Synchronization and rhythmic processes in physiology

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Complex bodily rhythms are ubiquitous in living organisms. These rhythms arise from stochastic, nonlinear biological mechanisms interacting with a fluctuating environment. Disease often leads to alterations from normal to pathological rhythm. Fundamental questions concerning the dynamics of these rhythmic processes abound. For example, what is the origin of physiological rhythms? How do the rhythms interact with each other and the external environment? Can we decode the fluctuations in physiological rhythms to better diagnose human disease? And can we develop better methods to control pathological rhythms? Mathematical and physical techniques combined with physiological and medical studies are addressing these questions and are transforming our understanding of the rhythms of life.

Physiological rhythms are central to life. We are all familiar with the beating of our hearts, the rhythmic motions of our limbs as we walk, our daily cycle of waking and sleeping, and the monthly menstrual cycle. Other rhythms, equally important but not as obvious, underlie the release of hormones regulating growth and metabolism, the digestion of food, and many other bodily processes. The rhythms interact with each other as well as the outside fluctuating, noisy environment under the control of innumerable feedback systems that provide an orderly function that enables life. Disruption of the rhythmic processes beyond normal bounds or emergence of abnormal rhythms is associated with disease. Figure 1 shows several examples of complex physiological rhythms.

The investigation of the origin and dynamics of these rhythmic processes — once the sole province of physicians and experimental physiologists — is coming under increasingly close examination by mathematicians and physicists. Mathematical analyses of physiological rhythms show that nonlinear equations (see Box 1) are necessary to describe physiological systems[1–4]. In contrast to the linear equations of traditional mathematical physics (for example, Maxwell's equations, the heat equation, the wave equation or Schrödinger's equation), nonlinear equations rarely admit an analytical solution. Consequently, as Hodgkin and Huxley realized in their classic analysis of the properties of ionic channels in the membranes of squid nerve cells, numerical simulations are one essential feature of quantitative studies of physiological systems[5]. A complementary approach is to analyse qualitative aspects of simplified mathematical models of physiological systems. This involves a mathematical analysis of those features of physiological systems that will be preserved by classes of models that are sufficiently close to the real system. For example, periodic stimulation of a squid giant axon gives rise to a wide variety of regular and irregular rhythms that can be modelled by simple as well as complex mathematical models[6–8].

Although we know that deterministic equations can display chaotic dynamics, it is not straightforward to distinguish deterministic 'chaotic' dynamics from 'noisy' dynamics in real experimental data. The problems were underscored by Ruelle: "Real systems can in general be described as deterministic systems with some added noise"[9]. Although in some carefully controlled situations it is possible to obtain good evidence that a system is obeying deterministic equations with a small amount of noise[6–8,10], more usually the origin and the amount of 'noise' is not easy to determine. In this review, I concentrate on three fundamental issues related to synchronization and rhythmic processes in physiology: origins of complex physiological rhythms; synchronization of physiological oscillations; and the function of noise and chaos in physiological processes with particular emphasis on stochastic resonance. Finally, I discuss the potential applications of these ideas to medicine.

Origins of complex physiological rhythms

Physiological rhythms are rarely strictly periodic but rather fluctuate irregularly over time (Fig. 1). The fluctuations arise from the combined influences of the fluctuating environment, the 'noise' that is inherent in biological systems, and deterministic, possibly chaotic, mechanisms. In most natural as opposed to laboratory settings, there is continual interaction between the environment and the internal control mechanisms, so that separation of dynamics due to intrinsic rather than extrinsic mechanism is not possible. Independent of the mechanism for the fluctuation, it is usually not clear whether the fluctuations are essential to the physiological function, or whether the physiological functions are carried out despite the fluctuation.

At a subcellular level, ionic channels in cell membranes open and close in response to voltage and chemical changes in a cell's environment. An ionic channel lets a specific ion pass through it provided there is a concentration gradient of that ion between the intracellular and extracellular medium and the channel is open. Because histograms of open and closed times of ionic channels are often well fit by an exponential or a sum of exponentials, theoretical models of channel activity often assume that the dynamics of channel opening and closing are governed by simple random processes such as the Poisson process[11–13]. Figure 2a shows a schematic representation of five channels, each of which is open at time 0 and each of which closes randomly with a fixed probability of 0.1 ms^{-1}. Figure 2b shows the fraction of open channels as a function of time for a membrane with 5, 50 and 500 channels. As the numbers of channels in a membrane increases, the falloff of the fraction of open

