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Commentary

What is physiologic complexity and how does it change with aging and disease?

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1. Introduction

A defining but elusive feature of physiologic systems is their daunting complexity. This complexity arises from the interaction of a myriad of structural units and regulatory feedback loops that operate over a wide range of temporal and spatial scales, enabling the organism to adapt to the stresses of everyday life. Quantifying and modeling the remarkable and often bewildering repertoire of behaviors exhibited by living organisms is one of the major challenges of contemporary science [4,7]. The combination of nonlinearity and nonstationarity, more the rule than the exception in the output of physiologic systems, poses a major challenge to conventional biostatistical assessments and standard reductionist modeling stratagems. To describe and quantify the mechanisms of these "nonhomeostatic" behaviors, investigators have employed new techniques derived from complexity theory, including fractal analysis and nonlinear dynamics. The appropriate application and interpretation of such metrics, however, remains incompletely explored. What is clear is that reliance on any single test may give a misleading representation of physiological complexity.

In this issue, Vaillancourt and Newell critique and suggest modifications to a general dynamical model of pathophysiology that we and others have elaborated over the past two decades [5,6,8,10,13,14,16,20,21,27]. The theory of complexity loss in aging and disease, as currently formulated, has two central postulates:

1. The output of healthy systems, under certain parameter conditions, reveals a type of complex variability associated with long-range (fractal) correlations, along with distinct classes of nonlinear interactions;
2. This type of multi-scale, nonlinear complexity breaks down with aging and disease, reducing the adaptive capabilities of the individual.

The term *nonlinear* applies to systems whose components interact in a non-additive way. Nonlinear coupling may lead to an extraordinary range of dynamics, including different classes of abrupt changes, (such as bifurcations), deterministic chaos, nonlinear phase transitions, pacemaker entrainment and resetting, stochastic resonance, wave phenomena (including spiral waves, solitons, and scroll waves), emergent phenomena, and certain types of fractal scaling. Understanding the specific classes of nonlinear interactions seen in healthy physiology and characterizing their perturbations with aging and disease is just beginning [4,16,27].

The term *fractal* applies to complex-like objects, which may be generated by stochastic or nonlinear deterministic mechanisms. Fractal objects show self-similarity (scale-invariance), such that the smaller-scale structure resembles the larger-scale form [10]. Examples in anatomy include the His-Purkinje network and the tracheobronchial tree. The fractal concept also extends to complex processes that lack a characteristic, or a single, time scale. Fractal processes generate fluctuations over multiple time scales, and their frequency spectra typically show an inverse power-law (1/*f*-like) scaling pattern. Of particular interest is a class of fractal processes that demonstrates long-range correlations. This type of "memory" effect has been identified in the fluctuations of the healthy heartbeat, as well as in the interstride interval fluctuations in the walking patterns of healthy adults [14,15,21,22].

A central caveat when applying concepts and techniques from complexity theory to biomedicine is the recognition

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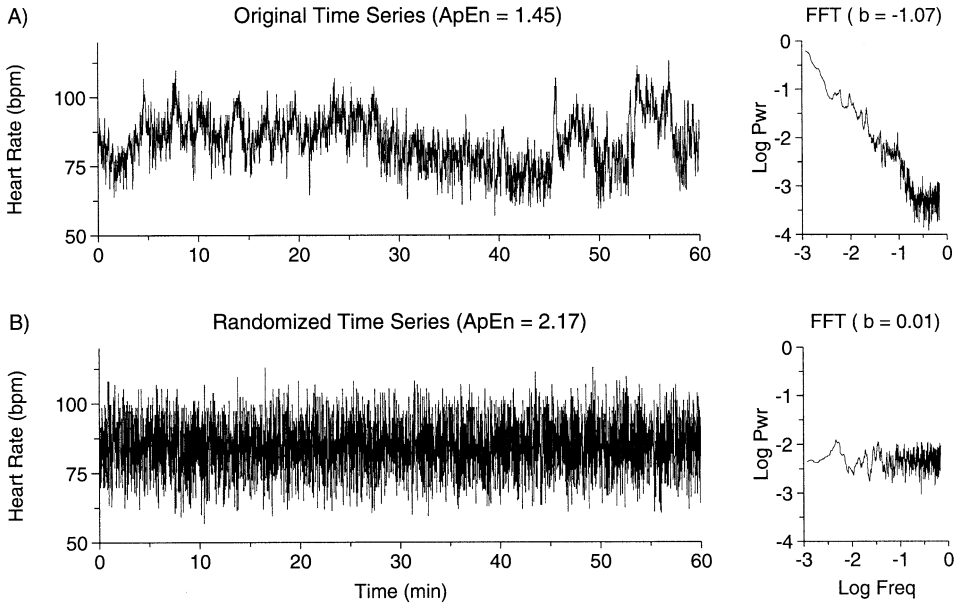

