Complexity modeling: Identify instability early

? analogous to supermaneuvrability in jet fighters? i.e., unstable, nonlinear aerodynamics

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Biological systems are innately complex, display nonlinear behavior, and respond to both disease and its treatment in similar complex ways. Complex systems display self-organization and predictive behavior along a range of possible states, often referred to as chaotic behavior, and can be both characterized and quantified in terms of this chaotic behavior, which defined strange attractors (ρ) and variability. In this context, disease can be characterized as a difference in a disease state ρ and a healthy ρ. Furthermore, effectiveness of treatment can be defined as a minimization problem to decrease the phase-state difference between disease and health ρ values, such that effective treatment is defined as the ability to restore the healthy ρ. Importantly, this approach will be effective without anything being known about the physiologic processes that define health or disease. The implication is that this approach is a powerful tool to define the determinants of instability as compared with normal variability, to answer why disease is not healthy, and to identify all potentially effective treatment options independent of known pharmacology and physiology. (Crit Care Med 2010; 38[Suppl.]:S649–S655)

Key Words: outcome prediction; nonlinear analysis; complexity of disease

We live in a complex interdependent physical world in which seemingly minor actions at one end of the globe can have profound effects on the weather on the other side of the world. Similarly, biological systems are also highly interdependent and have evolved with interconnectiveness that is poorly understood, regulated in an intrinsic and reactive manner, altered by trauma, disease, and aging, and influenced in seemingly different ways by medical treatments that display a dizzying degree of variability from one subject to the next. This reality has been termed the *butterfly effect* and underscores the inability of physicians to accurately predict patient outcomes despite advanced monitoring and knowledge of physiology. Importantly, these realities have a science devoted to them: complexity theory and its schizophrenic twin, chaos, as linked by fractal analysis. Recent advances in medicine by using tools developed to understand nonlinear complexity demonstrate its power in medicine. We and others have used this approach to diagnose cardiorespiratory insufficiency at the bedside several hours (on average) before conventional linear warning systems gave similar alerts. However, before describing these approaches, a brief primer on chaos, fractal geometry, and complexity theory will make the vocabulary and subsequent discussion clearer. This review was gleaned as a distillate from other sources and is in no way exhaustive or definitive, but it does cover the major aspects of the field. Readers interested in this topic are referred to more advanced texts for greater discussion of these concepts and their associated mathematical proofs (1–5).

A brief primer on chaos, fractals, and complexity theory

Chaos Theory and the Butterfly Effect. The term *butterfly effect* itself is related to the work of Edward Lorenz and is based on chaos theory and a sensitive dependence on initial conditions. It was first described by Jacques Hadamard in 1890 and popularized by Pierre Duhem's 1906 book *La Théorie Physique: Son Objet et sa Structure*, which holds that for any given set of observations, there is an innumerably large number of explanations. The idea that one butterfly could eventually have a far-reaching ripple effect on subsequent historic events seems to have first appeared in a 1952 short story by Ray Bradbury about time travel. In 1961, Lorenz was using a numerical computer model of 12 interconnected equations derived from fluid mechanics to predict weather patterns. When he reran this weather prediction a second time, he used a shortcut by entering 0.506 instead of the full decimal 0.506127. The result was a completely different weather scenario (6). What he realized was a defining moment in chaos theory and of a concept previously unknown. Specifically, systems in which tiny variations in initial conditions can produce large differences in later states of the system are known as *chaotic systems.* Lorenz noted that "one meteorologist remarked that if the theory were correct, one flap of a seagull's wings could change the course of weather forever." Later speeches and papers by Lorenz used the more poetic butterfly to replace the seagull, to the consternation of ornithologists everywhere. According to Lorenz, upon failing to provide a title for a talk he was to present at the 139th meeting of the American Association for the Advancement of Science in 1972, Philip Merilees concocted the title, *Does the Flap of a Butterfly's Wings in Brazil Set Off a Tornado in Texas?* The Wikipedia description of the butterfly effect summarizes this concept as follows: "The flapping wing represents a small change in the initial condition of the system, which causes a chain of events leading to large-scale alterations of events. Had the butterfly not flapped its wings, the trajectory of the system might have been vastly different. Although the butterfly does not cause the tornado in the sense of provid-

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ing the energy for the tornado, it does cause it in the sense that the flap of its wings is an essential part of the initial conditions resulting in a tornado, and without that flap that particular tornado would not have existed."

