Nonlinear Systems in Medicine

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MEDICAL REVIEW

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Many achievements in medicine have come from applying linear theory to problems. Most current methods of data analysis use linear models, which are based on proportionality between two variables and/or relationships described by linear differential equations. However, nonlinear behavior commonly occurs within human systems due to their complex dynamic nature; this cannot be described adequately by linear models.

Nonlinear thinking has grown among physiologists and physicians over the past century, and nonlinear system theories are beginning to be applied to assist in interpreting, explaining, and predicting biological phenomena. Chaos theory describes elements manifesting behavior that is extremely sensitive to initial conditions, does not repeat itself, and yet is deterministic. Complexity theory goes one step beyond chaos and is attempting to explain complex behavior that emerges within dynamic nonlinear systems.

Nonlinear modeling still has not been able to explain all of the complexity present in human systems, and further models still need to be refined and developed. However, nonlinear modeling is helping to explain some system behaviors that linear systems cannot and thus will augment our understanding of the nature of complex dynamic systems within the human body in health and in disease states.

INTRODUCTION

A system is a collection of interacting elements. Behavior of the system is distinct from the behavior of its parts or elements (Figure 1). These elements interact with each other directly and indirectly to modulate the system function.

The reductionist or mechanistic view of nature involves reducing systems into their component parts (elements) in an attempt to understand them [1]. This is the basis of linear system analysis, where output is proportional to or can be determined through applying simple differential equations to the input. Yet systems within nature, including the human body, frequently lack mechanical periodicity or linear dynamics and thus are referred to as nonlinear systems [2]. Within nonlinear systems, output is usually not proportional to input, and output for the same input value may not be constant over time [3]. Furthermore, in contrast to linear systems, breaking a nonlinear system down into its elements (parts) and analyzing those parts under controlled conditions does not accurately reflect the complex behavior present, nor capture the dynamic relationships operating between

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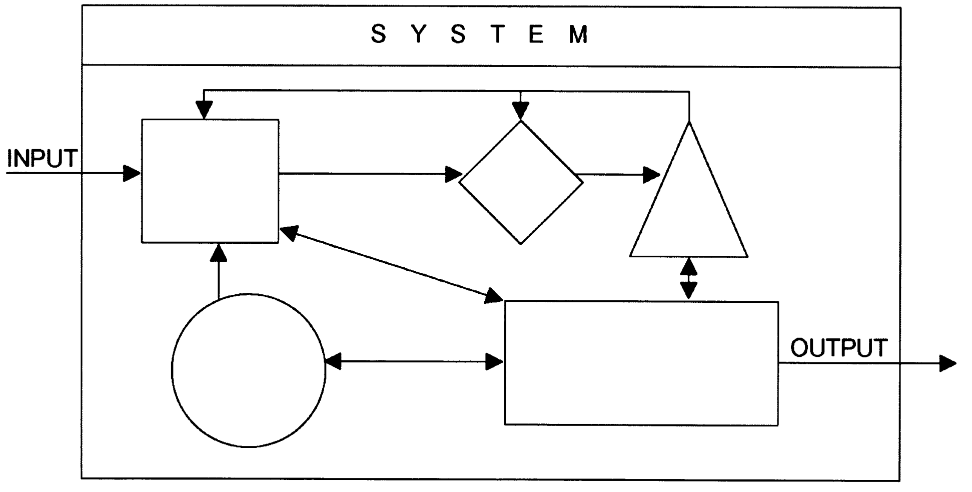

Figure 1. A system is composed of elements or parts (circle, square, rectangle, triangle, diamond) that manifest their own behavior, and can interact with each other (arrows). In addition, feedback loops may be present between elements (triangle output feeds back to diamond and square). The interaction and modulation of these elements under different conditions and different times result in a dynamic system, which can respond to the input at a particular time under particular conditions with a specific output.

various elements [4, 5]. By analogy, knowing the structure of water (H_2O) gives you no clue as to why water goes down a plughole in a vortex [6]. Likewise, with all the knowledge of the individual musicians and their instruments in isolation, one could never predict the high degree of interdependence and harmony of an orchestra playing Beethoven's Fifth Symphony [7].