Fig. 1. A. Heartbeat time series from a healthy individual showing multi-scale, complex patterns of variability. The frequency spectrum (log power vs. log frequency) shows a 1/*f*-like scaling pattern (exponent b ~ 1) consistent with long-range (fractal) correlations. B. The same time series in A has been shuffled so the data points are randomized. The flat spectrum (exponent b ~ 0) indicates uncorrelated (white) noise. However, note that ApEn is higher for the less physiologically complex time series in B, in which the fractal and nonlinear properties have been destroyed by the randomization procedure. This example illustrates one of the limitations in relying on a single mathematical measure, such as ApEn, to assess physiologic complexity.

that no single statistical measure can be used to assess the complexity of physiologic systems. Instead, a "toolkit" of extensive, still-evolving (and as yet undiscovered) metrics is needed to probe different aspects of these extraordinarily complicated behaviors under both healthy and pathophysiologic conditions [7]. A case in point is approximate entropy (ApEn). This measure was designed to quantify the degree of predictability of a series of data points [9,24–26]. Therefore, ApEn is fundamentally a "regularity" statistic, not a direct index of physiologic complexity. Further, ApEn does not probe the nonlinear properties of the signal, nor does it quantify fractal scaling behavior. Vaillancourt and Newell themselves acknowledge that an increase in ApEn is not necessarily synonymous with an increase in physiologic complexity. The following experiment demonstrates this point (Fig. 1). Take a sequence of data points representing the interbeat interval time series of a healthy heartbeat, an output that has recently been found to represent one of the most complex (i.e. multifractal) processes in nature [16]. Next, shuffle the order of the data points, creating a randomized surrogate dataset. The ApEn value of the new dataset will increase. However, this reordered or randomized white noise signal – in which the fractal correlation properties, as well as the nonlinear interactions, have been destroyed – is *less*, and not *more* physiologically complex by the definition given above. In this case, a loss of physiologic complexity (despite an increase in ApEn) is better assessed using scaling techniques and other measures that can detect and quantify the presence of long-range correlations in nonstationary time series, as well as possible nonlinear interactions [16,21,22]. *Thus, increased irregularity does not imply increased physiologic complexity* [5].

Previous and recent work by our group and others has demonstrated the utility of fractal scaling measures as one class of tools to help quantify certain features of physiological complexity [2,5,16–18,21–23,28]. We [21,23] have noted, specifically, that the breakdown of long-range (fractal) correlations in a physiological system can ultimately lead to at least three dynamical "end-states": (1) highly periodic (predictable) behavior (e.g. Parkinsonian tremors) [6,20]; (2) a random walk (brown noise) (e.g. fluctuations in the center of pressure when a patient with a balance disorder stands on a force-plate) [3]; or (3) completely uncorrelated (white) noise (e.g. short-term heart rate variability in atrial fibrillation) [5]. States 1 and 2 both indicate only trivial long-range correlations. State 1, emphasized in our 1992 paper [20], cited by Vaillancourt and Newell, will indeed be associated with reduced ApEn. However, State 3 will be associated with increased ApEn, despite the fact that it represents the degradation of normal physiologic control mechanisms governing healthy function (Fig. 1).

Vaillancourt and Newell seek to modify the original complexity loss theory of disease and aging by proposing that the complexity of physiologic signals may not only decrease, but also actually *increase* under certain pathologic conditions. They base their latter claim primarily on data showing increased irregularity in the output of certain perturbed systems. For example, ApEn values computed for cortisol fluctuations in subjects with Cushing's disease were found to be higher than those of healthy controls [11].

