Controlling chaos in biology

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We describe various techniques to control the dynamics of strongly nonlinear systems. These procedures are remarkably successful in stabilizing regular dynamic behaviours, as well as in directing chaotic trajectories rapidly to a desired state. Further, we highlight some interesting and potentially important applications to biological systems.

A variety of physical and biological systems are well modelled by coupled nonlinear equations[1]. In most cases such systems are capable of displaying several types of dynamical behaviour: fixed points, limit cycles, bistability, birhythmicity or chaos, for instance. Typically the nature of the motion depends on the value of one or more parameters. In real systems these may be quantities such as electric fields, temperature, pressure gradient, pH, molarity or kinetic rates. Generically the nature of the dynamics is governed by these parameters, and one can obtain a wide repertoire of dynamical patterns by tuning them[1].

Now these parameters can change (as a result of fluctuations in the environment, for instance) and this can push the system to drastically different kinds of dynamic behaviour. Thus it is of considerable interest to develop mechanisms of self-regulation or control in systems intrinsically capable of very complicated dynamics, so that it is guaranteed to maintain a fixed activity (the 'goal') even when subject to environmental perturbations.

The need for control mechanisms in order that a system is guaranteed to maintain fixed activity even when subject to environmental fluctuations has long been discussed in biology[2]. Situations wherein this is thought to play a role, include pupillary servomechanism[3], biological thermostats and regulation of cell reactions[2]. Although the details of the control mechanism operating in a given situation may be system-specific, from a theoretical standpoint it is important to study the general principles by which systems can be brought back to a desired state by self-regulation. The concepts developed rigorously through the study of model systems can then provide a framework for understanding the more complex mechanisms by which biophysical processes maintain a steady state.

Adaptive control algorithm

An adaptive control algorithm was recently proposed by Huberman and Lumer[4] and developed and extended by Sinha *et al.*[5,6]. It was demonstrated that the algorithm was a powerful and robust tool for regulating multidimensional, multiparameter, strongly nonlinear systems. The procedure *utilizes an error signal proportional to the difference between the goal output and the actual output of the system.* The error signal drives the evolution of the parameters which re-adjust so as to reduce the error to zero.

A general N-dimensional dynamical system is described by the evolution equation:

$$\dot{\mathbf{X}} \equiv \frac{d\mathbf{X}}{dt} = F(\mathbf{X}; \mu; t), \tag{1}$$

where $\mathbf{X} \equiv (X_1, X_2, \ldots X_N)$ are the state variables and $\mu = (\mu_1, \mu_2, \ldots \mu_M)$ are the parameters whose values determine the nature of the dynamics. The prescription for adpative control is through the additional dynamics:

$$\dot{\mu} = \varepsilon(X - X_s), \tag{2}$$

where X_s is the desired steady state value and ε indicates the 'stiffness of control'. For one-dimensional systems there is no ambiguity in eq. (2), but in higher dimensional cases X can in principle be any one of the dynamical variables characterizing the system.

This technique is very effective in bringing the system back to its original dynamical state after a sudden perturbation in the system parameters changes its dynamical behaviour drastically. For instance, when a parameter is perturbed, driving the system from a fixed point into the chaotic regime (say by changing the parameter instantaneously by an amount δ – a 'shock'), this control mechanism is capable of pulling the system rapidly back to the initial state. See Figure 1 for an example of the control dynamics in a complex (high dimensional, multiparameter) nonlinear system of biological relevance.

The scheme is called 'adaptive' as in this procedure the parameters (which determine the nature of the dynamics) *self-adjust* or *adapt* themselves to yield the desired dynamics. It is also sometimes called 'dynamic feedback control' in the literature. Since this adaptive principle is remarkably robust and efficient in generic nonlinear systems, it is of considerable utility in a large variety of phenomena, ranging from biological units to control engineering.

Huberman and Lumer[4] first studied adaptive control for a (discrete time) one-dimensional map, the logistic map, which is used as a prototype for chaos in a wide range of phenomena. It was first proposed by May[7] as a model for population dynamics, hence its name. The form of the map is given as:

$$X_{n+1} = \alpha X_n(1 - X_n), \tag{3}$$

where the nonlinearity parameter α determines the dynamical behaviour, which ranges from fixed points to chaos. It was found that the adaptive control mechanism, implemented through the equation:

$$\alpha_{n+1} = \alpha_n - \varepsilon(X_n - X_s), \tag{4}$$

was very successful in returning the system to any desired fixed point, X_s, even when perturbed to chaotic regimes quite far in parameter space. See Figure 2 for an example.

