LECTURE

Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside

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Clinicians are increasingly aware of the remarkable upsurge of interest in non-linear dynamics, the branch of the sciences widely referred to as chaos theory. Those attempting to evaluate the biomedical relevance of this subject confront a confusing array of terms and concepts, such as non-linearity, fractals, periodic oscillations, bifurcations, and complexity, as well as chaos.[1-4] Therefore, I hope to provide an introduction to some key aspects of non-linear dynamics and review selected applications to physiology and medicine.

Linear systems are well behaved. The magnitude of their responses is proportionate to the strength of the stimuli. Further, linear systems can be fully understood and predicted by dissecting out their components. The subunits of a linear system add up—there are no surprises or anomalous behaviours. By contrast, for non-linear systems proportionality does not hold: small changes can have striking and unanticipated effects. Another complication is that non-linear systems cannot be understood by analysing their components individually. This reductionist strategy fails because the components of a non-linear network interact—ie, they are coupled. Examples include the interaction of pacemaker cells in the heart or neurons in the brain. Their non-linear coupling generates behaviours that defy explanation by traditional (linear) models such as self-sustained, periodic waves (eg, ventricular tachycardia); abrupt changes (eg, sudden onset of a seizure); and, possibly, chaos.

One important class of abrupt, non-linear transitions is called a bifurcation.[1,4] This term describes situations in which a very small increase or decrease in the value of some factor controlling the system causes it to change abruptly from one type of behaviour to another. A common type of bifurcation is the sudden appearance of regular oscillations that alternate between two values. This dynamic may underlie various alternans patterns in cardiovascular dysfunction. A familiar example is the beat-to-beat alternation in QRS axis and amplitude seen in some cases of cardiac tamponade.[5] Many other examples of alternans in perturbed cardiac physiology have been described, including ST-T alternans that may precede ventricular fibrillation,[6] and pulsus alternans during heart failure.

Although the focus of much recent attention, chaos per se actually consists of only one specific subtype of non-linear dynamics.[1] Chaos refers to a seemingly random type of variability that can arise from the operation of even the most simple non-linear system. Because the equations that generate such erratic, and apparently unpredictable, behaviour do not contain any random terms—this mechanism is referred to as deterministic chaos.[1] The colloquial use of the term chaos (to describe unfettered randomness, usually with catastrophic implications) is quite different from this special usage. The extent to which chaos relates to physiological dynamics is being investigated and is controversial. At first it was widely assumed that chaotic fluctuations were produced by pathological systems such as cardiac electrical activity during atrial or ventricular fibrillation. However, this initial presumption has been challenged, and the weight of evidence does not support the view that the irregular ventricular response in atrial fibrillation or that ventricular fibrillation itself represents deterministic cardiac chaos.[7] An alternative hypothesis is that the subtle but complex heart-rate fluctuations seen during normal sinus rhythm in healthy individuals, even at rest, are attributable in part to deterministic chaos, and that various diseases, such as those associated with congestive heart failure syndromes, may involve a parodoxical decrease in this type of non-linear variability.[2] The intriguing question of the role, if any, of chaos in physiology or pathology remains unresolved.

