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Introduction to Controversial Topics in Nonlinear Science: Is the Normal Heart Rate Chaotic?

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In June 2008, the editors of Chaos decided to institute a new section to appear from time to time that addresses timely and controversial topics related to nonlinear science. The first of these deals with the dynamical characterization of human heart rate variability. We asked authors to respond to the following questions: Is the normal heart rate chaotic? If the normal heart rate is not chaotic, is there some more appropriate term to characterize the fluctuations (e.g., scaling, fractal, multifractal)? How does the analysis of heart rate variability elucidate the underlying mechanisms controlling the heart rate? Do any analyses of heart rate variability provide clinical information that can be useful in medical assessment (e.g., in helping to assess the risk of sudden cardiac death)? If so, please indicate what additional clinical studies would be useful for measures of heart rate variability to be more broadly accepted by the medical community. In addition, as a challenge for analysis methods, PhysioNet [A. L. Goldberger *et al.*, "PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals," Circulation **101**, e215–e220 (2000)] provided data sets from 15 patients of whom five were normal, five had heart failure, and five had atrial fibrillation (http://www.physionet.org/challenge/chaos/). This introductory essay summarizes the main issues and introduces the essays that respond to these questions. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3156832]

I provide a history of this controversial topic and a short summary of the main conclusions. Several different operational definitions of chaos are offered. Of the articles that comment on the question, "Is the normal heart rate chaotic?", most conclude that the evidence was inconclusive or negative, and several do not think the question itself is the right question to pursue. Several articles describe the application of new methods of time series analysis to help elucidate the complex dynamical features of heart rate variability. Many identify physiological mechanisms underlying heart rate variability which include stochastic processes at the cellular level, influence of respiration on the heart rate, and the interactions of the multiple feedback loops regulating the cardiovascular system. Several show that time series analysis can distinguish normals, heart failure patients, and patients with atrial fibrillation, and there is some discussion about the use of the time series analysis to assist in the diagnosis or treatment of patients.

Although, a small number of mathematicians and physicists had been aware that deterministic dynamical systems could display irregular dynamics since the time of Poincaré, only in the 1970s did recognition of these phenomena become widespread. Li and Yorke[33] used the term chaos to characterize some technical mathematical properties that were present in continuous one-dimensional difference equations that have a period-3 orbit, May[35] studied complex dynamics in ecological models and reviewed complex dynamic phenomena in simple one-dimensional difference equations, and Feigenbaum[13] demonstrated remarkable scaling properties present in quadratic maps. The rapid explosion of research was captured in the 1984 collection of technical papers in *Universality in Chaos*[11] and popularized by Gleick.[19] A prevailing view was that the concept of chaos could help us understand the irregular dynamics present in natural and man-made systems ranging from the weather to the stock market to the heart.

Now, chaos is generally accepted to correspond to aperiodic dynamics in deterministic systems with bounded dynamics and sensitive dependence to initial conditions. The sensitive dependence to initial conditions means that starting from any two arbitrarily close initial conditions, as time proceeds the trajectories will diverge and it is impossible to make predictions about exact dynamics other than some statistical characterization of the behavior.

But this deceptively simple definition contains a trap that makes it difficult to apply to real systems. Since real systems will necessarily always contain noise in both the measurements and in the dynamics of the system, real systems are not deterministic and, therefore, cannot satisfy the definition above. Nevertheless, in Cvitanović's collection,[11] 12 of the 41 papers describe complex "chaotic" dynamics in experimental systems, although not all papers made the claim for chaos! I was a coauthor on the only paper in this collection dealing with experimental studies on a biological system, which analyzed the effects of periodic stimulation on spontaneously beating chick heart cell aggregates.[24] Because the stochastic nature of real systems precluded a strict notion of determinism, we avoided calling the "irregular" rhythms observed at some stimulation frequencies chaotic. Yet in a probing review relevant to the current controversy, the mathematical physicist, David Ruelle, observed "when stimulated by a periodic signal, such aggregates produced a variety of types of dynamical behavior, including chaos. This is one of the rare cases of a biological system with well-understood nontrivial dynamics."[40] Although I think many other biological systems show "nontrivial" dynamics going back to classic studies by Hodgkin and Huxley on the nerve membrane, I also believe that the periodically stimulated heart cell aggregates do display chaotic dynamics.

