The meaning and measurement of physiologic variability?*

The history of physiology is really the story of oscillations in living systems (1). When asked to define physiology to nonprofessional, I have often responded, "If it wiggles, it's physiology; if it stops wiggling, it's anatomy!" Indeed, life implies activity and movement. At first blink, the common sine-wave oscillator can model many physiologic actions such as running legs or beating hearts. But on closer examination, we note that such smooth oscillatory behaviors are more often violated than obeyed by real living systems. Thus, in the time domain, repeated cycles within the same system are rarely identical except alone continuous. So much for the (boring) sine-wave model!

Fourier spectral techniques, developed from wave motions of the sea (2), transform time-series data into their frequency components. Cardiovascular researchers are familiar with the utility of spectral analysis of R-R intervals to quantify heart rate variability (3). But spectral techniques impose several limiting assumptions on the input time series, which must be linear and decomposable into sums of sines and cosines waves, stationary in time, and devoid of any data outliers. Violation of any of these assumptions, commonly displayed by physiologic systems, leads to spurious peaks in the frequency spectrum, defying interpretation.

When mathematical chaos hit the discipline of physiology some 20 yrs ago, many investigators climbed aboard the chaos wagon (4). The hubbub centered on simple deterministic models that displayed unpredictable, yet constrained irregularities in the signals, recognizable as fictive physiologic traces. In fact, it was even possible to describe the complexity of these signals in terms of Kolmogorov entropies, Lyapunov exponents, and fractal dimensions (5). But, alas, many of the successes won in the mathematical arena were just not amenable to physiologic dynamics. Why not? Simply put, physiologic systems are not stationary in time long enough for these mathematical solutions to converge to meaningful values. And come to think about it, if physiologic systems are fully deterministic in design, what then is the role of noise? We do live in a noisy world.

It is at this point that the article by Dr. Rassias and colleagues (6), published in this issue of Critical Care Medicine, becomes important. These investigators used a single complexity measure, approximate entropy (ApEn), to quantify the loss of variability of three diverse dynamic systems (R-R intervals, neutrophil phagocytosis, and plasma cortisol concentrations) in normal human volunteers subjected to intravenous endotoxin injections. Indeed, their results demonstrate significant decreases in ApEn values following exposure to endotoxin compared with paired saline controls, confirming the similar experiments of Codin et al. (7). There are several critical comments that could be leveled against this particular study, but I wish to focus on the big picture regarding the meaning of physiologic variability and how one might measure complexity.

Let me start with the second question first. We commonly aver that physiologic systems are variable and complex (looking), but how do we quantify variability in physiologic time series? The most common measure is the standard deviation (SD) of sequential time series points. However, the SD works only if the data are Gaussian distributed and stationary in time. Second, standard measures of nonlinear dynamics can be invoked, provided we have sufficient stationary data. Third, we could employ ApEn measures as did Dr. Rassias and colleagues (6), because this technique is purported to work on data sets as short as 50 points (8). Pincus (9), of course, originally devised ApEn as a statistic that quantifies the predictability (low ApEn) vs. unpredictability (high ApEn) of time series fluctuations. What must be appreciated, however, is that ApEn was first calibrated against three mathematically chaotic systems (Rossler, Logistic, Henon attractors), not physiologic time series. What is surprising to me is that as investigators have moved beyond chaotic thinking, they still employ ApEn methodology despite its well-known limitations. It is posited that a better nonlinear choice in this new millennium might be recurrence quantification analysis (10).

The mathematical details of ApEn(m, r, N) are easily found in the extant literature (9, 11) or ad hoc Web pages (Google searches). In brief, ApEn computations depend on the probability of repeating patterns (moving template) being present within the time series. But as Richman and Moorman (12) pointed out, ApEn does not exclude self-similarity matches. This bias renders ApEn heavily dependent on record length and, worse yet, prohibits quantitative comparisons between subjects. In addition, to the extent that the input data string is not stationary in time (e.g., presence of a simple baseline shift), ApEn values will be artificially high. Other problems center in the choice of the three variables: a) radius (r) is dependent on SD, which may itself be invalid; b) embedding (m of 2 or 3 may be too low); and c) length of record (N around 60 may be too short).

Now let us address my first question. Assuming it is somehow possible to measure physiologic variability (complexity) accurately, what does it signify? For physiologic systems ever on the move, we might assume that changes in variability somehow reflect changes in "state." Bold on the systems' horizon are Zblut's non-deterministic systems (terminal dynamics), which incorporate temporal alternations between deterministic trajectories and stochastic singularities (13). This experimentally supported mindset "chops" the dynamic into discontinuous pieces, obliterating the entrenched concept of full and continuous determinism. For such systems, chaos is out and piecewise determinism is in. Thus, each cycle of the system is unique, a new state, as it were. Each "next step" of the system becomes
environmentally meaningful, allowing the dynamic to negotiate our noisy world. To the extent that physiologic systems are indeed nondeterministic, physiologic variables will display variability that is contextually dependent. Much more could be stated, but if the context is an endotoxin challenge, heart rate variability may decrease through synchronization phenomenon (14), not the decoupling of systems (6).

The morals of this story are two-fold. First we must be cautious and discriminating in the choice of nonlinear tools, and second, we must be discerning and critical in the interpretation of complexity measures. Anyone can run their data through neat algorithms, but from the outset we need to know what we are doing and why we are doing it!

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REFERENCES