However, as noted above, an increase in the ApEn value for a given time series (implying an increase in irregularity/decrease in predictability) does not necessarily indicate an increase in physiologic or physical [29] complexity. Instead, this finding may simply be related to a breakdown in multiscale correlations, such as one sees in the example of the randomized heartbeat time series (Fig. 1), or due to more subtle perturbations in nonlinear control.

To support their contention that *physiological* complexity may increase with disease, Vaillancourt and Newell also cite data from our own laboratory [12,13] demonstrating a loss of correlations in inter-stride interval fluctuations in subjects with Huntington's chorea as compared to healthy controls. Here again, their definition of physiologic complexity is based entirely on an increase in unpredictability or irregularity, and fails to incorporate other essential features, such as the presence of long-range fractal correlations [21, 29]. Indeed, when one examines the fractal complexity of inter-stride interval fluctuations in health and disease, a *breakdown* of long-range correlation properties is observed [13], in keeping with the general complexity-loss hypothesis presented above.

Vaillancourt and Newell make two additional claims to support their speculations regarding possible bases for a paradoxic increase in biologic complexity with pathophysiology. First, they cite the healthy heartbeat as an example of a fixed-point attractor, in which the heart rate fluctuates around a homeostatic set point (steady state). Attractors are usually identified in phase-space maps that plot a given value in a time series (e.g. heart rate) against a subsequent value, separated by a fixed time lag. In fact, phase-space (delay map) representations of the healthy heartbeat reveal a very complex type of "attractor" [10]. In contrast, behavior resembling a limit cycle or fixed-point attractor is actually seen in the most severe pathologic conditions, including end-stage heart failure.[1] Second, the authors contend that healthy human gait can be modeled as a limit cycle attractor-type process. However, Hausdorff and colleagues [14, 15] have shown that fluctuations in inter-stride intervals during usual walking display a type of long-range correlation quite different from a limit cycle. Based on such findings, Hausdorff et al. [14,21] have proposed a reconsideration of classic central pattern generator oscillatory models underlying the control of locomotion.

The actual data supporting some of the cited reports on the complex dynamics of human heartbeat and gait are now available via the NIH-sponsored *Research Resource for Complex Physiologic Signals* [7] website (*www.physionet.org*). Readers may explore the original time series data from our own and other studies. We believe that the open-source availability of the actual raw signals, as well as the diagnostic algorithms, is essential to this purpose, and invite others to contribute their data and analytic source codes to the NIH PhysioBank and PhysioToolkit archives. For example, re-exploration of the original hormone assay datasets described by Vaillancourt and Newell (in which ApEn reportedly increased with disease) would help determine whether this pathologic increase in irregularity represents an actual increase in physiologic complexity, or is instead associated with a breakdown of correlation properties and alteration of nonlinear interactions, indicating a complexity-loss mechanism [5,16,21]. Availability of original data allows for continual reassessment of such invaluable datasets using new techniques as they become available, as well as modifications and refinements of older ones.

Finally, we note that the resolution of questions and debates regarding definitions of physiologic versus other types of complexity and their quantitative evaluation does not simply represent "in-house" sparring over semantic technicalities. Answers to these questions hold enormous promise for providing new understanding of the fundamental mechanisms underlying some of the most complicated signaling networks in nature and how they change with disease and aging. The elucidation of novel assays for drug effects and toxicities, as well as non-pharmacologic interventions, the development of "dynamical phenotyping" in the post-genomic era, and the description of new clinical diagnostic and prognostic measures in a wide range of life-threatening conditions all depend critically on this multidisciplinary, 21st-century enterprise.

[1] As noted, the healthy heartbeat, even in subjects at rest, has recently been shown to be a member of a special class of complex *multifractal* processes that require a large number of exponents to characterize their scaling properties [1,16]. The presence of such extraordinarily complicated behavior is more consistent with control mechanisms related to coupled cascades of feedback loops in a system operating far from equilibrium than it is with classic homeostasis and servomechanistic models of control [1,16,19].

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