It is useful to give concrete examples to serve as illustration. One could plot a simple time series of values based on a formula $x_{t+1} = ax_t[1 - x_t^2]\ y + 1/bz$, where x_t is a variable x at time t, a and b are constants, and y and z are related to x by the formula $x = c(y/z)$. If we use a number less than 1 as the initial x value, say 0.6200, and plot out the resultant x-y values, they would plot out a pathway that seems erratic but nevertheless behaves in a remarkably predictable pattern. Plotting the same time series but using 0.6201 as the starting value, merely 10^{-5} of a decimal point less, would show initially similar trends for the first 23 iterations but then diverge widely from the first series. Although initially the two graphs initially behave in a similar fashion, they rapidly diverge and seem to bear no relation to each other in terms of where they are at a specific point in time though they both track identical space, sort of like electrons around a nucleus. This quality defines that in non-linear systems the actual state one finds oneself is extremely sensitive on initial conditions. Second, despite apparent random behavior by the two graphs, they are both described by the same simple equation thus their behavior is highly deterministic. Accordingly, in chaos theory, three types of behaviors can be defined: *periodic*, which repeat themselves over some finite time interval, *chaotic*, which, while deterministic, demonstrate complex behavior and do not repeat themselves, and *random*, which are unpredictable and non-deterministic (7). Furthermore, the general shape of the two graphs is nearly identical, so while the exact position of a subject at any timepoint cannot be predicted with accuracy, one can accurately predict the phase space into which this subject will travel. This aspect of nonlinear systems is called *aperiodic behavior*.

Thus, chaos is not random but rather a highly structured behavior that is completely dependent on earlier states. This point has profound implications for science in general, and medicine in particular. Because the behavior is so sensitive on the initial state and since that may vary among subjects, even knowing exactly how systems interact, such as autonomic tone and blood pressure or heart rate, one is still unable to predict with any accuracy the behavior of the system. This is because of the inability in knowing the initial state with the degree of accuracy necessary to minimize subsequent variance. Regrettably, the intensive care unit bedside approach of trying to make measurements to within "an acceptable degree of measurement error" will not allow accurate predictions of subsequent behavior. Thus, highly predictive models of critical illness cannot rely on simple linear models of stimulus-response or output proportional to some degree of input but must embrace complexity in the development of predictive models. This is the logic for applying complexity modeling to identify the physiologic state and, by inference, disease.

Linear and Nonlinear Systems. Dynamics is the study of how a system changes with time, and hemodynamics is the study of how cardiovascular systems change with time. Systems are either linear or nonlinear. A simple linear system is completely described by linear equations, such as $x_{t+1} = ax_t + c$, where x_t is a variable x at time t, and a and c are constants. Importantly, linear relationships define straight-line relations where an increase in one value results in a proportional change in another. Another characteristic of a linear system is that the variables in a linear system are not interdependent. Thus, the overall behavior of any linear system containing many variables is the sum of the individual components. Relevant to life, linear systems are predictable at a given time if earlier conditions are known. Although linear systems are common in industry (e.g., internal combustion engine power output vs. piston gas flux), they are extremely rare in nature. Still, we teach physiology by using rules that presume hemodynamics and pharmacokinetics are linear. Drug metabolism is an example of linear mechanics. The determinants of drug levels in the blood include the initial loading dose and subsequent doses and their timing, route of administration, volume of distribution, and rate of metabolism or clearance. However, the volume of distribution is independent of the clearance rate, and both can be calculated independently of each other because they each reflect linear systems.

