Chapter 7

Chaos in Electrophysiology

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Abstract

Over the last fifteen years there has been much interest in the topic of chaos in biological systems. There are several hundred reports dealing specifically with electrophysiological systems. In this article, we review experimental and modelling work on chaotic dynamics in electrophysiology, concentrating on examples drawn from the cardiovascular and nervous systems, which have been the two systems most studied. We survey the techniques that have been used in claiming the existence of chaotic activity in these studies, giving a fairly comprehensive, but not exhaustive, list of the situations in which these techniques have been used. These techniques include: description of one-or-another of several well-characterized routes to chaos, extraction of a one-dimensional map from a time series ("return map"), examination of the power spectrum for a broadband component, reconstitution from the time series of a geometrical portrait of the strange attractor generating the chaotic behaviour ("method of time delays", "embedding"), construction of a Poincaré section (and perhaps a one-dimensional return map) from the reconstituted attractor, determination of the fractal dimension of the attractor and its Liapunov exponent(s), and testing for nonlinear determinism. We also give a few caveats along the way, including examples where the claim for chaos was wrong (or at best premature).

Chaos

One can find several definitions of chaos floating about in the literature. Many of these are mathematical in nature, and therefore of little use to an experimentalist or to a modeller carrying out numerical simulations (e.g. definitions involving the existence of an infinite number of unstable periodic orbits). A useful working definition of chaos might perhaps be something along the lines of aperiodic dynamics in a deterministic system demonstrating

sensitive dependence on initial conditions [143]. There are clear methodological problems if one takes a few moments to reflect on each of the three requirements in this definition.

Many experimentalists think of a trace as being chaotic when it is irregular or aperiodic (and obviously not just a periodic trace with some noise superimposed), but with some degree of determinism or predictability (i.e. not purely random or stochastic). It is not good enough to call a trace chaotic simply because it is aperiodic, as has been done in many published papers [125, 157]. An example of a behaviour that would not be viewed as chaotic at the present time is the irregular beating of a single pacemaker cell isolated from the sinoatrial node. The irregularity in this case can be accounted for by the fact that the electrical activity underlying spontaneous activity is being generated by a population of ion channels lying in the membrane, with each individual channel opening and closing in a random fashion [106, 288]. Note that while one cannot predict the exact time at which a particular channel that is presently open will close (or vice versa), the probability that it will do so is known, being controlled for most channels by the transmembrane potential.

Since Johnson, membrane, and sometimes synaptic noise are intrinsic to all electrophysiological systems, there are no electrophysiological systems that are purely deterministic (i.e. have no stochastic components). Thus, when one states that chaos exists in such a system, the underlying implication is that there is some deterministic mechanism at work that is responsible for generating the aperiodicity. A further implication is that this deterministic mechanism is in some sense more important to the production of the irregular dynamics than any stochastic processes that might be present. One way of demonstrating this deterministic contribution to the dynamics is to develop a realistic, physiologically-based, deterministic model of the system, and then to have that model generate chaotic behaviour resembling the experimentally observed irregular dynamics.

The third requirement in the definition (sensitive dependence on initial conditions) is not very often proven, or even tested, in experimental work. Demonstration of this property involves calculation of the largest Liapunov exponent. Among other things, this third requirement means that quasiperiodic phenomena - which are both aperiodic and deterministic - are not chaotic.

There are several recent publications specifically reviewing chaotic dynamics in the cardiovascular field [17, 49, 60, 127, 130, 140, 198] and in the neural field [60, 131, 152, 207, 210, 211, 220, 262]. Many publications summarize the broader physiological and biological literature [19, 47, 78, 80, 124, 143, 163, 197, 260, 287]. There has also been a great deal of discussion about the possible rôles of chaos in norrno- and patho-physiology [44, 86, 87, 140, 151, 163, 206, 238, 260, 287] and higher brain function [53, 60, 114, 151, 152, 186, 207, 210, 211, 258].

We now briefly consider the main techniques that have been used to provide evidence for the existence of chaotic dynamics in electrophysiological systems, along the way providing an entrée into the literature and pointing out some practical problems. We shall not go into the details of these techniques, since they are described in several recent review and tutorial articles [48, 49, 60, 80, 92, 127, 131, 137, 152, 163, 184, 210, 211, 217, 247, 250].

Routes to Chaos

One of the tests most frequently used to establish the existence of chaos is the determination that one of several well-characterized "routes to chaos" is being followed as some experimental parameter is systematically changed. There have been several routes to chaos described. These include period-doubling, intermittency, crises, period-adding,

Sil'nikov, and quasiperiodicity [20, 57, 97, 152, 252].

Period-Doubling Cascade

The period-doubling route to chaos is probably the route that has been the most reported. A period-doubling bifurcation occurs when there is a doubling of the period of a regular, periodic oscillation as some parameter is changed. It is well-known in mathematical work that a cascade of an infinite number of period-doubling bifurcations can lead to chaotic dynamics [20, 49, 60, 78, 143, 174, 252, 267]. Irregular rhythms seen in experiments on cardiac [36, 38, 76, 107, 109, 112, 122, 147, 244], vascular [98], and neural [116, 145, 173, 272] tissue can, and have been, interpreted in this light.