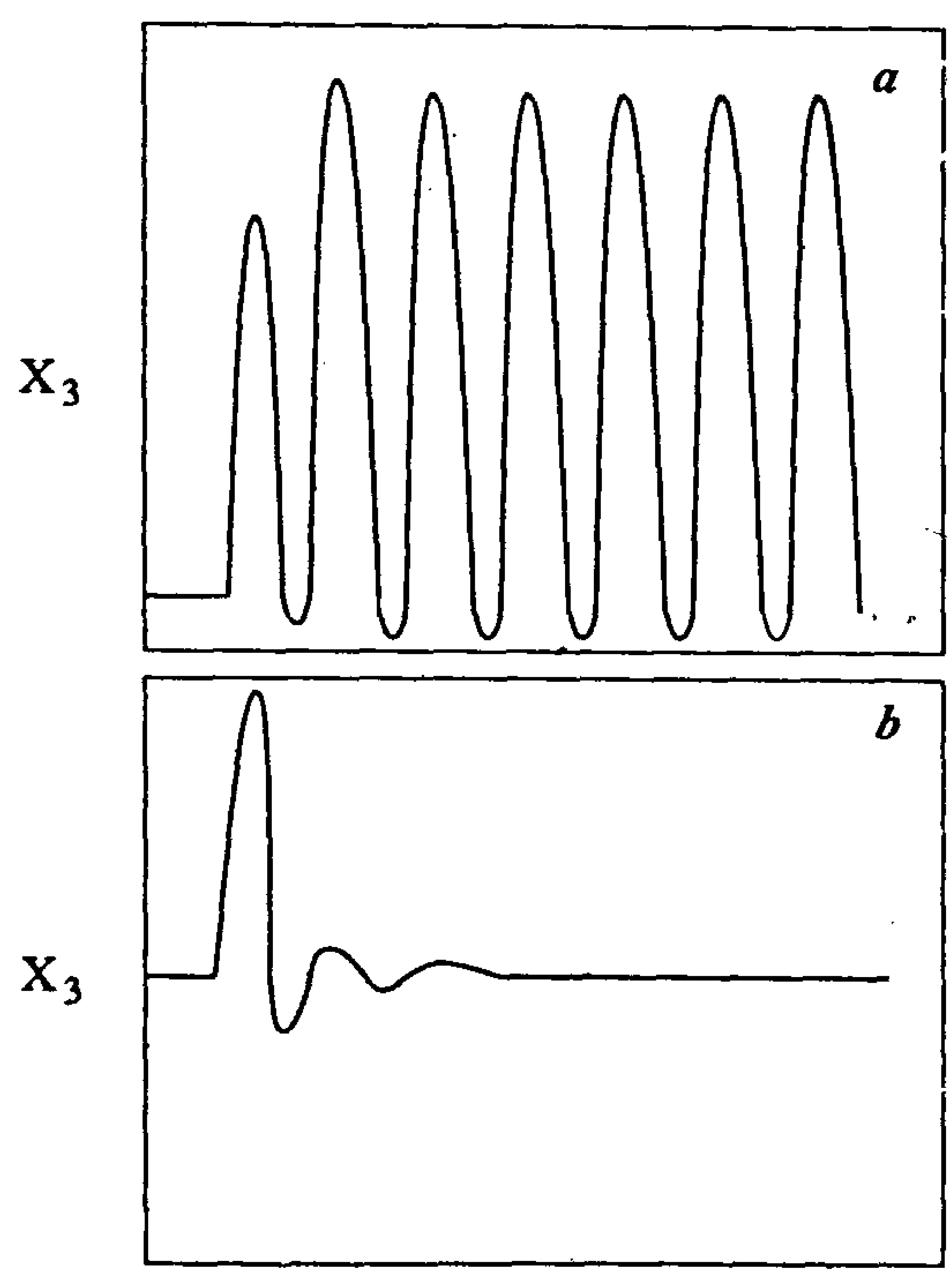

Figure 1. Dynamics of a complex nonlinear system modelling a biochemical network (given by eq. (10)) after a sudden perturbation changes a parameter value by a factor of 20: (*a*) without control, and (*b*) with adaptive control.

Sinha *et al.*[5] generalized the adaptive algorithm as follows:

$$\dot{\mu} = \varepsilon g(X - X_s), \tag{5}$$

where $g(X - X_s)$ is some suitable function with the property $g(0) = 0$. The adaptive control was checked for both discrete and continuous time dynamical systems, with several degrees of freedom and with more than one controlling parameter. In all cases it was found to be remarkably robust and efficient[5].

Now we present an analytical argument which guarantees that the control scheme will work for sufficiently small ε. Say we have a one-dimensional system:

$$\dot{X} = F(X; \mu) \tag{6}$$

with one parameter μ. The desired state (or 'goal') is X_s, which is a fixed point of the original system: i.e. $\dot{X} = 0$ at $X = X_s$.

The control dynamics leads to an augmented dynamical system consisting of the original dynamics and the additional control equation, which is coupled to the original system by feedback. By construction the desired state X_s is a fixed point of the control system, as $\dot{\mu} = 0$, when $g(X = X_s) = 0$. This formulation then assures us that the control is directed towards the desired dynamics.

Now, it can also be seen that the control process is stable. Examining the eigenvalues of the Jacobian matrix:

