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Local stimulation induces long-range order in spatio-temporal disorder

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A spatially extended model of diffusively coupled (bio)chemical oscillators creates spatio-temporal disorder (hyperchaos) characterized by complex and weakly correlated concentration patterns in space and time. Applying different types of local stimulation we show that the system forms stable patterns with well-defined global order for certain windows of parameters. Spatio-temporal hyperchaos thus supports efficient pattern control with minimum effort. A possible relevance of this mechanism for experimentally observed calcium wave patterns is pointed out. © *1999 American Institute of Physics.* [S0021-9606(99)71006-8]

I. INTRODUCTION

Diffusive coupling of (bio)chemical oscillators is a simple way to create spatio-temporal chaos.[1] That is, linear coupling of two nonlinear oscillatory units can yield an attractor with an infinite period and an infinite number of (unstable) periodic orbits. Such a chaotic attractor is low-dimensional with a fractal dimension smaller than 3 and a single direction of mean divergence, i.e., one positive Lyapunov characteristic exponent (LCE). We have shown that both the dimension of the attractor and the number of positive LCEs can increase if the number of diffusively coupled oscillators is increased.[2] This was verified for reaction kinetic oscillators based on autocatalysis (either implemented by backward activation or forward inhibition)[3] and for an oscillator without autocatalysis.[4] Starting from a chaotic system with two positive LCEs (composed of three diffusively coupled oscillators) one can easily find spatially extended systems (described by many diffusively coupled identical oscillators) with a high-dimensional and hyperchaotic (i.e., many positive LCEs) attractor in one and two spatial dimensions.[5]

The behavior of spatio-temporally hyperchaotic systems [sometimes referred to as ‘‘(bio)chemical turbulence’’] is strongly disordered with rapid decay of correlations both in space and time. We investigate the dynamics of such a hyperchaotic state with respect to local stimulation. The motivation of this study is the question whether a disordered spatial distribution of a (bio)chemical concentration can be organized into a well-defined ordered state without having to perturb the whole system. We find that the dynamically most complex state can in fact quite easily be made periodic by certain permanent local perturbations. We discuss this instance of pattern control as a prototype of dynamic information transduction in spatially extended (bio)chemical systems. A possible realization may be the patterns of cellular calcium waves that occur after local stimulation of receptors at the cell membrane as observed in frog eggs.[6]

II. MODEL

To build a spatio-temporal system we use the model for IP_3-induced Ca^{2+} oscillations proposed by Goldbeter *et al.*[7] in the following form:

$$\begin{aligned}\dot{X}&=f(X,Y)=a-m_2\frac{X}{1+X}+\frac{m_3Y}{k_1+Y}\frac{X^2}{k_a+X^2}+Y-kX,\\ \dot{Y}&=g(X,Y)=m_2\frac{X}{1+X}-\frac{m_3Y}{k_1+Y}\frac{X^2}{k_a+X^2}-Y,\end{aligned}\tag{1}$$

where X denotes the concentration of free calcium in the cytosol and Y denotes the concentration of calcium in IP_3-insensitive intracellular calcium stores. Parameter a denotes the flux of calcium from the inositol-1,3,4-trisphosphate(IP_3)-sensitive calcium stores due to a constant IP_3 level. The model Eq. (1) is a biochemical oscillator with autocatalysis of variable X. The bifurcation diagram with control parameter a increased from 0.31 to 0.34 (other parameters as in Fig. 1, except that $D_x=0$) shows a transition from fixed point to sinusoidal limit cycles with small amplitude in a Hopf bifurcation and a smooth transition to relaxation oscillations with (compared to the sinusoidal limit cycle) large amplitude.

To describe a spatially extended case N identical oscillators can be employed. Coupling is introduced by means of linear diffusive terms in the equations for cytosolic calcium,

$$\begin{aligned}\dot{X}_1&=f(X_1,Y_1)+D_x(X_2-X_1),\\ \dot{Y}_1&=g(X_1,Y_1),\\ \dot{X}_i&=f(X_i,Y_i)+D_x(X_{i+1}+X_{i-1}-2\cdot X_i),\\ \dot{Y}_i&=g(X_i,Y_i),\\ \dot{X}_N&=f(X_N,Y_N)+D_x(X_{N-1}-X_N),\\ \dot{Y}_N&=g(X_N,Y_N),\end{aligned}\tag{2}$$

for $i\in\{2,3,...,N-1\}$.