In experimental work on biological systems, it is very rare to find reports of a period-doubling bifurcation beyond a second consecutive period-doubling (which produces a period-4 orbit); a rare example of a period-8 orbit can be just barely made out in Fig. 5B of Hescheler & Speicher [122]. Thus, only one, two, or, very rarely, three period-doubling bifurcations have been described in biological systems before the irregular dynamics appears. There are probably two main reasons for this. First, the noise present corrupts higher-order period-doubled orbits that would presumably exist in the absence of the noise, producing a "bifurcation gap" [45, 81]. This gap exists because the small differences between the higher-order orbits that would occur in the noise-free system are within the background noise level, resulting in orbits that resemble at best a noisy period-2^n orbit, and which can be mistaken for "noisy periodicity" or "banded chaos" [166]. Secondly, since the range of the experimental parameter over which one would expect to encounter a period-doubled orbit decreases as the cascade is penetrated, it is often impossible to hold the experimental system stationary enough to allow period-doubled orbits of longer periods to be seen. This effect is accentuated in the presence of noise. However, this line of reasoning soon gets one into the hot water reminiscent of the famous question of Bishop Berkeley. Thus, it remains a matter of the individual investigator's judgment in a particular case as to when to claim that a cascade of period-doublings is leading to chaotically irregular dynamics [107, 111].

Evidence for the period-doubling route to chaos has also been found in modelling work on cardiac [24, 134, 160, 181, 281], neural [3, 4, 8, 25, 33, 34, 108, 116, 129, 135, 283, 284], and pancreatic [31] systems, as well as in modelling work on tremor [5].

Alternans is a rhythm seen on the electrocardiogram (ECG) in which there is a beat-to-beat alternation of one or more of the electrocardiographic complexes. It is often assumed that the alternans arises out of normal sinus rhythm *via* a period-doubling bifurcation. Alternans can be seen in the setting of acute myocardial ischaemia, and often precedes the phase of induction of malignant ventricular arrhythmias [229, 235, 265, 279]. It is thus tempting to speculate that the alternans might be the first sign of a period-doubling cascade that would eventually lead to chaotic dynamics, which would correspond to ventricular fibrillation [264]. Since the transition from ventricular tachycardia to ventricular fibrillation can be thought of as being due to the breakup of a spiral wave into multiple spirals [148], a recent report in which spiral breakup occurs when the system is sufficiently close to alternans is especially intriguing [148].

Caveats

1. As a single parameter is changed, it is mathematically possible for chaos to be seen following one [176, 276] or two [160] period-doubling bifurcations. It can also appear abruptly, not being preceded by any period-doublings, producing "instant chaos" [195]. Thus the interpretation proffered above of noise corrupting an infinite cascade is not necessarily the explanation when one sees chaotic dynamics following a finite number

of period-doublings in the presence of noise.
2. An incomplete cascade of period-doublings can occur, sometimes followed by a symmetrical cascade of reverse period-doublings ("period-halvings"), producing a bifurcation diagram containing "bubbles" ([100], Figure 5). Since such partial cascades can exist, it is prudent not to assume that chaotic dynamics must necessarily ensue if a sequence of a few period-doublings is seen [278].
3. The first period-doubled orbit shows up in the time series as a simple cycle-to-cycle alternation between two components in the waveform. When one sees such an alternation, it is thus tempting to claim that the rhythm has been produced by a period-doubling bifurcation. However, this is not always the case. A nice example of this is in 2:1 atrioventricular heart block. If one records from within the atrioventricular node, one can see a beat-to-beat alternation in action potential morphology. However, this is not the result of a period-doubling, since the transition from the period-1 rhythm is not direct, but rather, from a mathematical point of view, involves an infinite number of other periodic rhythms, which are termed Wenckebach and reverse Wenckebach rhythms [102, 257].
Another example would be when one sees alternation in the force of contraction of a multi-cellular muscle (cardiac, smooth, or skeletal), in which one [72] or two [182] subpopulations of cells are contracting on every other response, with perhaps the majority of cells contracting on each response. If the 2:1 response in the subpopulation(s) arises out of a Wenckebach sequence, the alternating rhythm cannot be said to have arisen out of a period-doubling bifurcation. It is difficult to rule out this possibility in an experiment in which one simply has an isolated trace showing an alternans rhythm, since it is technically difficult to measure from all - or indeed even a few - sites in a multicellular preparation. The best that can be done here perhaps is to vary a parameter and see whether intermediate rhythms can be seen during the transition from normal rhythm to alternans rhythm.

Intermittency

There are three types of intermittency (types I, II, and III). These are found when the system is chaotic, but close to (i.e. a relatively small change in a parameter will produce) a saddle-node, Hopf, or period-doubling bifurcation respectively [20, 205, 252]. The characteristic feature of a waveform showing intermittency is that, as time proceeds, there is a switching back-and-forth between two forms of behaviour, which appear very different: a laminar phase, in which the waveform looks quite regular (with some sort of slow drift), and a turbulent phase, in which the waveform is much more irregular.

Type I intermittency has been reported in neurons [116, 120] and axons [270], as well as in periodically driven heart cells [83]. Type III intermittency has been seen in the squid giant axon [173, 270] and in the elecroencephalogram [215]. There also is a report of intermittency, which might be of type I, in vascular smooth muscle [98]. We are not aware of any reports of type II intermittency in electrophysiological systems (reports of this type of intermittency are very rare in the literature on physical and chemical systems).

Caveat

1. Part of the definition of intermittency is that the system be close to the appropriate kind of bifurcation. However, this is a necessary, but not sufficient, condition. For example, systems that can have only periodic and quasiperiodic behaviours, and no chaotic behaviour - e.g. a limit-cycle oscillator subjected to periodic forcing of sufficiently low amplitude [82] - can display a form of behaviour which can be misidentified as type I intermittency when the system is close to a saddle-node bifurcation. We have previously termed this phenomenon "tangency" [20, 100]. Thus, showing a slow drift in a

waveform is not enough to establish the existence of a chaotic intermittency ([118], Fig. 1(b); [83], Fig. 11.4).