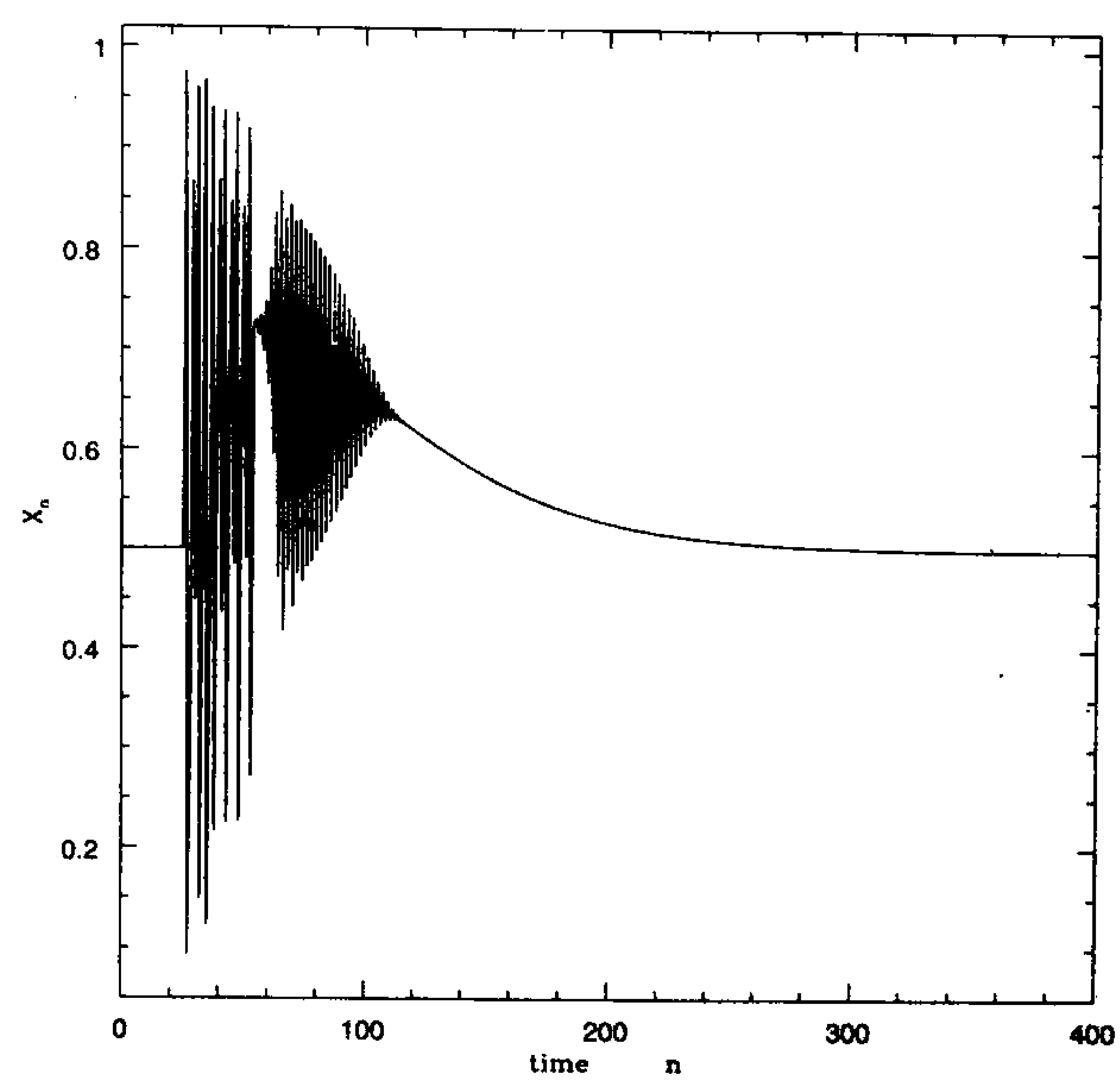

Figure 2. Dynamics of the controlled logistic map (given by eqs. (3, 4)) after a sudden perturbation almost doubles the value of the nonlinearity parameter α. It is clearly evident that the adaptive control is very successful in recovering the original desired state $X_s = 0.5$.

$$J = \begin{vmatrix} \dfrac{\partial F}{\partial X} & \dfrac{\partial F}{\partial \mu} \\ \varepsilon \dfrac{\partial g}{\partial X} & 0 \end{vmatrix} \tag{7}$$

we obtain, in the limit $\varepsilon \to 0$, the relevant eigenvalue of J to be $(\partial F/\partial X)$. Now $|\partial F/\partial X| < 1$ at X_s, as the desired state is a stable fixed point of the system. So in the limit of low ε, the evolution towards the goal dynamical state, is completely stable[6].

Recovery time, defined as the time required to reach the desired state within finite precision, is crucially dependent on the value of ε. Numerical experiments show that for small ε the recovery time is *always* inversely proportional to the stiffness of control.

An argument to account for the universality of the linear relationship between recovery time and stiffness of control, observed in a wide class of systems, is as follows: The key point is that when ε is small compared to the timescales in the original dynamical system, we can use an adiabatic approximation, as $\dot{\mu} \to 0$. So eq. (1) yields $X(\mu)$ as a solution, plugging which into eq. (2) gives $\dot{\mu} = \varepsilon[X(\mu) - X_s]$, from where it simply follows that recovery time will be proportional to $1/\varepsilon$ (ref. 6). Beyond an optimal stiffness however, in many systems, increasing the stiffness actually retards recovery. See Figure 3 for examples of recovery time vs stiffness of control, in multiparameter systems (from ref. 5).

This crucial dependence of recovery times on the stiffness of control, inspired a scheme to enhance the efficacy of the adaptive control algorithm[6] by tuning ε to some optimal value at each point of time. The idea is as follows: we would like to optimize progress towards the goal by making frequent suitable changes in the stiffness of control. The purpose is to achieve a predetermined accuracy in minimum time. Ideally the algorithm should ensure that the system tip-toes by many small steps through treacherous parameter regimes and in a few big strides speeds through smooth safe terrains. In ref. 6 we suggest how this can be done 'experimentally'. We monitor at each step how far we can safely increase the value of ε for the next step. The implementation involves a test which returns information on the error incurred in taking higher ε. If this is within pre-assigned acceptable limits of accuracy we increase the stiffness of control for the next adaptive control step. The resulting gains in efficacy (versus the algorithm with fixed ε) can be factors of two, tens or more! (See Figure 4.)