System behavior may be simple or complex, static or dynamic. Simple systems follow basic rules; thus with knowledge of the elements that make up the system and the rules that govern them, one can accurately predict the system behavior under various conditions.

In contrast, a complex nonlinear system has been defined as "a system or whole consisting of an extremely large and variable number of component parts, where the individual components display marked variability over time, and are characterized by a high degree of connectivity or interdependence between variables" [8]. Rather than exhibiting random behavior, most complex nonlinear systems will tend towards and manifest certain states more often, called "attractors." This leads to "Emergence," which describes the order that arises from what on initial inspection appears to be disorder; further, such emergence can arise from local and simple rules within the system [6].

The immune system, for example, consists of various elements (macrophages, monocytes, neutrophils) that interact with each other by means of messengers or signals (immunoglobulins, cytokines, interleukins). This system is forever in a state of flux, with complex offensive and defenses maneuvers mounted against a foray of invaders. Even when exposed to an identical stimulus, this system can respond differently and various behaviors emerge depending on multiple external and internal influences.

Behavior of the elements (parts) of the system may be periodic, chaotic, or random. In addition, one element can exhibit one or more types of behavior depending on the state of the other elements of the system and the overall system status at the time examined.

Not only are nonlinear systems important to the collection and interpretation of data, but such nonlinear connectivity and variability within a system may be a requisite for health. Breakdown of these normal nonlinear rhythms may produce "pathological rhythms," which may underlie disease states [9]. Improved identification and recognition of such rhythms may help in diagnosing illness at an earlier stage [7]. In addition, timely interventions may augment healthy rhythms and suppress pathological rhythms and so maintain health [10-13].

MATERIALS AND METHODS

In preparation for this paper, a review of the English-language scientific literature was performed primarily by searching the MEDLINE and EMBASE databases for the time period 1966 through 2002. Keywords used in the search included "complex," "dynamic," "systems," "nonlinear," "linear," "chaos theory," and "complexity theory." In addition, the bibliographies of articles found were also searched for relevant articles. Also, standard texts on nonlinear systems and chaos theory were reviewed, as were nonlinear and complex systems web sites.

HISTORY OF NONLINEAR SYSTEMS

In attempt to understand system structure and function, different approaches have been used. The reductionist or mechanistic view of nature, which has been referred to as the "Newtonian Paradigm," "Cartesian reductionism," or simply "reductionism," involves reducing systems into their component parts in an attempt to understand them. This approach is fundamental to linear modeling [1].

One of the first to allude to nonlinear systems was James Clerk Maxwell, who late in the Nineteenth Century, discussed the idea of infinitely small variations in present states having effects leading to future unstable and unpredictable system behavior [14]. Further, Henri Poincaré concluded after observing bodies within the solar system, that similar influences on a dynamic system at different times do not produce similar effects [15].

In the Twentieth Century, nonlinear theory came into the spotlight by accident. In 1961, Edward Lorenz, a mathematician-meteorologist working at the Massachusetts Institute of Technology, observed what he believed was order masquerading as randomness [16]. He used a simple mathematical model of weather patterns and a computer capable of performing multiple iterations (repetitions). After accidentally inputting an incorrect decimal point in a number, he noted that small variations in initial conditions (temperature or atmospheric pressure) would cascade through various iterations into remarkably different output (weather conditions) [12, 17].

This and other observations by Lorenz were the earliest reference to chaos theory [18]. Robert May wrote about chaos in regard to deterministic nonlinear behavior in 1974, but he credits James Yorke with using the term "chaos" to describe behavior manifesting similar features to what Lorenz had observed a decade earlier [19, 20].

After penetrating much of the physical sciences, only recently has nonlinear systems theory been seriously investigated and applied within the biological sciences. Specifically, nonlinear systems are those where output is not directly proportional to input, or cannot be described by linear differential equations; such output generally cannot be modeled easily if at all [3, 21, 22]. A brief description of system element behavior will be followed by a discussion of chaos theory and complexity theory, with examples from medicine, and concluding remarks.

