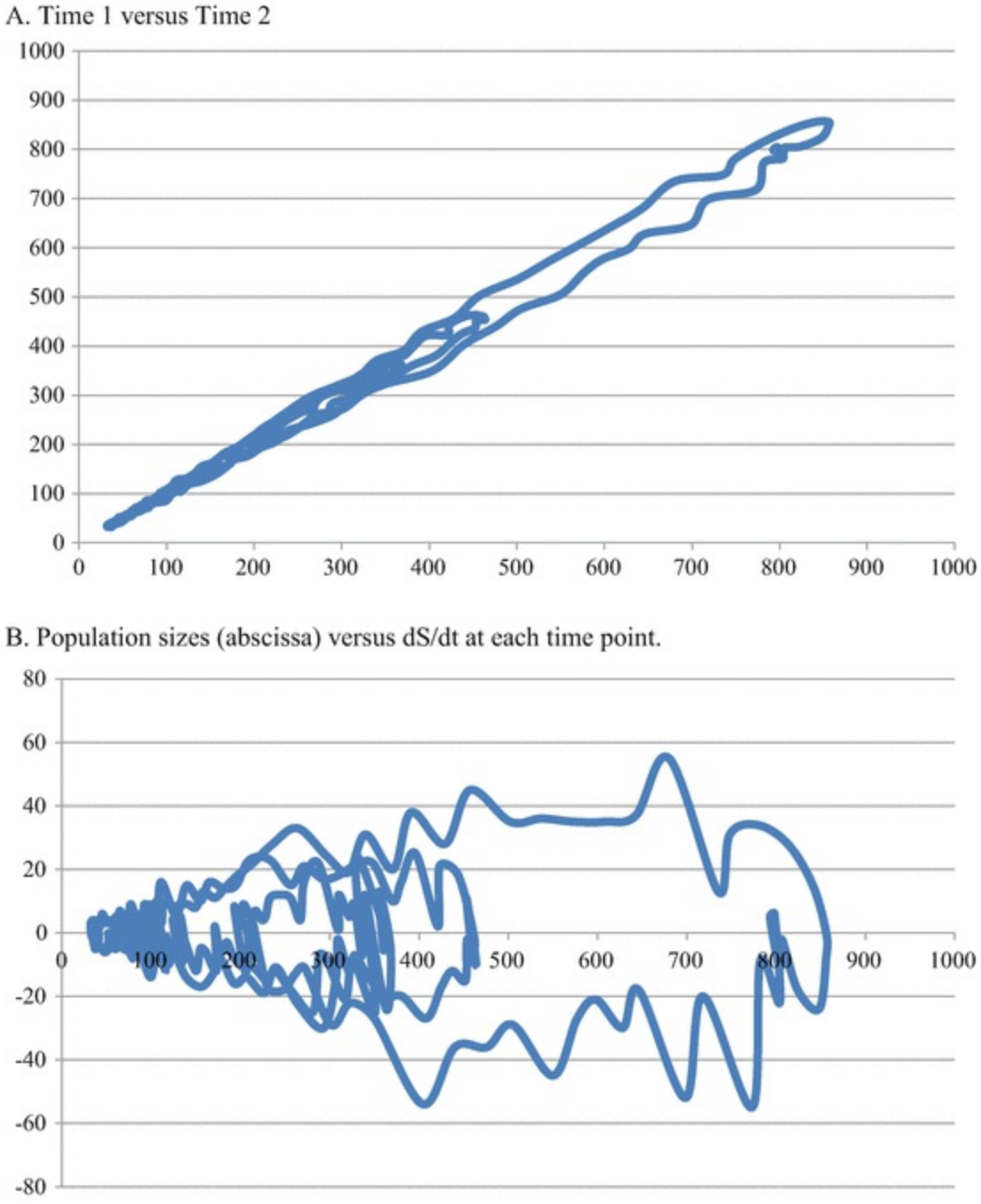

Fig. 16.4 (**a**) Sheep *t*1 versus *t*2; and (**b**) Sheep d*x*/d*t* versus *t*1. B. Population sizes (abscissa) versus d*S*/d*t* at each time point

Figure 16.5 shows the equivalent Phase Response Curves for changes in the wolf population. Figure 16.5a shows the mapping of each time population (ordinate) onto its immediate prior time (abscissa). The curve is much more stable with periodic cycles and no occurrence of wide cycle variations, with the repeating cycles forming a diagonal line. Figure 16.5b shows a PRC comparing the change in population number d*W*/d*t* (ordinate) versus population size *S* (abscissa). Just as with the sheep PRC, the wolf PRC for this comparison provides greater resolution for the periodicities in

population change. Also, just as with the sheep differential PRC , there are much wider variations in population from one time to the next for large populations. Therefore, both sheep and wolf populations are highly susceptible to rapid changes at large population sizes, a finding that is consistent with actual population studies such as Christian and Davis (1964).