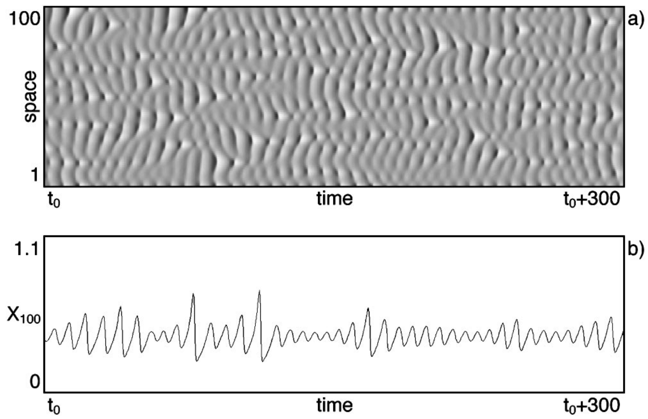

FIG. 1. Spatio-temporal concentration pattern in Eq. (2) with $N=100$ for $a=0.325$, $m_2=20$, $m_3=23$, $k_a=0.81$, $k=k_1=0.8$, $D_x=0.6$. $t_0=$arbitrary time after transients have faded. (a) Gray scale encoding of concentrations X_i as a function of time; white $=0.2$, black $=1.0$. (b) Time series of variable X_{100}.

Biochemical oscillators of this autocatalytic type are known to produce spatio-temporal hyperchaos when coupled diffusively.[3] For example, diffusive coupling of 5 calcium oscillators [$N=5$ in Eq. (2)] yields 4 positive Lyapunov characteristic exponents with zero-flux boundary conditions for the autonomous system (diffusion coefficient $D_x=0.06$, other parameters as in Fig. 1). Similar to the cases studied earlier,[2,3,4] if the number of coupled calcium oscillators is increased, both the number of positive LCEs and the (fractal) dimension of the attractor can increase. Figure 1 shows a plot of a spatio-temporally hyperchaotic state and a time series of one variable in a chain of 100 oscillators for a set of parameters where an isolated single cell is in an oscillatory state. Such a high-dimensional attractor with many positive LCEs has a strong decay of correlation both in time and space.

III. INDUCED ORDER IN ONE SPATIAL DIMENSION

In this section, we study the one-dimensional chain of 100 oscillators with zero-flux boundary conditions, Eq. (2), and parameters as in Fig. 1. We apply various types of external stimulation to the spatio-temporally hyperchaotic state of Fig. 1.

The first external stimulation studied is a sine wave of constant amplitude and frequency which is added to the first oscillator by replacing parameter a in the first oscillator according to

$$a \rightarrow a \cdot (1 + A \sin(\omega t)). \tag{3}$$

This forcing mimics a periodic stimulation of the IP_3 level in the first oscillator of Eq. (2). If the amplitude A of the sine wave exceeds a threshold and the forcing frequency is appropriate (e.g., approximately the frequency of the isolated cell), then the local periodic perturbation immediately starts to spread to neighboring cells until the whole array is ordered into a periodic state (Fig. 2). The final stable state consists of periodic waves propagating from the point of stimulation to the other end of the chain. The amplitude of

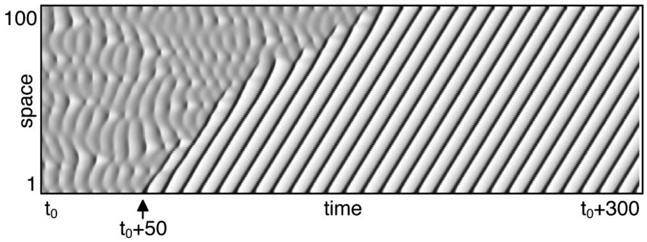

FIG. 2. Spatio-temporal concentration pattern in Eq. (2) with $N=100$. At $t=t_0+50$: start of sinusoidal stimulation of first oscillator according to substitution (3) with $A=0.3$ and $\omega=0.7$. Other parameters and gray coding as in Fig. 1.

the propagating wave is larger than both the amplitude of a single oscillator and of an oscillator in the hyperchaotic state of Fig. 1.

Figure 3 shows the signal of the last oscillator in the chain (X_{100}) as a function of the stimulation frequency ω. Distinct frequency windows are found in which the stimulation signal is able to propagate through the oscillator chain, while for other frequencies the local stimulation exhibits no global effect on the system. These windows can easily be identified by their larger amplitude. In the region where local stimulation leads to a globally ordered state, the dynamics of the last oscillator either follows a period-one limit cycle or a period-two limit cycle (both indicated by numbers in the figure). In the frequency regions where signal propagation fails the dynamics of the last oscillator is in a highly chaotic state with much smaller average amplitude.