However, nonlinear systems occur more commonly in nature. Examples include the innate immune response to foreign antigen, blood flow distribution, heart rate variability (HRV), and localized cortical neurologic activity. Just like the weather, the behavior of a nonlinear system may be impossible to accurately predict. Because nonlinear systems behave in a chaotic fashion, such systems are difficult if not impossible to understand by using simple linear models. This reality underlying the difficulties underlying research into complex systems like heart failure, sepsis, and multiple systems organ failure. Thus, if we are to truly understand disease and its response to therapy, we require a new set of modeling tools and mathematical principles to be able to understand and predict biological behaviors. The initial model developed by Lorenz to explain chaotic behavior required only three interconnected equations:

$$dx/dt = -\sigma\ (x_t + y_t)$$

$$dy/dt = -x_t z_t + r\ x_t - y_t$$

$$dz/dt = x_t y_t - b\ z_t$$

for variables x, y, and z and constants σ, r, and b, where σ is called the *Prandtl number* and ρ the *Rayleigh number*. All values of σ, ρ, and β exceed 0, but usually $\sigma = 10$, $\beta = 8/3$, and ρ is variable. The system exhibits chaotic behavior for $\rho = 28$ but displays knotted periodic orbits for other values. All three equations are interdependent having, at a minimum, variables x and y in x, y, and z space (three dimensional). Plotting real values of these equations relative to a specific system, like blood flow or blood pressure, describes each system's aperiodic behavior. A system that is plotted through all its potential states is called its *phase space*. Of importance, when plotting such phase space, it may describe one of three different patterns. The behavior may simplify down to a constant repeated value, at which time the system is said to be in a steady state. Furthermore, it may create a racetrack of cycling values over time referred to as *periodic behavior*. Both steady-state and periodic behavior regions in phase space are known as *attractors*. However, more commonly, the solution to the equations creates an ever-changing pattern that resembles a butterfly-like figure that never exceeds certain values but never repeats itself either (Fig. 1). The butterfly shape is called a *Lorenz strange attractor*. It also defines the third law of chaos, namely, that chaotic systems "are confined to a certain range of values and the value of the system does not repeat." Such constant variation that occurs within defined limits is the rule rather than the exception in nature. HRV and

