Review

Insights for cardiology from chaos theory

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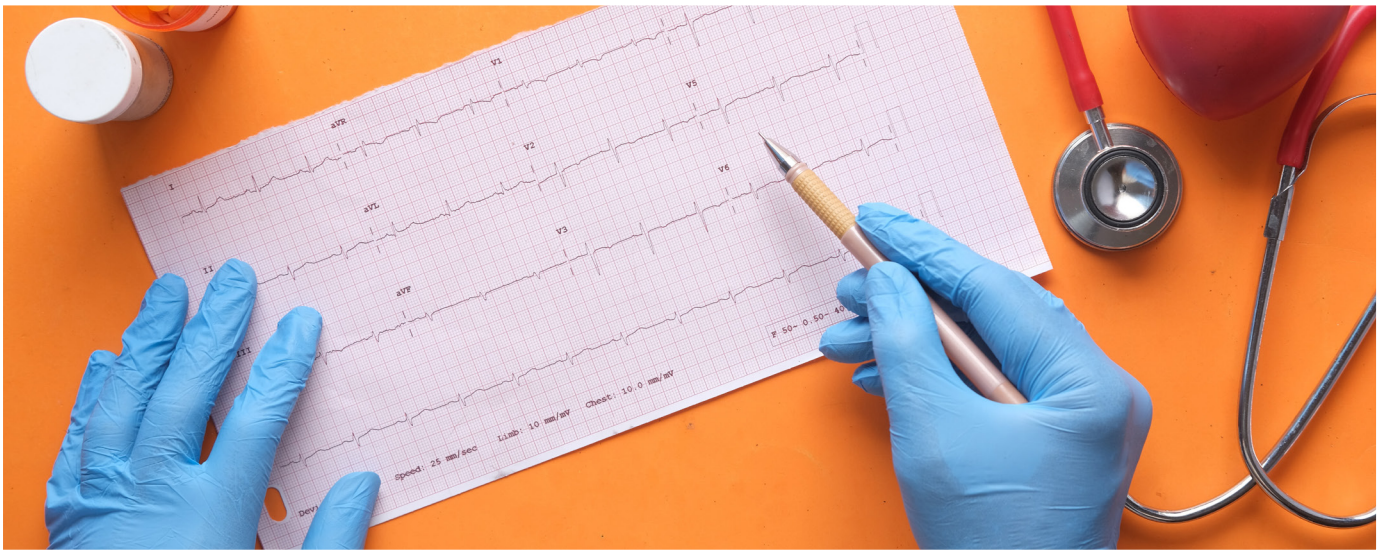

Abstract

Non-linear mathematical models uncover features of physiological systems that are missed by linear approaches. Chaos, a type of non-linear motion, is an inherent feature of health. Its study provides insights into several fields, including neurology, epidemiology, and cardiology. However, chaos is largely unknown in health science and when it is known, it is not actively investigated due to its mathematical complexity and computational demands. This review introduces chaos theory to health researchers without a formal background in the physical sciences to address the interdisciplinary learning barrier. Comparisons between chaos theory and classical linear systems are drawn to provide an accessible, qualitative introduction to chaos before exploring its genesis and consequences in the cardiovascular system. Breakup of spiral wave action potentials (SWAPs) is shown to be identical to mechano-electrical feedback (MEF) as a route to cardiological chaos. SWAP breakup contributes to arrhythmogenesis alongside tissue heterogeneities and the complex perfusion geometry resulting from ischaemia. Together with the recent success of novel chaotic metrics for obstructive sleep apnoea (OSA) and haemodynamics, a widespread adoption of non-linear systems theory in the health sciences is encouraged to complement existing linear methods.

Abbreviations

AP - Action potential
BR - Border region
CD - Correlation dimension
DFA - Detrended fluctuation analysis
EC - Ephaptic coupling
ECG - Electrocardiogram
FD - Fractal dimension
gPC - Generalised polynomial chaos expansion
HRV - Heart rate variability
MEF - Mechano-electrical feedback
MLE - Maximal Lyapunov exponent
OSA - Obstructive sleep apnoea
PS - Phase synchronisation
SCD - Sudden cardiac death
SR - Sarcoplasmic reticulum
SWAP - Spiral wave action potential

Introduction

Chaos theory may provide ground-breaking solutions to previously unsolved problems in physiology. Originating from the physical sciences, this non-linear model offers insight through its ability to uncover emergent phenomenology and hidden dynamics that are missed by linear methods.[1] Current health science literature employs linear models almost universally while non-linear methods remain largely unknown. Despite this, chaos theory has diverse biomedical applications, including in epidemiology, neurology, and healthcare organisation.[2]

In the cardiovascular system, chaotic analysis may be used to investigate cardiac instabilities, such as alternans, arrhythmia and heart rate variability (HRV), cardiomyocyte coupling, and unique metrics for diagnosis.[1,3,4] However, chaotic networks are mathematically complex, containing numerous intricate interactions between system elements. Efficient simulations of large chaotic networks are therefore difficult to study without significant computational power.[5] Mathematical approximations are often used to overcome this issue, at the expense of simulation accuracy. Despite these shortcomings, perhaps the greatest limitation of chaos theory is the interdisciplinary learning barrier it poses to health scientists.