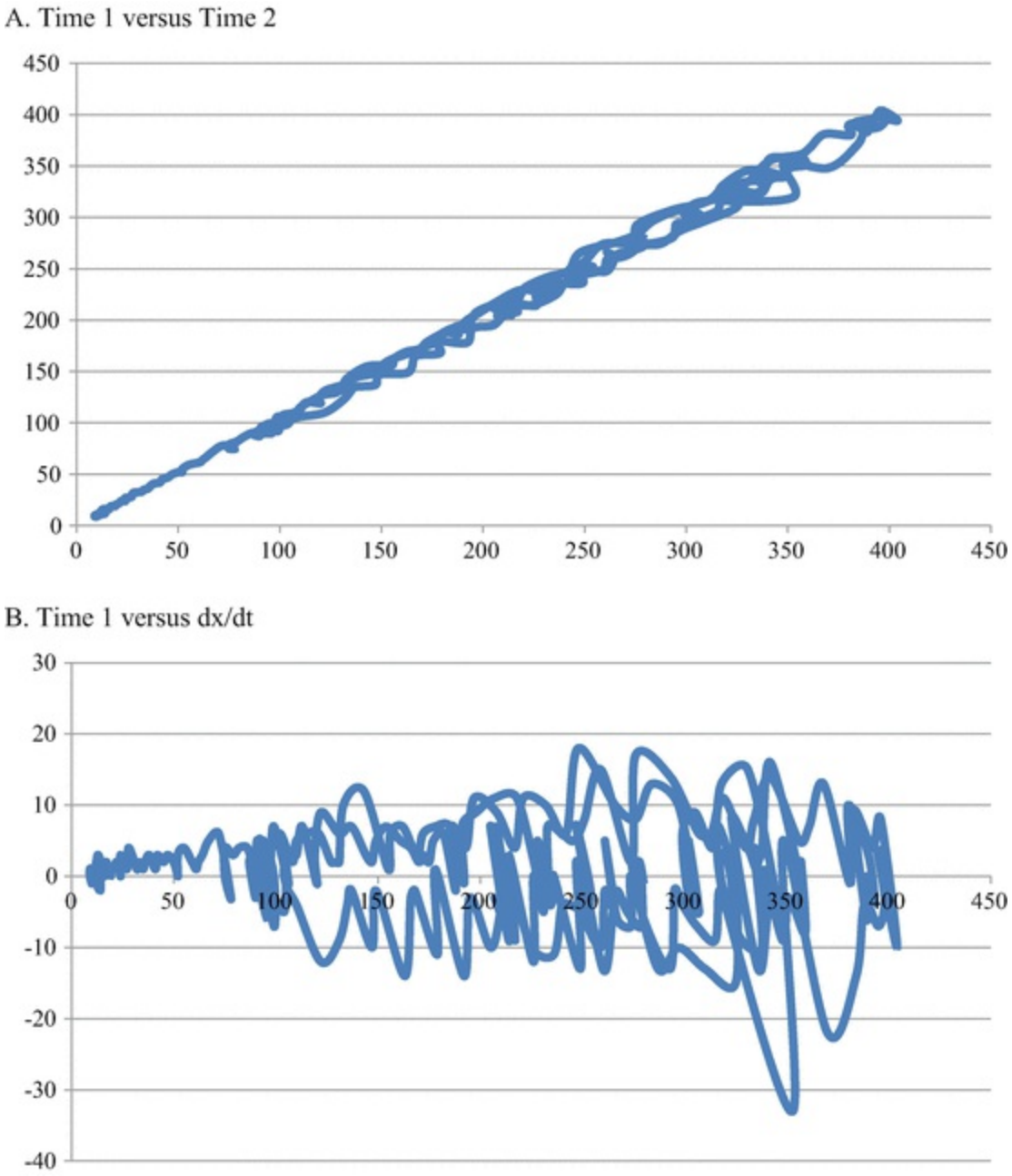

Fig. 16.5 (**a**) Wolf *t*1 versus *t*2; and (**b**) Wolf d*x*/d*t* versus *t*1

The high population instabilities provide a sobering consideration for human population health with world overpopulation approaching 8 thousand million people with a mid-late twenty-first century peak projected at 10–12 thousand million people.

Just as with the Wolf Sheep Predation model, the Lotka-Volterra equations, including Eq. 16.1 for this scenario, are valid in repeated studies of animal and other species interactions, including microbial pathogens. The growing, more mobile human population can promote the spread of emergent bacterial and viral pathogens, further compounded by the increased high resistance to most antibiotics by various bacterial species, including tuberculosis . Approximately 30% of all humans have been exposed to tuberculosis, once a major killer worldwide prior to the advent of antibiotics, yet multiple antibiotic-resistant strains of *Mycobacterium tuberculosis* already exist and are spreading in poorer areas of the world that lack proper public health infrastructures. Furthermore, we have no cure for any viral disease, only the estimation of the most virulent influenza strains each year for hopefully effective vaccine preparation. Additionally, climate changes and human activities have led to the distribution of parasitic insect and other species worldwide, so that insect vectors for pathogens can spread protozoan diseases such as malaria and deadly viruses such as Zika .

Associated with the Phase Response Curves are the Lyapunov exponents λ that measure trajectory changes in cyclic phenomena, including populations , human behaviors , and health conditions. Figure 16.6 shows the spectrum of Lyapunov exponents for changes in the sheep population (Fig. 16.6a) and for changes in the wolf population (Fig. 16.6b). The exponents for the sheep population over time cycle themselves and form a pattern of increasing and decreasing variation. The sheep population change exponents are small around $t = 5$ and then increase and oscillate at wider variation, approaching chaotic levels around $t = 82$ (close to the $t = 91$ inflection point where wolves first overtake the sheep in Fig. 16.3), before thinning around $t = 145$. The cycle exponents intensify again, approaching chaotic levels around $t = 199$ and again at $t = 262$, before thinning again. There may be repeating cycles within cycles based upon this pattern, a finding that has been observed in fractal analysis of processes and structures (Wolfram, 2002) and in the Fourier analysis of harmonics in cycling systems (Bracewell, 1965).