Crises

A crisis occurs when an unstable periodic orbit collides with a chaotic attractor [94]. Crises come in two flavours: interior and boundary. The former results in the sudden widening or narrowing of a pre-existing chaotic attractor, while the latter converts transient chaos into chaos, producing a chaotic attractor (or vice versa). Unlike the case in theoretical work or numerical simulation, it is usually impossible in experimental work to track an unstable orbit as a parameter is changed. Thus, it is virtually impossible to obtain *prima faciae* evidence for a crisis in experimental work, since one will simply see the sudden appearance, disappearance, or change in size of a chaotic attractor, and there is always the alternative explanation of bistability between a periodic orbit and a chaotic attractor, or between two different chaotic attractors.

While crises have been documented in many physical systems, there are very few reports in the physiological literature. For example, an interior crisis can be seen in the periodically driven FitzHugh-Nagumo model [283], which is a simplifed version of the Hodgkin-Huxley equations for squid axonal membrane, and a crisis has been associated with the transition from beating to bursting in a model of a pacemaker neuron [284]. We have previously noted that crisis-induced intermittency has several characteristics reminiscent of the behaviour displayed by single ionic channels, whose kinetics are taken to be stochastic at present [103, 162].

Quasiperiodicity

Quasiperiodic behaviour occurs when the trajectory of the system lies in the surface of a torus, producing a motion made up of two or more frequencies that are incommensurate [20, 48, 96, 143, 152, 252]. A chaotic attractor can occur when quasiperiodic motion on a torus of dimension three [194] or higher [234], which results in a quasiperiodic waveform with three or more incommensurate component frequencies, is destabilized by a nonlinear perturbation [57, 96, 152]. One nice aspect of this scenario is that the chaotic strange attractor produced is structurally stable: i.e. it will persist despite changes in parameters in the system, provided that they are sufficiently small.

We know of only one report claiming this quasiperiodic route to chaos in electrophysiology, which will be discussed below. This relative lack of evidence might simply be because this route is not well-appreciated by experimentalists, and so there may not have been many serious attempts made to find it or produce it experimentally. However, the majority of physiological variables (e.g. heart rate, blood pressure) are controlled by systems with many different characteristic response times. The weak interaction of these many different control systems would lead to N-tori with N large [96]. One might thus expect chaotic behaviour arising from the Newhouse Ruelle-Takens scenario to be quite commonplace *in vivo*, since these control systems are generally nonlinear and interact in a nonlinear fashion. However, unlike the case in the physical systems where this scenario has been described [20, 96, 252], it might be difficult to provide direct experimental evidence for this route, since to do so one would have to set up a stationary quasiperiodic behaviour with three or more component frequencies. In addition, one would then have to subject the system to the appropriate nonlinear perturbation, which might have to be very carefully chosen, especially when the perturbation is small [96]. An additional consideration to be borne in mind in this case is that this route might be intrinsically rare, since it was not seen very often in a numerical study of one particular system in which a search was made over a wide range of randomly chosen parameters [96]. In addition, while the theory says that chaos should occur for an infinitesimally small, but appropriately chosen perturbation, it was found in this study

that the chaotic attractors became increasingly common as the amplitude of the perturbation was increased.

Caveats

1. Quasiperiodicity is a mathematical concept that cannot be proven in an experimental or numerical setting, having, like chaos, fundamental methodological problems inherent in its definition (e.g. irrational numbers). In a noisy system, it becomes impossible to discriminate between quasiperiodic orbits and periodic orbits of long period ([83], Figs. 11.7 and 11.8). In addition, a fundamental conflict between the measure-theoretic and generic points of view has been pointed out [100].
2. Should the nonlinear perturbation be preexisting (i.e. not added *after* the 3-torus is established, as in the Newhouse-Ruelle-Takens scenario), it is possible that only two frequencies would be seen as a parameter is changed before the chaotic attractor would appear, since the 3-torus that would otherwise occur would not come into existence because of the destabilizing effect of the nonlinear perturbation [252]. For this reason, chaotic activity seen following a 2-frequency quasiperiodic motion has been interpreted in terms of the Ruelle-Takens-Newhouse scenario in experimental work on physical systems [20, 252]. Unfortunately, diagnosis of the Newhouse-Ruelle-Takens scenario cannot definitely be established in this circumstance, unless one could somehow remove the perturbation and show that a 3-torus would result instead of the strange attractor in the absence of the perturbation.
3. It is possible to obtain chaos from a 2-torus, e.g. in the Curry-Yorke model [20]. This route is probably connected with another very-well studied "route to chaos" involving quasiperiodicity in one-dimensional maps [20, 152]. There are also several other reports in which there are still other routes to chaos involving tori - e.g. period-doublings of tori [9, 66].
4. In the one report that we have been able to find in the electrophysiological literature in which the quasiperiodic route to chaos was claimed [98], there was apparently a transition to a period-doubled rhythm, and then to a quasiperiodic rhythm, and then to chaos. This is not consistent with the classic Newhouse-Ruelle-Takens scenario (unless some variant of the situations described in caveats 2 or 3 above existed).

The Šil'nikov Scenario

The Šil'nikov scenario (or bifurcation or phenomenon) is a very complex phenomenon in which the system generates an infinity of periodic and aperiodic orbits as a parameter is changed away from a value at which the system admits a homoclinic orbit (an orbit of infinite period) associated with a saddle-focus type of equilibrium point. As one changes a parameter away from the one precise value where the homoclinic orbit exists, there is an explosion producing an infinite number of periodic orbits, each of which undergoes a cascade of an infinite number of period-doubling bifurcations leading to chaos. There is numerical evidence that this scenario is being followed when "mixed-mode" rhythms containing action potentials and delayed afterdepolarizations are seen in numerical work on an ionic model of the sinoatrial node [105]. It is also possibly occurring in other situations in which delayed afterdepolarizations are seen in cardiac ([101], see also references therein) and neural [104, 113, 285] oscillators, as well as in still other situations in which early afterdepolarizations [29, 30] or internal calcium oscillations [278] occur. The Šil'nikov scenario has also been invoked to account for phenomena seen in respiration [240] and in human neuromuscular coordination [151].

