PHYSIOLOGICAL MODELS SURVEY

PHYSIOLOGICAL MODELS, DEVELOPMENT

This article illustrates some basic principles of modeling in the physiological sciences, with emphasis on a salient feature that receives more and more attention, namely the issue of *variability,* measurable as fluctuations or oscillations (1–3). Along these lines one may also consider the experimental application of so-called perturbation techniques that induce instabilities in a system, while the observed response reveals important information about the characteristics of such a system (4, 5). Also, circadian rhythms and their implications for physiological processes are well recognized and intensively investigated today, both in animals and in humans. Heart rate variability (*HRV*) refers not only to variations in rhythm, but has also (possibly teleological) consequences for filling and ejection of the cardiac ventricles. In the future we may learn whether the fundamentals of homeostasis pertain to oscillations rather than to pure equilibrium. Is the oscillator a source for control or just a clockwork as already conceived by Descartes. What matters most, entropy or order? And how can intrinsic rhythms be duly implemented in the physiological models?

Time patterns, therefore, seem to play a fundamental role in normal functioning. There is emerging evidence that independently operating systems within the body may yet tend to be phase locked: for example, the coupling between cardiac and locomotor rhythms (heart rate becomes entrained with walking and running cadence at some speeds) is a physiological phenomenon (6). Similarly, although not discussed in this article, a novel and fascinating area of investigation is the technological and even surgical coupling of different tissues or organ systems. An example of the therapeutic implications of the first type is the auditory biofeedback in the treatment of strabismus (cross eye). In this process voltage signals proportional to vergence eye position are transmitted from the eye movement monitoring system to an audio oscillator that converts the signal to tones proportional to horizontal eye position, that is, the patient "hears" the vergence eye movements. An example of a surgical advance based on physiological models that enhances our understanding of underlying mechanisms is the cardiomyoplasty procedure in which a skeletal muscle is wrapped around a malfunctioning heart chamber to assist in the process of contraction (7). These remarkable applications demonstrate the potentially wide range and impact on clinical practice, based on insight derived from sound physiological models.

The functional importance of variability in physiological modeling deserves attention. Already in 1865 the famous French investigator Claude Bernard stated that in physiology we must never make average descriptions of experiments, because the true relations of phenomena disappear in the average (8). Apparently, his remark has gained new impetus over the last decade, and the notion of intrinsic variability may turn out to provide a practical tool in distinguishing physiologic from pathophysiologic states.

A PRIMER OF CONTROL SYSTEMS IN PHYSIOLOGY

Physiology is the biomedical discipline that investigates, describes, and interprets the mechanisms of functioning pertaining to the normal (healthy) living being and intgrates this knowledge in the clinical sciences. Living systems and their components are continuously controlled (and occasionally even perturbed) by internal and external stimuli. Therefore, a short discourse about physiological control systems seems appropriate.

Basically, biological control systems do not differ much from technological controllers. Physiological control systems often feature the intrinsic property of small oscillations or fluctuations, meaning that a moderate degree of instability is desired in order to react to even small perturbations effectively. This prominent property occurs in various organ systems, for example, the variability of the heart rhythm, skin temperature oscillations, the small fluctuations of the resting transmembrane potential, the management of instability during dynamic exercise, and saccadic movements encountered in vision research. Small fluctuations actually may prevent sudden large overshoots that could prove fatal.

The principle of minor instability for promoting smooth operation is familiar to engineers who have developed advanced technological devices, as for example, the booster engines of a rocket, which continuously rotate during takeoff to prevent tumbling. Also, from everyday life we know that a stick placed on a finger will surely fall if one attempts to keep the hand rigid; small circular movements (teasing the Coriolis force?) assist in keeping the stick in an upright position. Experienced tennis players make clearly visible lateral oscillating movements with their whole body, in order to anticipate and initiate a rapid sprint in either direction when the ball is being served by the opponent.