BEHAVIOR OF ELEMENTS OF A SYSTEM

Three types of behaviors of elements within a system have been described and include periodic, random, and chaotic behavior.

Periodic or Orderly behavior describes behavior that tends toward a particular state(s), i.e., having a fixed-point or periodic attractor (state to which the element eventually settles). Over the course of time and iterations, the element will tend towards either one particular value (a fixed-point) or periodically oscillate between one or more attractors.

Random behavior is that in which each item of the element has a certain probability of being manifest, described by a uniform or non-uniform probability distribution, with negligible deterministic effects, i.e., based on current knowledge and technology, we cannot predict the elements future behavior or output from input.

Chaotic behavior or that behaving according to "chaos theory" describes dynamic behavior that is sensitive to initial conditions, and parameter changes, deterministic (described by rules), aperiodic (does not repeat itself), and restricted within certain parameters. Chaos theory is being applied more and more to nonlinear medical systems and will thus be expanded on now.

CHAOS THEORY AND CHAOTIC BEHAVIOR

A general definition of chaos is "Chaos is defined as the quality of a deterministic mathematical system in which an extreme sensitivity to initial conditions exists" [23]. The mathematical calculations involved in modeling chaos theory requires large numbers of calculations, often iterated (repeated), thus this field has blossomed in parallel with the computer revolution [3]. The main properties of chaotic behavior are summarized in Table 1.

Important features relating to components of the human body include the ability to determine this behavior using mathematical calculations (deterministic), as well as that of being very sensitive to initial conditions. Also, elements behaving according to chaos theory never repeat exactly and manifest the effects of any small perturbation. In addition, many anatomical structures appear to have fractal organization.

Elements that exhibit chaos behavior often have a multiplicity of components, functions, feedback loops, and diverse links among variables (both micro- and macro-level) existing across different scales of organization [2]. Another interesting feature of chaos is that it is cumulative, such that when two elements manifesting chaos are coupled together, they are more likely to manifest chaos and unpredictability than if they remain apart [24]. Applications of chaotic behavior in medicine occur within the basic and clinical sciences, and examples are presented in Table 2.

Many believe that behavior governed by chaos theory underlies many human systems; some believe that "physiology is chaos" [70]. In the case of normal physiologic variability, this has been proven in several examples within the human body; however, not all physiological elements behave chaotically. In addition, although increased variability in many physiological systems correlates with health, e.g., heart rate variability, this is not always the case. Importantly, Que et al. [38] and others have demonstrated increased variability in respiratory impedance in patients with asthma. Thus, increased or decreased variability are associated with illness states.

One hypothesis regarding the importance of this variability involves uncoupling of biological oscillators and proposes that loss of connection of elements in a complex system removes various fine controls and feedback loops on their behavior, thus they revert back to an uncoupled basic, nascent or escape rhythm [71]. This rhythm is often periodic or orderly.

Are there therapeutic potentials from chaos? Perhaps. Sensitivity to initial conditions has been used by one group to convert a chaotic pattern of arrhythmia (unstable) to a low-order periodic pattern (stable) by single intermittent stimuli using a "proportional perturbation feedback" method: by delivering an electrical impulse at the right time and place, it is possible to bring about an alteration in the heart's electrical dynamics [39, 72]. In addition, it is possible to move from non-chaos to chaos in some systems by altering period and