Note that adaptive control is remarkably robust with respect to variation in the form of the control function (g in eq. (5)). In realistic systems, the functional form of the control dynamics arises from the physio-chemical or engineering design considerations specific to the system. It is thus necessary to determine whether recovery is sensitive to the specific choice of the

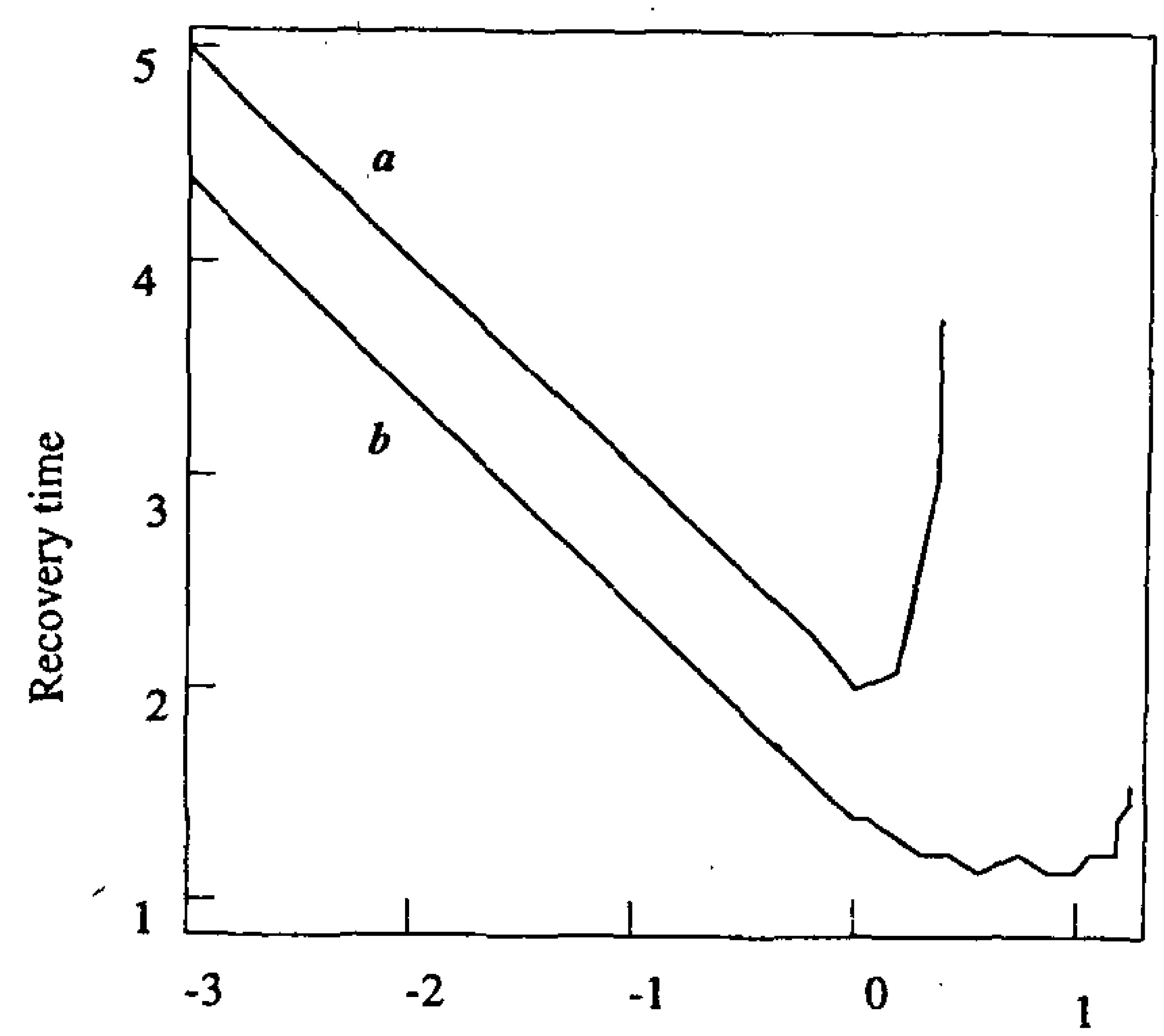

Figure 3. Recovery time τ versus stiffness of control ε for discrete multiparameter nonlinear systems: (*a*) a system of interest in population dynamics[7], given by:

$$X_{n+1} = \alpha X_n (1 + X_n)^{-\beta}.$$

(*b*) a two-dimensional discrete map of coupled oscillators which has been used to model SQUIDS and convection in conducting fluids (details in ref. 5).

