Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 4938–4942, July 1989
Biophysics

On the dynamics of a forced reaction–diffusion model for biological pattern formation

(chaos/dynamical systems/attractors)

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Communicated by Susumu Ohno, March 20, 1989

ABSTRACT **Ideas from the theory of dynamical systems are applied in biological pattern formation. By considering a simple reaction–diffusion model subjected to an external excitation, we find that the system can give rise to a great variety of periodic, quasiperiodic, and chaotic evolutions.**

The generation of spatial patterns constitutes one of the most important problems in developmental biology (1). The first detailed theoretical account of how patterns can be generated was provided in 1952 by Turing (2), who proposed that an initially homogeneous system of chemicals (morphogens) may become nonhomogeneous through reaction of the chemicals with each other and diffusion. These nonhomogeneous chemical distributions form a prepattern out of which the ultimate pattern or structure will emerge. The above concept constitutes the basic philosophy behind the reaction–diffusion models for biological pattern formation, largely developed by Meinhardt. Using the reaction–diffusion concept, Meinhardt (3) has presented models that account for pattern formation in several biological processes. More recently, Meinhardt and Klingler (4) were also able to simulate the pigmentation patterns on shells of molluscs. The model can be described by two reactions, one autocatalytic and one that acts antagonistically to the autocatalysis. Any vital molecule for the generation of a particular pattern (i.e., the pigment deposition for shell patterning) is the activator, α, which stimulates its own production (autocatalysis). The antagonistic reaction can be caused by the inhibitor, h. This interaction is commonly modeled by two nonlinear coupled partial differential equations that give the evolution of a row of adjacent cells. A possible and widely used mathematical formulation of a reaction–diffusion model for biological formation is given by the following equations:

$$\frac{\partial \alpha}{\partial t} = \frac{c(\alpha^2 + c_0)}{h} - \mu\alpha + D_\alpha \nabla^2 \alpha \qquad [1a]$$

$$\frac{\partial h}{\partial t} = c\alpha^2 - \nu h + D_h \nabla^2 h, \qquad [1b]$$

where t is time, α is the activator concentration, h is the inhibitor concentration, D_α is the rate at which the activator diffuses from cell to cell, D_h is the rate at which the inhibitor diffuses from cell to cell, μ is the decay rate of the activator, ν is the decay rate of the inhibitor, c is the source density, and c_0 is an activator-independent activator production.

Eqs. **1a** and **1b** provide the concentration change of α or h in a time interval. Adding these changes to some initial values (steady state) gives new concentrations at a later time. Repeating this procedure, one can derive the time evolution of α and h in a one-dimensional array of cells. If the steady state is unstable to small fluctuations the above procedure will give rise to simple periodic patterns. More complex patterns (oblique lines, branching, checkerboard or mesh-like patterns, etc.) have been obtained through manipulation of the above model by adding new terms or even more equations (3, 4). This approach, even though rather phenomenological, has provided excellent evidence in support of the reaction–diffusion concept in biological pattern formation. In biology, however, a system can be often influenced by several periodic external forces that have not been taken into account by the above models. An external force could be anything of biological significance, such as temperature or pressure variations or a certain product of a gene that obeys a periodic fashion of expression.

In this paper we will present results showing that a variety of patterns ranging from periodic to quasiperiodic and chaotic can arise naturally from the dynamics of a simple forced reaction–diffusion model. The formulation of this model is exactly the same as above, but with the term $A \sin \omega t$ added to the first equation. The parameter A indicates the amplitude of the forcing and ω the angular frequency of the forcing. The period of the forcing, $\mathfrak{p}$, is therefore $2\pi/\omega$ and the frequency, f, in cycles per unit of time is $1/\mathfrak{p}$. Similar transitions have been observed in the study of the so-called forced Brusselator (5–8). The Brusselator (9) is a model for an oscillatory chemical reaction that, when subjected to an external forcing, gives rise to quasiperiodic and chaotic solution. While some similarities exist in the formulation of the forced Brusselator and the forced reaction–diffusion model for biological pattern formation, differences in the evolution may be significant due to differences in the nonlinear terms.