Table 1. Main properties of chaotic behavior

Property	Definition
Deterministic	Equations of motion, variables, and parameters are specified exactly by some rule and can be applied to the element, e.g., by differential equations or other mathematical formula(e).
Sensitive dependence on initial conditions	Small variations in initial (starting) conditions result in large, divergent and dynamic transformations in outputs (concluding) events. Exemplified by the "butterfly effect," i.e., does the flap of a butterfly's wings in Brazil set off a tornado in Texas? This curious question is unproven in meteorology since buffer systems can dampen out small effects.
Emergent order	Have a sense of order, structure, and an emerging pattern (even though it may appear random on casual inspection).
Fractal organization	Have self-similarity (magnified images of fractals are essentially indistinguishable from unmagnified versions) and fractal-dimensions (follow a particular formula) e.g. The Koch Snowflake: starting with an equilateral triangle, each side is divided into thirds, the middle third segment is removed and a new smaller equilateral triangle is inserted into the middle third, and so on.
Strange attractors	The tendency for nonlinear networks to occupy a limited number of stable states out of the theoretically huge numbers of states available to them, e.g., the "Lorenz Attractor" with a weaving back and forth motion between its two wings.
Constrained values	Constrained to a relatively narrow range of values, thus the signal does not become infinitely large or small. This feature is characterized by trajectories diverging exponentially with time, but restricted within a finite area in phase space (an abstract mathematical space on a graph of two or more axes in which coordinates represent the variables needed to specify the phase or state of an element at a particular time).

amplitude modulation. This is a route to chaos termed the "quasiperiodic transition to chaos" first suggested by Ruelle and Takens; such maneuvers may help to restore chaos in systems and thus provide a new therapeutic approach to some conditions [39].

As mathematics is frequently used to model physiology, investigators have been able to apply models of chaos to living systems, some with success. Yet, this enthusiasm must be tempered by the knowledge that this is still a model, and a model can never replace the real thing, only approximate it. I will now detail a few examples of applying chaos theory within medicine.

CYTOKINES

Cytokines are small protein or glycoprotein messenger molecules that convey information from one cell to another. Over 200 have been identified including the interleukins, growth factors, chemokines, and interferons [37]. Receptors for cytokines are present on many cells, including endothelial cells, neutrophils, cytotoxic T cells, monocytes, macrophages, natural killer cells, and others. A panoply of feedback loops operates within this complex cytokine-cellular system that appears to behave in a complex nonlinear manner [8].

Table 2. Manifestations of chaotic behavior in medicine

Field	Example [Reference]
Anatomy	• Fractal structure of arteries, veins, cancellous bone tissue, nerves, pulmonary alveoli, tracheobronchial tree [25-27]. • Regional myocardial blood flow heterogeneity follows a simple fractal relation [28].
Cellular biology	• Properties of ion channel proteins [29]. • Stem cell differentiation [30]. • Calcium oscillations and intracellular signaling [31].
Molecular biology	• Fractal dimension to exon structures of DNA [32].
Oncology	• Abnormal mammographic parenchymal fractal pattern to screen for breast cancer [33]. • Fractal dimension in positron emission tomography scanning to detect melanoma [34]. • Fractal analysis in detection of colon cancer [35]. • Fractal dimension analysis in evaluating response to chemotherapy [36].
Internal medicine	• Cytokine behavior exhibiting emergent patterns [37]. • Variability in respiratory impedance in Asthma [38].
Cardiology	• Atrial fibrillation can arise from a quasiperiodic stage of period and amplitude modulation, i.e., "quasiperiodic transition to chaos" [39]. • Chaos control of arrhythmias in human subjects by stabilizing an unstable target rhythm [40]. • Endothelial function behavior [7]. • Heart rate variability: - Low-dimensional chaos associated with health [41, 42]. - Reduced fractal behavior associated with increase in sudden cardiac death [43]. - Predicting mortality following myocardial infarction [44]. - Inhibition of autonomic tone modulates heart rate variability [45]. - Congestive heart failure decreases chaos and increases morbidity [46, 47]. - Beta-blockers improve the fractal behavior in patients with advanced congestive heart failure [48]. - Gender differences in fractal measures of heart rate behavior [49]. - Coronary artery disease can alter circadian heart rate variability [50]. - Decreased heart rate variability following heart transplantation [51].
Neonatology	• Premature babies at risk for sudden infant distress syndrome have diminished nonlinear heart rate variability, which may reflect abnormal autonomic system development [52].
Pharmacology	• Pharmacodynamics of drugs and their effects can alter chaos dynamics of human systems [53, 54].
Neurology	• Epilepsy: - Epileptogenic zone location [55-57]. - Antiepileptic drug effects [58, 59]. - Predicting seizure activity [60, 61]. • EEG activity in Alzheimer's disease and vascular dementia [62]. • Neural networks manifest chaos [2].