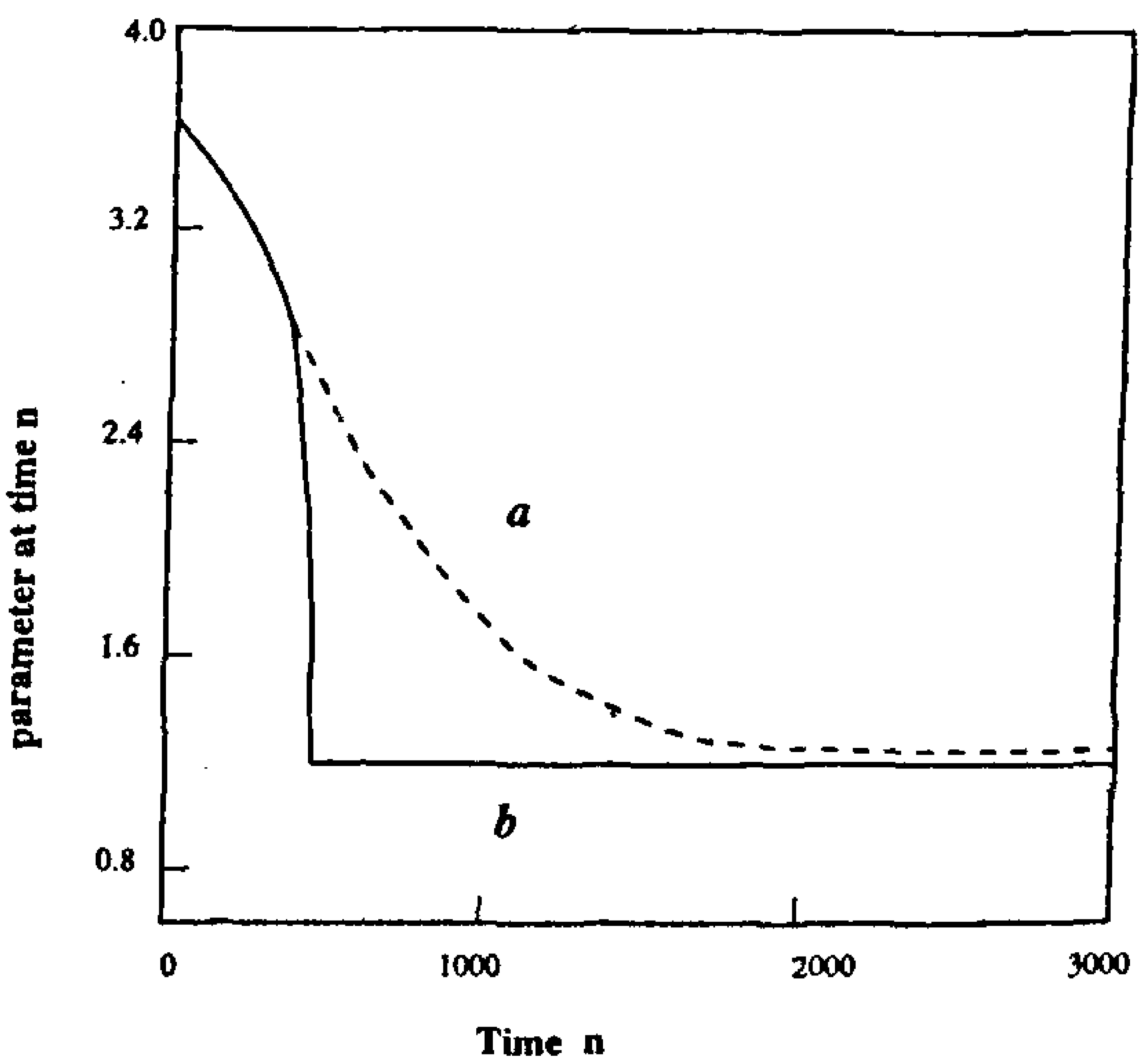

Figure 4. Evolution of parameter α of the logistic map (given by eq. (3)) under control dynamics given by (*a*) the 'fixed ε' algorithm (- - -); and (*b*) the 'variable ε' algorithm (—). Clearly the variable stiffness scheme (ref. 6) yields much faster recovery.

control function. In ref. 5 several forms were tried, like $g(y)=y^2$, $y^{1/2}$, $\sin y$, $1-e^y$ and $y(1-y)$, where $y=(X-X_s)$. In all cases control remained effective and rapid, with recovery times scaling as $1/\varepsilon$.

The sensitivity of adaptive control to background noise (which is inevitably present in most real life situations) was also investigated[5]. See Figure 5 for an example of control in the presence of random additive background noise. For small noise strengths, recovery times with and without noise are virtually identical. So the adaptive control method is clearly robust with respect to background fluctuations.

Now we will discuss two examples of adaptive control of relevance to biology[5].

Hopf bifurcation

Hopf bifurcations are believed to underlie the oscillations observed, for instance in Cheyne–Stokes respiration, some types of muscle tremor and hematological disorders[8]. The Poincare oscillator given as:

$$\dot{r}=\alpha r-r^3$$
$$\dot{\theta}=w \tag{8}$$

shows a supercritical Hopf bifurcation (soft excitation) as α is varied. The sign of α determines the dynamics: when $\alpha<0$ the system evolves to a fixed point ($r=0$), and when $\alpha>0$ the system evolves to a limit cycle of radius $r_c=\alpha^{1/2}$ (ref. 9). The control dynamics is determined by the error signal, i.e. the difference between the goal output and the actual output:

$$\dot{\alpha}=\varepsilon(r-\langle r\rangle), \tag{9}$$

where $\langle r\rangle$ is the desired steady state value of r.

This system was analysed by Sinha *et al.*[5], and the results indicated that the control scheme efficiently brought back the system, both to the fixed point ($r=0$), and to cycles of any radius. The recovery time was inversely proportional to the stiffenss of control ε.

A biochemical network

Sinha *et al.*[5] also studied the adaptive control mechanism for a complex dynamical system which describes various biochemical processes responsible for coherent behaviour observed in spatio-temporal organization[10].

$$\dot{X}_1=\frac{a_1}{a_2+X_3^n}-KX_1$$
$$\dot{X}_2=a_3X_1-\phi(X_2,X_3)$$
$$\dot{X}_3=a_4\phi(X_2,X_3)-qX_3\,, \tag{10}$$

where

$$\phi(X_2,X_3)=\frac{TX_2(1+X_2)(1+X_3)^2}{L+(1+X_2)^2(1+X_3)^2} \tag{11}$$

and a_1, a_2, a_3, a_4, L, T and n are parameters. Such equations are typically thought to describe a variety of processes occurring in living cells. The system gives rise to a range of behavioural patterns.

In this complex multiparameter system adaptive control can be implemented, say on parameter K, as:

$$\dot{K}=-\varepsilon(X_1-\langle X_1\rangle), \tag{12}$$

where $\langle X_1\rangle$ is the desired state. This control is very effective in returning the system back to its original state when perturbations in some parameter give rise to irregular dynamics (see Figure 1). The recovery time is again proportional to ε^{-1}.

Note that in most generic higher dimensional systems, one can use any variable X_i in the error indicator (for instance, we use X_1 above). This ambiguity in choice can be removed though, by employing AND logic in the control, i.e. by requiring that *all* variables reach their steady state values: X_i^s, $i=1,2,\ldots N$. The equation for control then becomes:

$$\dot{\mu}=\varepsilon\sum_{i=1}^{N}(X_i-X_i^s).$$

This control scheme works efficiently and is completely general and robust as well[5].