A control system is an arrangement of components (such as sensors, comparators, and actuators) that are designed to govern a particular process. A well-known and relatively simple example is the heating control used in a room or house. A typical diagram is presented in Fig. 1 and consists of a heating unit that can be switched on and off by comparing the desired temperature (set point) with the actual temperature sensed at the thermostat. Obviously, the dynamics of such a control system depend on many internal and external factors including weather conditions, capacity of the heater, and possible routes for leakage. A similar setup operates in biological systems, although the anatomical and physiological details are more complex. The simplest setup refers to a "reflex loop" 1 in which a certain (effective) stimulus elicits a particular response according to a standard protocol, for example, the *blinking reflex* in which the eyelid is quickly closed when a suddenly approaching and threatening object is seen. Apart from temperature, many other conditions and functions are controlled in living organisms, for example, locomotion, blood pressure and flow, composition of body fluids, release of hormones, and vision.

Three features of the control system just described deserve further attention:

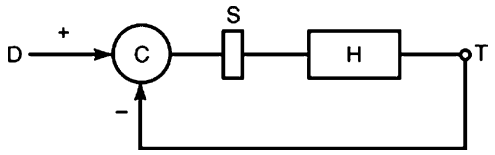

Figure 1. Diagram of a relatively simple control system. D is the dial to set the desired temperature. C the comparator, H the heater, T the thermostat, and S the switch to turn the system on and off.

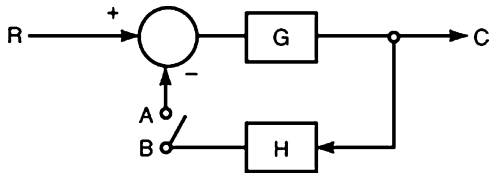

Figure 2. A control system with a feedback loothat can be interrupted, thus permitting the estimation of the so-called open-loop gain.

1. In order to keep a process under control, information must be received about the actual status of that process, that is, the comparator must get "feedback" about the outcome of its regulatory action. Feedback rcuits result in either a negative or positive action; in the terminology of physiology these effects are referred to as inhibitory and excitatory, respectively.
2. The on–off switch clearly introduces *nonlinearities* in the behavior of the system. Such discontinuities are not uncommon in biology. Sometimes a linearized approach is selected for simplicity, which still yields useful results.
3. The regulatory capabilities of a control system depend on the wiring (i.e., how the various elements are connected), and the gain. When the feedback is interrupted (a so-called *open-loop state*) during an experiment or due to a particular disease, the performance may be different from that under the normal closed loop condition, (Fig. 2). Apart from how powerful a control system is (gain) one may also consider the time course of a change imposed on the system. This is generally done by calculating a *time constant* that indicates the typical rate by which the system is regulated.

MODELING IN BIOLOGY

Mathematical and graphical models are convenient because they aid in organizing the pattern of thinking and thus facilitate communication among colleagues. Also, they are relatively inexpensive and often applicable to the description and analysis of complex systems. In addition, they potentially enhance insight by providing suggestions about clues to critical experiments and validation of methods.

In the mathematical approach an analytical expression is formulated that indicates how one variable depends on other parameters. The equation may be precise, based on a formal derivation, or may be a convenient approximation for the sake of simplicity. A graphical representation may be multidimensional, with linear or (semi-) logarithmic axes, depending on the nature of the process(es) considered.

Various mathematical tools are used for the description and analysis of physiological models and signals, including time-domain and Fourier analysis (frequency-dependent approach). The spectral power density provides a measure of the distribution of the average power in a signal at different frequencies.

SIMULATION IN PHYSIOLOGY

Elementary models combined with knowledge about their control systems can be fruitfully employed to simulations in physiology. Such endeavors may mimic or even predict the outcome of a particular process under well-defined conditions, either normal (i.e., physiological) or pathological. In general, simulations yield results that resemble observed phenomena but do not necessarily reflect physiological properties. For example, the arterial tree can be simulated by a two-element electrical analog, the so-called *Windkessel* (air bellows), consisting of a resistor (representing the presumed stiff peripheral vessels) and a capacitor (which stores energy in systole and discharges during diastole; it is formed by the compliant aorta). A later improved model includes the characteristic impedance of the aorta by adding another resistor in series with the previous two components. It was also shown that a nonlinear three-element *Windkessel* model has no advantages over the traditional version, (9) although the pressure dependence of compliance can be demonstrated.