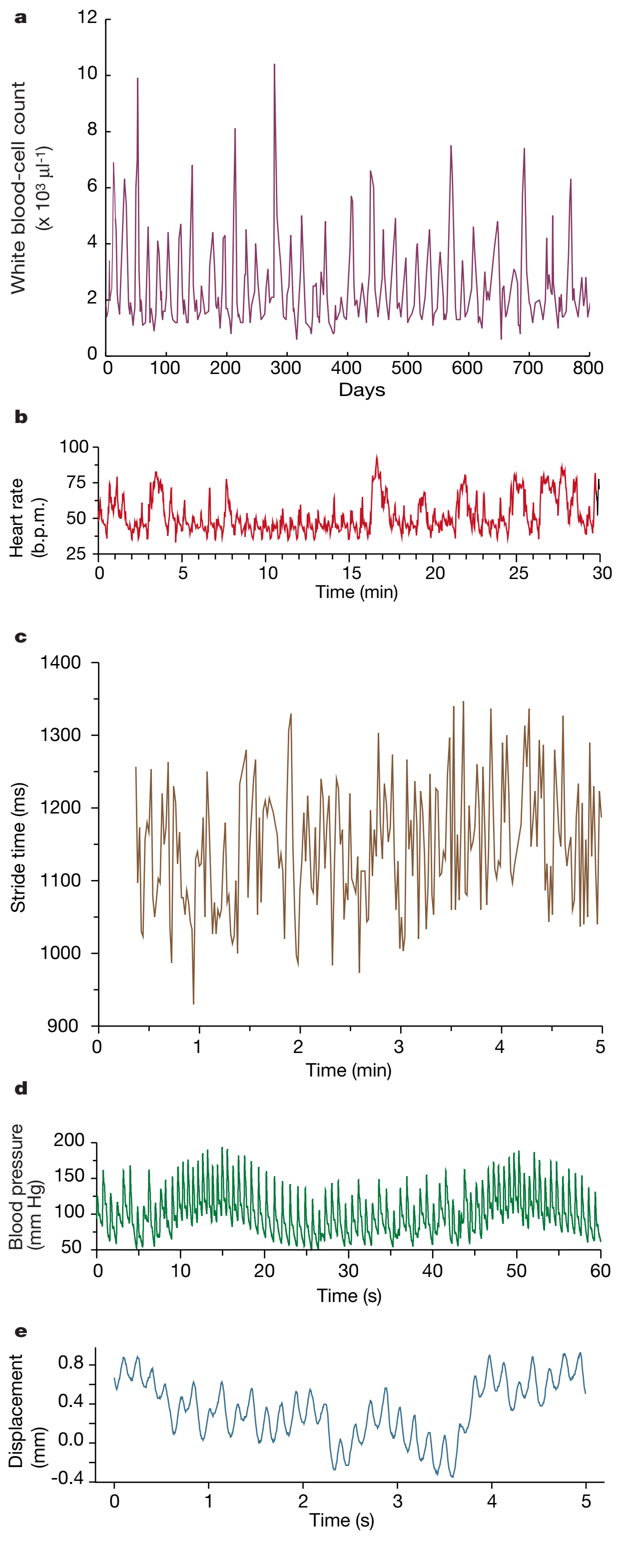

Figure 1 Representative physiological time series. **a**, White blood-cell count in a patient with cyclical neutropenia (tracing provided by D.C. Dale, C. Haurie and M. C. Mackey)[31]. **b**, Heart rate in a subject at high altitude (adapted with permission from the British Heart Journal)[85]. **c**, Stride time in a patient with Huntington's disease (tracing provided by J. Hausdorff)[86,87]. **d**, Blood pressure in a patient with sleep apnoea (tracing provided by A. Goldberger). **e**, Parkinsonian tremor measured from a finger (tracing provided by R. Edwards and A. Beuter[79]). (The traces in panels **c** and **d** are adapted with permission from the Research Resource for Complex Physiologic Signals at http://www.physionet.org.)

Box 1

Properties of nonlinear equations

Nonlinear dynamics is a well developed discipline with many outstanding results[89]. Three concepts are central — bifurcations, limit-cycle oscillations and chaos.

Bifurcations are changes in qualitative properties of dynamics. For example, as a parameter changes, steady states can become unstable and lead to stable oscillations, or a system with one stable steady state can be replaced by systems with multiple stable steady states. Physiological correlates are immediate. Drugs may lead to changes in control systems so that an abnormal, unhealthy rhythm is replaced by a more normal one. Mathematically, the drug induces a bifurcation in the dynamics, and as such, the actions of the drug can be analysed in a theoretical context. Often, the same type of bifurcation can be found in a host of different mathematical equations or experimental systems, and it is common to consider the 'universal' features of such bifurcations. Because many diseases are classified and identified by physicians based on characteristic qualitative features of dynamics, there is a natural match between the emphasis on qualitative dynamics in both mathematics and medicine.

Stable limit-cycle oscillations are a key feature of some nonlinear equations. Following a perturbation, a stable limit-cycle oscillation re-establishes itself with the same amplitude and frequency as before the perturbation. A perturbation to a linear oscillation may lead to a new amplitude of oscillation. For example, there is an intrinsic pacemaker that sets the rhythm in human hearts. If one or more electric shocks are delivered directly to the heart near the intrinsic pacemaker, the heart rhythm is modified transiently but re-establishes itself with the same frequency as before within a few seconds.

Chaos refers to aperiodic dynamics in deterministic equations in which there is a sensitivity to initial conditions. This means that even in the absence of stochastic processes, irregular rhythms can be generated. Although it is easy to consider mathematical systems in which all stochastic influences have been eliminated, in real physical and biological systems it is impossible to eliminate stochastic inputs. Thus, although chaotic dynamics is a clear mathematical concept, application of this concept to real biological systems is a difficult undertaking.

channels approaches the exponential distribution $e^{-0.1t}$. Although most models of channel opening and closing assume a stochastic mechanism such as the one above, deterministic chaotic models might also be consistent with the observed channel dynamics[2,3].

It is remarkable that the irregular openings and closings of ionic channels underlie all neural and muscular activities, including those that require great accuracy and precision such as reading this sentence, playing a violin concerto or carrying out a gymnastics routine. Because typical cells have of the order of at least 10^3 ionic channels of each type, deterministic equations can be used to model cells even though the underlying mechanism is probably stochastic[11–13]. This notion is supported by studies of heart pacemaker cells in which channel dynamics have been modelled by random Markov processes. The resulting dynamics are similar to those generated by the deterministic models with an added 'noisy' fluctuation of period similar to what is observed experimentally[14,15]. Additional regularization of dynamics can arise as a consequence of coupling of cells with irregular dynamics or cells that are heterogeneous[15–17].