The Unforced Model

From Eqs. **1a** and **1b** we can define the concentrations α_0 and h_0 of the steady state by setting $\partial\alpha/\partial t = 0$, $\partial h/\partial t = 0$, $\nabla^2\alpha = 0$ and $\nabla^2 h = 0$:

$$c(\alpha_0^2 + c_0)/h_0 = \mu\alpha_0 \qquad [2a]$$

$$c\alpha_0^2 = \nu h_0. \qquad [2b]$$

From Eqs. **2a** and **2b** it follows that

$$\alpha_0^3 - (\nu/\mu)\alpha_0^2 - c_0\nu/\mu = 0 \qquad [3a]$$

$$h_0 = (c/\nu)\alpha_0^2. \qquad [3b]$$

Eq. **3a** is a cubic equation whose discriminant is greater than zero for all values of μ, ν, c and c_0. Thus, Eq. **3a** has only one real solution. Then (considering also **3b**) it follows that the steady-state solution (α_0, h_0) is always uniquely defined. If this steady state is unstable to small perturbations it can give rise to a periodic pattern.

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Fig. 1*a* shows the evolution from a slightly perturbed unstable steady state of a cell randomly selected out of a one-dimensional array of size 20. The solutions are obtained numerically by using the explicit approximation (10). The margins (boundary conditions) of the array are considered impermeable. The evolution of the cell is described by a trajectory in the state space, which is defined as a coordinate system whose coordinates are the necessary variables needed to completely describe the evolution of the system. In our case the necessary variables are two—namely, the activator concentration and the inhibitor concentration. As we can see from Fig. 1*a* the cell's evolution becomes periodic via a Hoph bifurcation. The trajectory approaches and remains on the limit cycle, which is the attracting submanifold of the available state space. In fact, all trajectories from slightly different initial conditions are finally attracted by the limit cycle. Thus, a periodic pattern will emerge. Fig. 1*b* shows the spectral density (power spectrum) of this periodic evolution. It shows peaks at integer multiples of the natural frequency of the system, f_1, which is approximately equal to 0.012.

The Forced Model

In this section we investigate the response of the forced system in the case where the unforced system has a limit cycle. The investigation will be carried out with the help of the state space, Poincaré sections, and power spectra.