Caveats

1. There are many problems with establishing the existence of the Šil'nikov scenario. As recently emphasized, it is not sufficient to simply show that a homoclinic orbit exists [233]. Determination of the amplitude of the real parts of the eigenvalues of the saddle-

focus equilibrium point is one of the key measurements to be made in establishing this scenario. Unfortunately, while this calculation can be carried out in modelling work [105], it has not been done in experimental work.

2. There is one experimental report on a chemical reaction in which mixed-mode oscillations occurred, but with no sign of chaotic activity [171]. Modelling work on this reaction reveals that the range of the parameter over which the chaos exists is exceedingly small, and the chaos itself can be on such a fine scale that it would almost certainly not be observable in the corresponding - necessarily noisy - experimental system ([226], Fig.17). This "chaos on a fine scale" is presumably what accounts for the lack of aperiodic behaviour in the modelling work hitherto carried out on ionic models of heart and nerve (references above).
3. Noise can produce rhythms reminiscent of the mixed-mode rhythms expected from the Šil'nikov scenario in situations where this scenario cannot exist [35, 165].

Power Spectrum

The power spectrum of many chaotic signals has a background level that is significantly above the instrumental noise floor. In this context, the power spectrum has been determined in experimental work on the cardiovascular [98, 244, 291, 292, 294, 295, 296], neural [1, 117, 173, 177, 202, 249, 270], respiratory [239, 240], and hormonal systems, as well as in reports on human speech [191] and periodically driven plant cells [121]. Spectral analysis has also been employed in modelling work on periodically stimulated cardiac cells [134] and axons [133], as well as on bursting pacemaker neurons [25] and spiral waves in an excitable medium [297].

While the lack of a broadband component in the power spectrum of ventricular fibrillation has been taking as evidence for concluding that fibrillation is not chaotic [86], it is possible to construct chaotic models that have a narrow-band spectrum similar to that seen in fibrillation [139]. In contrast, the spectrum during atrial fibrillation has been reported to be broad-band in nature [146].

Caveats

1. One should be cautious in concluding that a system is chaotic simply on the basis of the existence of a broad-band spectrum computed from a single time series. The evidence is more convincing if one can show a sequence of bifurcations involving periodic orbits, with the *sudden* emergence of a large-amplitude broad-band component in the spectrum, coinciding with the transition from periodic to aperiodic behaviour [25, 133, 244].
2. It has been known for some time that chaotic systems can have a $1/f^{\alpha}$-like spectrum [126, 170, 214]. While cardiovascular [136, 142, 153, 188, 190, 200, 201, 242, 256, 282] and neural [75, 188, 189, 193, 209, 243] systems can also have a $1/f^{\alpha}$-like spectrum, caution is indicated in so far as drawing a causal connection, i.e. implying or concluding that the electrophysiological system is therefore chaotic [256]. In this respect, we must note that stochastic systems can have a $1/f^{\alpha}$ spectrum [41, 65, 199], and that there exist strange (i.e. fractal) attractors that are not chaotic [95]. Caution is also suggested in cases when their seems to be some fractal structure in the signal - e.g. fractal clustering in auditory spike trains [271] and in ventricular extrasystoles [266]. Finally, a $1/f^{\alpha}$ spectrum can be replicated by a system whose component parts individually have appropriately chosen Lorentzian spectra [243]. Thus, as previously stated [106, 142], the $1/f^{\alpha}$ falloff in heart-rate and blood-pressure spectra could conceivably be simply the result of many different control systems working over widely different time scales. It is thus not necessarily correct to deduce that there is some form of fractal process simply because there is a $1/f^{\alpha}$-like spectrum [190].
3. Fractal anatomy does not imply chaotic dy-

namics [249], nor does the existence of a $1/f^{\alpha}$ spectrum imply the existence of a fractal anatomy [21, 37, 161], as has been claimed for the cardiac His-Purkinje system ([85, 287], and references therein).

Attractor Phase-Portrait

This technique has been particularly attractive to many investigators, in no small measure because it is very simple. A time series of a measured variable x(t) is sampled at an interval Δt producing the discrete data set $\{x(0), x(\Delta t), x(2\Delta t), ..., x(N\Delta t)\}$. One then forms n-tuplets (often triplets for purposes of illustration) of points $(x(i\Delta t), x((i+1)\Delta t), ..., x((i+(n-1)\Delta t)))$, $i \geq 0$ and plots the trajectory traced out by these n-dimensional points in the n-dimensional phase space. This method of reconstructing or reconstituting a phase-space trajectory is called "the method of time delays" or "embedding". Alternatively, a phase portrait can be obtained by plotting one measured variable against another, or a two-dimensional phase-plane plot can be obtained by plotting the first derivative of a variable *vs.* the variable itself.