Given the difficulty of analysing the origin of temporal fluctuations on a subcellular or cellular level, it is not surprising that the analysis of physiological rhythms in intact organisms provides added difficulties. In some cases, for example, for electrical activity of the

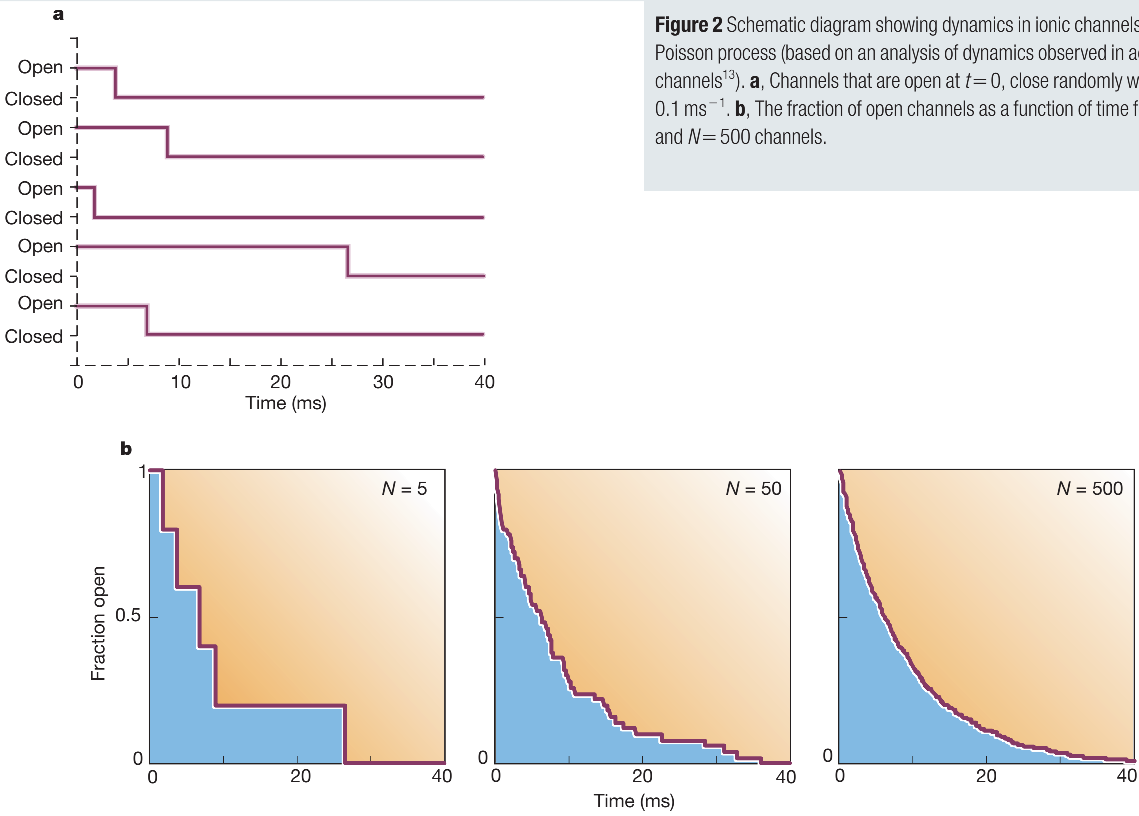

Figure 2 Schematic diagram showing dynamics in ionic channels that deactivate by a Poisson process (based on an analysis of dynamics observed in acetylcholine channels[13]). **a**, Channels that are open at $t=0$, close randomly with a probability of 0.1 ms^{-1}. **b**, The fraction of open channels as a function of time for $N=5$, $N=50$ and $N=500$ channels.

brain and the heart, the data can be collected easily using electrodes on the body surface, and computers provide a means for rapid analysis of large data sets. In other areas, such as endocrine function, determination of hormone fluctuations is difficult and expensive, requiring drawing blood at frequent intervals and performing expensive assays on the blood samples.

Consider the timing of the normal heartbeat as a paradigmatic example of physiological rhythm. Maintaining an adequate blood flow to the brain is essential to life. The heartbeat is generated by an autonomous pacemaker in the heart, but its frequency is mediated by neural activity controlled in turn by a large number of different feedback circuits all acting in parallel. As a consequence, the normal heart rate displays complex fluctuations in time in response to environmental factors such as breathing, exercise, changes in posture and emotion[18]. Diseases that impair heart function, for example damage to the heart caused by a heart attack or high blood pressure, lead to impaired pumping ability of the heart. In such cases, because the normal heart rate would not pump adequate blood to the brain, the heart generally beats more rapidly, and many of the normal fluctuations of heart rate are blunted. Lacking clearly defined and widely accepted operational definitions for chaotic dynamics, it is not surprising that agreement is lacking about whether or not normal heart dynamics are chaotic[19] or not chaotic[20,21]. Various tests of time variation have been applied to heart-rate variability to show that heart-rate fluctuation displays $1/f$ noise[22], fractal dynamics with long-range correlations[23,24], and multifractal dynamics[25]. Although similar dynamics in physical systems have been associated with self-organized criticality[26], in the biological context it is impossible to assert a mechanism based on the current observations. Indeed, it is possible that many of the properties observed reflect the response of individuals to a changing environment, and the environmental inputs themselves have interesting scaling properties[27].