Controlling limit cycles

Many biological processes depend on the stabilization

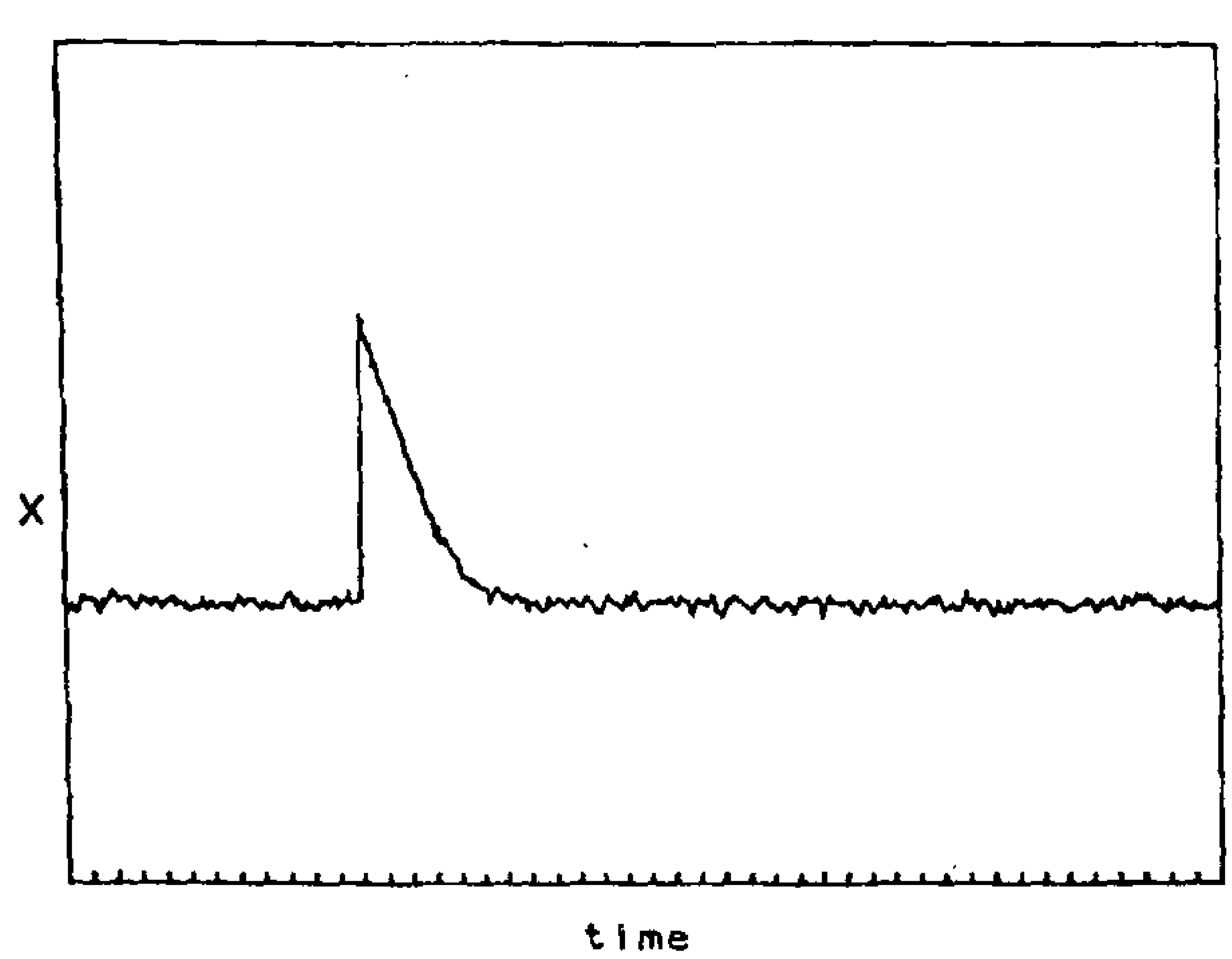

Figure 5. Control dynamics of a nonlinear system in the presence of background noise (strength of noise $\sigma=0.005$).

of cyclic patterns (for example in glycolytic oscillations, peristaltic waves, electrical activity of the cortex, circadian rhythms, population dynamics, etc.[7,8]). Ref. 5 addresses this very relevant issue of controlling complex periodic behaviour.

Now, the adaptive control algorithm can be extended to control periodic behaviour, by suitably modifying the error signal in the feedback loop. For discrete dynamical systems, an effective error signal can be devised using the logical OR structure[5]. That is:

$$\dot{\mu} = \varepsilon \prod_{i=1}^{k} (X - X_i^c), \tag{14}$$

where k is the order of the stable cycle being controlled, and X_i^c are the values of the different points in the orbit. This implies that the desired state is either $X = X_1^c$ or $X = X_2^c$ or $\ldots$, $X = X_k^c$. This method works very well even for high order cycles. (See Figure 6 for examples.)

Conclusion

From the study of systems of varying complexity it appears that adaptive control can provide efficient regulation of the steady state of nonlinear systems. The procedure utilizes an error signal proportional to the difference between the goal and the actual output of the state variables.