Examination of the phase-portrait sometimes reveals a banded structure that is reminiscent of "strange attractors" (described below) seen in numerical simulations of mathematical systems that are commonly accepted as being chaotic (e.g. Lorenz, Rössler attractors). Whether this resemblance is of any significance, or merely superficial, is unclear. In the area of neurophysiology, portraits have been constructed in one of the three ways mentioned above for the EEG [12, 13, 50, 67, 68, 177, 211, 216], multi-unit recordings from the tectum [192], the H-reflex [245], the electro oculogram [1], visual evoked potentials [249], epileptiform hippocampal bursts [117], respiration [238, 239, 240], speech [191], bursting molluscan neurons [116, 186], driven neurons and axons [2, 62, 115, 116, 117, 119], and models of axonal and neuronal membrane [3, 116, 169]. There are also many articles in the cardiovascular field, dealing with normal sinus rhythm [12, 26, 50, 123, 178, 187, 225, 295], atrial fibrillation [123, 146, 196], ventricular fibrillation [139, 224, 225], irregular rhythms in periodically driven preparations [36, 38, 244], irregular blood flow and blood pressure [99, 230, 282, 292, 294], and models of cardiac cells [24, 181] and of spiral waves [297]. Portraits have also been made for periodically driven plant cells [121] and for activity in a model of respiration [238]. Finally, of great interest to electrophysiologists, it is apparently possible to reconstruct a chaotic attractor that is generating a spike train via an integrate-and-fire mechanism from a record of the spike train itself [241]. Embedding is now perhaps most frequently used as a preliminary step in obtaining a Poincaré section or in calculating the correlation dimension or Liapunov exponent.

Caveats

1. The visual appearance of the attractor can change depending on the choice of embedding time delay Δt (see [12] for the ECG; [80] for the heartrate). One of the very few places where one can find nice systematic illustrations demonstrating this point in an experimental system is in an article on a chaotic chemical reaction ([231], Figs. 2,3). An incontrovertible example of the effect of choice of time delay on the reconstituted attractor can be seen when one embeds a time series obtained from a deterministic set of equations: in this case, the reconstituted strange attractor can be made to look very different from the real strange attractor ([282], Fig.3).
2. Filtered noise can sometimes give a reconstituted trajectory that looks similar to a strange attractor, in that it appears to contain some "structure" ([216], Fig. 3). In some situations in which the existence of low-dimensional chaos (and therefore a strange attractor) is claimed, the phase portrait is comparable to a "ball of string" or "tangle of spagetti" ([26], Fig.1; [67], Fig.1a; [87], figure on page 48; [292], Fig.6), that is reminiscent of the phase por-

trait constructed from a random system ([73], Johnson noise from a resistor in Fig.3; [216], Fig.4). In such an instance, the possibility also exists that there has been a misdiagnosis of low-dimensional chaos, and that there is instead an orbit (which might or might not be chaotic) of very high dimension ([73], summated output of 12 oscillators in Fig.3).

3. Interaction between two approximately periodic processes at different frequencies (e.g. respiratory sinus arrhythmia) can produce a quasiperiodic rhythm, which, in the presence of noise, can sometimes result in a portrait that superficially has the banded shape characteristic of many strange attractors (e.g. the Rössler attractor). The same sort of phenomenon can occur in periodically stimulated cells that have some sort of "memory", the time constant of which is long with respect to the period of the stimulation.
4. In modelling work, reconstitution of an attractor can still be carried out using the method of time delays, even though one can plot the phase-space trajectory directly [24, 116].

Poincaré Sections

Once an attractor has been reconstituted, it is possible to take a Poincaré section of that attractor. This is done in a three-dimensional reconstruction, for example, by placing a plane tangential to the overall direction of the trajectory in that region of the phase space, and keeping track of where successive passes of the orbit pierce that plane (a nice example of this is in a study on a chaotic chemical reaction - [231]). One can then sometimes also extract out a one-dimensional return map. Poincaré sections have been taken for the ECG [12, 291], experiments on neural [2, 116, 117, 186] and cardiac [244] tissue, respiration [239], vocalization [180], and modelling of cardiac [24, 181], neural [116, 284], respiratory [238], and multiloop feedback [79] systems.

Return Map

Perhaps the simplest context in which one can visualize and appreciate chaotic behaviour is in the setting of a one-dimensional finite-difference equation or map [78, 143, 174]. It is therefore not surprising that the approach of reducing consideration of experimentally or numerically obtained data to consideration of the properties under iteration of a one-dimensional map has been very popular. This procedure can be carried out in two ways. The method most commonly used is to construct a return map directly from the time-series showing the chaotic behaviour. Less commonly, what one might call a "forward map" may be constructed from an experiment independent of the experiment producing the chaotic trace [23, 38, 39, 82, 107, 108, 131, 160, 280].

A return map can, in turn, be produced in one of two ways. As described in the section just above, one can construct a Poincaré surface of section for a reconstituted attractor and then keep track of where this surface is pierced on successive passes of the trajectory. Alternatively, one can simply measure some characteristic feature of the waveform on each "cycle" of the waveform (or on each cycle of the waveform of a periodic forcing stimulus, yielding a "stroboscopic map") and plot successive values as a function of the immediately preceding value. This latter approach results in an approximately one-dimensional first-return map in experiments on plant [118, 121], cardiac [38, 76, 82, 107, 109, 112] and neural [3, 115, 117, 119, 120, 145, 179] preparations, as well as in the cries of newborn infants [180]. A one-dimensional map has also been extracted in this way in work modelling cardiac [160, 181, 281], neural [2, 25, 129], and pancreatic [31] activity. In other situations, when a first-return plot is made, one or more clouds of points showing little or no hint of one-dimensional structure results [12, 40, 71, 74, 76, 106, 110, 164, 238, 240, 246, 289]. This result is variously ascribed to the existence of random or chaotic dynamics. In some cases - digitalis-in-

toxicated cardiac muscle [71], hipppocampal bursting [246], and ventricular fibrillation [289] - the interpretation is that there is a two- or higher-dimensional map underlying the process. The extracted two-dimensional return map has then been used in "controlling chaos" [255] in neural [246] and cardiac [71] preparations in which the authors claim the existence of chaotic activity ([40], for an alternative interpretation).