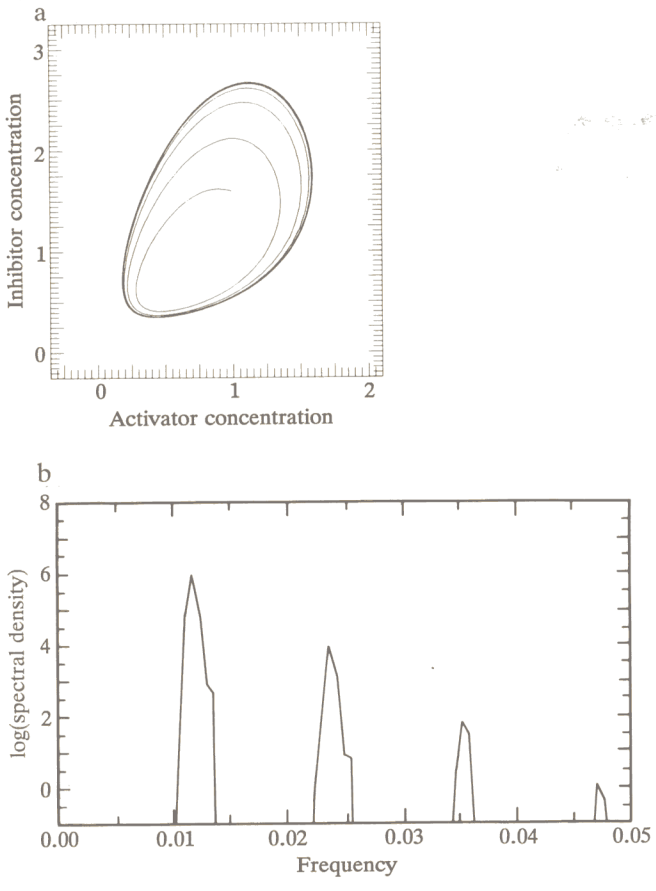

FIG. 1. (*a*) Evolution of a randomly selected cell according to the unforced model with $c = 0.1$, $c_0 = 0.1$, $\mu = 0.1$, $\nu = 0.05$, $D_\alpha = 0.15$, and $D_h = 0.05$. Under such conditions the steady state is unstable. Thus, for a slight perturbation the trajectory, via a Hoph bifurcation, approaches and stays on a limit cycle. The evolution is periodic. (*b*) Power spectrum of *a*. The natural frequency of the above unforced model is $f_1 \approx 0.012$. The peaks at integer multiples of f_1 indicate a periodic evolution.

As was mentioned above, the state space depicts the evolution of a cell in time. Fig. 2*a* shows an example where the forced system exhibits a limit cycle (periodic evolution). This type of oscillation is also called period-1 oscillation because the trajectory repeats itself every cycle exactly. The corresponding power spectrum (Fig. 2*b*) presents peaks of frequencies that are integer multiples (harmonics) of the driving frequency, which in this example is approximately equal to 0.016. For a given trajectory we can follow the evolution and mark the trajectory at times that are integer multiples of the forcing period ($2\pi/\omega$). In this way a sequence