How can experimental systems that obviously contain stochastic terms controlling the dynamics be called chaotic? All the experimental papers in Ref. 11 display irregular dynamics under controlled laboratory conditions and often as parameters vary leading to bifurcations in the dynamics. One or more of the following properties are observed: The dynamics follow bifurcations that are consistent with a transition to chaos in theoretical models; a deterministic model of the system enables prediction of chaotic dynamics in the absence of stochastic terms; embeddings of the time series in two or more dimensions show evidence of organized structure consistent with a strange attractor; and it is possible to derive an approximately one-dimensional return map consistent with chaos from analysis of the experimental data. Subsequent years have witnessed many other experimental demonstrations of chaos using similar criteria.

In parallel with these early studies, various theoretical measures were applied to characterize time series including measures developed to characterize chaotic systems. Classic measures include the power spectrum, the Lyapunov exponent, the dimension, and the presence of nonlinear predictability. Of these, the Lyapunov exponent is perhaps the most important since in a bounded deterministic dynamical system, the Lyapunov exponent gives a measure of the rate of divergence of neighboring trajectories and a positive Lyapunov exponent reflects sensitive dependence to initial conditions and can be taken as a definition of a chaotic system.[40] Yet, computer algorithms for the Lyapunov exponent have many subtleties that are not always appreciated. For example, a small amount of noise in a limit cycle oscillation could yield a positive Lyapunov exponent if the trajectory has regions with large slopes. Other feature characteristics of chaotic dynamics that may be revealed by time series analysis include a broad power spectra, fractal dimension, and short term predictability. However, these features may also be present in nonchaotic systems, so positive identification of chaos based on these measures is not possible.[17]

Nevertheless, identification of chaos in cardiac and neural systems using time series analysis methods attracted a great deal of public attention. A short essay in Science suggested that "chaos may provide a healthy flexibility to the heart, brain, and other parts of the body" and quoted a number of research scientists including Ary Goldberger, Walter Freeman, Agnes Babloyantz, Paul Rapp whose research supported that position.[37] Similar points were made shortly afterward in high profile journals.[21,44] However, if there was chaotic dynamics, then it would naturally follow that deterministic models elucidating the mechanisms of these rhythms should be possible. Although deterministic models of cardiac and neural dynamics in well controlled laboratory settings did show chaotic dynamics that in a few cases were confirmed by experiment,[17] analysis of complex dynamics in the more realistic settings did not yield similar insights. A few years later, Rapp[39] recounted some of this early history concluding "it is now clear that many of the earlier demonstrations of chaos in biological data are spurious." Although I expect it was rather hard to publish papers that declaimed "the heart rate is not chaotic," some papers did just that.[10,27]

But the controversy was far from over. From early studies, it has been clear that if a time series is generated by a chaotic system, then it should be possible to predict the future for short times.[1,12,45] Indeed, since predicting the future even for short times could be very lucrative if translated into financial markets, some researchers from nonlinear dynamics migrated to finance;[6] others attempted to exploit these methods to analyze cardiac dynamics. Papers in this journal investigated determinism and predictability in heart rate time series[22,31] and argued for chaotic dynamics.[23] This approach has been significantly extended in recent years by Poon and co-workers.[5,38,47] Their basic method compares the ability of linear and nonlinear regression models to predict the future for short times without noise and with noise. If the nonlinear predictor is better without the noise and is comparable after some amount of noise is added, the dynamics are called chaotic. In some low dimensional deterministic dynamical systems, the amount of added noise in this noise titration method varies in similar fashion to the Lyapunov exponent of the associated deterministic process independent of small amounts of noise that might corrupt the original signal. However, despite claims that these methods constitute a sufficient condition for chaos, recent papers have demonstrated that the "noise titration test" identifies chaotic dynamics in stochastic systems which do not fulfill the property of determinism that is intrinsic to most definitions of chaos.[14,32] Perhaps more importantly, the noise titration test can give a positive indicator for chaos, even in systems in which there is not sensitive dependence to initial conditions, see example in Fig. 1 in Freitas *et al.*[14] as reflected by a negative Lyapunov exponent.