Caveats

1. The fact that there is no one-dimensional structure apparent on a return map does not necessarily imply that the system is stochastic. For example, if the map is determined from a Poincaré section, it might be that the surface of section is inappropriately placed: changing the location of the plane of section might result in a more one-dimensional map ([231], Figs. 9,10). Perhaps more importantly, there is no requirement that chaos must have some sort of one-dimensional description, since one might expect this only in systems in which the flows are strongly contracting.
2. Establishing that a period-3 orbit exists on a return map has been used to claim the existence of chaos in periodically driven plant cells, since the existence of such an orbit implies that the system "is chaotic in the sense of Li & Yorke" [118]. However, the existence of chaos in the sense of Li & Yorke is of questionable significance, since what one invariably sees in experimental or modelling work is the stable period-3 orbit, and not the aperiodic orbits that theoretically coexist with that orbit. Thus, the correspondence between Li-Yorke chaos and the irregular experimental trace obtained by Hayashi et al. [118] is not as direct as these authors claim.

Fractal Dimension

The irregular waveform produced by a chaotic system is a reflection of the aperiodic trajectory traced out by the state-point of the system. This trajectory is a consequence of the existence of a *strange attractor* in the phase-space of the system [234]. This object is termed an *attractor* since it attracts trajectories starting from a set of initial conditions (its *basin of attraction*). It is termed *strange*, since its geometric properties are not those of a simple curve, surface, or volume, but rather those of a more exotic structure, such as a Cantor set. One can calculate the dimension of this fractal object using one of several different algorithms [63, 64, 92, 137]. This determination of some form of dimension is probably the most commonly used basis on which claims of chaotic dynamics have been made in biological systems. This is undoubtedly due in no small part to the ease with which many of these algorithms can be implemented on the computer. Another reason for the widespread use of this approach is that in situations where one only has a single time-series and cannot systematically change a parameter in the system, one cannot apply some of the other tests mentioned above (e.g. establishing a route to chaos or demonstrating an increase in the background level of the power spectrum). The most widely-used algorithm to date is that due to Grassberger & Proccacia [90, 91], which estimates the correlation dimension ([137], for a nice introduction to this algorithm).

Since the initial reports in the mid-1980's [11, 13, 56, 175], there have been on the order of a hundred papers published in which the fractal dimension of the electroencephalogram (EEG) has been calculated (see references cited immediately below and also [15, 16, 54, 84, 131, 132, 175, 207, 210, 212, 275]). These articles deal with the influence on the calculated dimension of the EEG of several factors, including smoking [213], intelligence [167], state of consciousness [11, 13, 50, 68, 177, 178], mental tasks [177] and various diseases [11, 50, 68, 187]. Staying within the field of neurophysiology, dimension calculations have also been made for the magnetoencephalogram [177, 237], nystagmus [1, 253], olfaction [67, 183], vocalization [180, 191], the H-reflex [245], tremor [69, 154, 178], postural sway [43], visual

perception [159, 192], visual evoked potentials [249], auditory event-related brain potentials [220], respiration [137, 203, 238, 239, 240], single-unit recordings from monkey motor cortex [219], molluscan neurons [186], periodically stimulated squid axon [173], model neural networks [84], and a model of respiration [238].

In the cardiac field, there have been many reports of the fractal dimension of normal sinus rhythm, including investigation of the effect of circadian rhythms, cardiac transplantation, the autonomic nervous system, altitude, stage of development, and various diseases [12, 22, 26, 50, 70, 123, 136, 144, 158, 178, 259, 261, 277, 291, 295]. One interesting finding is a decrease in dimension with age [144].

Estimates of dimension have also been made for atrial flutter [123]. Two studies on ventricular fibrillation showed that the dimension is very high or that fibrillation is random [139, 224]. In contrast, in some instances of atrial fibrillation, the algorithm yields a low-dimensional estimate [123, 196]. The suggestion has been made that the lack of low-dimensional behaviour in ventricular fibrillation is due to the fact that the correlation length is small when compared to the size of the ventricles [18]. It has been reported that the dimension falls during the early stages of myocardial ischaemia in pigs, and falls still further just before fibrillation ensues [261]. A reduction in dimension also occurs in patients before ventricular fibrillation occurs [156, 259, 263]. In contrast, another report on three clinical cases found that the dimension gradually rose as normal sinus rhythm was replaced sequentially by non-fibrillatory ventricular arrhythmias (extrasystoles, bigeminy, tachycardia), coarse fibrillation, and finally fine fibrillation, which was not low-dimensional [225]. In a model of a single hypermeandering spiral wave, which might be a mechanism involved in ventricular fibrillation [93], there is also a low correlation dimension [297].

In addition to heart and brain, there have been applications to systems in which smooth or skeletal muscle is involved: blood flow [98, 99, 282, 292, 294], electromyography [6], vocalization [180, 191], tremor [69, 154, 178], and finger tapping [154]. Finally, the correlation dimension has been calculated for hormonal levels [208].

Caveats

1. It has been known for a long time that there are significant methodological problems with calculation of the fractal dimension. These centre around the choices of sampling rate, time delay, amount of data, precision of A-D converter, filter characteristics, surrogate data set, and length of scaling region, as well as problems due to stationarity, noise, and geometrical effects [14, 51, 56, 59, 61, 92, 137, 177, 185, 199, 211, 216, 221, 224, 225, 232, 250, 273]. The technical quality of the studies cited above runs from fatally flawed to "state-of-the-art" at the time study conducted. Indeed, for the former group, one might well take the point of view recently expressed: "One of our conclusions is that for a number of problems the only meaningful solution will be not to report a dimension at all" [137].
2. In an attempt to control for some of the above problems, the method of "surrogate data" has been employed. Data is scrambled in some way so as to randomize it (producing e.g. phase-randomized, Fourier-shuffled, or Gaussian-scaled surrogates), but keeping intact some property of the original signal [27, 245, 247 (with source code for algorithms), 274] . The dimension is then calculated for both the original and the surrogate data sets, and various null hypotheses concerning the two data sets can then be tested. However, this method is not foolproof, and has its own problems: for example, there can be spurious identification of noise as chaos [223, 274], there can be comparable incomplete saturation in both the original and the surrogate data [136, 158], and there is at least one report where the surrogate data is identified as being of low-dimensional origin

while the original unscrambled data is not [245]. In addition, this author has methodological reservations about the practice of the technique of surrogate data, since the "random number generator" used to scramble the data is almost invariably a pseudo-random number generator, which uses a deterministic algorithm that has more in common with a chaotic process than with a stochastic one [106]. A similar criticism can be made for studies in which "random" signals are constructed using pseudo-random number generators and used for testing-out dimension algorithms [221], or for showing that putatively chaotic systems are in fact probably stochastic [40, 46, 106].