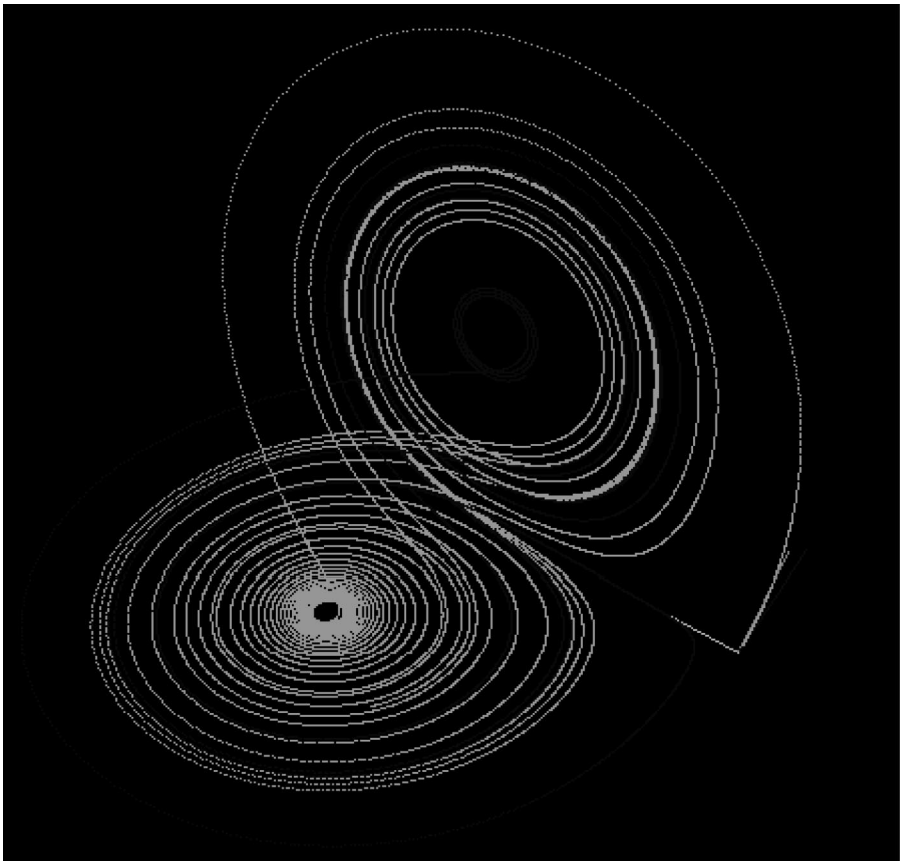

Figure 1. This figure, made using $\rho = 28$, $\sigma = 10$ and $\beta = 8/3$, shows three time segments of the evolution of trajectories in the Lorenz attractor. Reproduced from Wikipedia [Lorenz attractor] with permission.

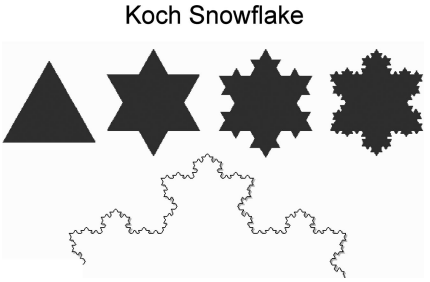

Figure 2. Fractal geometry with increasing complexity shown as a Koch snowflake.

varying breathing patterns represent two obvious examples, but blood pressure variability, microcirculatory flow phase among capillaries, and ventricular contraction synchrony also represent Lorenz strange attractors (8–12).

Fractal Geometry. The Lorenz strange attractor is one example of a fractal object. In 1975 Mandelbrot described the concept of *fractals* as the geometry of irregular shapes that look the same on all scales of length (13). A fractal structure exhibits *self-similarity*, i.e., no matter how closely one inspects it, a structure is apparent on a small scale that is identical to the large-scale structure of the object. A geometric example of a fractal is provided by the Koch snowflake (Fig. 2). Start with an equilateral triangle, and, taking the middle third of each side, attach an equilateral triangle with sides one third the length of the large triangle. The result is a Star of David. The process is repeated on all 12 sides of the star and then repeated again on all straight sides of the new figure, and so on indefinitely. No matter what scale of length under which one examines the snowflake, it will have the same appearance. In biology the obvious examples of fractal structure are the vascular tree, repeatedly branching and dividing from aorta to the smallest capillary, and the bronchial tree down from the trachea to the alveolar ducts (14).

Complexity Theory. Complexity deals with the capacity of systems composed of simple units at any level (atoms, molecules, neurons, computer processors, or people) to self-organize and evolve in time. This has been the topic of several novels and a few recent movies expanding on the potential that self-organization implies. In reality, self-organization surrounds us at all levels, and it is this self-organization that allows complexity theory to be used to predict state and thus identify instability in at-risk patients. The concept is that by following a set of amazingly simple rules, entire armies of termites create defined structures in a matter of minutes. In medicine, the traditional macroscopic descriptions of signs and symptoms have given way during the latter part of the 20th century to pathologic descriptions of microorganisms, cellular processes, and organ-system interactions. Although the reductionist approach has been successful to date and forms the majority of logic used at present in scientific publications, it cannot provide a complete description of the universe, our own world, populations, organisms, or subatomic particles.

Reductionist science depends on analyzing objects and phenomena in isolation. This is the essence of laboratory science, wherein a complex relationship is artificially abstracted into simple yes-no, up-down solutions to a high degree of accuracy. For example, a myocardial infarction is assessed relative to the interaction between energy delivery (blood flow) and metabolic demand (myocardial oxygen requirements). However, as described below, most myocardial infarctions present specific signature changes in R-R intervals long before any actual flow-induced ischemic changes occur to the cardiac myocytes. Expanding on this further, the stress causing the myocardial infarction has known external contributors, like social stressors, depression, and personality characteristics. Although paying lip service to these factors, reductionism usually excludes all but the most direct factors in defining ischemic risk and outcome from an acute coronary syndrome.