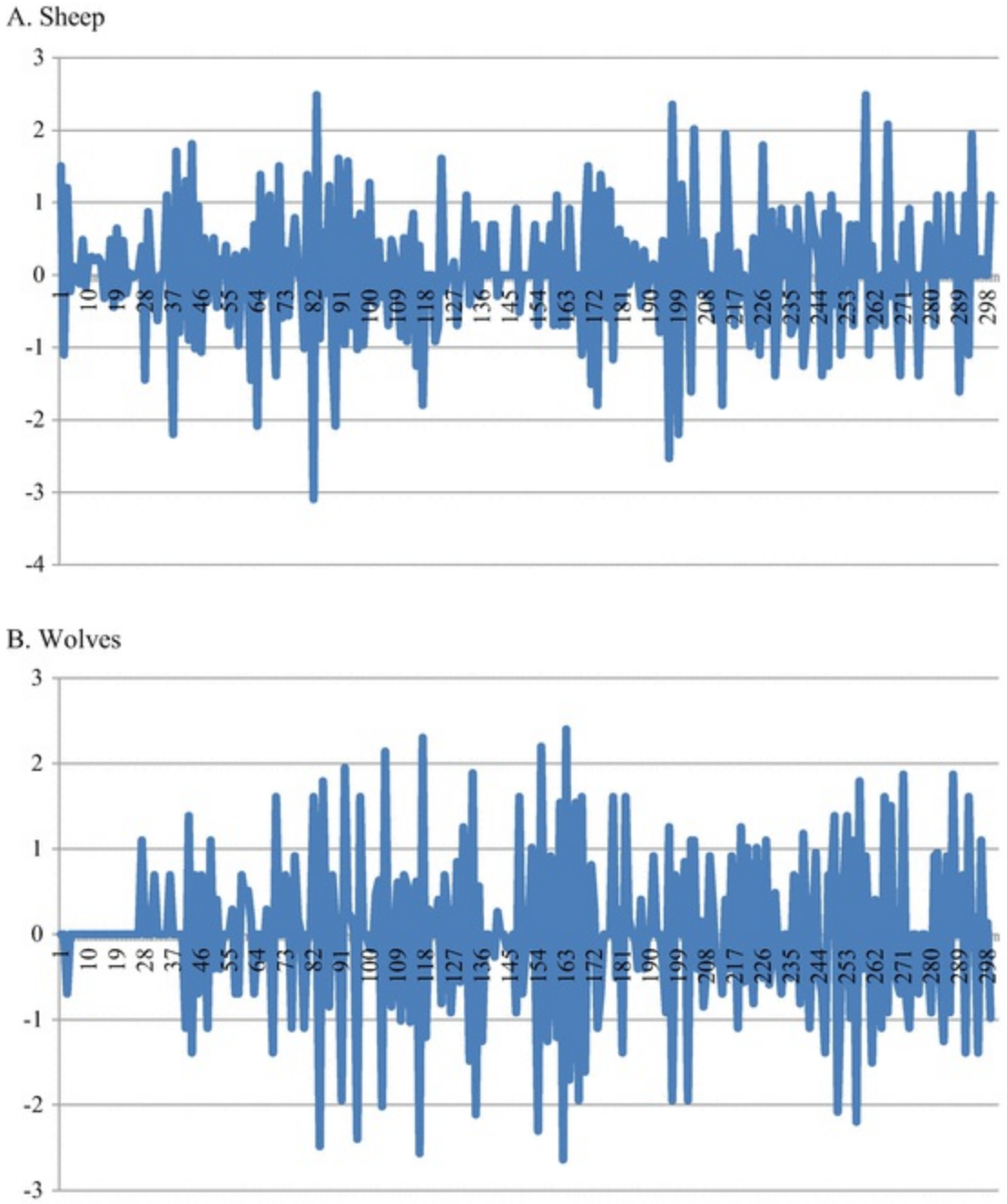

Fig. 16.6 Lyapunov Exponents (ordinate) for changes in populations of Sheep (**a**) and Wolves (**b**) across the first $t = 300$ time points

Similarly, for the wolf population changes (Fig. 16.6b), the Lyapunov exponents cycle with the pattern of variation peaking when the sheep variation is decreasing, consistent with their population overlaps in the model and in nature. The changes become almost chaotic with wide variation at $t = 118$ and again at around $t = 163$. The early time periods have relatively flat variation, then the spectrum of variation increases, then thins around $t = 140$, followed by increases and further thinning around $t = 275$. Therefore, the wolf population changes as reflected by subsequent time Lyapunov exponents cycles with broader cycles. There are cycles within cycles, again

consistent with experimental measures of natural processes.

If we slightly change one variable in the NetLogo model (Fig. 16.1), the pattern of cycles over time may be different. In Fig. 16.7, we alter "grass regrowth time" from 30 to 50, perhaps simulating drought conditions to some extent. The result, shown in the Fig. 16.7 NetLogo simulation output graph, has sheep and grass cycling. However, the wolves are in trouble from the beginning, falling in numbers by $t = 30$ and wavering at only a few individuals up to about $t = 150$ when they become extinct. Meanwhile, the sheep and grass oscillate around a stable carrying capacity, albeit much lower than the conditions in Fig. 16.1. At $t = 159$, there are zero wolves, $S = 191$ sheep (increasing), and 131 small grass patches (decreasing). The display shows scattered sheep and grass patches with considerable barren land.