The aims of this review are to introduce the topic of chaos qualitatively, to explore cardiology from a non-linear perspective using recent literature, to demonstrate the usefulness of chaotic analysis and to propose new directions for cardiology research.

Methodology

The PubMed and Google Scholar databases were used to source relevant and timely material. Initially, the Boolean search terms "chaos" and "cardiology", "cardiovascular" or "cardiac" (with all variations) were employed and 612 articles were identified. General research into chaos did not constrain articles by publication date. Cardiology research required material to be published between October 2018 and April 2020. Of the remaining 40 articles, 12 were disregarded as they did not investigate or utilise mathematical chaos. Of these, a total of 16 articles were selected to be analysed based on content and scope for comparison; these articles primarily focussed on the alleged role of chaotic dynamics in arrhythmogenesis.

Chaos: an introduction

Physiological systems can demonstrate five levels of mathematical order: equilibrium, periodicity, quasi-periodicity, chaos, and random motion.[6] The first three levels of order are linear, meaning any change to an input variable results in a well-behaved systemic response. Simply, small changes produce small effects while large changes produce large effects. Chaos, however, is neither fully linear nor fully random. Instead, it occupies a niche middle-ground, containing features of both extremes.

> *Chaotic systems appear disorderly yet, like linear systems, their ability to be captured by mathematics makes them fully deterministic; any future state can be calculated from an initial, or indeed any other, state.[2] Chaotic systems are therefore described as non-linear.*

Like all non-linear systems, chaos is extremely sensitive to initial conditions. A vanishingly small change to the initial state of the system produces errors that accumulate over time, resulting in large qualitative changes in dynamics.[6] Any attempt to predict the system trajectory in the future will also attract errors. A calculated final state will therefore contain a high degree of uncertainty. In other words, although chaotic motion may be described deterministically using equations, exponential error growth means it is unpredictable overall. The resulting dynamics evolve erratically and, to the uninitiated, appear fully random. An intuitive example of this behaviour is that of the double pendulum (**Figure 1**). Some key differences between conventional linear systems and their chaotic counterparts are outlined in **Table 1**.

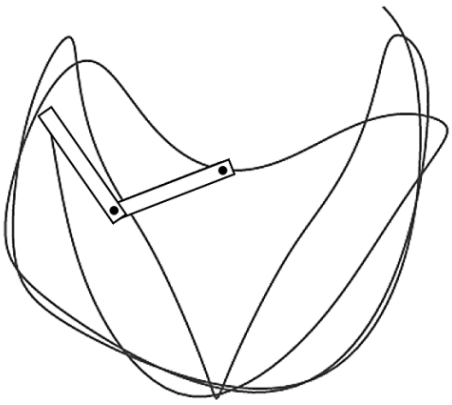

Figure 1. A possible trajectory of the chaotic double pendulum. The position of the system at a future time can be calculated from its initial position (deterministic), but with little certainty (unpredictable) due to errors from initialisation that grow over time. In cardiology, this motion is naturally seen in heart rhythm. This figure was produced using a Python simulation.

Table 1. Key features of linear and chaotic systems.

	Linear systems	Chaotic systems
Equations	Always described by simple equations.	Sometimes described by simple equations. Sometimes described by intricate equations. May be approximated as linear systems (linearisation).
Exponents	All terms are linear; all variables are raised to first power only.	At least one term is curved; at least one variable raised to non-unity power.
Behaviour of solutions	Gradual changes in behaviour; time series are regular. Any solution may be written as the sum of linearly-independent components.	Abrupt changes in behaviour; time series are erratic and have fractal nature. Time series therefore appear similar at different scales (self-similarity).
Determinism	Fully deterministic and predictable.	Fully deterministic. Predictable in the absence of error (pure mathematics). Unpredictable otherwise (simulations, human physiology).
Sensitivity	Uniformly sensitive: changes to the initial state are reflected equally by system dynamics.	Extremely sensitive: changes to the initial state cause large, unexpected changes to dynamics.