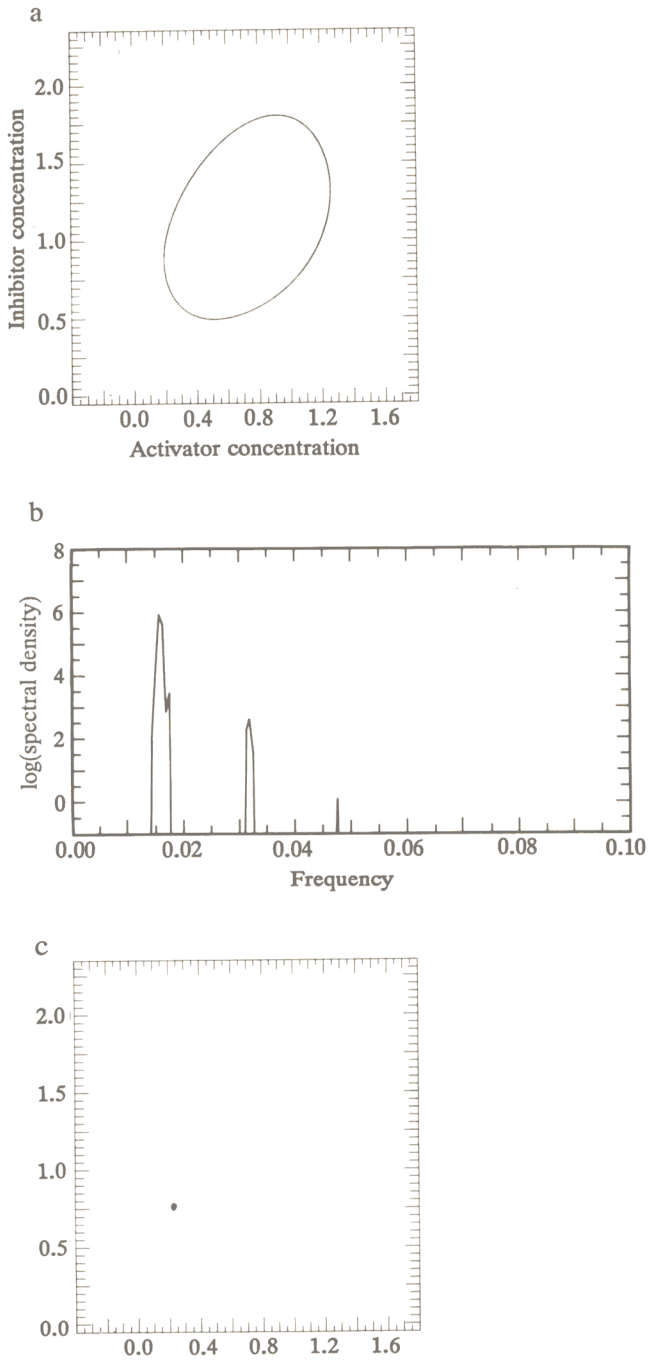

FIG. 2. (*a*) Period-1 oscillation of a randomly selected cell according to a forced model with $A = 0.02$ and $\omega = 0.1$. The other parameters are the same as in Fig. 1*a*. (*b*) Power spectrum of *a*. As in the case of Fig. 1*b* it indicates a periodic evolution with peaks at integer multiples of the driving frequency $f_2 = 0.1/2\pi \approx 0.016$. (*c*) Poincaré section of *a*. The presence of only one point indicates that the evolution is periodic of order 1.

of strictly comparable points is accumulated. Proceeding to simplify the picture, we can erase the trajectory and keep the so-called strobed points. The assembly of these points defines the Poincaré section (11). Apparently, if the evolution of a cell is periodic of order 1 with the frequency of the forcing, the strobed points will be the same point repeating forever (5). This is illustrated in Fig. 2*c*, which shows the Poincaré section of the periodic evolution shown in Fig. 2*a*. If the trajectory is a subharmonic oscillation of order n (repeating exactly every n cycles), the Poincaré section will consist of n dots repeating forever in the same order. In this case the power spectrum will still show sharp peaks at integer multiples of the driving frequency but will also show $n - 1$ less-intense peaks between any two harmonics, indicating the subharmonics.

By varying the parameters A and ω, transition to a quasiperiodic or to a chaotic evolution may be obtained. In a quasiperiodic case a periodic motion is modulated by a second motion, itself periodic but with another frequency. The combination of frequencies will produce a time series