3. There is a much more fundamental question that is intimately tied in with the above technical problems. It is now becoming increasingly clear that the reservations that some members of the community have held for a long time are in fact well-founded: there are real problems in the calculation of dimension and in the interpretation of the resulting number. Perhaps most tellingly, when the input to the algorithm is coloured noise, there can be spurious identification of a low-dimensional attractor [137, 199, 221]. Perhaps the clearest statement of this view to date has been by Osborne & Provenzale [199]: "This in turn implies that the determination of a finite and non-integer value for the fractal dimension is in general not sufficient to indicate the presence of a strange attractor."

   Thus, a revisionist school of thought is now developing, in which investigators reexamining the question are now finding no evidence for the existence of low-dimensional chaos, or else reinterpreting the evidence of earlier studies that suggested the existence of low-dimensional chaos based on estimation of fractal dimension. In electrophysiological work, this has been true thus far for the EEG [84, 202, 212, 216, 274, 275] and for normal sinus rhythm [136, 158]. In addition, studies on binocular rivalry [159], respiration [137], postural sway [43], neuromuscular jitter [74], and the H-reflex [245] in human beings could find no evidence for low-dimensional chaotic dynamics using attempted calculation of the fractal dimension. Similar work with other signals will undoubtedly follow. This observation perhaps accounts for the trend in many of the most recent articles to banish the term fractal dimension or correlation dimension, and replace it instead with innocuous terms such as "dimensional complexity parameter" [177], "dimensional complexity" ([210] and references therein), "complexity" [144, 277] and "apparent correlation dimension" [22, 277].
4. As mentioned above, many physiological systems have a $1/f^{\alpha}$ falloff in their power spectra. Random systems with this kind of spectrum show spurious evidence for the existence of low-dimensional dynamics [199].
5. When the dimension algorithm shows no indication of low-dimensional chaos [137, 202], this can indicate either that the system is stochastic or that there is a high-dimensional chaotic attractor. The highest dimension that has been reliably reported in experimental work is 12, but this involved reconstructing an orbit that was not chaotic using 10^7 points in a physical system (a collection of 12 electronic oscillators) that has low noise by biological standards [73].
6. Another context in which the word "fractal dimension" appears in the literature is when one makes a measurement of the fractal dimension of the waveform itself, treating it as a fractal curve. Thus, by one measure [150], a straight line has a dimension of one, while a very wiggly curve will have a dimension closer to 1.5. Variants of this kind of "length of coastline" analysis have been carried out for the EEG [150], respiration [128], heartrate [88, 89, 293], individual normal and abnormal electrocardiographic complexes [150], blood flow [230], ventricular ectopy [266], the EMG [6], and postural sway [43]. In the majority of the above investigations, surrogate data sets

were not constructed. However, in one case where a surrogate data set was constructed - for the human H-reflex [245] - it was found that there was no difference between the original and the shuffled data. We reiterate the point that "the existence of fractal properties in the irregular line does not of itself imply underlying deterministic dynamics (e.g. chaos)" [89].

7. It has been stated several times that fractal anatomy can lead to fractal dynamics [249]. However, there is at least one case on record where it has been shown that this conclusion was prematurely taken [21, 37, 161].
8. The dimension of the attractor provides a lower bound on the dimension of the state-space. It thus provides no added information about the dimension of the state-space (i.e. the number of variables) in a physiological system, which is known *a priori* to be very high. Thus the statement that one commonly encounters to the effect that "the dimension is the number of independent variables or degrees of freedom necessary for explaining the system's *total* [emphasis in original] behavior or dynamics" [262], while true, is highly misleading. For example, all periodic phenomena in the physical and biological world have a dimension of one. The majority of experimentalists would take exception to the conclusion that the dynamics are thus "explained" in these various systems.
9. Not all "chaotic" attractors are "strange" [96], and vice versa [95].

Liapunov Exponent

The Liapunov exponent is a measure of sensitive dependence on initial conditions. An n-dimensional system has n Liapunov exponents, and chaos occurs when at least one exponent is positive. There are several algorithms for estimating the Liapunov exponents directly from a time series ([290]; [84, 92, 217, 250], for references to more recent methods). Calculation of the most positive exponent has been carried out for several cases in electrophysiology: e.g. EEG [11, 13, 68], respiration [52], tremor [69], vocalization [191], postural sway [43], molluscan neurons [186], periodically driven squid axon [62] and hippocampus [47], ECG [12, 79], ionic models of neural [10, 25, 33, 133] and cardiac [134, 281] cells, blood pressure and flow [282], hormonal levels [208], neural network models [4], and a model of a hypermeandering spiral wave [297]. A simpler approach is to extract a one-dimensional return map from the time series, or formulate a forward map, and then to calculate the Liapunov exponent from iterations of the map [160]. The Liapunov exponent has also been calculated in a model of tremor formulated as a one-dimensional map [5].