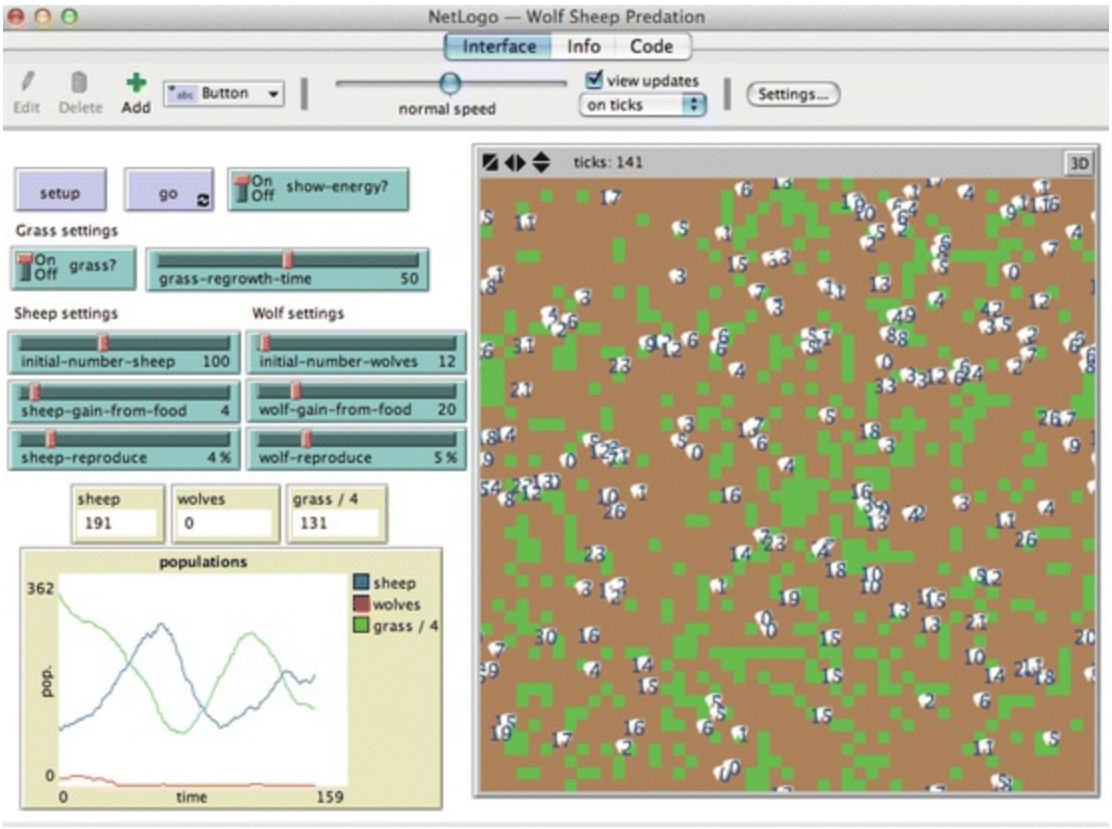

Fig. 16.7 Changing one variable in Fig. 16.1 Sheep Wolf Predation

Therefore, the modified single variable impacting grass substantially changes the overall landscape, and it is fatal for an indirect target: wolves. Less grass means fewer sheep for the wolves to eat. There is sensitive dependence on initial conditions for all trajectories. Perhaps additional factors could be measured as well, such as lack of water leading to dehydration and potentially other diseases that could impact the wolves. While limited in time, the experimental data could be extracted to an Excel spreadsheet, and we could analyze the phase response curves and Lyapunov exponents

just as before, perhaps adding grass as a third species with oscillatory behaviors .

16.4 Simulations in Trajectory Change

Therefore, so many factors can impact changes in trajectories for populations, including human populations . The Lotka-Volterra Eq. 16.1 provide us with comprehensive mathematical models for simulating real-world processes from bacterial growth to human interactions and health conditions. The equations demonstrate the principle of driving and dissipative forces for the growth of populations, whether or not those entities are actual individuals, bacteria , or cancer cells. Lotka and Volterra had developed these descriptive differential equations early in the twentieth century, and their model stands as a solid framework for our analysis of changing systems across biological and physical processes. Lotka (1956) recognized the value of phase response curves at a time when much of science had forgotten Poincare's earlier work on nonlinear dynamics . This is rather surprising since many of the advances in the twentieth century science had a focus on quantum mechanics , fluid mechanics , and the thermodynamics of processes. The phase response curves and trajectory analysis did regain traction in the physical sciences, but these methods were largely ignored in the biological and social sciences, with the exception of ecology , which continued the tradition of mathematical models to describe the recognized complexity of interacting natural systems.

Part of this lag came from the differential growth in knowledge for these fields as well as the delay in the wide distribution of electronic computers for analysis and simulation. The physical sciences were mathematically based, of necessity, from the early twentieth century breakthroughs in quantum mechanics , seemingly overthrowing the less explanatory classical mechanics. The biological sciences became entrenched in the methods of statistics, valuable in its own right, and the social sciences followed suit. This is not to underestimate the importance of statistics in studying differences between populations , or Thom's (1977) "cloud of points." Our argument is that simulation, trajectory analysis using differential equations, and the many powerful tools of statistics can be used together for theory development, model testing, and then testing against actual data. Furthermore, the results can be directly applied to health policies and interventions to improve human health. We use the proper tools to address the appropriate scientific problem.

Simulation and differential equations are needed for continuous, longitudinal data, information that to the present has been more widely available in the physical and ecological sciences. Obtaining longitudinal data on humans has been far more difficult due to the slower technological developments to continuously monitor people during their everyday activities without violating ethics and respect for individual rights and privacy, something that is much less of a problem with chemical reactions, animals, and

plants, although research protocols fortunately have become more ethical toward animals as we have increasingly recognized their cognitive/emotional capacities and need for protections.

Advances in computer technology and gaming have made simulations valuable for scientific research. Such programs have been available for many decades but were accessible only to scientists with large, mainframe computers prior to the widespread availability of computers and their miniaturization during the late 1980s through the present. With innovation and consumer demand, simulation programs have become more sophisticated and have moved toward freeware or reduced cost accessibility to the general public and to researchers across diverse scientific disciplines.

16.5 Implications for Health Trajectory Analysis

The Wolf Sheep Predation model and Lotka Volterra equations illustrate one scenario for how human population , physiological processes, behaviors , spread of disease, and spread of health promotion, etc. can be theorized and developed into programs that accurately describe human conditions for the action of the human health system. Currently, public health researchers are evaluating Healthy People 2020 objectives for the health of 330 million Americans and are developing Healthy People 2030 objectives for the next decade as the American population and world population continue to grow and to face new, emergent health problems and continuing needs across the globe. Simulation can help us to model proper interventions.

Nevertheless, no model is perfect despite the number of variables and rate parameters that we introduce. Therefore, there is a need for health researchers to increasingly collect accurate health information over longitudinal periods so that trends can be evaluated and modeled, including our emphases upon driving and dissipative forces in the trajectories of individual and group health behaviors . The development of personalized genomics will further complicate this problem, as every person will become an outlier on some variables to an extent due to each person's genetic and epigenetic uniqueness. NetLogo and other powerful simulation programs offer large suites of sample scenarios (e.g., altruism, addiction , virus spread in populations , etc.) that can be manipulated to create new models and to inspire innovation for new conceptualizations to evaluating problems . This work will go hand-in-hand with the greater accessibility to longitudinal physiological and behavioral data on humans that they can consent to provide using mobile app and other health measurement devices, all with an ethical focus.

16.6 Summary

NetLogo and other simulation programs for Agent-Based Models (ABM) utilize

differential equations to model real-world processes. They can be used for theory development and testing in comparison to natural systems. Combined with statistical methods and trajectory analysis, they can validate health models for a tremendous variety of situations and conditions, measuring the causative driving and dissipative forces for processes that can inform medical and health interventions.