In order to estimate the robustness of the system's response to external signals, we stimulated the first oscillator with a deterministic chaotic signal [Fig. 4(a)]. Parameter a of the first oscillator in Eq. (2) (the IP_3 level) was modulated with an external variable (x_1)

$$a \rightarrow a \cdot (1 + A \cdot x_1), \tag{4}$$

where x_1 is calculated from a modified Rössler system

$$\begin{aligned} \dot{x}_1 &= (-x_2 + 0.205 x_1)\,\omega_R, \\ \dot{x}_2 &= (x_1 - x_3)\,\omega_R, \\ \dot{x}_3 &= (0.1 + 4 x_3 (x_2 - 2))\,\omega_R. \end{aligned} \tag{5}$$

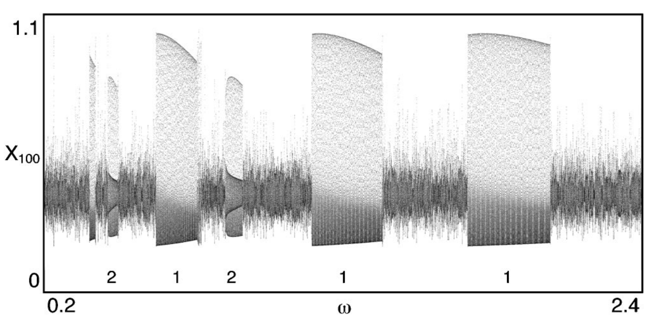

FIG. 3. Concentration of variable X_{100} as a function of forcing frequency in Eq. (2) with $N=100$ and a forcing of the first oscillator according to substitution (3) with $A=0.3$. Other parameters as in Fig. 1. The numbers inside the plot indicate whether last oscillator follows a period one or period two limit cycle.

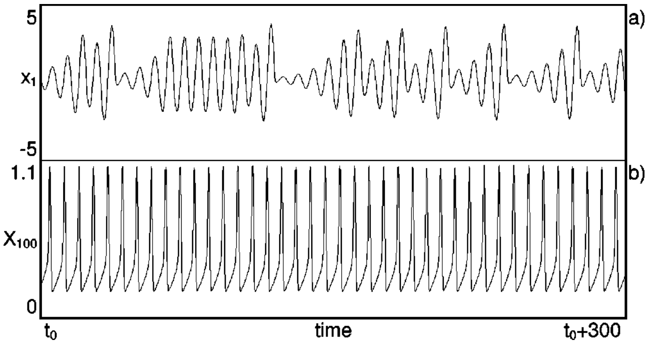

FIG. 4. Forcing of first oscillator in Eq. (2), $N=100$, with the chaotic x_1-variable of Eq. (5), with $\omega_R=0.62$. Oscillator parameters as in Fig. 1. (a) Time series of forcing signal. Forcing according to substitution (4), $A=0.15$. (b) Time series of concentration of variable X_{100} after transients had died out.

Variable x_1 varies in an aperiodic fashion strongly in amplitude and in a narrow range of frequency around a constant mean [Fig. 4(a)]. The chaotic forcing of the strongly hyperchaotic state of coupled oscillators also leads to a synchronization of cells and to a stationary (almost) periodic pattern (except in a small neighborhood of the forced cell) if the mean frequency of the external chaotic signal is approximately the frequency of the sinusoidal forcing applied in Fig. 2 [Fig. 4(b)]. As in the previous cases, by such a local forcing of the first oscillator the dynamics of the last oscillator in the chain may be significantly altered. This can be seen by comparing Fig. 4(b) with the dynamics of the last oscillator in the unforced system [Fig. 1(b)].

So far, we have considered systems with external forcing. Next we studied an autonomous system of 100 coupled oscillators, where parameter a of the first cell is chosen to be different from parameter a in all other cells, simulating a locally altered IP_3 level. This means that the intrinsic frequency of the first oscillator differs from that of all other oscillators in the chain. Figure 5 shows the result as a function of parameter a in the first cell. The left margin corresponds to the value of a in all other oscillators. As in the simulation of Fig. 3, distinct windows are found in which the local periodic stimulation is spread as a regular pattern over the whole chain of oscillators. In particular, a broad window with period one oscillations (in the left half of the figure) and a window of period two oscillations (middle of the figure) can be seen.

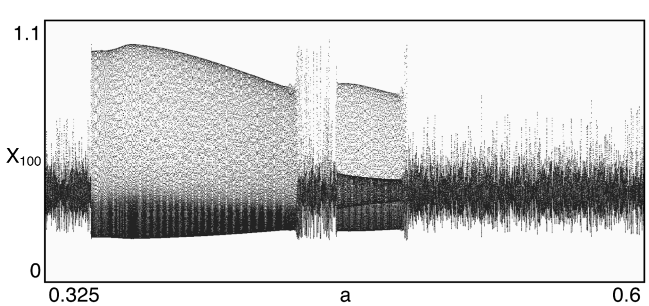

FIG. 5. Concentration of variable X_{100} in Eq. (2) with $N=100$ as a function of parameter a of the first oscillator. $a=0.325$ for all other oscillators. Other parameters as in Fig. 1.