The central feature of complex systems is their inherent ability to self-organize. This is referred to as emergent behavior. This collective behavior of complex systems occurs spontaneously. What can emergent systems do that other systems cannot? First of all, they are robust and resilient. There is no single point of failure, so if a single unit fails, becomes lost, or is stolen, the system still works. Second, they are well suited to the real world. Human-engineered systems may be optimal but often require effort to design and are fragile in the face of changing conditions. Importantly, complex systems do not need to have complete knowledge or understanding to achieve a goal. Finally, they find a reason-

able solution quickly and then optimize. Since, in the real world, time matters, this quality is extremely well suited for adaptive biological systems because decisions need to be taken while they are still relevant. For example, computer algorithms tend to not produce a useful result until they are complete; for an organism this may be too late. Complexity theory attempts to analyze this self-organization aspect of dynamics and use it to define useful and maladaptive behaviors. Because order emerges spontaneously in complex systems, this will have a survival advantage for that system in a changing environment. I previously used to claim that *intelligence* was the ability of an organism to adapt to a changing environment. That definition must now be modified to say that intelligence is the effective use of complexity by a biological system to adapt to a changing environment.

From a Darwinian perspective, there is a clear survival advantage for an organism which remains in a state capable of self-organization so that it may adapt. From the above discussion about chaos theory, it is clear that such systems follow nonlinear dynamics and their processes are interconnected. In essence, we have just described the human body. However, chaos and continued adaptation are energy-requiring processes; although adaptive, they are by their very nature not stable but are in a type of equilibrium. Clearly, certain biological processes do better when their behavior is well defined, such as bone stiffness, muscle-ligament orientation, and neuron-vascular reflex arcs. On the other hand, other systems such as thought, the immune system, and blood flow distribution require a more adaptive perspective to sustain a survival advantage.

The Edge of Chaos. From the above discussion it is clear that some systems function better when they are constantly changing, whereas others do best in a more stable state. From this perspective came the concept of living at the *edge of chaos*. The paradox created by the above construct is that if a complex system generates order spontaneously, then how does it avoid becoming too ordered and lose its future ability to adapt? Similarly, if it is too disordered, it would not have the minimal structure necessary to sustain complex functions, such as blood flow and thermal regulation. How is it that complex systems avoid the extremities of stability and random behavior? In his book *At Home in the Universe*, Kauffman (2) proposes that life should be considered a complex ordered system sitting near the transition between order and chaos. Such a placement of life would have many advantages. It would allow for rapid sensing of change and coordinate adaptation with a minimal amount of delay and cost, while providing enough structure to insure stability. If this hypothesis is correct, then it would drastically change the concept of evolution as postulated by Darwin. Darwinian evolution opines that random mutations occur in the species which are either adaptive or maladaptive. Those that are adaptive and provide a survival advantage are passed on to their offspring, whereas those that are not adaptive die off before having offspring. Mutations by this process are random events of nature. However, if complexity theory is correct, then life arose not randomly as a few nucleic acids formed by thermoelectric activity in the primordial swamp but by spontaneous organization. Accordingly, the resultant life forms would not be accidents of nature but the product of the environment that they were born into. Although creationists will have my head for this, it allows for an accelerated evolution of species beyond that predicted by random mutations and without intelligent design.

Using complexity theory to define health and identify disease

Traditional medical teaching has always held that health represents a steady state at rest, whereas disease reflects the wildly uncontrolled and deregulated processes of maladaptation. However, under normal resting conditions, healthy reactive biological processes, such as the nervous, immune, and hemodynamic systems, are not static and unchanging but, as will be shown below, display continual change of a minor but characteristic nature. Importantly, this reality flies in the face of traditional views that health is defined by a steady-state equilibrium. In fact, normal homeostasis is often a restless search of physiologic systems, such as blood pressure and blood flow distribution, for the optimal state within boundaries from which to operate. These slight variations may seem random but, when analyzed by using complexity theory that quantifies order and entropy, can be clearly demonstrated to be chaotic. Interestingly, the traditional concept of disease is that it fluctuates widely, whereas studies of disease using complexity theory demonstrate that, if anything, disease is characterized by a loss of chaos and an increasingly constant behavior. In a sense, disease reflects a loss of the ability to adapt. Similarly, external stressors such as exercise, thermal challenge (hypo- or hyperthermia), and anxiety (15) markedly decrease the intrinsic variance of many biological systems including the immune, vascular, and limbic systems. Clearly, there is no condition more stable and static than death. This may be the reason why subjects with depression have an increased risk of cancer and infection and why a positive attitude is an important component of the arsenal for recovery. For a detailed discussion of this topic and specific references, the reader is referred to recent review articles (16, 17).