There have been extensive quantitative analyses of data from many other physiological systems. In some instances the original motivation for the analyses was to determine whether the system dynamics was chaotic, although I believe the answer to this remains unclear. But the data do reveal extraordinarily rich dynamics, and I mention several examples briefly. Electroencephalographic data reflect integrated activity from large numbers of cells in localized regions of the brain. A seizure shows characteristic changes in electroencephalographic records typified by larger-amplitude, regular and sustained oscillations reflecting broad synchronization of neural activity[28]. Standard clinical interpretation of electroencephalographic data has been supplemented by a variety of quantitative analyses motivated by nonlinear dynamics[29,30]. Analysis has also been carried out of a variety of normal and abnormal rhythms of blood-cell levels. Some blood disorders are characterized by pronounced fluctuations in levels of circulating white blood cells[31]. Blood-cell levels are controlled by feedback loops with long time delays and theoretical models have succeeded recently in analysing the effects of various manipulations. Endocrine function also provides a challenging area in view of the difficulty of obtaining temporal data, although sustained efforts have generated time series of various hormones including parathyroid hormone[32], growth hormone[33] and prolactin[34].

These initial studies indicate extremely rich dynamics with differences between normal individuals and patients. The issue of whether or not the dynamics reflect chaos is much less interesting than elucidating the underlying mechanisms controlling the dynamics.

Synchronization of physiological oscillators

Although many cells in the body display intrinsic, spontaneous rhythmicity, physiological function derives from the interactions of these cells with each other and with external inputs to generate the rhythms essential for life. Thus, the heartbeat is generated by the sinoatrial node, a small region in the right atrium of the heart composed of thousands of pacemaker cells that interact with each other to set the normal cardiac rhythm[14,15]. Nerve cells generating locomotion synchronize with definite phase relations depending on the species and the gait[35]. And the intrinsic sleep–wake rhythm is usually synchronized to the light–dark cycle[1,36]. In general, physiological oscillations can be synchronized to appropriate external or internal stimuli, so it is important to analyse the effects of stimuli on intrinsic physiological rhythms. Even the simplest theoretical models (see Box 2 and Figs 3, 4) show the enormous complexity that can arise from periodic stimulation of nonlinear oscillations.

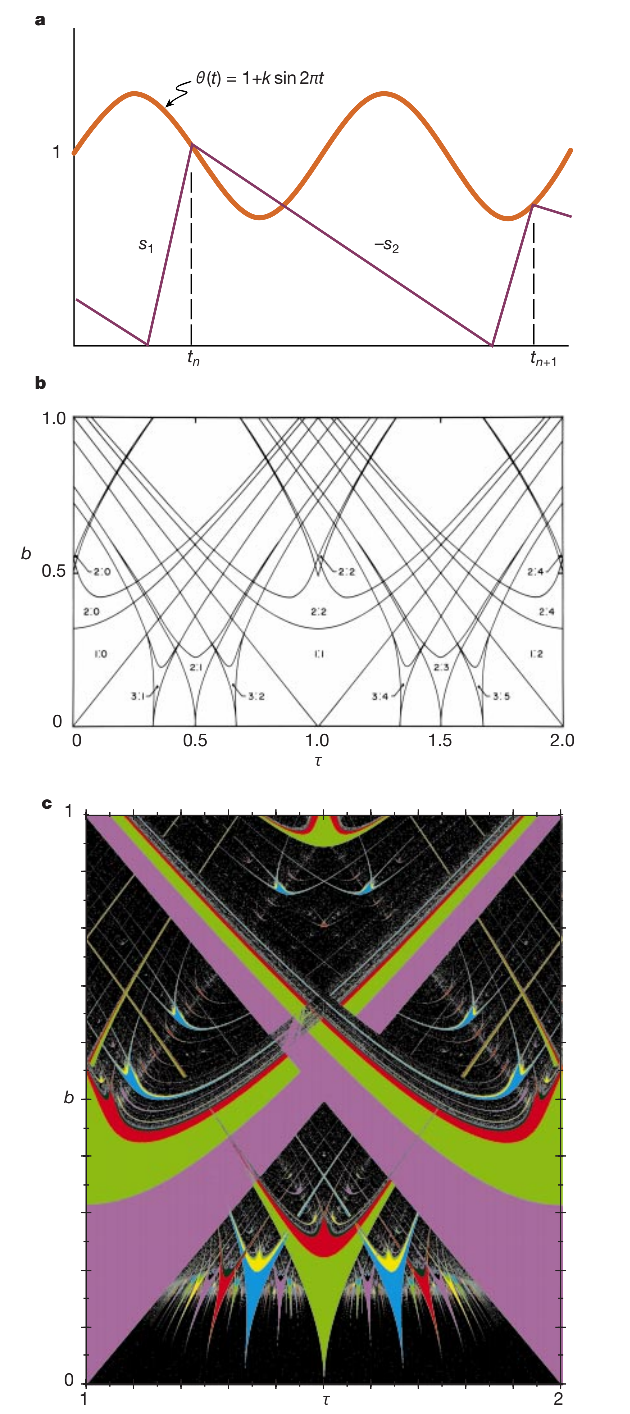

Figure 3 Integrate and fire model and locking zones. **a**, An activity increases linearly until it reaches a sinusoidal threshold and then decreases linearly. The successive times when the activity reaches threshold are determined iteratively. **b**, Schematic picture of the main Arnold tongues for the sine circle map (equation (3) in Box 2). N:M locking reflects M cycles of the sine wave and N cycles of the activity. Chaotic dynamics are found only for $b > 1/2\pi$. **c**, Colour representation of a region of **b**. The colours code different periodic orbits (compare with **b**). The delicate geometry and self-similar structures are more evident in this representation. (Panels **a** and **b** modified with permission from ref. 88; colour version of the locking zones provided by J. Gallas.)