Mechanical models simulating the systemic circulation and successfully applied in animal experimental setups were developed by Westerhof (10) and by Kerkhof (11) An analog distributed model of the human systemic circulation was given by Westerhof in 1969, and in 1978 reduced by Noordergraaf (12). O'Rourke and Avolio proposed a T-shaped model in relation to the anatomical design, and other investigators developed single and multiple tube models, thus lumping a small or large portion of the individual elements (13).

BASIC TYPES OF NEURAL CONTROL SYSTEMS

Connections within the nervous system are realized by using synapses, which are electrical coupling sites in which a specific transmitter substance released from the presynaptic ending will induce a voltage change at the opposing postsynaptic membrane. An excitatory signal induces a depolarization, whereas an inhibitory signal causes hyperpolarization. This design permits the construction of a variety of regulatory circuits, all based on the following four prototypes (where the signal travels from left to right side):

- A divergent circuitry [Fig. 3(a)], in which distributes a signal to various effectors
- A convergent circuitry [Fig. 3(b)], which has an additive effect with possible threshold features

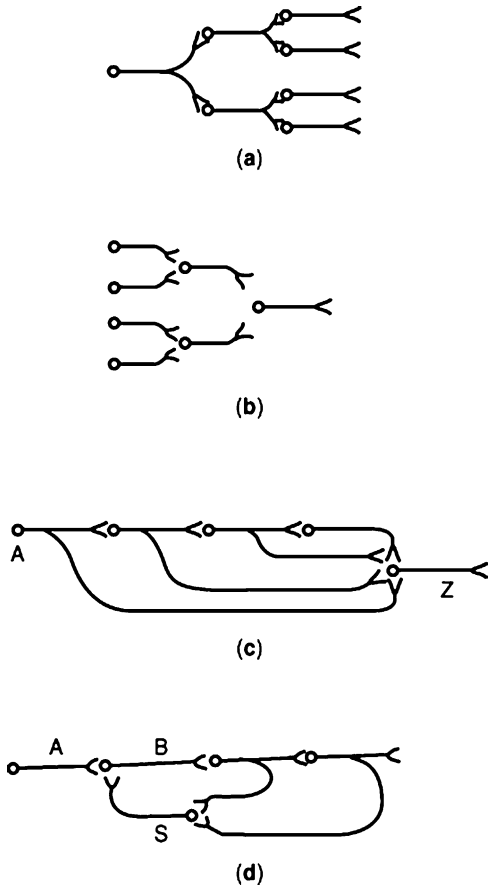

Figure 3. (a) A divergent (branching) synaptic circuitry, where the circle denotes a neuron and the v shape ending a synaptic connection; (b) a convergent circuitry; (c) a parallel circuitry; (d) a reverberating system.

- A parallel circuitry results in a repetitive sequence at point Z after a single initiating impulse originating at A, because every synapse introduces a certain delay [Fig. 3(c)]
- A reverberating circuitry with feedback capabilities, possibly resulting in endless loops with a particular clock frequency; the signal from point A travels to the junction in B where some delay occurs, and then it is rerouted via the switching neuron S and arrives again at its point of origin at A [Fig. 3(d)].

The combination of one neuron plus one synapse is a simplification introduced for convenience of explanation. In fact, numerous synapses may connect to a single neuron, permitting both temporal and spatial summation. These phenomena illustrate the probabilistic nature of signal transmission in the nervous system, where crossing a critical threshold for excitation is a matter of the delicate interplay of inputs from numerous sources. Another striking example is formed by the neuromuscular synapse in which miniature endplate potentials originate from spontaneous release of transmitter molecules from presynaptic vesicles, thus contributing to the likelihood of impulse transport.

FLUCTUATIONS OF THE MEMBRANE POTENTIAL

Excitable tissues (such as nerve cells and muscle fibers) feature the property of a potential difference across the membrane during the resting condition. This state is generally referred to as *polarization*. The electrical potential stems from (unequal) distributions of several ions, mainly sodium plus chloride (in the extracellular medium) and potassium (within the cell). During rest a potential difference of about −80 mV (inside with respect to outside of the cell) is maintained by the action of an ion pump. Small spontaneous fluctuations (possibly to be regarded as intrinsic perturbations) around this average potential have been recorded and described as $1/f$ noise, that is, exhibiting a spectral intensity obeying a relationship proportional to f^{-1}, where f is the frequency in hertz (14). The fluctuations imply that signal transmission in the nervous system is a highly probabilistic process. The French scientist and 1965 Nobel prize winner Jacques Monod elegantly explained the importance of probability in the field of (molecular) biology when he applied cybernetics to molecules (15). Thus the phenomenon of variability is present at a cellular level and represents a characteristic element in physiology.