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17. Review of Basic Principles

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Abbreviations

PRC Phase response curve

SETI Search for extraterrestrial intelligence

In this book, we have combined the traditional multiple variable statistical analysis approach to health research with the study of nonlinear dynamics and trajectories from mathematics, the physical sciences, and ecology . Research from many different scientific disciplines has been merged with health topics and research, consistent with the universality of the nonlinear trajectory analysis and Wilson's (1998) concept of consilience , "the unity of knowledge." The primary objectives have been to (1) demonstrate the applications of nonlinear dynamics , particularly the Jacobian matrix , Lyapunov exponent λ, Phase Response Curves (PRC), and coherence lengths ξ, to the analysis of physiological and behavioral longitudinal data; (2) emphasize the systems perspective and hypercycles of connected systems in health conditions and functioning; and (3) to demonstrate the universality of systems change, stability, energetics, and catastrophes across multiple levels/scales of human health (molecular to human interactions) and even in nonliving processes. Change is continuous for all systems because of the overlap or correlation between interacting individuals, objects, events, and electromagnetic radiation. The only way to avoid change is complete isolation at a temperature $T = 0$ Kelvin, or $T = -273.15$ °C, at which atoms and molecules theoretically stop all motion.

The need for this approach stems from the advances in nonlinear trajectory analyses in the physical sciences and ecology , where continuous data analysis provides trends in periodic living and nonliving processes with the action of independent variables at specific time points to drive or dissipate trajectories. For health care, this means increased telemetry and longitudinal data collection plus analysis of comprehensive

systems of variables, having both direct and indirect effects according to the method of path coefficients. It involves an improved understanding of epidemiological cause-and-effect mechanisms between variables as well as moving beyond the arbitrary classification of characteristics within variables and the statistical analysis of Thom's (1972, 1977) "cloud of points" toward a four-dimensional (time included) topology of health processes, physiology, functioning, and behaviors as continuous processes following trajectories over manifolds /surfaces . Most importantly, Trajectory Analysis will be essential for the future of health care, when researchers, clinicians, and policy makers will have to merge health assessments and interventions/treatments with individualized genomics , epigenomics , metabolomics, and the diverse microbiome inhabiting the body.

17.1 Principles

The major principles that comprise Trajectory Analysis include the following:

1. Change is continuous and often cyclic /periodic in nature, with angular frequencies measuring the phase of a health process or condition;

2. Multiple correlating variables with direct and indirect effects contribute to the trajectories of health outcomes, either driving (facilitating) or dissipating (inhibiting) the health condition or behavior;

3. Variable effects can be positive, negative, or neutral, and they can include both actions and non-actions (negative probabilities);

4. Body systems are resilient, but with specific circumstances (e.g., low immune function, high stress), health can change and conditions emerge due to sensitive dependence on these initial (or new) conditions;

5. Longitudinal health trajectories continuously change, but their return paths usually return to normal within a brief but finite time, or they may diverge, with the Jacobian matrix and its characteristic root Lyapunov exponents measuring the change;

6. Health varies, but a genuine transition from a positive health state to a negative health state, or vice-versa, that is maintained requires a Type 0 Phase Shift as measured by a Phase Response Curve (PRC).

7. All health processes operate via energy potentials, such that the two optimum strategies to achieve a Type 0 Health Phase Shift are: (1) a Rankine–Hugoniot Jump with the input of energy or resources (and maintenance thereafter), and (2) superimposition of correlating driving variables with the health condition to shift and maintain the desired condition; and

8. Poor health is associated with molecular and system instabilities /chaos , as measured by a Lyapunov exponent $\lambda > 0$ and especially approaching $\lambda \sim 3$, or a decreasing coherence length ξ.

Hayflick (2007) and Davies, Demetrius, and Tuszynski (2012) argued molecular instability as central characteristics of aging and cancer . Pecora and Carroll (1990) demonstrated that chaotic systems can be stabilized by synchronizing their aberrant oscillations with driving signals, forcing the chaotic system to superimpose and correlate with the introduced signal. Similarly, Ott, Grebogi, and Yorke (1990) argued that small disturbances to a chaotic system can nudge the system into varied periodic cycles. From an applied perspective, Buzsáki and Wang (2012) provided evidence that gamma oscillations (35–45 Hz) might be useful in regulating various neurological conditions, including sleep/wake cycles. Applications of cardiac arrhythmia phase resetting via cardiac catheter electrical stimulation of the heart were described in Chap. 14.

The above eight principles are universal for living and nonliving processes. Thus, they represent an experimental approach to support current and epidemiological methods for improving health research, policy, and clinical practice. They provide us with approaches to conceptualizing physiological as well as psychological health processes.

17.2 Methods

The central approaches to measuring changes in health trajectories involve the collection of continuous, longitudinal data with many time points so that trends can be plotted, mapped, and analyzed. The contributions of multiple driving and dissipative variables can be assessed via multiple regression statistical analysis and higher order structural equation models as well as hierarchical linear models . For trajectory analysis , we move further with the analysis of cycles, return maps , and deviations from trajectories. We utilized differential equations, which we have simplified to focus on Jacobian matrices and the calculation of Lyapunov exponents and system phases.

Cvitanovic et al. (2004, pp. 132–134) defined the Lyapunov exponent λ as the

positive diagonal elements of the Jacobian matrix and that can be calculated as (see Chap. 12, Eq. 12.2):

$$\lambda = (1/t) \ln (|\delta x(t_1)|/|\delta x(t_0)|) \quad (17.1)$$

which matches closely the Glass and Mackey (1988, p. 54) derivation of λ (Eq. 11.10). For system phase, Glass and Mackey (1988, p. 105–106) defined the initial system state or phase as $\theta_0 = 0$, shifted phases following a disturbance are $\theta_n = t_n/t_0$, and the change of phase (see Chap. 11, Eq. 11.8):

$$\Delta\theta = (t_n - t_0)/t_0 \quad (17.2)$$

Using Eq. (17.2), we can map the change of phase $\Delta\theta$ (ordinate) versus each phase point over time t (abscissa) to construct a Phase Response Curve (PRC). A Type 1 phase shift will be cyclic , whereas an effective Type 0 phase shift will show separation of curves.

Finally, the deviations of trajectories follow hyperbolic mappings of pressure curves at critical transition points , such that λ = 0 corresponds to a circle, whereas increasing positive λ topologically corresponds to the increasing eccentricity ε of a stretching circle. As λ positively increases, the circle becomes elliptical, then parabolic. It becomes hyperbolic near λ ~ 3 and the phase response curve pattern of chaos . Simultaneously, λ is inversely proportional to the coherence length ξ, as two resonating systems in stability have greater correlations or coherence when λ is near zero. Therefore, we have our final relationship for understanding trajectory change:

$$\lambda \sim \varepsilon \sim \xi^{-1} \quad (17.3)$$

This relationship also is proportional to Kolmogorov entropy for a system and to the fractal dimension of repeatability at various levels within a system.