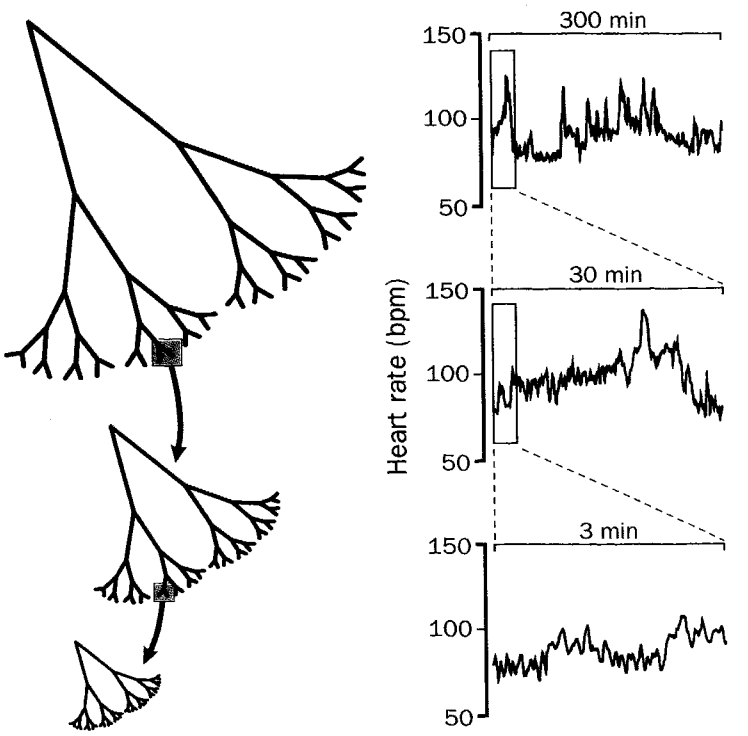

Figure 1: **Schematic representations of selfsimilar structure (left) and selfsimilar dynamics (right)**
The tree-like fractal (left) has selfsimilar branchings such that the small scale (magnified) structure resembles the large scale form. A fractal process such as heart rate regulation (right) generates fluctuations on different time scales (temporal magnifications) that are statistically selfsimilar.

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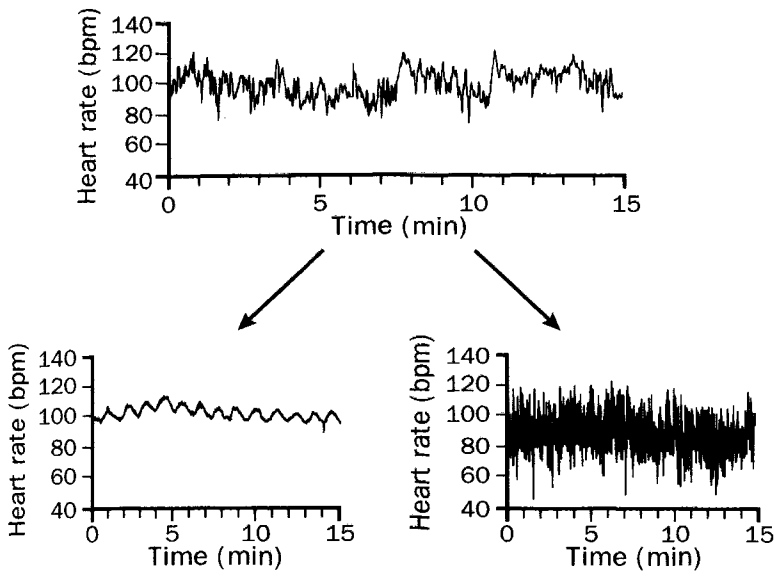

Figure 2: **Healthy dynamics (top), showing multiscale, long-range order; pathological breakdown of fractal dynamics, leading to single-scale (bottom left) or uncorrelated randomness (bottom right)**

Top heart-rate time-series is from a healthy individual; bottom left is from patient with heart failure, and bottom right from patient with atrial fibrillation.

The term fractal is a geometric concept related to, but not synonymous with, chaos.[2,3] A fractal is an object composed of subunits (and sub-subunits) that resemble the larger scale structure, a property known as self-similarity (figure 1). Examples of fractal-like anatomies include the arterial and venous trees, the branching of certain cardiac muscle bundles, as well as the ramifying tracheobronchial tree and His-Purkinje network. Mechanistically, these self-similar structures all serve a common physiological function: rapid and efficient transport over a complex, spatially distributed system. Various other organ systems contain fractal structures that serve functions related to information distribution (nervous system), nutrient absorption (bowel), as well as collection and transport (biliary duct system, renal calyces).

The fractal concept can be applied not only to irregular geometric or anatomical forms that lack a characteristic (single) scale of length, but also to complex processes that lack a single time scale. Fractal (scale-invariant) processes generate irregular fluctuations on multiple time scales, analogous to fractal objects that have a wrinkly structure on different length scales. For example, in figure 1 the time series of heart rate from a healthy individual is plotted on three different scales. All three graphs have an irregular wrinkly appearance, reminiscent of a coastline or mountain range. The irregularity seen on different scales is not visually distinguishable, an observation confirmed by statistical analysis.[7]

Complex fluctuations with the statistical properties of fractals have not only been described for heart-rate variability but also for fluctuations in respiration,[8] systemic blood pressure,[9] human gait,[10] and white blood cell counts,[11] as well as certain ion-channel kinetics.[3] Furthermore, if scale-invariance is a central organising principle of physiological structure and function, we can make a general, but potentially useful, prediction about what might happen when these systems are severely perturbed. If a functional system is selforganised in such a way that it does not have a characteristic scale of length or time, a reasonable anticipation would be a breakdown of scale-free structure or dynamics with disease. How does a system behave after such a pathological transformation? The antithesis of a scale-free (fractal) system—ie, one with multiple scales—is one that is dominated by one frequency or scale. A system that has only one dominant scale becomes especially easy to recognise and characterise because such a system is by definition periodic—ie, it repeats its behaviour in a highly predictable (regular) pattern (figure 2).