CONTROL OF MOVEMENT AND LOCOMOTION

The delicate interplay between macroscopic and microscopic structures such as muscle fibers, bones, nerves, and tendons permit the maintenance of posture as well as the control of movements of humans and most animals. In contrast, some creatures such as spiders use no muscles to extend their legs. Instead, they extend them hydraulically, and the blood pressures involved may exceed 450 mmHg.

For vertebrates, the so-called motor unit forms the basic entity for skeletal muscle action (Fig. 4). Such a unit consists of a motor neuron (located in the spinal cord) plus all muscle fibers that it serves; physiologically this implies that a distinct group of muscle fibers contracts simultaneously once a single motor neuron fires (i.e., generates an action potential). A skeletal muscle consists of a multitude of such parallel fiber groups, and total force development depends on the number of simultaneously active motor units. At the level of muscle fibers we also observe the phenomenon of variability, called *jitter*, which refers to the variation in the time interval between consecutive discharges of muscle action potentials of two fibers from the same motor unit.

Biomechanics is the branch of biophysics that is concerned with the effects of forces on the motion of a living organism or one or more of its parts, such as a leg. Forces, torques, fulcrum, and lever action form the basic ingredients of biomechanics. The center of mass (*CM*) of the standing human body is centrally located in the abdomen at the level of the navel. The *CM* obviously shifts, for example, when carrying a load with one arm. Performing dynamic exercise causes the body to become unstable. Therefore, sports such as running, cycling, and skating imply the management of instability.

Because a complete description of a real biological system in terms of its movements is often extremely complex,

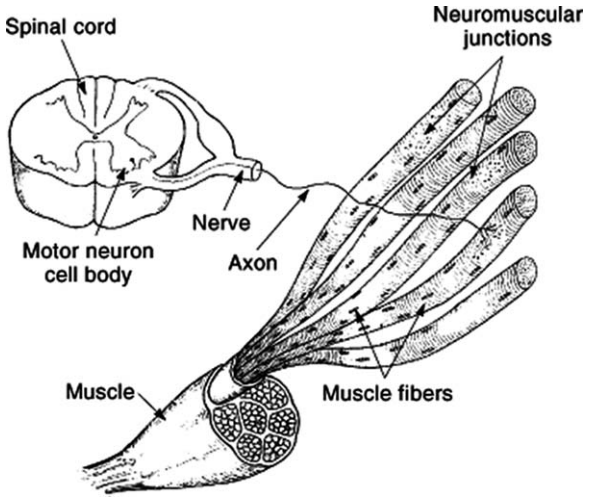

Figure 4. Schematic representation of a motor unit, consisting of a motor neuron plus all connected muscle fibers and intermediate structures such as collaterals of the efferent nerve fiber and neuromuscular synapses that functionally connect the nerve fiber endings with the corresponding muscle fibers.

many researchers employ reduced models that nevertheless provide enough insight into the problem under investigation. A simple model of a control system encountered in locomotion will be presented. In general, the current contraction state of a particular muscle is reported to the motor center (feedback loop), but the anticipated action is also considered (feedforward control). Furthermore, information is routed to the antagonistic muscle, enabling a smooth and balanced movement pattern. A defective coordination of movement (loosely referred to as clumsiness) actually covers a spectrum of abnormalities. Thus, there may be a number of potential defects in the control systems that would involve substantial consequences. For example, dysdiadokokinesis is a defect in which an individual lacks the ability to perform rapid movements of both hands in unison.