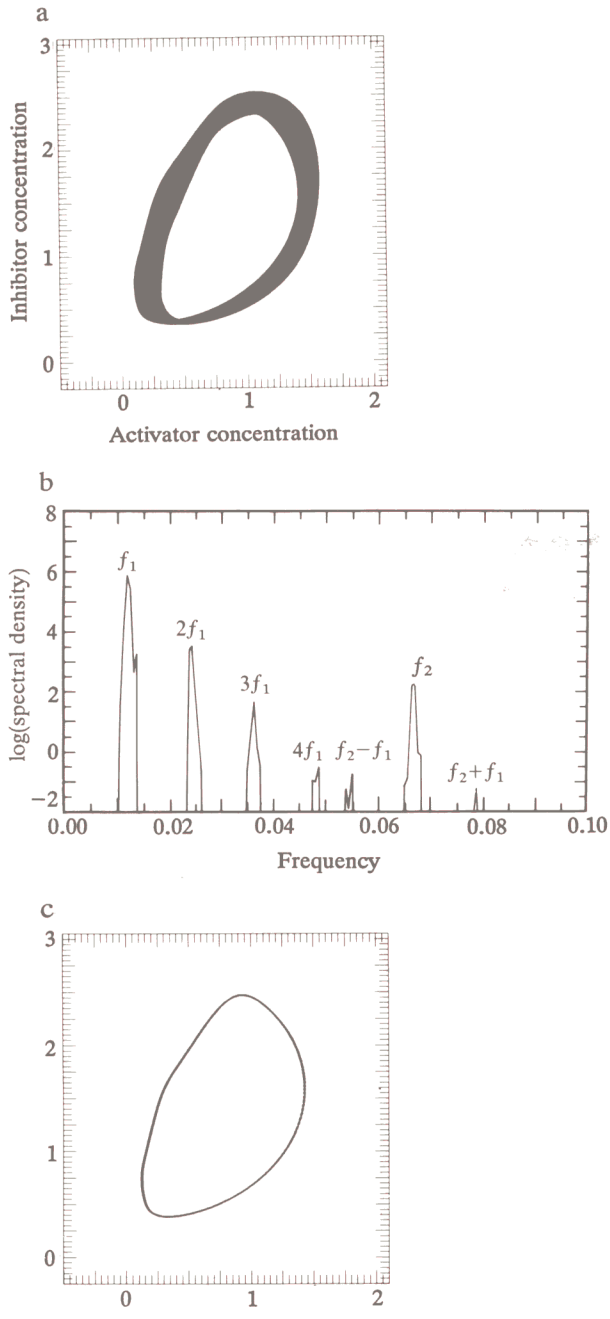

FIG. 3. (*a*) Quasiperiodic evolution of a randomly selected cell according to a forced model with $A = 0.0431$ and $\omega = 0.41888$. The other parameters are as in Figs. 1*a* and 2*a*. (*b*) Power spectrum of *a*. All the peaks can be explained by the two basic frequencies $f_1 \approx 0.012$ and $f_2 = 0.41888/2\pi \approx 0.0666$. (*c*) Poincaré section of *a*. The strobed points follow a closed curve as expected from a quasiperiodic trajectory that fills a torus in the appropriate state space.

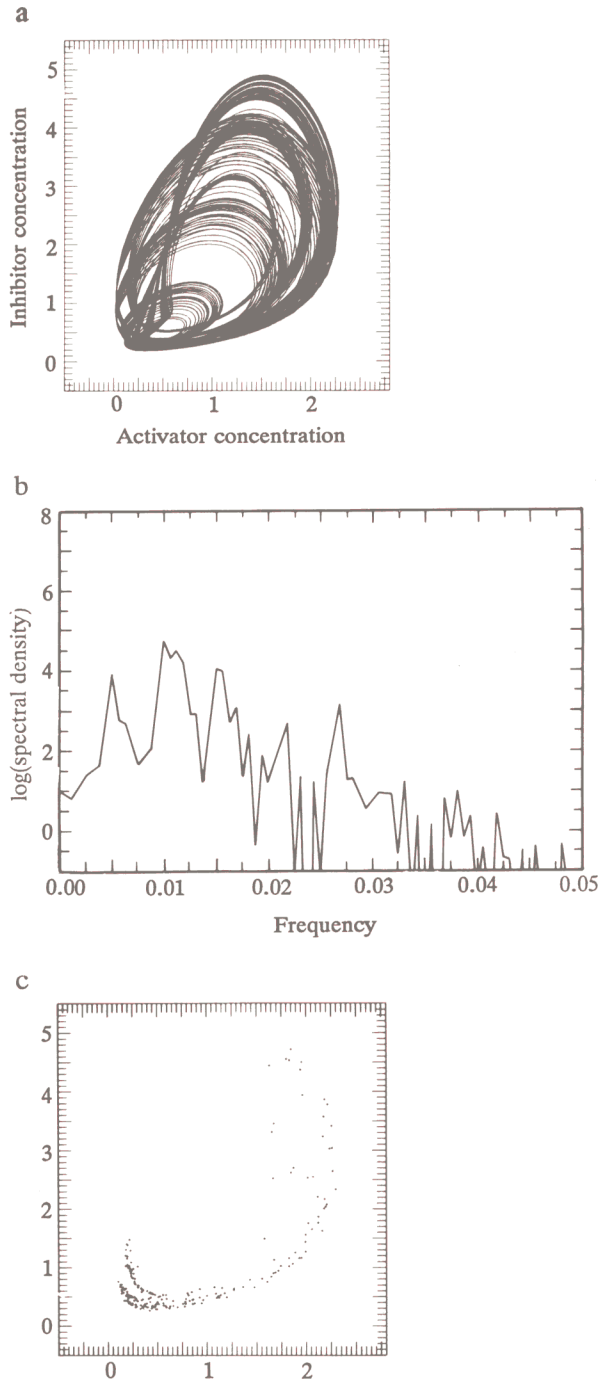

FIG. 4. (*a*) Chaotic evolution of a randomly selected cell according to a forced model with $A = 0.03$ and $\omega = 0.0321$ and the remaining parameters as in Figs. 1*a*, 2*a*, and 3*a*. The trajectory follows an irregular path on a "strange" submanifold of the total available state space. (*b*) Power spectrum of *a*. It shows some peaks on a continuous background. No preferred frequency is apparent. This suggests that a strange attractor may be present. (*c*) Poincaré section of *a*, indicating the presence of a strange attractor. Note the different picture from those in Figs. 2*c* and 3*c*.