Table 2. Manifestations of chaotic behavior in medicine (continued)

Field	Example [Reference]
Epidemiology	• Effects of pulse vaccination in simple epidemic model [63]. • Population dynamics modeling [64].
Psychiatry	• Reduced chaos on electroencephalogram may occur in altered moods, behavior, and with alcohol consumption [65, 66]. • Treatments for depression may restore biological chaos in the brain [67]. • Bipolar disorder — one model suggests this may result from strong fluctuations in energies between different brain structures which produce turbulence "chaotic attractors" which can suddenly switch between opposite states, and create new and more complex structures [68, 69].

Cytokines exhibit interdependence, pleiotropy (multiple effects), redundancy (multiple cytokines have the same effect), and can dampen or amplify the effects of other cytokines or cells [8]. Given their multiplicity and complexity of functions, it is likely that their behavior follows nonlinear dynamics. For instance, typical cytokine dose-response curves show an initial threshold (no effect below a certain concentration), followed by an exponential response, and then a plateau maximum response [37]. In healthy individuals, tumor necrosis factor-alpha causes neutrophilia at low doses but neutropenia at high doses [73]. Attractors with great stability have also been demonstrated in systems containing cytokines; when cytokine concentrations were measured within a system not in equilibrium, the system eventually converges to an equilibrium point. Additionally, by varying the activation levels of the cytokines and thus simulating what may occur in antigenic stimulation (such as an exposure to an inflammatory mediator), several stable and unstable equilibrium points have been noted experimentally [37]. Thus, it has been demonstrated that in a relatively simple system consisting of four components: effector cells, regulatory cells, cytokines, and an inhibitor — nonlinear interactions manifest chaotic behavior [37].

HEART RATE VARIABILITY

Heart rate variability (HRV)[b] involves analysis of the standard deviation of spontaneously varying interbeat intervals (R-R intervals), which can be represented in the time domain, the frequency domain, as well as recurrent patterns in higher dimensions [74, 75].

After generation by the sinoatrial node, the heartbeat is modulated by many feedback circuits from various systems. The normal heart rate displays complex fluctuations in response to breathing (heart rate increases with inspiration), exercise, changes in posture, and emotion [9]. High degrees of HRV signify health, whereas illness is manifested by reduced variability [5, 41, 42]. For example, decreased HRV has been noted in patients suffering from congestive heart failure [46, 76], and also predicts higher arrhythmic death and total mortality following myocardial infarction [44, 48, 77]. Nonlinear dynamics present in the control mechanisms of the electrical system of the heart give rise to the complex variability it manifests.

In subjects at high risk of sudden death, including those with heart failure, fractal organization along with certain nonlinear interactions breaks down; thus application of fractal analysis may provide new approaches to assessing cardiac risk and forecasting sudden cardiac death [78]

Suggested etiologies for reduced HRV include loss of neural modulation of the sinoatrial node as well as a sympathovagal imbalance [51, 79]. The vagal component appears to be of greater importance in maintaining variability [80]. Indirect evidence for these etiologies comes from several small studies. In one non-controlled study of patients with congestive heart failure, beta-blocker therapy (atenolol) was used to suppress sympathetic activation and improved HRV [48]. In another study of ten healthy men and women, low-dimensional HRV was modulated by inhibition of autonomic tone (using propranolol and atropine) and by exercise [45, 81].

Another reason for reduction in HRV may be and isolation "uncoupling" of the heart from its interaction with other organs or "biological oscillators" [71, 82]. In other words, increased system isolation may be reflected by greater signal regularity [13]

Why is a reduction in HRV deleterious? Sympathetic activation and/or reduced vagal tone may make the heart period less adaptable, thus making the heart less able to cope with a frequently changing hemodynamic and autonomic environment [5, 83].