CLOSED LOOP DRUG DELIVERY

The field of pharmacokinetics concerns the analysis of factors that affect absorption, distribution, and elimination of drugs in the body. In contrast, pharmacodynamics refers to interactions at the receptor site. Drugs may primarily act locally (the so-called topical type such as eye drops or inhaled aerosols) or they may more or less simultaneously (intentionally or not) influence many organs in the whole body (i.e., systemic type). Obviously, temporal as well as spatial considerations are relevant in pharmacokinetics. The route of administration mainly determines where a pharmacological substance exerts its primary action. Because of the frequently occurring side effects of almost all drugs, it is also important to gather information about the distribution and uptake of a drug at a site that is not the primary target. Apart from the site of administration, it is important to have some estimate about the optimal speed of delivery at the desired location. Injection into the bloodstream is fast and potentially transient, while application on the skin (transdermal route) is slow but has the advantage of being long-acting and rather constant. In particular, in iontophoresis a drug is delivered transdermally by using an electric field to enhance the transport of small, poorly absorbed ionic drugs across the skin surface with the advantage that only a low dosage of the drug is required (16). All these considerations make clear that it is useful to develop models that incorporate the various (anatomical and physiological) compartments that are spatial and chemical in nature in order to predict the concentration and time pattern at a target site dependent on the location of introduction of the substance, as well as the particular time sequence (e.g., bolus versus repeated doses) of administration.

VISION RESEARCH AND EYE MOVEMENT

Various aspects of eye movement have been extensively described in PHYSIOLOGICAL MODELS, DEVELOPMENT by T. Bahill. Therefore, we focus here on our main theme, namely fluctuations, instability, and variability as observed in the oculomotor control system. Basic concepts of the neuromuscular system controlling movement of hands and limbs also apply to eye tracking. The task of permanently centering a moving image on the fovea is realized by a multilevel system involving reflex loops, volitional control, and predictors. Saccades are rapid successions of conjugate steps of eye rotation that permit the positioning of a target image onto the fovea. The eyes voluntarily move from one fixation point to another, as can be observed during reading. They are preceded by a reaction time of about 0.20 s and follow a typical course of rapid acceleration and subsequent deceleration with occasionally a small overshoot. Accommodation (focusing) is driven by a blur of the target image on the retina. Smooth pursuit involves a slow but continuous following movement needed to perform a smooth tracking task. Disjunctive movements of both eyes permit vergence (binocular fixation system resulting in convergent or divergent movement). Accommodation and vergence form an interactive dual-feedback system. Physiological nystagmus (min eye movements) are repetitive fast and slow movements that adds to the visual acuity by preventive bleaching while shifting to different receptors. Acceleration of the body requires the vestibulo-ocular reflex to become operational. It is believed that (white) noise enhances stability (as in *HRV*), while fluctuations affect accommodation. Hung described a nonlinear static model, containing the depth of field (as a dead-space operator for accommodation) as well as Panum's (17) fusional area (as a dead-space operator for vergence), and found that these operators are able to account for the discrepancy between results using the phoria and fixation disparity methods (18).

RESPIRATORY CONTROL

During inspiration, air enters the lungs from the nasal passages (conchae) or the mouth via a branching system of tubes ending in numerous small but highly elastic hollow structures (alveoli). These elastic elements are in contact with small blood vessels and are therefore the sites of gas

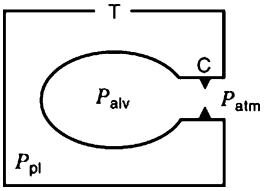

Figure 5. There is increased local obstruction at point C in case of asthma, whereas in emphysema the trajectory between C and the alveoli shows a permanent decrease of diameter.

exchange. Expiration implies transport in the opposite direction, from the lungs towards the final tube (the windpipe or trachea). Expansion of the lungs is normally realized by muscular activity of both the diaphragm and the intercostal muscles (19).

The dynamics of respiration are commonly described in terms of a pressure–volume relationship (to study restrictive diseases such as interstitial fibrosis and pulmonary edema) and derived quantities such as flow (Q, to study obstructive diseases such as lung emphysema) and compliance (the ratio of volume changes resulting from variations in pressure). In contrast to emphysema, asthma is a reversible obstructive airway disease, because it is caused by an increase in smooth muscle tone in the large bronchi. Figure 5 illustrates the nature of these abnormalities in a lumped parameter model, consisting of the thoracic wall (T), an overall spherical elastic element with alveolar pressure (P_{alv}) inside, atmospheric pressure (P_{atm}), pleural pressure (P_{pl}), total airway resistance (R_{aw}), and C is the usual point of collapse of the airways acting as a Starling resistor (i.e., a collapsible tube affected by the pressure of its surroundings). It can be derived that

$$Q\,(\text{inspiration}) = (P_{stm} - P_{alv})/R_{sw} = -\text{Q(expiration)}$$

The stimulus to breathing is controlled by a particular area in the brain stem called the respiratory center. The rhythmical contraction of the diaphragm and intercostal muscles determine the inspiration sequences, that is, the brain generates alternating cycles of firing and quiescence in the responsible motor neurons.