whose regularity is not clear. The power spectrum, however, should consist of sharp peaks at each of the basic frequencies with all its other prominent features being combinations of the basic frequencies (11). Geometrically a quasiperiodic trajectory fills the surface of a torus in the appropriate state space. Thus, the Poincaré section will consist of an assembly of points along an invariant closed curve (12). Fig. 3*a* shows such an evolution. Note how the trajectory fills the surface of our two-dimensional torus, which is the attracting submanifold of the total available state space. The Poincaré section (Fig. 3*c*) is a closed curve and the spectral density (Fig. 3*b*) presents peaks at the two basic frequencies ($f_1 \approx 0.012$ and $f_2 \approx 0.0666$) and at frequencies that are multiples or combinations of the basic frequencies ($2f_1$, $f_1 + f_2$, etc.).

In a chaotic evolution the trajectory seems to "wander" on a so-called strange attractor, which is not a limit cycle or a torus, but some complicated submanifold of the available state space that is not topological (13, 14). A chaotic motion is neither periodic nor quasiperiodic (strictly speaking a chaotic evolution is periodic with an infinite period). An example of such an evolution is shown in Fig. 4*a*. Because the motion is nonperiodic, the oscillation has no preferred frequency and thus the corresponding power spectrum (Fig. 4*b*) shows some peaks on a background of a continuous spectrum (broadband noise). The power is simply distributed among an infinite number of frequencies. The Poincaré section (Fig. 4*c*) is made up of points that neither fall along a closed curve nor repeat indefinitely in the same order. The points simply repeat in an irregular fashion.

In addition, we find that for a given set of parameters the type of the dynamics may not be affected by the size of our cell array. This is demonstrated in Fig. 5, where we show the evolution of a randomly selected cell from an array of size 100. For this simulation, the parameters are the same as in the case of Fig. 4. By comparing Figs. 4*a* and 5 we see that the corresponding attractors (and therefore the evolution) are very similar.

In this paper we chose to present our results by displaying the dynamics of a randomly selected cell. The reason for this is that the dynamics of a randomly selected cell seem to be representative of the evolution of all cells. In a given situation all cells are undergoing one type of evolution only. Situations where some cells undergo chaotic evolution, some cells undergo quasiperiodic evolution, and some cells undergo some periodic evolution were not observed. Fig. 6 shows the evolution of another randomly selected cell from the experiment with the cell array of size 100 discussed above and in Fig. 5. By comparing Figs. 5 and 6 we see that both cells undergo a chaotic evolution. The two trajectories are not identical, however. This indicates that even though all cells undergo a certain type of evolution, spatial gradients may be present in the resulted pattern. A detailed study of the spatial structure of these patterns was beyond the scope of this paper and will be investigated in the future. It will be interesting, for example, to assess the role of the external forcing and spatial inhomogeneities in biological pattern formation. Finally, we should mention that experimentation indicates that even with small changes in the parameters, differently shaped attractors are obtained. Thus, for all practical purposes an infinite number of patterns may emerge from the model used here.