Currently, applied applications of trajectory analysis in health care are scarce due to the lack of extensive continuous, longitudinal data on individuals that is representative, consistent, and offering informed consent of study participants. Epidemiological trend and time series analyses do exist and are extremely useful to health policy experts and clinicians. However, the periodicities of these trends and the contributions of many independent variables have not been widely addressed in these models.

Simulation and Agent-Based Models have a rich history for theory development and modeling system behaviors (Dresden & Wong, 1975; Grimm & Railsback, 2005). These approaches represent the mainstay of current trajectory analysis , although we are seeing their direct applications in cardiology and neuroscience (Chap. 14).

17.3 The Future

Public health and medicine face many challenges with growing, diverse human populations that are living longer. Figure 17.1 shows Gompertz mortality curves with

increasing age for American males (Fig. 17.1a) and females (Fig. 17.1b). The mortality rates are provided on a logarithmic scale to linearize the relationship (Gompertz, 1825; Riklefs & Finch, 1995). Examining each curve in Fig. 17.1, the increase in the probability of dying stays relatively flat with only slight increases from age 20 to 40, after which there is a doubling of the probability roughly every 7 years for both males and females. Gompertz' (1825) work is the basis for the actuarial tables that life insurance companies use to compute premium rates, besides individual risk indicators. The curves are remarkably consistent across race, culture, and nationalities, although the curve is more compressed toward younger ages for disadvantaged countries and regions (Riklefs & Finch, 1995).

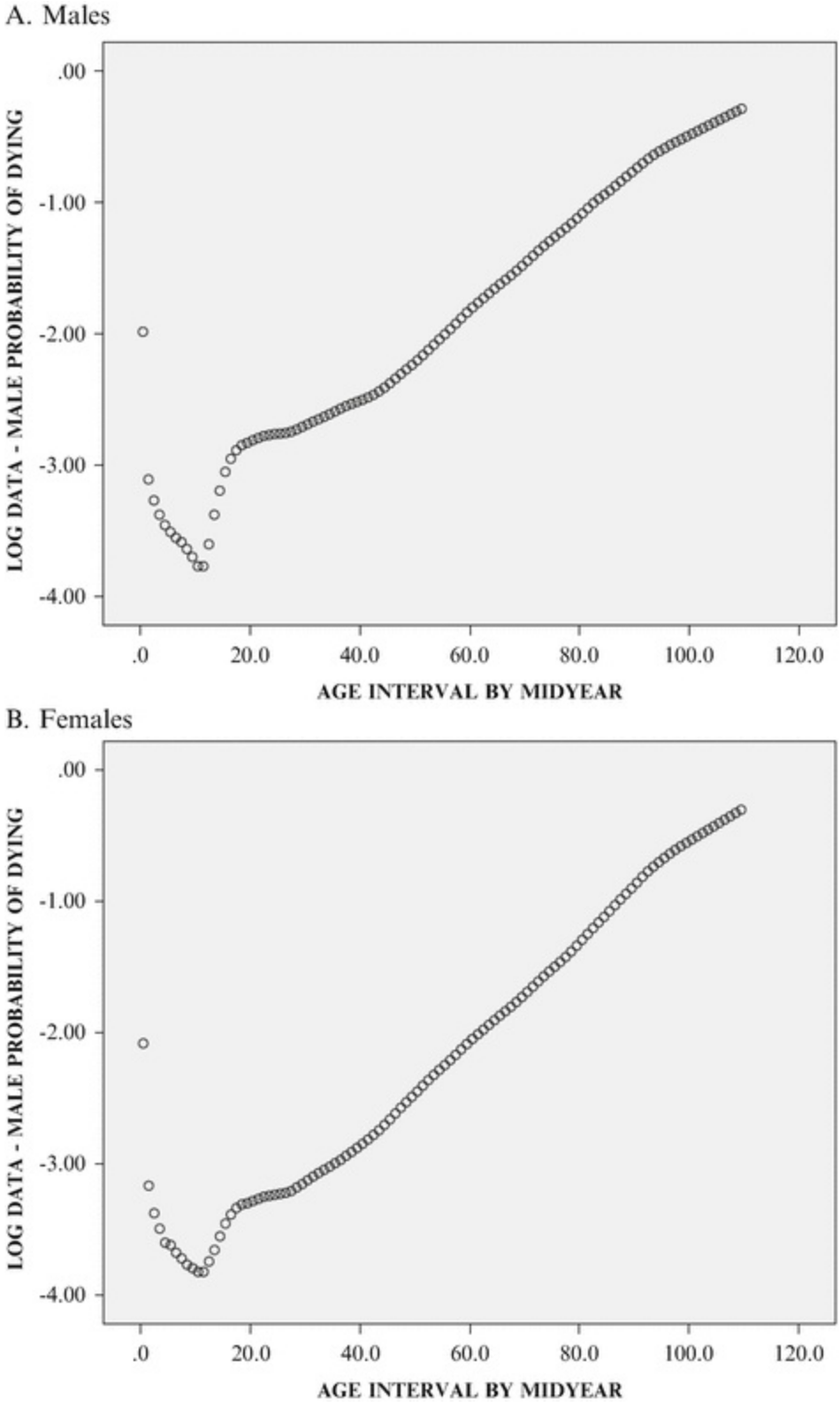

Fig. 17.1 Gompertz logarithm mortality rate curves by age in years for American males (**a**) and females (**b**). Data from the CDC National Center for Health Statistics 2002 Death index plotted by the author using SPSS version 18.0

What is most striking about the mortality curves is the age range 14–24. This range represents the largest increase in the probability of dying for the entire lifespan, and this

bump exists for all populations studied (Riklefs & Finch, 1995). The probability of dying for males increases fourfold, and the probability of dying for females doubles during this life period. The probable causes include variations in cognitive development maturation, raging hormones, reproductive competition , and especially engagement in risk behaviors and experimentation, including the impact of these behaviors on others. While most people survive this period, some people do not. The instabilities of this age range are clearly defined along with the probable causes. Therefore, trajectory analysis with longitudinal interventions (education, support mechanisms) certainly applies for this sensitive period of human development as well as for the entire lifespan. With the 7-year doubling period past age 40, we can examine the variables that promote increased risk to physical decline, disease, and disability so that more individuals experience healthy aging instead of accumulating conditions (Hayflick, 2007).