Setting aside the difficulties in documenting chaotic dynamics in naturally occurring biological time series, researchers have pursued other methods of time series analysis in an effort to identify complex features of heart rate variability. In the current series of essays, most have focused on developing new methods of time series analysis that address other aspects of heart rate variability than those intimately related to chaos and suggest that these other methods may provide important insights about the underlying physiological processes. Many of these other approaches can be traced back to studies in the early 1980s that identified significant peaks in the power spectra associated with different physiological functions and found $1/f$ scaling of the power spectrum at low frequencies.[2,30] These observations stimulated a large body of research into mechanisms of heart rate variability, as well as analyses directed toward the scaling properties of the normal heart rate. An early paper described a technique called *detrended fluctuation analysis* in which the mean square deviations of fluctuations around a trend line were computed as the time scale of the trend line varies over wide intervals. This work indicated the presence of different scaling exponents for different time scales.[36] In the current volume, these results are extended by introducing time lags into the detrended fluctuation analysis with the goal of identifying physiological time delays present in the various cardiac feedback control loops.[3] Different methods of getting at these multiple time scales associated with physiological feedback have been further pursued by identifying multifractality in heart rate time series.[26] In the current volume, two of the papers develop the theme and carry out analyses of heart rate variability that is consistent with the notion that the heart rate is nonchaotic, nonlinear, and multifractal.[4,42] Apart from the current essays, Costa *et al.*[9] presented a recent review of these methods and extensions. Finally, there is interest in extending the insights from the multifractal approach to traditional nonlinear measures. An earlier paper in this journal documented scaling of the correlation sum (used to compute the correlation dimension).[41] In the current volume, Hu *et al.*[25] utilized a scale-dependent Lyapunov exponent to analyze heart rate variability.

Many of the contributors to this issue come from fields other than physiology or medicine and focused on technical aspects of the time series methods rather than the physiological implications. However, several of the papers deal with physiological mechanisms. There are three main themes: stochastic influences, respiratory influence, and multiple feedback loops. In a purely theoretical investigation of a model for the modulation of the normal sinus rhythm, Zhang *et al.*[48] demonstrated that stochastic release of the regulatory agent acetylcholine in the neighborhood of the sinus node could lead to an irregular rhythm that might be identified as chaotic using some algorithms. It is widely known that respiration influences the heart rhythm—the heart rate speeds up during inspiration and slows down during expiration.[43] Wessel *et al.*[46] used regression methods to investigate this coupling and concluded that most of the variability of the heart rhythm is directly caused by fluctuations of the respiratory rhythm. Buchner *et al.*[8] investigated the bidirectional coupling between respiration and heart rate control using stochastic methods. Finally, studies of the scaling properties suggest that the multiple feedback loops operating over different time scales would lead to the observed scaling properties.[3,4,42] This is an important idea that I think needs further theoretical and experimental investigation. An early theoretical model of multiple negative feedback loops and time delays showed chaotic dynamics over limited parameter ranges,[18] but not the rich fluctuations commonplace in normal heart rate variability documented in the volume.

In this volume several papers showed that time series analysis could distinguish between the three groups of patients made available by PhysioNet[20] and demonstrated ways in which the methods could be used to derive insight into the underlying physiological control.[3,4,42,25,46,8,15] Although these methods may be helpful clinically, the potential utility of time series analysis methods was not a key focus of any of the papers. However, several groups in the past have presented evidence that time series analysis could provide information about risk stratification for sudden cardiac death,[7,28,34] or perhaps even be able to predict an imminent sudden cardiac death.[44] While time series analysis methods have appeared to have great potential utility in assessing human health and the risk for sudden cardiac death, there is still a need for sharp predictions based on understanding fundamental mechanisms that are translated into clinically useful procedures. A promising direction that emerged from a nonlinear dynamics perspective is the assessment of the shape of the T-wave on the electrocardiogram,[29] rather than heart rate variability *per se*.

The fascination of chaotic dynamics to me, and to many in my generation, is the unexpected appearance of irregular dynamics in very simple deterministic systems. The discovery of universal routes to chaos in mathematical models and then in the laboratory has been a triumph of scientific imagination, mathematics, and experiment. My conclusion is that the normal heart rate variability does not display chaotic dynamics. The various claims to the contrary are based on operational definitions that do not capture the defining properties of chaotic systems outlined at the start of this essay. However, even though I have helped perpetuate it, I do not believe the debate itself is of interest unless it leads to new insights into mechanisms of heart rate control and the transitions that lead from health to disease.

In a 1990 essay, I concluded, "The real question is not, 'Is cardiac chaos normal or abnormal?' but rather, 'What are the mechanisms underlying complex cardiac rhythms and how are they manifest in the laboratory and clinic?' Nonlinear dynamics offers powerful new mathematical tools to help sort out these issues, and we are sure to see dramatic advances in the future."[16] Although there have been some spectacular advances in understanding the nonlinear dynamics of complex arrhythmias, the application of these insights into clinically useful procedures and devices has been more difficult than I imagined.

Readers and authors are invited to continue the debate at a website set up by Chaos (http://blogs.aip.org/ControversiesInChaos).

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