The paradoxical appearance of highly periodic dynamics in many disease states (disorders) is one of the most compelling examples of the notion of complexity loss in disease. Complexity here refers specifically to a multiscale, fractal-type of variability in structure or function. Many disease states are marked by less complex dynamics than those seen under healthy conditions. This decomplexification of systems with disease seems a common feature of many diseases, as well as of ageing.[12] When physiological systems become less complex, their information content is degraded. As a result, they are less adaptable and less able to cope with the exigencies of a constantly changing environment.[2] Remarkably, the output of many severely pathological systems has a nearly sinusoidal appearance. An example is the sinus-rhythm heart-rate variability sometimes seen in patients with severe congestive heart failure (figure 2) or with the fetal distress syndrome.

Generally, the practice of bedside diagnosis would be impossible without the loss of complexity and the emergence of such pathological periodicities.[2,13] It is these periodicities and highly-structured patterns—the breakdown of multiscale fractal complexity under perturbed conditions—that largely allow clinicians to identify and classify many pathological features of their patients. Familiar examples include periodic tremors in neurological conditions, AV Wenckebach patterns, the sine-wave electrocardiogram pattern in hyperkalaemia, manic-depressive alternations, and cyclic (Cheyne-Stokes) breathing patterns in heart failure. The panel summarises three major classes of pathological periodicities with representative examples.

Although fractals are irregular, not all irregular structures or erratic time series are fractal. A key feature of the class of fractals seen in biology is a distinctive type of long-range order.[7] This property generates correlations that extend over many scales of space or time. For complex processes, fractal long-range correlations are the

Panel: **Features of periodic disease syndromes**

A **Intermittent flare-up or recurrence of some symptom or symptom-complex at periodic intervals**
eg: periodic flares of peritonitis in familial Mediterranean fever; periodic fevers in Hodgkin's disease; periodic variants of arthritis

B **Periodic oscillations of one or more physiological variable**
eg: cardiopulmonary oscillations in heart failure (Cheyne-Stokes breathing); white blood cell oscillations in some cases of chronic myelogenous leukaemia; periodic heart rate dynamics preceding some cases of sudden cardiac death

C **Loss of normal structural variability or emergence of some highly patterned (stereotypic) morphological appearance or behaviour**
eg: granuloma pattern formation; target lesions of the skin in allergic drug reactions; patterned behaviour during episodes of partial-complex seizures

mechanism underlying a memory effect; the value of some variable—eg, heart rate at a particular time—is related not only to immediately preceding values, but also to fluctuations in the remote past. Certain diseases are marked by a breakdown of this long-range organisation property producing an uncorrelated randomness similar to white noise. An example is the erratic ventricular response in atrial fibrillation (figure 2).

Practical applications of non-linear dynamics are likely to arise within the next few years. Probably the first bedside implementations will be in physiological monitoring. Several indices derived from chaos theory have shown promise in forecasting those at high risk of electrophysiological or haemodynamic instability, including: (1) automated detection of the onset and offset of pathological low frequency (<0·10 Hz) heart-rate oscillations[4] (figure 2); (2) detection of subtle ST-T alternans;[6] (3) detection of a breakdown in fractal scaling[7]; and (4) quantification of differences or changes in the non-linear complexity or dimension of a physiological time series.[14] In addition to these diagnostic applications, perhaps the most exciting prospects are related to novel therapeutic interventions.

Chaos theory also holds promise for the elucidation of several major problems in contemporary physiology and molecular biology. Appreciation for the rich non-linearity of physiological systems may have relevance for modelling highly complicated signal-transduction cascades involved, for example, in neuroendocrine and immune dynamics in which interactions and cross-talk occur over a wide range of temporal and spatial scales, as well as for understanding complex pharmacological effects. Fractal analysis of long DNA sequences has revealed that non-coding sequences have long-range correlations among nucleotides.[15] Finally, findings from non-linear dynamics have also challenged conventional mechanisms of physiological control based on classic homoeostasis, which indicates that healthy systems seek to attain a constant steady state. By contrast, non-linear systems with fractal dynamics (such as the neuroautonomic mechanisms regulating heart-rate variability) behave as if they were driven far from equilibrium under basal conditions. This kind of complex variability, rather than a single homoeostatic steady state, seems to define the free-running function of many biological systems.[2,7]

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