COMPLEXITY THEORY AND COMPLEX SYSTEMS

Complexity theory or "complexity" is a new and evolving nonlinear systems theory that has attempted to capture what happens beyond what chaos theory describes, into the realm of creating new systems from existing ones, as well as the emergence of order from disorder [84]. One suggested definition is that "Complexity is the property of a real world system that is manifest in the inability of any one formalism being adequate to capture all its properties. It requires that we find distinctly different ways of interacting with systems. Distinctly different in the sense that when we make successful models, the formal systems needed to describe each distinct aspect are not derivable from each other" [85].

A useful analogy for complexity is poetry, in that poetry is the nonlinear use of language where the meaning is more than just the sum of the parts (the words). Complexity involves various elements whose collective behavior manifests at the border between order and randomness, termed "the edge of chaos" [4]. Whereas chaos is predictably unpredictable, complex behavior is unpredictably unpredictable.

Complexity science has grown out of a general lack of satisfaction with traditional scientific practices and their failure to capture anything but a shadow of complex reality [86]. In spite of the many impressive advances, the observations and explanations of biological phenomena may have been viewed through lenses polarized by a mechanistic and reductionist view, with its attendant constraints and boundaries. Complexity science demands that such barriers and constraints be removed in order to gain a more complete view of nature [86].

Complexity often describes self-organizing systems that function far from thermodynamic equilibrium and thus they require a continuous source of external energy, which they dissipate to create and maintain order [87]. The development of such order diminishes the system's entropy, a measure of the amount of disorder and randomness of the system; thus the energy is used to decrease entropy, and order is created [38].

Another feature is that out of complexity come self-organization and emergence, the links between order and disorder [4]. In other words, behaviors of many simple parts interact in such a way that the behavior of the entire system becomes complex and cannot be predicted solely on structure and function of its parts. In addition, within an entire system, complexity at one level, e.g., atoms forming a complex system on a planet, may manifest simplicity on another level, e.g., the planet orbiting the sun [88]. Paradoxically, the science

Table 3. Main properties of complex systems

Property	Example — The nervous system
Heterogeneous elements	Nerve cells (neurons), nerve fibers, dendrites, and a supporting tissue (neuroglia).
Interactions	Synapses, electrochemical interactions, no characteristic scale, no simple "on-off" switching or "all-or-none" responses.
Formation & operation	Multiple steady states, highly adaptive, plasticity, nondeterminism, dimensionality.
Diversity & variability	Fast and slow neurons, changing ecosystem of supporting cells.
Environment	Effected by local (e.g., calcium, caffeine) and general environment (e.g., autonomic nervous system tone, temperature).
Activities	Behavior, learning, language, thought.

of complexity purports that the complex patterns we see in the world are the result of underlying simplicity [6].

The study of cellular automata (or cellular automaton) has formed a major part of complexity research. Cellular automata are dynamic systems that are discrete in state, space, and time [89]. In the simplest case, a cellular automata model consists of a one-dimensional lattice of identical cells, each of which can be in one of a number of states, e.g., "on" or "off" [90]. Using various algorithms, cellular automata can provide a way of viewing interactions that arise within a population or system under different conditions [91]. This modeling is hoped to furnish new understandings of population dynamics, evolution, as well as system organization and function.

Within the medical field, systems that involve many elements simultaneously interacting are beginning to be modeled based on complexity theory. For example, the endothelial cell and its response to internal and external stimuli behaves as a complex system. Endothelial function may be altered by neurobehavioral changes, temperature, organ dysfunction, circadian rhythm, host-pathogen interactions, drugs, oxygen content, cytokines, physical stress, thrombus, and all of the cardiovascular risk factors. While dissecting out and examining the individual effects of such exposures on the endothelium (mainly *in vitro*) have increased our understanding, attempts to translate such findings to clinical management or therapeutic manipulations have generally been unsuccessful [7], i.e., applying linear models to complex nonlinear systems doesn't usually work. In addition, several researchers are discovering large numbers of transcriptional activators that interact with cytokines and other inflammatory pathways in a manner suggesting complex nonlinear system function [7].