17.4 Context

At the beginning of the twentieth century, all human populations were susceptible to infectious diseases, poverty, and associated suffering. Figure 17.2 shows an eroding 111-old creek stone that was used as a grave marker for one of the author's ancestors, who died at the age of 4 years. Her mother chiseled a barely perceptible eulogy into the flat stone, "Our Little Darling at rest." Such a scenario was not uncommon even in the Western World during the early twentieth century. Fortunately, the advent of antibiotics and drug discovery, public health programs, immunizations, water sanitation, medical technologies, and standardization of best clinical practices revolutionized health care in the West and globally. However, health disparities remain widespread due to poverty, even in Western nations, and due to environmental catastrophes, wide socioeconomic disparities , war, and other human crises worldwide.

Fig. 17.2 A forgotten child's grave in 2017 after 111 years. Photograph by the author

The remarkable process of life represents a far-from-equilibrium, nonholonomic maintained system (Courbage, 1983; Nicolis & Prigogine, 1981) that has been continuous, without interruption for approximately 3.8 billion years on the fragile biospheric film covering the earth's solid and liquid surfaces, the only known planet where this process has occurred around approximately 10^{23} stars in the universe (van Dokkum & Conroy, 2010). This continuous process has survived numerous biogeochemical crises and accompanying massive extinctions of both terrestrial and extraterrestrial origins (Vernadsky, 1997; Brenchley & Harper, 1998; Hoffman, Kaufman, Halverson, & Schrag, 1998; Erwin, 2008), today producing tremendous variation both within and between species (Darwin, 1859; Wilson, 1975). Despite the mass dominance of prokaryotes (i.e., bacteria) throughout the history of life, the past 600 million years of life have been characterized by the emergence of multicellular, endosymbiotic living network development having high complexity in the eukaryotes: protists, fungi, plants, and animals (Maynard Smith & Szathmary, 1999; Seielstad, 1989; Wilson, 1975).

All life and all physical events in the universe are predicated on energetic potentials and driving forces to maintain these potentials. The earth is not a closed system, nor is the solar system despite the staggeringly vast interstellar distances and near complete vacuum conditions between even nearby stars. For our solar system, the sun (Fig. 17.3) overwhelmingly is the driving energetic force, releasing 2.4 × 1039 MeV s-1 of energy and 1.8×10^{38} neutrinos s^{-1} isotropically (Rolfs & Rodney, 1988, p. 491). About

64×10^9 neutrinos cm^{-2} pass through the earth's surface each second, although it is the dissipated energy that drives all life on earth. Furthermore, the sun, its planets, a trillion comets, and other orbiting objects orbit over 250×10^6 years at 2.5×10^{17} km distance the central black hole singularity of the Milky Way galaxy at a relative velocity of 16.5 km s^{-1} and oscillating above and below the galactic plane at a periodicity of 66×10^6 years (Bash, 1986; Frisch, 1993), the latter no doubt affected by some unknown external driving force from the galaxy's past.

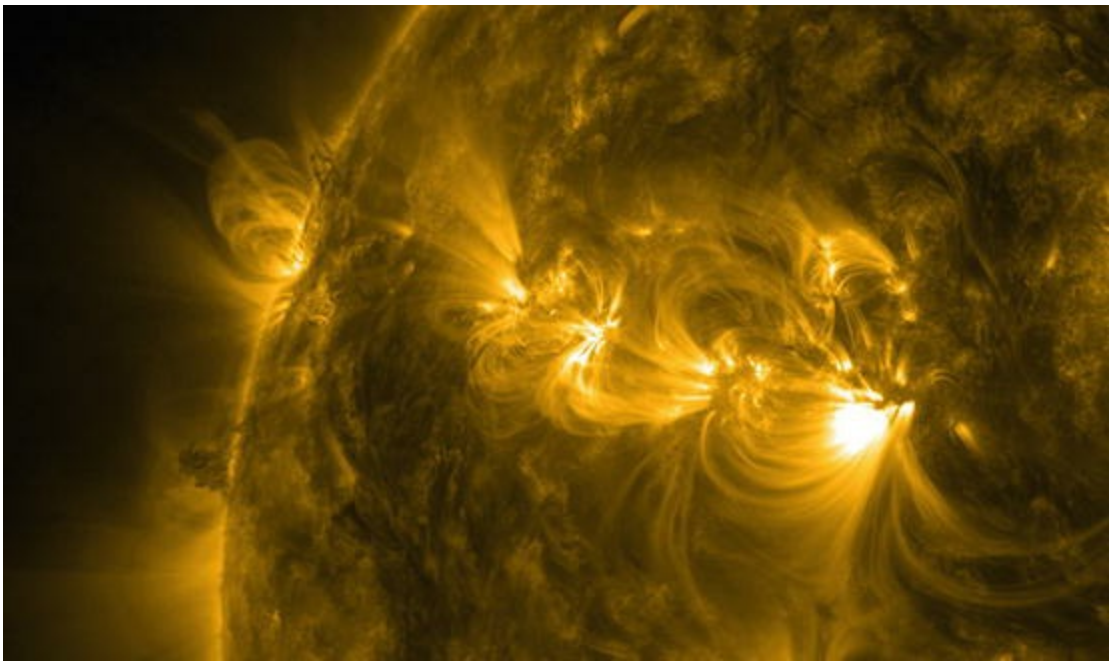

Fig. 17.3 The Sun, 4:28:10 GMT on 8 February 2016. Photograph captured and enlarged on 8 February 2016 using the open source software JHelioviewer® (www.jhelioviewer.org), European Space Agency and National Aeronautics and Space Administration