In vitro experiments in cardiac and neural tissue have clarified the effects of periodic stimulation in biological systems. Heart and nerve tissue are examples of excitable tissue[4]. This means that in response to a stimulus that is sufficiently large they will generate an event called an action potential. Following the action potential, for a time interval called the refractory period, a second stimulus does not elicit a second action potential. During periodic stimulation there are both periodic synchronized rhythms and aperiodic rhythms (see Box 2). Periodic stimulation of biological systems can give also give rise to aperiodic rhythms. For weak stimulation, it is common to find quasiperiodic rhythms, in which two rhythms with different frequencies march through each other with little interaction. Other aperiodic rhythms are chaotic. Identification of chaotic dynamics in periodically stimulated heart and nerve tissue is made more certain by the derivation of deterministic, theoretical models that are accurate both quantitatively and qualitatively and that correspond closely to both the regular and irregular dynamics observed experimentally[6–8,10]. As the frequencies and amplitudes of the stimulation are varied, there is a characteristic organization of the phase-locking zones. However, if the dynamics are dissected on a fine scale, the detailed bifurcations in model systems differ from one another over some amplitude ranges. In experimental systems it is difficult to carry out locking studies in which stimulation parameters are varied finely because living preparations can be affected by stimulation and may change over the lengthy times needed to carry out the stimulation.

External inputs can often synchronize biological rhythms. Plants and animals display a circadian rhythm in which key processes show a 24-hour periodicity. This periodicity is usually set by the 24-hour light–dark cycle, but if this is removed by placing the organism in a constant environment, a cycle length different from 24 hours is observed. Thus the light–dark cycle entrains the intrinsic rhythm. If there is shift of the light–dark cycle, for example as might be generated by visiting a different time zone, then a time lag occurs until there is a new synchronization Such phenomena have been modelled by both integrate and fire models and limit-cycle models[36–39].

Other circumstances in which physiological rhythms are stimulated by regular, periodic inputs occur in the context of medical devices. A mechanical ventilator assists breathing in experiments and in people who have respiratory failure. Such devices can be used in a variety of modes, but in the simplest, the physician sets the period and amplitude and the mix of gases for the ventilator, which then periodically inflates the patient's lungs. The resulting periodic lung inflation can interact with the person's intrinsic respiratory rhythm. In some instances, the respiratory rhythm will be entrained to the ventilator, but in other cases the patient will breath out when the ventilator is in the inflation phase[40–42].

These examples illustrate the effects of an external periodic input on intrinsic physiological rhythms. But the physiological rhythms also interact with one another. An example is the increase of the heart frequency during inspiration. Although the interactions between the respiratory and cardiac rhythms are not strong enough usually to lead to synchronization, such synchronization has been demonstrated in healthy high-performance swimmers[43].

It seems likely that many bodily activities require synchronization of cellular activity. For example, synchronization seems to be an essential component of many cortical tasks — coherent oscillations at 25–35 Hz are found in the sensorimotor cortex of monkeys[44] and 40–60-Hz oscillations are found in the visual cortex of cats[45].

Many different sorts of mathematical models have been proposed to account for synchronization in diverse systems. For example, synchronization has been observed in mathematical models of populations of cells that generate the heart beat in leeches[16], the respiratory rhythm in rats[46], gamma and beta rhythms in the brain[47], and the circadian rhythm[48]. However, because coupled oscillators show robust behaviour in which units tend to become synchronized[49], the observation of synchronization in models is not in itself a strong indicator of the suitability of the models.

Given the enormous numbers of connections between different cells and organs in the body, perhaps the biggest puzzle is not why bodily rhythms may in some circumstances become synchronized to each other, but rather why there seems to be so much apparent independence between rhythms in different organs.