To illustrate some of the core underlying principles of complexity theory, and using the nervous system as an example, the main properties of complex systems are described in Table 3 [7, 88].

CONCLUSIONS

While applying linear models to human systems and their elements has improved our understanding of their structure and function, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems. Such models may help in dissect-

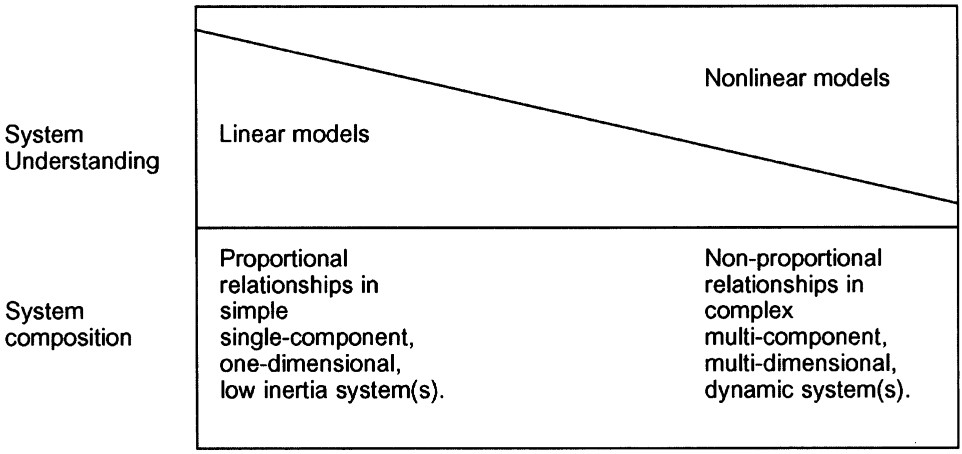

Figure 2. Role of linear and nonlinear models in understanding different systems. Amount of system understanding is represented pictorially by the two-dimensional area. Linear models may better help to explain simple proportional relationships, whereas nonlinear models may better explain complex dynamic systems.

ing and analyzing individual components of a system. However, by measuring these components under specific, ideal or standard conditions, this restricts the system to only one of its possible states and assumes a static system and a specific output, which may fail to reflect the true output of a dynamic system.

In contrast, nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux, whose output varies depending on the system state, element states, and complex interactions at the time of the input.

Nonlinear models will probably help to fill in some of the results not as yet adequately explained using linear models. Yet, not all medicine is nonlinear, so linear modeling should not be abandoned. Together, both models take us closer to a complete understanding of a systems behavior, particularly in the case of complex dynamic systems. Thus, it is believed that linear and nonlinear modeling will serve a complementary role in explaining simple and complex system behavior manifest within human systems (see Figure 2).

Chaos theory is providing new insights into understanding normal as well as abnormal behavior within systems. Applications of chaos, especially fractals, may detect disease in its early stages or "early warning."

Cytokine dynamics appear to behave in a nonlinear way, and nonlinear dynamics have a great potential for illuminating their complex dynamic applied physiology. Appropriate HRV that manifests chaos behavior is associated with health, whereas loss of this nonlinear variability portends morbidity and mortality.

Knowledge of chaos may also prove valuable in managing illness. Intervention and/or modulation of a disordered system may result in reestablishing a connection between that system and other systems, and a returning to its normal state of connectivity and variability, so called "recoupling." Such recoupling may maintain chaos when desirable, e.g., appropriate heart rate variability, and eradicate it when detrimental, e.g., cardiac arrhythmias.

Complexity theory is attempting to provide an explanation for the very origin of systems as well as how complex behaviors may arise from a relatively simple set of rules. Stuart Kauffman, a pioneer in the field, believes that complexity theory will play a major role in elucidating complex biological systems and refers to it as "the physics of biology" [6].

Finally, the notion of complex adaptive systems, "complexity theory," that is, systems that "learn" from interactions are being actively pursued. Genetic encryption of the environment in the context of biological evolution, cellular automata, and modulation of protein production using biological pulse signals are examples of ongoing complexity theory research [6, 23, 92].

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