Some of the tiny but relatively substantial percentage of energy that reaches the earth's surface is absorbed by the thylakoid membranes of photosynthetic bacteria and algal/plant chloroplasts, with the natural semiconductor chlorophylls, carotenoids, and xanthophyll's triggering a series of coupled oxidation/reduction reactions that ultimately reduce nicotinamide-based cofactors for further coupling to water, carbon dioxide/oxygen, glucose, and other metabolic cycling reactions in cells. Without thylakoids to capture solar energy , animals, protozoans, and fungi steal glucose and metabolites from plants and from each other to further couple metabolic activities and the reverse cellular respiration activities (oxidation/reduction potentials again) that drive energy release in eukaryotic mitochondria or bacterial cell membranes. Therefore, living systems cycle energy along potential gradients in order to survive (Eigen & Schuster, 1979), thereby driving each other, with the predominantly ultimate driver being the sun (Fig. 17.3). We have hypercycles of periodic events and order impacting

each other throughout the universe, either directly or indirectly, via chemical and physical processes of photosynthesis , cellular respiration , and solar nucleosynthesis. This connectedness and the ramifications for subtle changes in each of us over the course of our lives are staggering.

We detect minute radio signals from distant stars, galaxies, and quasars, even potential evidence of extraterrestrial intelligence (Seielstad, 1989) using radiotelescopes such as the instrument shown in Fig. 17.4 that astronomer Frank Drake used for the first SETI experiment during the early 1960s. These large telescopes collect tiny photons of electromagnetic radiation that have traveled for millions and even billions of years. How much more readily available are the health measurement tools that are at our disposal!

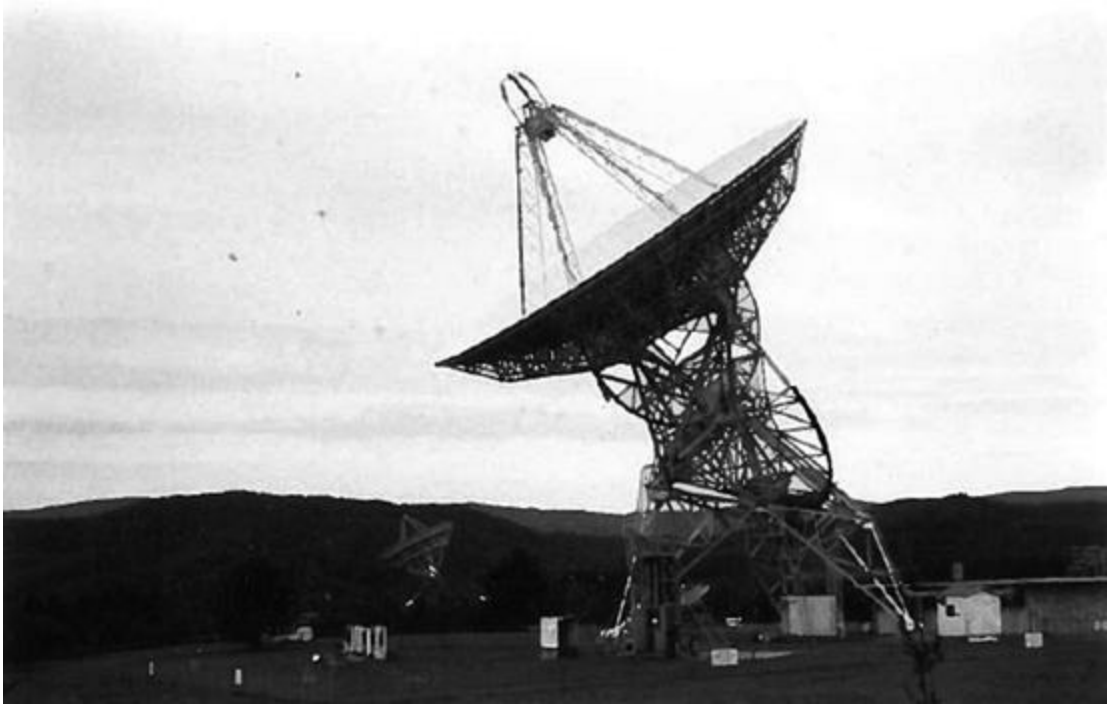

Fig. 17.4 Two radiotelescopes at the National Radio Astronomy Observatory, Green Bank, West Virginia. Photograph by author, May 1988

Trajectory analysis illustrates the wide effects of many variables both direct and indirect. With increasing complexity , we are seeing that even complicated classical systems exhibit quantum behaviors (Vattay, Kauffman, & Niiranen, 2014) that are consistent with Nicolis and Prigogine's (1981) arrow of time and the irreversibility of correlating (coherent) systems that lead to change at all levels. Except for our spiritual aspects that are beyond measurement, we physically are part of the universe and are subject to all of its effects. Health conditions are not limited to arbitrary classifications that currently are intensively studied. Instead, we need to focus on multiscale events and processes that create change in health, many conditions that can be mediated or

moderated based upon our mapping of these dynamic events.

17.5 Perspective

Lightman and Gingerich (1991, p. 255) defined a scientific anomaly as "an observed fact that is difficult to explain in terms of the existing conceptual framework," and they suggest the use of retrorecognition as a psychological tool to address unexplained facts/givens within new frameworks and to provide improved theories of knowledge. As we perform health research, taking alternate perspectives and employing tools from other scientific disciplines (i.e., benchmarking) enables us to see problems and potential solutions in new lights.

Kahneman (2003) challenged researchers and clinicians to engage in increased Systems 2 Reasoning as we critically attack problems and fallacies in decision-making and problem-solving. Trajectory analysis requires new conceptual frameworks to study complex systems of variables that interact and affect health or any type of action in the universe.

17.6 Summary

We described eight basic principles of Trajectory Analysis that are applicable to health care. The science of nonlinear and trajectory dynamics is growing rapidly, although it remains mostly theoretical. Cardiology and neuroscience have introduced these concepts to improve human health. Our next steps are to expand this science into health care to support current statistical and epidemiological methods.

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Mortality
Multiple-drug resistant Staphylococcus aureus (MRSA)
Myocytes

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National Center for Health Statistics (NCHS)
National Health and Nutrition Examination Survey (NHANES)
Necrosis factor
Negative probabilities
NetLogo
Neural networks
Neurology
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Nicotinamide adenine dinucleotide (NAD)
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