HRV. Perhaps the most widely studied example of the clinical utility of complexity theory comes from its use in identifying those subjects at risk of an impending acute coronary syndrome. Cardiologists have long been interested in studying cardiac rhythm and examining the R-R interval variation, referred to as HRV. HRV is currently quantified in the time domain and by using Fourier analysis in the frequency domain. However, both of these forms of quantification reflect linear analysis (18, l9). Time domain analysis is based on statistical manipulation of R-R intervals, whereas frequency domain analysis (or spectral analysis) looks at the variability around a particular heart rate value. A spectrum of values is produced with peaks around highly variable values, such as respiratory frequency, as this reflects the normal autonomic influence of respiration on vagal tone. Spontaneous inspiration causes immediate vagal withdrawal and cardiac acceleration, referred to as *respiratory sinus arrhythmia*. This can be quantified by using Fourier transformations of the R-R intervals into the time domain and examining the harmonics coincident with the respiratory rate. This approach demonstrated that diabetic neuropathy first manifests itself as loss of respiratory sinus arrhythmia; its reemergence coincides with recovery of tight glucose control (20). Similarly, cardiac transplantation, which creates a denervated heart, does not completely abolish respiratory sinus arrhythmia but does reduce its power by 100-fold (21). These linear modeling methods provide excellent analyses of such periodic influences on heart rate. However, there are also nonperiodic influences such as exercise,

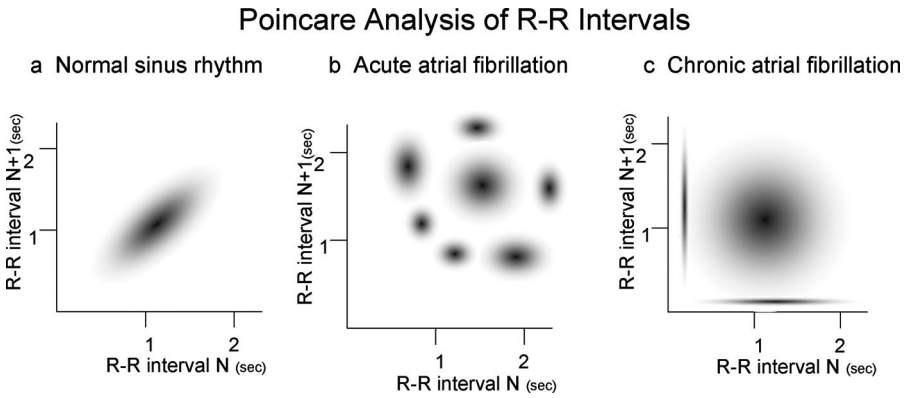

Figure 3. Hypothetical Poincare analysis of R-R intervals for normal sinus rhythm (*a*) acute atrial fibrillation (*b*), and chronic atrial fibrillation (*c*). Note the order seen for the R-R intervals during acute atrial fibrillation (chaotic), whereas chronic atrial fibrillation has random R-R intervals.

thermal stress, psychological state, and baroreceptor activity, which are not characterized by this form of analysis because they do not take into account beat-to-beat variations in heart rate.

Using nonlinear dynamics as a modeling tool, several groups have examined the intrinsic R-R variability of normal sinus rhythm (Fig. 3) (19, 22). Using Poincare plot analysis to analyze R-R interval variations, Woo et al (23) demonstrated that the complexity seen in normal subjects was lost in heart failure independent of changes in heart rate. Poincare plotting examines the frequency of one event with the next and then that one to its subsequent event. Relevant to acute medicine, decreases in HRV occur not only with aging and congestive heart failure but also with sudden cardiac death (24–26). HRV can be quantified by many means. The simplest is the SD of the mean of all nonectopic R-R intervals. Loss of the low-frequency HRV by Fourier analysis is also a measure of decreased complexity. Myocardial infarction decreases HRV and, at the extreme, is associated with sudden cardiac death (27).