CONTROL OF HEART AND CIRCULATION

The tracing of an electrocardiogram (*ECG*) is one of the most popular icons displayed whenever referring to the field of medicine. From a clinical point of view, the measurement of the *ECG* is attractive because it involves a noninvasive procedure that can be performed quickly using either portable or fixed equipment. The cardiac system can best be described as a mechanical pump system that is triggered and synchromized by electrical signals. Because of its noninvasive nature, the *ECG* is helpful in providing some preliminary information on cardiac rhythm, electrical conduction, and its disturbances. Figure 6 shows the preferential pathways for conduction of the excitation wave, which closely follows functional anatomy of the heart, that is, starting at the sinus node in the right atrium, traveling towards the apex of the ventricles, followed by a spread towards the outflow tract. This route implies that the blood

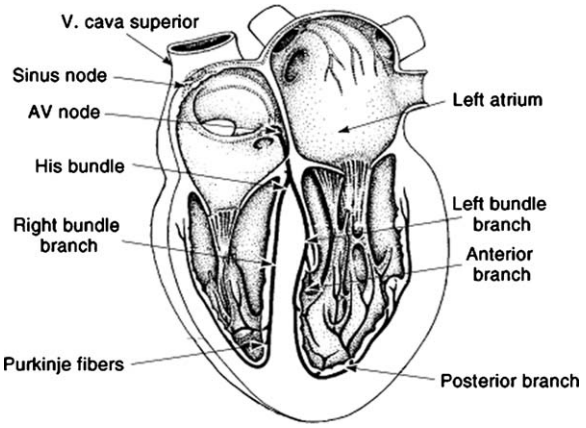

Figure 6. A cross-sectional view of the heart, showing the two ventricles and both atria, along with the conduction system for the electrical impulse running from the sinus node towards the apex and then upwards along the muscular walls of the ventricles.

is expelled from the ventricles similar to the optimal direction for squeezing out the contents of a tube of toothpaste, that is, running from the very bottom up towards the opening at the opposite site.

The rhythm of the healthy heart is not constant but exhibits a certain degree of *HRV* (20). Many studies have employed advanced mathematical techniques to analyze the cardiac rhythm and estimate the relative contribution of the sympathetic and parasympathetic drives, respectively (21, 22). But the perpetual change of the rhythm has also profound mechanical consequences: An increase in cycle length implies facilitation of ejection both by increased filling (i.e., elevated preload) and reduced opposing pressure at the time of the valve opening (i.e., lower afterload), while during the next beat with a shorter interval the opposite applies. In other words, impeded and facilitated beats appear to alternate, thus possibly improving stability of the complete circulatory system.

The left ventricle has often been modeled as a sphere or prolate ellipsoid, but neither geometry conforms with reality. Independent of geometrical assumptions, Beringer and Kerkhof (23) have shown that a fairly linear relationship exists between end-systolic volume (*ESV*) and end-diastolic volume (EDV). This notion has been verified in human patients and also in their experimental investigations when studying the volume regulation in physiologically operating chronically instrumented dogs (24). The regression coefficients appear to be characteristic of ventricular volume regulation and are sensitive to inotropic intervention (i.e., adrenergic agonists and blockers). This relationship implies that a clinically important cardiac performance indicator, namely ejection fraction (*EF*) is inversely related to *ESV* (25). Furthermore, using the Suga-model, myocardial oxygen consumption can potentially be predicted from a single noninvasive determination of *ESV* Quite similar to the description of pulmonary dynamics, the dynamics of heart and vessels are also characterized by pressure–volume (P–V) relationships. Flow (Q) equals the time derivative of a changing volume. Another frequently employed derived index is elastance (E), the reciprocal of

compliance, which is defined as the material property that enables resisting deformation. In analytical form,

$$E = P/(V - V_0)$$

where V_0 is the unstressed volume. This is analogous to Hooke's law (length–tension relationship), which states that tension (i.e., force per unit area) equals Young's modulus times the relative change in length.