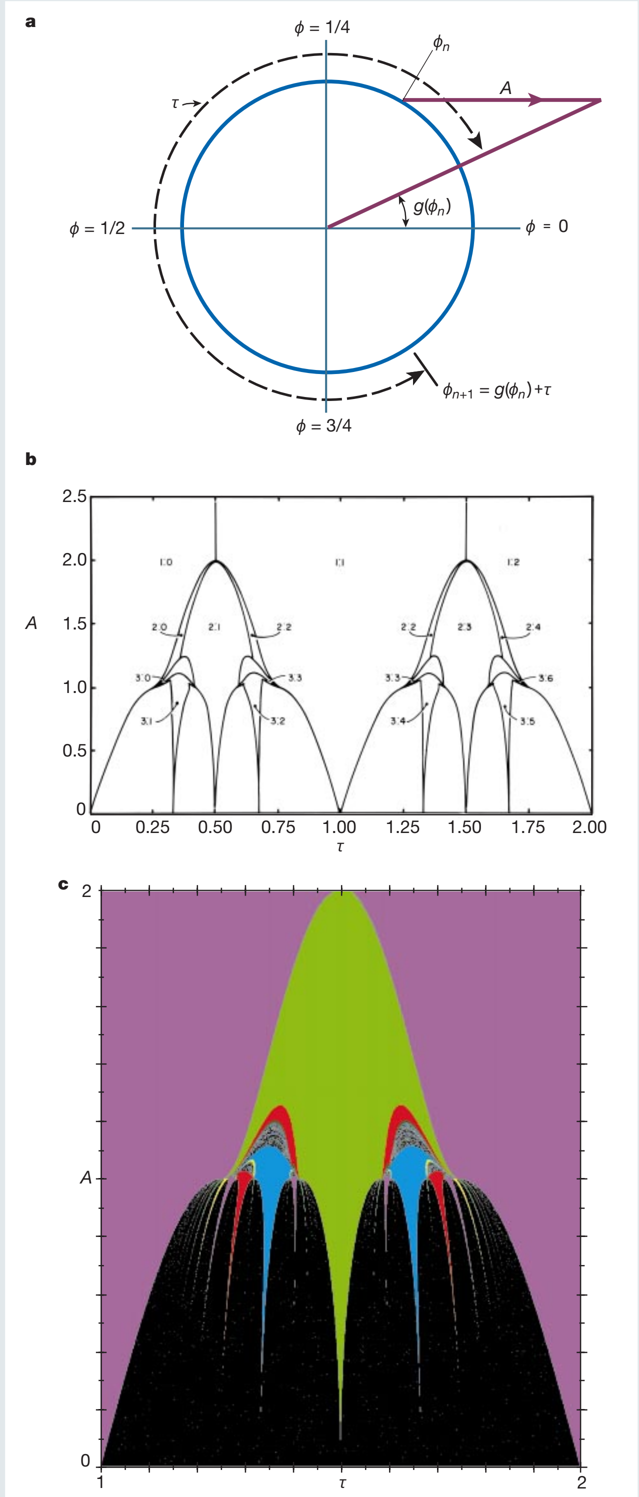

Figure 4 Poincaré oscillator model and locking zones. **a**, A stimulus of amplitude *A* delivered to the limit-cycle oscillator in equation (4) (Box 2) resets the phase. **b**, Schematic picture of the main Arnold tongues for the periodically forced Poincaré oscillator (equations (4) and (5) in Box 2). *N*:*M* locking reflects *N* stimuli for *M* cycles of the limit cycle oscillation. The Arnold tongue structure is present for $0 \leqslant A \leqslant 1$. **c**, Colour representation of a region of **b**. (Panels **a** and **b** modified with permission from ref. 88; colour version of the locking zones provided by J. Gallas.)

The function of noise and chaos in physiological systems

When looked at carefully, all physiological rhythms display fluctuations. Do the physiological systems function well despite these fluctuations, or are the fluctuations themselves intrinsic to the operation of the physiological systems? And if the fluctuations are essential to the functioning of the systems, is there some reason to believe that chaotic fluctuations would provide added function over stochastic fluctuations? There are no clear answers to these questions.

Chaotic dynamics might underlie normal function. In chaotic dynamics, there are typically many unstable periodic orbits, and there is also a sensitive dependence on initial conditions so that small, well-timed perturbations could lead to strong effects on the dynamics. Scientists have learned how to control chaotic dynamics[50] and nonlinear dynamics[51] in model equations and in the laboratory. Electrical stimulation of complex dynamics in cardiac[52] and neural[53] systems using chaos-control techniques has led to the regularization of complex rhythms, although the mechanisms of these effects are not certain[51]. Rabinovich and Abarbanel suggest that chaotic dynamics might be easier for the body to control than stochastic dynamics[16]. Another way the body might exploit chaos is by associating different unstable orbits with different percepts. Skarda and Freeman[54] proposed that the spatiotemporal fluctuations observed in the olfactory bulb in rabbits are chaotic. Each different odour is associated with and selects a different unstable spatiotemporal pattern of oscillation. However, in view of the difficulties associated with recording and interpreting spatiotemporal dynamics in living biological systems, and the huge gaps in understanding complex physiological functions involved in cognition and control, these claims remain intriguing hypotheses rather than established fact.

In normal circumstances, detection of signals is hampered by noise. For example, because the aesthetic and practical utility of sounds and images is reduced as noise level increases, designers of devices for recording and playback of sound and images make strenuous efforts to maximize the signal-to-noise ratio.

In other circumstances, however, the presence of noise and/or chaotic dynamics can improve detection of signals. Stochastic resonance refers to a situation in which the signal-to-noise ratio is maximum at an intermediate level of noise[55–58]. For example, in tasks that are at the threshold of perception, the addition of noise can improve threshold detection. To illustrate this, consider a 'leaky' integrate and fire model[59] in the presence of noise as a model for stochastic resonance (Fig. 5). Assume that an activity (here a membrane potential of a nerve cell) x is governed by the differential equation

$$\frac{dx}{dt} = -cx + I + \xi \qquad (1)$$

where c is a decay constant, I is constant input and ξ is added random noise. The activity rises to a threshold $f(t) = 1 + k\sin 2\pi t$, which represents an oscillating signal. If $c = 0$, then x increases linearly to the threshold (as shown in Fig. 3 and Box 2). When the activity reaches the threshold it elicits an action potential indicated by the arrows, followed by an immediate reset of the activity to zero. With $\xi = 0$ the maximum value of x is I/c. Consequently, if $(1 - k) > I/c$ and there is very low noise, then the activity would never reach threshold (Fig. 5a). But if there is moderate noise the activity can reach threshold, and this tends to occur at the troughs of the sine wave (Fig. 5b). Of course, if the noise is too great, then the activity is no longer as concentrated at the troughs (Fig. 5c). Thus, at intermediate values of the noise, the activity is well synchronized to the sinusoidal input, but rather than occurring on every cycle, there is a stochastic element resulting in a skipping pattern of activity in which excitation tends to occur at random multiples of a common divisor. Although the mechanisms are not well understood, similar rhythms, which may represent a 'stochastic phase locking', are observed frequently in physiological data[56,57].

Box 2
Simple models for synchronization of nonlinear oscillators

Because biological oscillators are stable nonlinear oscillations, many of the general features of the interactions between the periodic input and the ongoing rhythm can be predicted without knowing precise details of the nature of the oscillator or the input. Simple toy models of synchronization show a host of phenomena shared by more complex models and real systems[2,4,49,59,88,90–92].