Caveats

1. The big problems here are the large amount of stationary data needed [59] and the corrupting influence of noise on the estimate [92, 250, 274]. It is also essential that appropriate choices of delay time and embedding dimension be made: e.g. there can be an artefactually large Liapunov exponent if too small an embedding dimension is chosen, so that trajectories that are really widely spaced lie close together on the reconstituted attractor [290]. This is especially true in "stiff" systems, where the trajectory moves alternately on faster and slower time scales (e.g. action potentials or electrograms): - a nice picture of this for the ECG is shown in Fig.6 of [84].
2. Although there have been many reports published on the calculation of the Liapunov exponent for the EEG, there is one investigator working with the EEG who has recently made the frank statement: "I have not been able to measure Lyapunov exponents with our biological data" [217]. As with calculations of the fractal dimension, the technical quality of the studies cited above varies dramatically.
3. Stochastic systems can have a positive Liapunov exponent ([184], and references therein). There is also the somewhat paradoxical result that addition of noise to a cha-

otic system can convert the sign of the Liapunov exponent from positive to negative [172].

Entropy

Various kinds of entropies [92, 204, 250] have been estimated for the EEG ([68]; other references in [211]), EMG [221], the H-reflex [245], respiration [238], normal sinus rhythm [12, 123, 144, 204, 236, 293], atrial flutter and fibrillation [123, 196], periodically driven ventricular cells [122], hormonal levels [204, 208], and models of respiration [238]. As with fractal dimension, there is a trend to replace the term "entropy" with "complexity". Two interesting findings are that heart-rate entropy decreases with age and that women have a greater "complexity" in their heartrate than do men [236].

Tests for Nonlinear Determinism

The problems noted above in using estimation of the fractal dimension and Liapunov exponent to establish the existence of chaos have led - at least in some people's minds - to a questioning of the interpretations of results obtained from these methods [48, 59, 77, 79, 80, 84, 233]. This fact might account for the recent upsurge of interest in developing algorithms that carry out the lower-level task of simply providing evidence for determinism in a time series, since determinism is one of the three components in the definition of chaos given earlier. Several of these tests are now available: e.g. nonlinear prediction [268], local flow [141], local dispersion [286], and exceptional events [138]. Further information on these and other related methods can be found in four recent review/tutorial articles ([28]; [92]; [217]; [247] (with code for implementing algorithms)). As with estimation of fractal dimension, surrogate data sets are constructed to test a null hypothesis.

One or more of these tests have been applied to recordings of normal sinus rhythm [84, 136, 158, 291], ventricular fibrillation [289], the EEG [84, 187], the MEG [187], hippocampal evoked responses [241, 248], local field potentials arising during visual responses [192], binocular rivalry [159], monosynaptic spinal cord reflexes [27], spike trains from sensory neurons [164], and neural network models [84]. In addition, prediction has been carried out using tessellation and neural networks in data obtained from the forced squid giant axon [179]. In several of the above cases, the conclusion is that there is no evidence for nonlinear determinism in the data.

Caveat

1. Coloured noise can produce results similar to those from a chaotic system when nonlinear forecasting is used [158, 268].

Spatial Considerations

The majority of the clinical and experimental reports cited above that claim the existence of chaos are in situations in which the system variables are functions of both space and time. Each of these systems is thus described by a system of partial differential equations rather than by a system of ordinary differential equations. It is therefore perhaps surprising that the chaotic dynamics in these cases, where the phase-space is of infinite dimension, can often be reduced to the examination of the dynamics of a one- or two-dimensional map. It is our view that the reason for this is that there must exist an inertial manifold, on which the dynamics is finite-dimensional [228]. The flows in the resultant finite set of differential equations (the inertial form) must then be strongly contracting, so that a low-dimensional finite-difference equation provides a good approximation to the system.

In addition, in these spatially-distributed systems, measurements are typically made at a single site. Thus, there has been virtually no experimental investigation of spatiotemporal chaos in electrophysiological systems, recording from multiple sites. However, since it is no more difficult to "record" from multiple sites

than from a single site in modelling work, there are several numerical studies of chaos in spatially-distributed systems [7, 129, 160, 181]. One of these studies raises the interesting possibility of controlling spatiotemporal chaos [7].

The ability to record from multiple sites also opens up the possibility that multichannel reconstruction of the attractor can be carried out. In this process, one uses signals simultaneously acquired from several different spatial locations to produce a phase-space portrait of the system, and to then perhaps estimate fractal dimension and the Liapunov exponent [58]. This procedure has been carried out both for the EEG [50, 55, 211] and for the ECG [12, 50].

Time delays

A time-delay differential equation arises naturally when one considers the systems (intrinsic, neural, and hormonal) controlling the activity of cardiac, skeletal, and smooth muscle, as well as when one considers information processing in the nervous system. It has been known for some time that chaos can arise in a time-delay differential equation [168], and that one can calculate return maps, power spectra, fractal dimension, Liapunov exponents, etc. of such systems. Nevertheless, like spatiotemporal chaos, this remains an almost completely unexplored area in electrophysiology.

Conclusions

As mentioned early on in this article, a fundamental problem in establishing the existence of chaos in an electrophysiological system is that noise is present in all such systems. This random noise can be due to membrane noise, synaptic noise, or simply Johnson noise. There are now several modelling studies showing that experimentally observed irregular traces are consistent with random (or at least pseudo-random) mechanisms involving populations of single channels [32, 42, 46, 106, 254, 288]. Thus, unless a deterministic interpretation can be put on single channels kinetics [103, 162] and vesicular release [155], one is left with the fact that a stochastic mechanism is at the base of all phenomena seen in experimental work, including "chaotic" ones. Perhaps a view recently expressed by Ruelle [233] is the one that we should all adopt: "In fact we should not be obsessed by chaos: The whole of the dynamics of a real system is interesting, and not just the occurrence of chaos".

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