Biological situations where control is believed to play a crucial role include, for instance, the maintenance of homeostasis[8] (that is the relative constancy of the internal environment with respect to variables such as blood pressure, pH, blood sugar, electrolytes and osmolarity). Clinical experiments on animals show, for example, that following a quick mild haemorrhage (a sudden perturbation in arterial pressure) the blood pressure is restored to equilibrium values within a few seconds[11]. The control of fixed points, explored in detail in ref. 5, thus has potential utility in such physiochemical contexts. Cycles are also central to a variety of biophysical and bio-

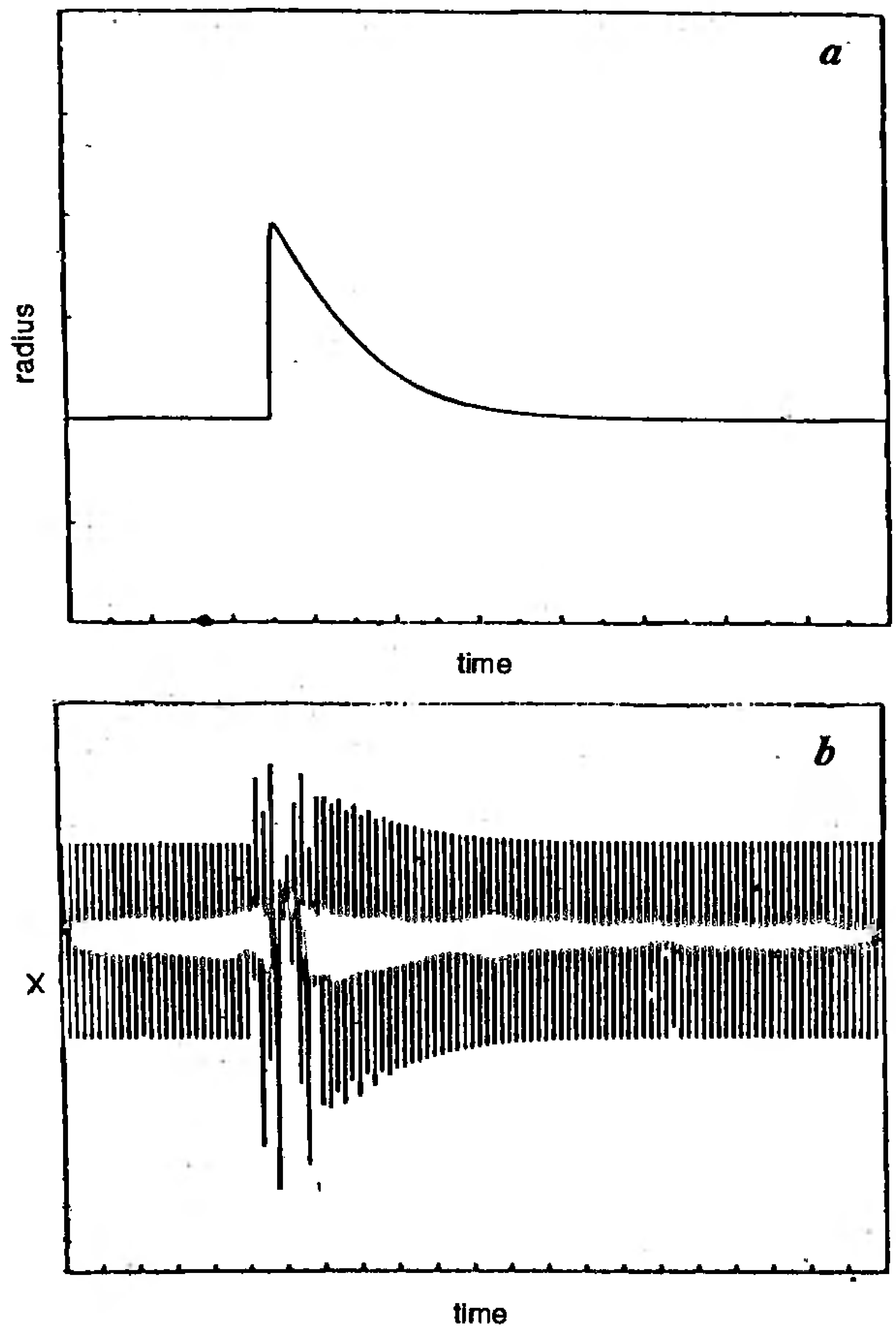

Figure 6. Dynamics of controlling a limit cycle in two systems: (*a*) a continuous time system, the Poincare oscillator, given by eq. (8); (*b*) a discrete time system, the logistic map, given by eq. (3).

chemical processes. Variations in these – for example, the replacement of periodic by aperiodic behaviour, or the emergence of new cycles – are often associated with disease[8]. The adaptive control of cycles discussed above, then has applicability in the regulation of biologically significant oscillatory phenomena.

Using small perturbations to control chaos

Now we describe another class of recent control methods, which cleverly exploit the extreme sensitivity of chaotic systems to tiny perturbations (a characteristic, known as the 'butterfly effect') to control trajectories using small feedback[12-16]. The research broadly fits into two categories. First, one can select a desired behaviour from the inifinite variety of behaviours naturally present in chaotic systems, and then stabilize this behaviour by applying only tiny changes to an accessible system parameter. One can also switch between behaviours as circumstances change, again using only tiny perturbations. This means that chaotic systems can achieve great flexibility in their ultimate performance. Second, one can use the sensitivity of the chaotic system to direct trajectories rapidly to the desired state.

One of the fundamental aspects of chaos is that many different possible motions are simultaneously present in the system. A particular manifestation of this is the fact that there are typically an infinite number of unstable periodic orbits that co-exist with the chaotic motion. These orbits are not obvious in free running chaotic systems, as vanishingly small perturbations will take the orbit away from the periodic point exponentially fast. But the existence of these periodic orbits embedded in the chaos can be used for control.