Spontaneous oscillations of arteries have also been observed, with a period ranging from 45 s to 60 s for the radial artery diameter under resting conditions, resulting in an almost twofold change in distensibility (26). A general model of the properties of a muscular blood vessel at varying levels of contraction predicts that the vessel becomes unstable at high levels of contraction (27). A lumped model of the arterial tree can also be considered, similar to the lumped model for the lungs as presented before. Imagine that the arterial bed with all its branches is replaced by a single vessel with a diameter similar to the human aorta and encompassing an identical hemodynamic resistance (R). How long would this hypothetical noncollapsible aorta be? From Poiseuille's law we know that $R = 8\eta l/\pi r^4$. If the radius r = 1 cm, the blood viscosity η = 3 cP, and R is the mean driving pressure divided by mean flow, that is, 100/5 mmHg·min/L, then the length l turns out to be approximately 200 m.

Obviously, the real circulation consists of various vascular beds that supply blood to the various organs such as brains, kidneys, skeletal muscles, and intestines. One powerful regulatory mechanism used to accommodate varying needs in a single organ is based on the principle of redistribution of flow within the body by local vasodilation and constriction of arterioles. Another phenomenon, called autoregulation, is based on vasoactivity that maintains the flow at a particular level even during acute changes in pressure.

Arterial blood pressure is well controlled by several systems. Figure 7 presents a survey with emphasis on time course and gain for each subsystem involved (28). Hypertension can then be interpreted as a disorder in which the set point is altered while the control systems continue to regulate towards an erroneously determined set point. This view also explains the chronic nature of a condition in which blood pressure even at rest is elevated. Going back to Fig. 1 this abnormality would be equivalent to a situation in which the heater feedback system continues to maintain a given (wrong) set point.

FRACTAL AND WAVELET ANALYSIS OF CARDIOVASCULAR PARAMETERS

The design and function of the cardiovascular system is commonly described in terms of a muscular pump and a network of branching vessels. This traditionally implies an interpretation in terms of the laws of physics (12, 13). More recently, analysis using the fractal properties of physiological observations has been employed. This appears to have a great potential for the study of physiology at scales of resolution ranging from the microcirculation to the entire organism. Other new techniques include wavelet analysis and nonlinear approaches. They are mentioned here to let the reader become aware of the existence of these tools.

Fractal analysis

The values of the measured properties of many physiological systems seem random. This view originates from the tools that have been used when analyzing the details of organs. Nowadays there are new methods to analyze seemingly random experimental data, such as a time-series approach. These methods use many of the properties and ideas of fractal analysis. The mathematician Mandelbrot chose the word *fractal* to denote objects or processes with multiple-scale properties, that is, the ever finer subdivisions of objects or processes as they are viewed at progressively higher magnification. Until recently, our ability to understand many physiological systems was hampered by our failure to appreciate their fractal properties and to interpret scale-free structures (29).

Wavelet analysis

Fourier analysis (i.e., decomposition of a signal into sinusoidal waveforms) is not suitable for signals with discontinuities. This type of computational headache can be successfully treated by wavelet (*ondolettes*) analysis, a powerful technique developed by Mallat and Meyer in France (30). Later, Daubechies (at Princeton) discovered the dual family, representing the high-frequency range and the smooth parts (low frequencies). Wavelet analysis owes its efficiency to the fast pyramid algorithm, reducing the number of calculations by down-sampling operations, that is, steps that remove every other sample at each operation (halving the data each time). The method has vital applications in compression of signals and images, in addition to noise reduction (a common problem in biomedical recording, in particular in magnetic resonance imaging). The current popularity of wavelet analysis may be exemplified by the commercially available software "Wavelets for Kids" developed at Duke University.