A low HRV (as measured by the SD of the mean of all nonectopic R-R intervals) is strongly associated with mortality, independent of other indices such as ejection fraction or exercise tolerance. It is now widely accepted that myocardial infarction causes a decreased HRV and that this, in turn, is associated with sudden cardiac death. Although these changes define that complexity is lost in disease, its usefulness primarily comes from predicting events and identifying disease before treatments to reverse processes become ineffective. Thus, the focus on HRV analysis has been on identifying those patients who develop arrhythmias and those at increased risk of sudden cardiac death. Several methods have been proposed (28–30) but, regrettably, no noninvasive technique is presently accurate enough to be used as a bedside tool. Analyzing the variability of the Q-T interval does however seem promising.

Several investigators have opined that although complexity theory dictates that chaotic states are exquisitely sensitive to their initial state, making accurate predictions of outcome impossible, that same sensitivity makes them highly susceptible to control with minor interventions. In support of that concept, cardiac pacing at times defined by a computer program that analyzed the R-R interval changes and paced to offset chaos progression prevented asystole in an isolated cardiac muscle preparation prone to cardiac toxicity, whereas fixed pacing had no effect (12). Whether or not such analyses can be applied to intact hearts *in situ* remains to be seen.

Complexity modeling and sepsis

Sepsis, septic shock, and the development of multiple organ failure reflect the major challenge confronting critical care medicine specialists since the start of their specialty (31). Perhaps the most exciting, although most speculative, of the applications of nonlinear dynamics to medicine has been its integration into a model of the pathogenesis of multiple organ dysfunction. In this regard, Burykin and Buchman (32) have been thought leaders in this field. Our understanding of most of the complex processes associated with critical illnesses comprises grouping symptoms and signs and calling them syndromes. Thus, we understand acute lung injury as the acute respiratory distress syndrome and multiple seemingly unrelated organ failures associated with profound critical illness as multiple organ dysfunction syndrome (MODS). Because these syndromes commonly occur in critically ill patients and when present are associated with increased mortality, they are presumed to follow common pathways that include activation of the inflammatory systems. Our thinking on this process has slowly evolved. First, MODS was thought to involve a massive proinflammatory response. However, it was subsequently shown that persistence of a generalized inflammatory response, rather than its magnitude, was the primary driver for its development (33). Subsequent studies revealed that MODS was associated as much with immune suppression as the proinflammatory state alone, as the anti-inflammatory processes overwhelmed normal innate immune defenses (34, 35). This evolved to an understanding that mitochondrial damage and apoptosis were central effector arms in the process of death from critical illness (36). Considering the complexity of these biological systems, their interconnectivity, the differing states in which patients present, and their baseline physiologic state before therapy, is there any surprise that monotherapy with even the most potential anti-inflammatory and immunomodulating agents is only minimally effective at best?

Godin and Buchman (37) address this problem by using complexity modeling. They reasoned that because the order and stability found in biological systems depends on the connections between the system's constituents, the progression from an initial systemic inflammatory response to MODS abolishes the connections between organs, resulting in a loss of complexity. If so, then linkage between HRV and breathing is lost, baroreceptor tone sensing and vasomotor tone is lost, and endocrine homeostasis is blunted. All these effects are central characteristics of septic shock and MODS. The strength of their reasoning came with the final step in their logic. They predicted that irreversibility may be due either to irreversible organ damage or to irreversible effects on connections. This implies that, to restore health, we need not only restore organs to a functional state, but also restore a state of connectedness between individual organs. In support of this concept, liver transplant patients with acute rejection and acute respiratory distress