Information derived from Rickles et al, 2007[2] and Sharma 2009.[6]

Chaos appears to be a physiological determinant of health while a loss of chaos is associated with a loss of health.[2]

> *Within cardiology, chaos manifests itself in heart rhythm regularity; a mathematically complex heart rhythm is generally healthy.[7] However, if incoherent electrical activity leads to a loss of chaos, complexity can remain despite new-found cardiac pathologies.[8]*

It is this promise of emergent phenomenology that often motivates the study of chaos; can specific parameter values give rise to previously unseen phenomena?

Cardiovascular origins of chaos and irregular cardiac dynamics

Dynamical chaos arises through several mechanisms in cardiac electrophysiology. The breakup of spiral wave action potentials (SWAPs) is particularly relevant due to its alleged role in arrhythmogenesis.[5] SWAPs propagate through cardiac tissue with a

three-dimensional spiral geometry (**Figure 2**) and become unstable when perturbed. This instability leads each SWAP to fragment and reform. The resulting waves compete with activity from the sinoatrial node and are described as re-entrant; they traverse around the same anatomical circuit.[9,10] Consequently, irregular cardiac dynamics and cardiac instabilities arise.

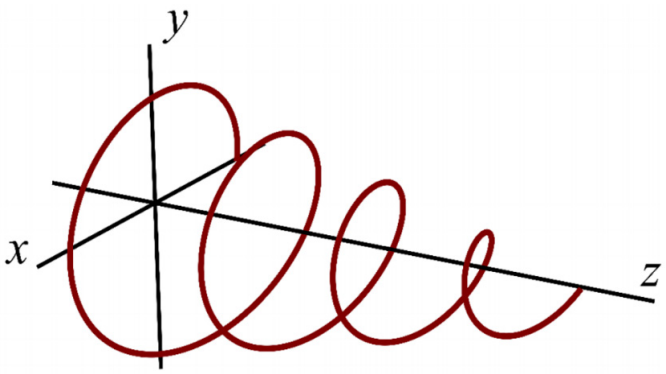

Figure 2. SWAPs occur naturally within the heart and have a corkscrew-like shape. The SWAP tip is the point of intersection between the wave and the *z*-axis. This figure was produced using a Python simulation.

The introduction of time delays to cardiomyocyte Ca^{2+} channels has recently been found to cause SWAP breakup.[5] Alternations in the amplitude (amplitude alternans) or time intervals (temporal alternans) between successive electrocardiogram (ECG) peaks arise from this approach[11] and are associated with arrhythmia and sudden cardiac death (SCD).[3]

A new approach using delay differential equations appears promising.[5] It drastically simplifies highly non-linear SWAP systems whilst maintaining important qualitative features of the dynamics. The model is therefore simple and well-optimised, making the study of SWAPs accessible to health scientists who lack powerful computer hardware or a mathematical background. Additionally, two independent treatments of SWAP propagation may provide novel approaches to instability research; a non-localised model[9] and a statistical model.[12]

Re-entrant wave breakup is however not the only route to chaos. Mechano-electrical feedback (MEF) occurs when tissue deformation affects action potential (AP) propagation. One study reports that MEF induced by pacing cardiac cells at sufficiently high rate resulted in an alternating AP duration.[3] This is consistent with the temporal alternans that pre-empt ventricular fibrillation and SCD.[13] The rate of AP repolarisation initially accelerated before slowing, prolonging the pre-peak time and decreasing the post-peak time.[3] This result may be reinterpreted; we can conceive that each AP instead experienced an effective time delay due to the change in polarisation speed.

> *The authors' results are therefore consistent with the delay differential equation approach,[5] showing MEF and delay-induced SWAP breakup have an identical effect on electrophysiology and instability development.*

Fluctuations in sarcoplasmic reticulum (SR) load have been shown to cause amplitude alternans.[14] The mechanism involves non-linear interactions between Ca^{2+} release and local voltage. Continuous phase transition to alternans occurs at a high rate of SR Ca^{2+} re-entry. By comparing with other studies,[3,5,13] it appears that alternans develop when charge movement in cardiac tissue surpasses a threshold frequency, though this insight requires confirmation by future research.

Cardiac dynamics are also affected by external sources.

> *Cardio-respiratory coupling during respiratory sinus arrhythmia has been quantified using a new model of chaotic phase synchronisation (PS): a measure of the degree to which two or more time series may be superimposed.[15]*

Both the simulated and experimental respiratory signals utilised in one study[7] had an insignificant effect on cardiac dynamics, a result that supports the hypothesis that the vascular system has a greater effect on cardiac dynamics than the respiratory system.[15] Some of the authors' assumptions should be questioned however.[7] White and red noise were used to randomise respiration and heart rate, respectively. The use of two different noise colours is never justified by the authors and others report that white noise is not applicable to heart rate.[9] Unequal inhalation and exhalation durations are also acknowledged in some studies,[15] but not in others.[7] Cardio-respiratory interplay should therefore be investigated further.