The integrate and fire model assumes that there is an activity that rises to a periodically oscillating threshold[59,90] and then resets to a lower threshold. Depending on the setting, the activity might represent a nerve membrane potential, a substance that induces sleep or a neural activity associated with the timing of inspiration. There are also many ways in which one might model the activity. It could be modelled by a function that increases linearly in time, or by a function that saturates, or perhaps even by a biased random walk. One of the simplest embodiments of the integrate and fire model is to assume an oscillatory threshold $\theta(t) = 1 + k\sin 2\pi t$ and an activity that increases linearly to the threshold, followed by a linear decrease to zero (Fig. 3a). To illustrate some of the properties of this model, consider the situation in which there a jump from 0 to the threshold, followed by a linear decay (slope of $-s_2$) to zero. Let t_n be the time when the oscillation is at the threshold value for the nth time. Then

$$t_{n+1} = t_n + 1/s_2 + (k/s_2)\sin 2\pi t_n \quad (2)$$

If $\tau = 1/s_2$, $b = k/s_2$ and $\phi_n = t_n$ (mod 1), we obtain

$$\phi_{n+1} = \phi_n + \tau + b\sin 2\pi\phi_n \pmod 1 \quad (3)$$

This difference equation — sometimes called the sine circle map — displays an incredible array of complex rhythms[91]. One type of rhythm is synchronization of the activity to the sine function in an N:M phase-locked rhythm so that for each M cycles of the sine wave the activity reaches the threshold N times. For low amplitudes ($0 \leq b \leq 1/2\pi$) of the sine-wave modulation, there is an orderly arrangement of the phase-locking zones, called Arnold tongues. For fixed values of b, as τ increases all rational ratios M/N are observed and there are quasiperiodic rhythms in which the two rhythms march through each other with slight interaction. For $b > 1/2\pi$, the simple geometry of Arnold tongues breaks down and there are chaotic dynamics as well as bistability in which two different stable rhythms exist simultaneously. Figure 3b,c gives a hint at the complexity of the organization of the locking zones.

A second prototypical oscillator was described originally by the French mathematician Poincaré

$$\frac{dr}{dt} = cr(1-r), \quad \frac{d\phi}{dt} = 2\pi \quad (4)$$

where the equation is written in a radial coordinate system (r, ϕ). In this equation, there is a stable limit cycle at $r = 1$. More realistic models of biological oscillations also have limit cycles, but the variables in these models would reflect the mechanism of the underlying biological oscillation. For example, more realistic models of biological oscillators might be written in terms of ionic currents or neural activities. Because there are certain features of the qualitative response of biological oscillators to single and periodic stimulation that depend solely on the properties of nonlinear oscillations[1], the tractable analytic properties of the Poincaré oscillator make it an ideal system for theoretical analysis. We assume that the stimulus is a translation by a horizontal distance A from the current state point, followed by evolution according to equation (4) (Fig. 4a). If c is sufficiently large, then after the periodic perturbation there is a very rapid return to the limit cycle, and the dynamics can be described approximately by[92]

$$\phi_{n+1} = \tau + g(\phi_n, A) \pmod 1, \quad \text{where } g(\phi, A) = \frac{1}{2\pi}\arccos\frac{\cos 2\pi\phi + A}{(1 + A^2 + 2A\cos 2\pi\phi)^{1/2}} \quad (5)$$

Although for $0 \leq A \leq 1$ there is again a simple Arnold-tongue geometry that is the same topologically as that found in the integrate and fire model for low amplitudes, for higher amplitudes the detailed geometry is radically different (Fig. 4b, c).

Although noise is helpful in this artificial example, various proposals have been made suggesting that signal detection might be facilitated in physiological systems by similar mechanisms in which noise was either added externally or present intrinsically. Several reports indicate that added noise seems to enhance signal detection in *in vitro* preparations[58], in animal experiments[60,61] and in human perception[62–64]. Because noise is an intrinsic property of human physiological systems, a compelling question is whether or not noise may be acting to aid function in normal activities in a manner similar to the way it can act to enhance the detection of subthreshold activities.

Prospects for medical applications

In the physical sciences, advances in basic science have inevitably led to new technology. Although many technological innovations in medicine, such as X-ray imaging and nuclear magnetic resonance imaging, have derived from advances in the physical sciences, the recent mathematical analyses of temporal properties of physiological rhythms have not yet led to medical advances, although several directions are under active consideration.

There is a wide spectrum of dynamical behaviour associated with both normal and pathological physiological functioning. Extremely regular dynamics are often associated with disease, including periodic (Cheyne–Stokes) breathing, certain abnormally rapid heart rhythms, cyclical blood diseases, epilepsy, neurological tics and tremors. However, regular periodicity can also reflect healthy dynamics — for example in the sleep–wake cycle and menstrual rhythms. Finally, irregular rhythms can also reflect disease. Cardiac arrhythmias such as atrial fibrillation and frequent ectopy, and neurological disorders such as post-anoxic myoclonus, are often highly irregular. The term 'dynamical disease' captures the notion that abnormal rhythms, which could be either more irregular or more regular than normal, arise owing to modifications in physiological control systems that lead to bifurcations in the dynamics[65]. What is most important in distinguishing health from disease is that