Nonlinear analysis

Heart rate (HR) and blood pressure (BP) are controlled by several central nervous system oscillators and different control loops (see Fig. 7). Interactions among these units may induce irregular time courses in the processes they govern, but the underlying subprocesses also include deterministic behavior. These irregular time courses can be more accurately characterized by dynamic nonlinear analysis rather than by linear time series. Typically, one-dimensional time series data are transformed into multidimensional phase-space plots, thus filling selected regions. Two essential aspects of such plots include:

1. The correlation dimension, which is a measure of the complexity of the process studied, that is, the distribution of points in the phase space
2. The Lyapunov exponent, a measure of the predictability of the process, quantifying the exponential divergence of initially closed state-space trajectories.

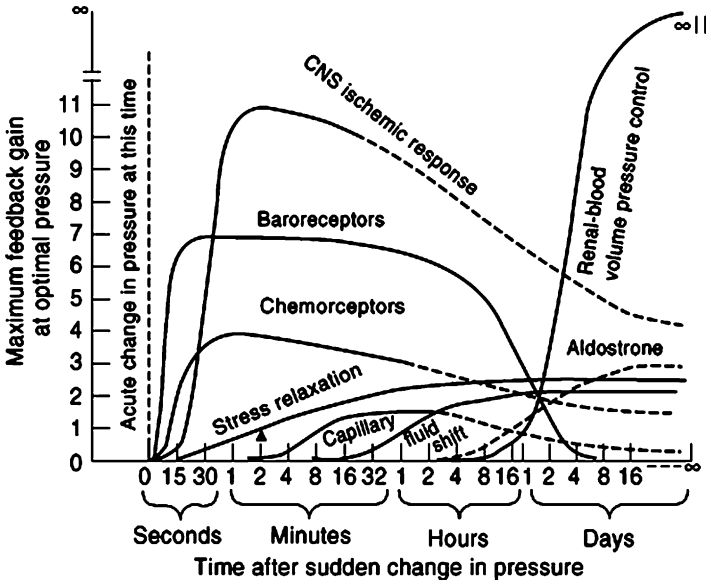

Figure 7. Gain of the various arterial pressure control mechanisms as a function of time after the onset of a disturbance. (Reproduced from A. C. Guyton, *Human Physiology and Mechanisms of Disease*, 5th ed. Philadelphia: W.B. Saunders, (1992, with permission.)

Significant nonlinear dynamics of HR fluctuations were found in rabbits and piglets. Such studies may improve the understanding of underlying physiological processes.

ENDOCRINOLOGY

Cells communicate by means of electrical coupling (e.g., direct contact interaction or neurocontrollers) and chemical interaction (i.e., endocrine control often for the long-distance type). These communication networks regulate vital processes such as growth, differentiation, and metabolism of tissues and organs in all living systems. The nervous system and the endocrine system are linked by the integrating function of the hypothalamus, a specific region of the brain.

The specific endocrine contribution to regulation forms the subject of this section. It involves signal generation, propagation, recognition, signal transduction, and response to a particular stimulus. In endocrine signaling, the pertinent cells release substances called hormones. The main endocrine glands are the hypothalamus, the anterior and posterior pituitary, the thyroid, parathyroid, adrenal cortex and medulla, pancreas, and the gonads (i.e., ovaries or testes). Hormones can be chemically classified into three groups: steroid hormones (e.g., estrogen and progesterone), peptide or protein hormones (such as insulin, prolactin, and the various releasing hormones), and a category derived from the amino acid tyrosine (i.e., thyroxine and triidothyronine). These substances are usually transported via the bloodstream. Therefore they are distributed within the whole body. Lifetime in plasma may range from seconds to days. In order to ensure a selective action at a special site, target cells exhibit sensitivity for a particular hormone and only in these cells will an appropriate response be induced. The ability of target cells to exclusively respond to specific hormones depends on the presence on the membrane of receptor proteins that are unique for a particular hormone. The action may take place on the cell surface (with or without an intracellular mediator—the second messengers, substances that serve as the relay from the plasma membrane to the biochemical machinery inside the cell), or only within the interior of the cell, at the nucleus level.

Besides negative and positive feedback circuits, the endocrine system features rhythmic control by pulsatile release of certain hormones leading to circadian variations. Also, endocrine control can be pharmacologically modified with the use of synthetic hormones. The modern field of molecular biology is also concerned in part with many aspects of the physiology of the endocrine system at the (sub)cellular level.

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