Separately, the study reports that chaos can originate from the autonomic control of local vasculature.[7] Two chaotic metrics were utilised: fractal dimension (FD), which tracks changes in dynamical complexity, and the maximal Lyapunov exponent (MLE), which evaluates system predictability. This result is well agreed upon.[15,16]

Pathological chaos and diagnostic metrics

In addition to SWAP breakup and alternans,[3,5] electrophysiological gradients cause arrhythmia[4] by interrupting AP propagation. Conduction is affected by the shape of the border region (BR) between perfused and non-perfused tissue in ischaemia and by a recently discovered conduction mechanism involving extracellular ion movement, known as ephaptic coupling (EC).[17] High BR complexity and strong EC were found to promote conduction in the ischaemic region, reducing the likelihood of arrhythmia.

The trajectory of SWAP tips is another determinant of arrhythmia. In homogeneous media, tip dynamics are stable and periodic. Circularly symmetric tissue heterogeneities can however transition SWAP tips to chaos. This result is independent of wave dynamics, and supposedly suggests SWAP breakup is not a prerequisite for arrhythmogenesis.[8] However, the authors also note that chaotic tip trajectories drive SWAP breakup itself. SWAP tips may therefore only cause arrhythmogenesis indirectly through breakup. Arrhythmia resulting from chaotic tip trajectories therefore require further study, with the inclusion of signal noise to better mimic real cardiac electrophysiology.

A recent article found that patients with obstructive sleep apnoea (OSA) are identified more readily using chaotic analysis of HRV time series than with ECGs.[1] In OSA, heart rate varies periodically between bradycardia and tachycardia. Conventionally, non-linear detrended fluctuation analysis (DFA) is used to analyse ECG data for OSA. Analysis of HRV time series with chaotic correlation dimension (CD), a measure of complexity, had an associated p-value of $p=0.003$, whereas ECG DFA had a p value of $p=0.044$. This result is statistically significant ($p<0.05$). In addition, the authors' conclusion that sympathetic responses increase during apnoea should be investigated further due to the aforementioned link with the development of cardiac instability.[7,16]

Evaluating the reliability of cardiovascular models is essential for clinical applications. Systems may be assessed using the polynomial chaos expansion (gPC). This novel technique provides information about prospective models by calculating the mean, standard

deviation, and other relevant statistics. gPC also measures system sensitivity to changing parameters, a defining feature of chaos, and provides an estimation of errors. Currently, gPC is finding success in several areas of cardiology. In studies of ventricular wall thickness,[18,19] conventional approaches and gPC agree to within 2%. A recent application used gPC to assess the decrease in blood pressure that occurs during arterial stenosis and found a similarly accurate result.[20] The technique was also noted to be far more efficient than traditional methods, completing instantly where other approaches required two weeks.

> *Not only does this overcome the computational barriers that are posed by chaotic simulations, gPC may eventually be used in diagnosis; patient-specific analysis has already been demonstrated in studies of blood flow.[21]*

Conclusion

Chaos theory offers new approaches in physiology. Recent simplifications to SWAP models have made the study of cardiological chaos accessible to health scientists. Functionally identical to MEF, delay-induced SWAP breakup is an important route to chaos as it produces alternans, through Ca^{2+} release and chaotic tip trajectories, that are associated with arrhythmia and SCD. Alternans also arise from the interaction of APs with ischaemic BRs or extracellular Ca^{2+} ions. Origins of irregular cardiac dynamics and instabilities are therefore numerous and varied.

In general, alternans appear to result from the oscillatory movement of charge above a frequency threshold, though this is unconfirmed. The effect of the respiratory system on cardiac dynamics and a causal link between tip dynamics and arrhythmogenesis, independent of SWAP breakup, are yet to be established.

> *The chaotic metrics of phase synchronisation (PS), fractal dimension (FD), maximal Lyapunov exponent (MLE), correlation dimension (CD) and polynomial chaos expansion (gPC) aid new research.*

In diagnosis, CD already improves on conventional methods to identify OSA patients, while gPC overcomes the limitation of simulation efficiency and demonstrates patient-specific use. Future literature is likely to locate similar uses for the other chaotic metrics as non-linear techniques become more widely utilised in health science.

Though broad prerequisite knowledge is often required, non-linear models clearly complement linear approaches and the success of chaos theory in current research justifies its future study.

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