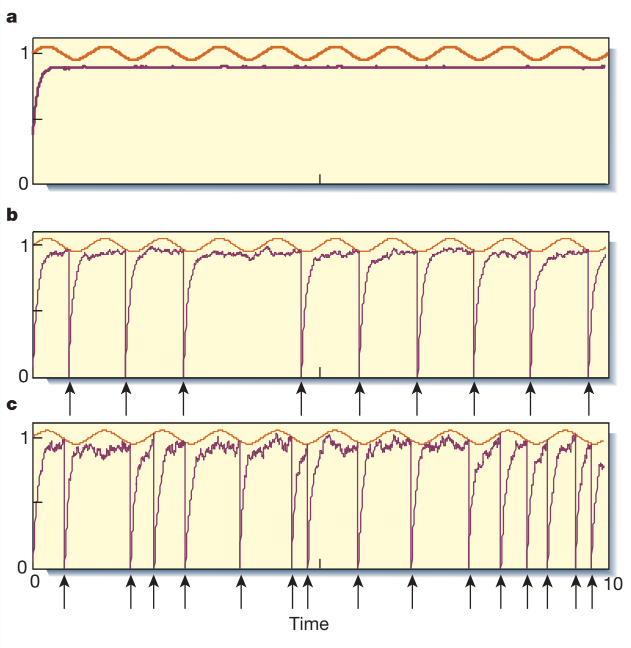

Figure 5 Schematic representation of a noisy, leaky integrate and fire model with three levels of noise. The activity rises to a sinusoidally modulated threshold following equation (1). **a**, The activity saturates and does not reach threshold. **b**, **c**, As the noise increases, the activity reaches threshold leading to an action potential (arrows). The ability to detect the frequency of the sine wave by the induced spiking activity will have a maximum efficiency at some intermediate level of noise. This illustrates the phenomenon of stochastic resonance[55,57].

there is a change in the dynamics from what is normal, rather than regularity or irregularity of the dynamics. Thus, generalizations such as "chaos may provide a healthy flexibility to the heart, brain, and other parts of the body"[66] must be considered warily.

Efforts are underway to develop better diagnostic and prognostic methods by analysis of dynamics of physiological rhythms. For example, in cardiology it would be extremely useful to have a measure that provides an independent predictor of significant cardiac events such as impending cardiac arrest. A variety of quantitative measures of cardiac activity derived from concepts introduced in nonlinear dynamics have been proposed as markers of increased risk of sudden death[67–71]. However, because algorithms must be tested on large populations, it is difficult to design and implement clinical trials to test the utility of the various proposed measures. One recent initiative, the development of open databases that could serve as a repository of clinical data that are difficult and expensive to obtain, provides an emerging strategy that should prove indispensable for testing competing algorithms[72]. Likewise, the public availability of powerful data-processing methods should advance research[73].

Similar efforts at analysis of dynamics of time series are also underway in neurology. The earlier debates about whether the electroencephalogram displayed chaotic dynamics have been superseded by predictions of the onset of seizures using a variety of measures derived from nonlinear dynamics[74–76]. Analysis of abnormalities in tremor and standing steadiness may provide a marker of heavy-metal toxicity[77,78] or the early onset of Parkinson's disease[79].

There are a number of ways in which knowledge about the synchronization of oscillators could be put to medical use. Because bodily functions show distinct periodicities, schedules for drug administration might be optimized. In cancer chemotherapy, treatments could be based on the circadian rhythm of cell division[80]. Intriguing strategies to minimize the effects of jet lag have been developed, based on experimental studies of resetting the circadian oscillator by modifying the exposure to light after travel[1,81], although I am unaware of any clinical studies that have assessed these proposals.

Medical devices that are used to regulate and artificially control cardiac and respiratory dynamics have been developed principally by engineers working with physicians. The empirical methods used to develop and test these devices have not included a detailed mathematical analysis of interactions of the physiological rhythm with the device. Indeed, devices usually have several adjustable parameters so that the physician can optimize the settings for operating the device based on direct testing in a patient. Recent work has investigated the application of algorithms motivated by nonlinear dynamics to control cardiac arrhythmias in humans (ref. 82 and D. J. Christini, K. M. Stein, S. M. Markowitz, S. Mittal, D. J. Slotwiner, M. A. Scheiner, S. Iwai and B. B. Lerman, unpublished results). Although there are not yet clinical applications, I anticipate that better understanding of the interactions between stimuli and physiological rhythms will lead to the development of better medical devices.

The recent identification of stochastic resonance in experimental systems has led to the suggestion that it might be useful to add noise artificially as a therapeutic measure. For example, in patients who have suffered strokes or peripheral nerve damage, detection tasks might be enhanced by addition of artificial noise to enhance tactile sensations[62]. Similarly, addition of sub-sensory mechanical noise applied to the soles of the feet of quietly standing healthy subjects reduced postural sway and seemed to stabilize the postural control (J. Niemi, A. Priplata, M. Salen, J. Harry and J. J. Collins, unpublished results). Another intriguing suggestion is that addition of noise might also enhance the efficiency of mechanical ventilators. The use of a variable inflation volume with occasional large inflations might act to prevent the collapse of alveoli and therefore maintain improved lung function in patients undergoing ventilation[83]. Finally, low-level vibratory stimulation of a premature infant seemed to eliminate long apnoeic periods. Although the mechanism is unknown, it was hypothesized that a stable fixed point, corresponding to no breathing in the apnoeic infant, coexisted with the normal limit-cycle oscillation that corresponded to breathing. The vibration destabilized that fixed point thereby eliminating the apnoeic spells[84].

Conclusions

Physiological rhythms are generated by nonlinear dynamical systems. *In vitro* experimental systems often yield dynamics that can be successfully interpreted using both simplified and complicated mathematical models. These models make predictions about effects induced by parameter changes such as changing the frequency and amplitude of a periodic stimulus. However, rhythms in intact animals in an ambient environment have so far defied simple interpretation. Bodily rhythms such as the heart beat, respiration and cortical rhythms show complex dynamics, the function and origin of which are still poorly understood. Moreover, we do not understand if the complex dynamics are an essential feature, or if they are secondary to internal feedback and environmental fluctuations. Because of the complexity of biological systems and the huge jump in scale from a single ionic channel to the cell to the organ to the organism, for the foreseeable future all computer models will be gross approximations to the real system. In the physical sciences, scientific understanding has been expressed in elegant theoretical constructs and has led to revolutionary technological innovation. If the advances in understanding physiological rhythms will follow the same trajectory, then we are still just at the beginning. □

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