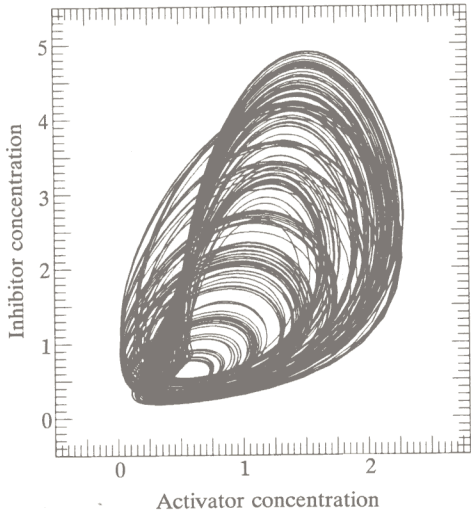

FIG. 5. Chaotic evolution of a randomly selected cell out of a one-dimensional array of size 100. All model parameters are as in Fig. 4*a*. The resemblance of the attractors in Fig. 4*a* and here indicates that the type of evolution and therefore the type of dynamics may not depend significantly on the size of the cell array.

Perspectives

The theory of dynamical systems provides the basis for the understanding of the states of order and disorder. More importantly, attractors provide a geometric framework to qualitatively and quantitatively compare different states. In biology, chaotic dynamics have already been used to analyze pathological situations such as cardiac arrhythmia or brain activities (15, 16). Periodic-to-chaotic transitions have been shown in several biochemical reactions, including the synthesis of cAMP and its effects on morphogenesis of *Dictyostelium discoideum*. It has been shown that upon aggregation of the cells, cAMP is emitted with a periodicity by the centers of the aggregation field. However, in a mutant of *D. discoideum* the emission from the aggregate is not periodic but represents chaos. The mutant develops with morphogenetic defects such as aberrant stalks and fruiting bodies (17, 18). Recently, Ohno (19) has found that periodic-to-chaotic transition is applicable to coding sequences of the genetic material and Nicolis (16) has shown that one-dimensional spatially asymmetric and information-rich sequences like the ones observed in biopolymers carrying biological information may be generated from a time-irreversible dynamics possessing a chaotic attractor. In this paper we have demonstrated the existence of periodic, quasiperiodic, and chaotic solutions of a simple forced reaction–diffusion model for biolog-

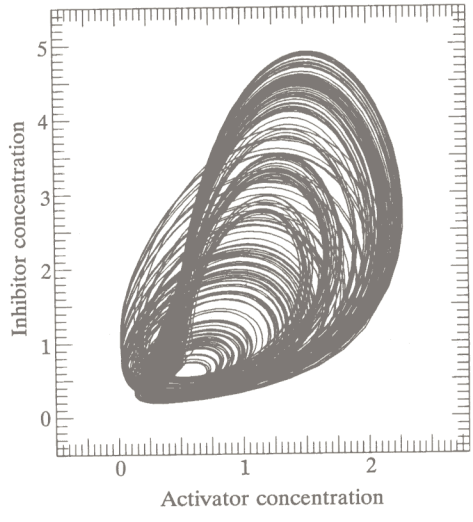

FIG. 6. Chaotic evolution of another randomly selected cell out of the one-dimensional array of size 100. All model parameters are as in Fig. 4*a*. The resemblance of the attractors in Fig. 5 and here indicates that both cells undergo the same type of chaotic evolution. However, the trajectories are not identical. This may indicate that spatial gradients may exist in the resulting pattern.

ical pattern formation. Our results suggest that a great variety of patterns can arise naturally through the interplay of a simple reaction–diffusion process and an external forcing. The application of chaos concepts to a set of partial differential equations (such as the ones used here) may seem at first beyond hope, as the state space of a partial differential equation must have an infinite number of degrees of freedom. The success of geometric ideas in partial differential equations may be attributed to the fact that the system in question is a dissipative system (11). Dissipation contracts volumes in the state space, often reducing the final motions in a low-dimensional state space. The model presented in this paper provides us with the tools to analyze the fate of a particular system of chemical reaction(s) that governs the generation of simple and complex structures and, therefore, to understand complexity in the generation of biological patterns. Lastly, in a broader, philosophical view, the chaotic transition of some systems may be the force of generation of complex structures in biological systems, controlled simply by periodic excitations and explainable within a simple mathematical framework.

We thank Professors R. O'Malley, R. Picard, and D. Snider of the University of Wisconsin–Milwaukee and Professor Norman Packard of the University of Illinois in Urbana–Champaign for valuable discussions and advice.

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