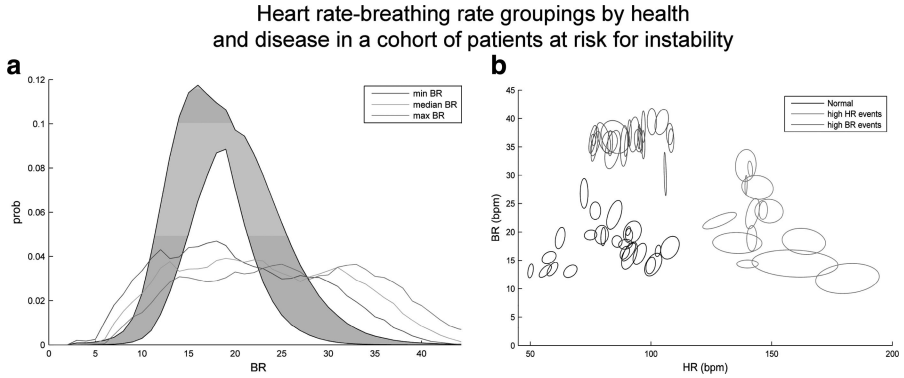

Figure 4. Analysis of 671 step-down unit patients continuous recordings of probability (a) probability (*prob*) distribution for breathing rate (BR) or respiratory rate of normal subjects (*shaded area* ± SD) and unstable subjects, minimum (*min*), median, and maximum (*max*) values and (*b*) BR-heart rate (*HR*) groupings per patient for normal patients, those with high heart rate, and those with high BR.

syndrome may completely recover within hours of receiving a new liver, which presumably alters the toxic effects of the interconnectivity.

Based on this logic we have studied the interconnections among heart rate, respiratory rate, pulse oxygen saturation (Spo_2), and blood pressure in patients at risk of developing cardiorespiratory insufficiency (38). In collaboration with Oxford BioSignals, we used their complexity model of instability defined as the *BioSignals index* (BSI). The data fusion method used to calculate BSI utilizes neural networking to develop a probabilistic model of normality in four dimensions, previously learned from a representative sample of a 150-patient training set. Variance from this data set is used to evaluate the probability that the patient-derived vital signs are considered normal. The generated BSI ranges from 0 (no abnormality) to 10 (severe abnormalities in all variables). A BSI of ≥3 is deemed to reflect significant cardiorespiratory instability requiring medical attention (39). Using this method, we studied all 326 patients admitted to one step-down unit over an 8-wk period, reflecting over 18,000 hrs of continuous monitoring. The nursing staff was blinded to the BSI data. Medical emergency team activation occurred seven times during this study interval. In each case the BSI signal would have alerted the nurses to the patient's instability a minimum of 30 mins beforehand and with a mean lead time of 6.2 hrs. Furthermore, the patterns of heart rate-respiratory rate between groups differed depending on whether or not they were unstable, having either primary cardiac problems or respiratory problems (Fig. 4). As shown in Figure 4, both the probability of a given heart rate distribution and the heart rate-respiratory rate groupings between stable step-down unit patients and those with instability were markedly different. These data suggest that dynamics of linkage between desperate physiologic variables exist during disease, and these linkages may be used to identify patients and define their primary illness. The potential application of this approach in the monitoring of the critically ill patient population remains untapped.

CONCLUSION

Nonlinear dynamics and complexity modeling reflect new and powerful tools that may allow us to see into the soul of disease. Complex systems are highly dependent upon initial state in determining the final state and are self-organizing. Thus, treatments may not need to fully restore health but merely make disease less attractive to the system for it to restore itself. The sensitivity of these forms of analyses to define state and its change should also allow for a more specific analysis of the effectiveness of novel and existing treatments and, as alluded to above, should define potential treatments not previously considered. Because one cannot use reductionist thinking to understand complex systems and their responses to change, it is important to understand and use these approaches proactively in the study of critical illness and its response to therapy. However, although complexity modeling can define complex systems and predict with accuracy the probability of events, they do require external validation as to what is considered good or bad. They allow linear descriptions of nonlinear issues without any insight into the processes that define a given physiologic state. Thus, without context this characterization of state, either health or disease, is purely descriptive and arbitrary.

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