The approach is as follows: first, we determine some of the low period unstable orbits that are embedded in the attractor. For each such orbit we determine the system performance that would result if that periodic orbit were actually followed by the system. (In laser, for instance, the relevant measure of performance is its output power at a given wavelength.) Typically some of the periodic orbits will yield improved performance compared to that of the free running chaotic motion. Small time-dependent controls are tailored in such a way as to stabilize one of the periodic orbits that yield improved performance.

Loosely speaking, the controls are small kicks that place the actual orbit back onto the desired unstable periodic orbit. We apply these kicks whenever we sense that the actual orbit has wandered slightly away from the desired orbit. Because chaotic orbits are ergodic on the attractor, they eventually wander close to the desired periodic orbit and then because of this proximity can be 'captured' by a small control. Once captured, the required control remains small – on the order of the inherent system noise.

Details of the technique[12]: Stabilization of an unstable periodic orbit in a suitably defined Poincare surface of section can be achieved by slightly adjusting the control parameter. In particular, suppose we wish to stabilize an unstable period-1 orbit contained in the chaotic attractor. As the control parameter is slightly varied the fixed point will shift from $X_s(\mu)$ to some $X_s(\mu')$. One can define a vector **g**:

$$\mathbf{g} \equiv \frac{\partial X_s(\mu)}{\partial \mu} \approx \frac{X_s(\mu') - X_s(\mu)}{\mu' - \mu}. \tag{15}$$

Near the periodic point and for small values of the control parameter one may write:

$$\delta X_{n+1} \approx M \cdot \delta X_n, \tag{16}$$

where M is a 2×2 matrix and $\delta X_n = X_n - X_s$, where X_n is the state of the system at the nth iteration. Let λ_u and λ_s denote the stable and unstable eigenvalues of the matrix M respectively, with $|\lambda_u| > 1$ and $|\lambda_s| < 1$. Thus $M \cdot e_u = \lambda_u e_u$ and $M \cdot e_s = \lambda_s e_s$ where e_s and e_u are the stable and unstable eigenvectors of M (i.e. the stable and unstable directions). Further, the contravariant basis vectors are defined by $f_s \cdot e_s = f_u \cdot e_u = 1$, $f_s \cdot e_u = f_u \cdot e_s = 0$. When the nth iteration X_n is close to X_s the value of the parameter is changed slightly such that X_{n+1} falls on the stable manifold of X_s. That is we choose the control $\delta\mu$ so that

$$f_u \cdot \delta X_{n+1} = 0 \tag{17}$$

which yields the control formula[12]:

$$\delta\mu = \frac{\lambda_u \, f_u \cdot \delta X_n}{(\lambda_u - 1) \, f_u \cdot g}. \tag{18}$$

The control is switched on only if $\delta\mu$ is less than the prescribed maximal allowed perturbation $\delta\mu_{max}$; otherwise $\delta\mu$ is zero.

Biological applications

An experiment on an *in vitro* rabbit heart septum used drug ouabain to induce arrhythmias in the autonomous beating of the heart tissue[15]. A discrete time embedding was constructed using the time interval between the heart beat as the system variable of interest. For this induced arrhythmia, the presence of deterministic chaos was confirmed by the observation of repeated approaches of the system state to a period one orbit, with each approach along the same stable direction, with the corresponding departures along the same unstable direction. In this case however it was not possible to find a system parameter that would move the system state point onto the stable manifold. But it was possible to intervene directly in the system by injecting a premature heart beat at an interval time to place the system state point onto the stable manifold. The dynamics of the system then naturally tended to carry it toward the (unstable) period-one motion. However, because it was possible only to shorten the interbeat interval and not to lengthen it, the control was at best period three. Further control experiments are studying an artificially perfused canine heart undergoing ventricular fibrillation.

Another example of this control method is a recently conducted experiment on the hippocampus of the temporal lobe of the rat brain[16]. When bathed in artificial cerebrospinal fluid containing high levels of potassium, the brain exhibits spontaneous bursts of synchronized neuronal activity in a portion of the hippocampus. These bursts can trigger seizure-like dischrages in a nearby region. As in heart experiments, inter burst intervals are plotted as embedding. Employing the same technique as in heart experiment, control was achieved.

Other ways to alter chaotic dynamics

One body of research seeks to control a nonlinear system, to follow a prescribed goal dynamics, without feedback[17]. If we denote the control dynamics by:

$$\dot{X} = F(X) + U(t), \tag{19}$$

where $U(t)$ is an additive controlling term, then the object is to choose $U(t)$ so that $|X(t) - g(t)| \to 0$ as $t \to \infty$, where $g(t)$ is the goal dynamics. To accomplish this a simple choice

$$U(t) = \frac{dg}{dt} - F(g(t)) \tag{20}$$

is made. Thus $X(t) = g(t)$ is clearly a solution of the controlled equations. However in this method the convergence to the goal dynamics is not clear, nor is its dependence on the choice of function F and initial condition $X(0)$. The method potentially works for nonlinear systems in general, and has the advantage of not requiring feedback. On the other hand, the applied controls are typically large and the convergence to the goal not assured.

Another body of research addresses the effects of periodic[18] and stochastic perturbations on chaotic systems[19]. As one might expect, the effect of such perturbations is difficult to predict in general, and these studies are not 'goal oriented' – in that a desired behaviour is not specified in advance and a generic technique for achieving a certain goal is not developed. Nevertheless dramatic changes in the dynamics of chaotic systems have been recorded using these methods: for example periodic or nearly periodic behaviour can sometimes be produced from originally chaotic dynamical systems.

In summary, these methods all serve as simple, powerful and robust control tools for regulating strongly nonlinear systems capable of exhibiting very complicated behaviour. These concepts can then serve as a paradigm for understanding the more complex regulatory mechanisms widespread in Nature, and have utility in designing clinically useful controls.

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