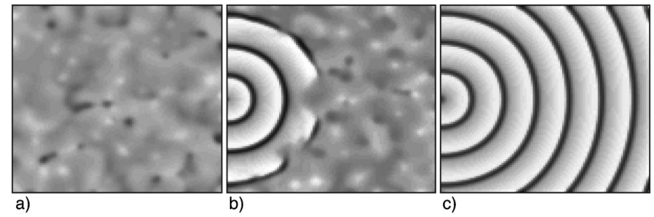

FIG. 6. Concentration pattern of variables X_{ij} of 100×100 oscillators as in Eq. (2) but arranged in a square grid with two-dimensional diffusive next-neighbor coupling. Parameters as in Fig. 1. (a) In the absence of external signal. (b) System of (a) with external signal according to substitution (3) applied simultaneously to two oscillators at center of left margin [coordinates (1,50) and (1,51)]. $A=1.0$, $\omega=0.67$, $t=t_0+60$. (c) Same as (b), except that $t=t_0+200$.

IV. LOCAL STIMULATION OF A TWO-DIMENSIONAL SYSTEM

In the following, we will consider a two-dimensional array of 100×100 oscillators instead of the one-dimensional chain. Each cell is diffusively coupled with its (maximally 4) nearest neighbors in a square grid. As in the previous section we chose zero-flux boundary conditions. Figure 6(a) shows a snapshot of a spatio-temporally hyperchaotic state in the array of 100×100 oscillators for a set of parameters where a single cell would be in an oscillatory state. After switching on the external stimulation according to Eq. (3) with $\omega=0.67$ in two adjacent oscillators in the middle of the left border, the concentration distribution in the two-dimensional system organizes to form periodic waves with the two forced oscillators as their origin [Fig. 6(b)]. Soon the waves cover the whole system yielding a stationary pattern of moving waves [Fig. 6(c)]. The periodic pattern of Fig. 6(c) is robust in the sense that it occurs for a finite window of parameters (e.g., forcing frequency and amplitude) and it also appears and is stable if a sinusoidal forcing with approximately two times the frequency used in Fig. 6 is applied [other parameters as in Fig. 6(c)]. Figure 7 shows another example with a forcing frequency of $\omega=0.43$. In this case the propagating pattern has a period of two cycles (compare the occurrence of period two oscillations in the frequency scan of the one-dimensional case, Fig. 3). With stimulation at the center of the field the respective complete target patterns are found.

As in the one-dimensional case, similar results were achieved in the autonomous system with a locally different value of parameter a (the level of IP_3) of two oscillators at

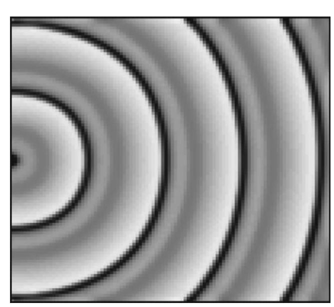

FIG. 7. Period two concentration pattern of 100×100 oscillators as in Fig. 6(c) except that $a=0.323$, $A=1.0$, and $\omega=0.86$.

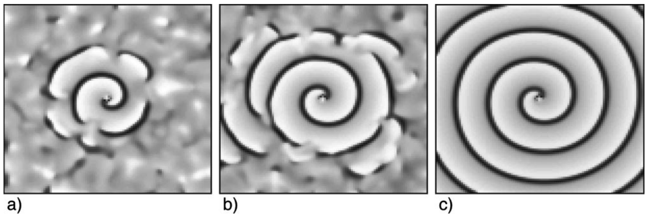

FIG. 8. Spiral concentration pattern of a system as in Fig. 7(a) with forcing at the center: unit (50,50) is pinned to zero, its eight neighbors are forced according to substitution (3) with a phase shift of $\pi/4$ between two adjacent units. $A=1.0$, $\omega=0.67$. (a) $t=t_0+30$; (b) $t=t_0+60$; (c) $t=t_0+120$.

the border. We found that in the two-dimensional case the stimulated synchronization is much easier to achieve when two neighboring oscillators are stimulated simultaneously (as compared to the stimulation of only one oscillator). Still, this can be considered a local stimulation compared to the 10^4 oscillators of the whole system.

Motivated by the experimental observation of spirals of cytosolic calcium[8] we examined whether spiral waves can be induced in our system with proper local stimulation. Figure 8 shows a successful result where 8 units at the center are forced sinusoidally at different phases. Within a certain frequency window a one-armed spiral is immediately induced and, after some time, spreads over the whole field. The spiral can be maintained as long as the forcing is turned on. Under other conditions we were able to induce two- and three-armed spirals in the hyperchaotic field.

V. DISCUSSION

Diffusive coupling of oscillators Eq. (1) can yield a spatio-temporally disordered state in one or two spatial dimensions [Figs. 1 and 6(a)]. This state is generic in the sense that it is not destroyed by slightly altered parameters or by slight deviations from the identity of all oscillators. The disordered state has a high fractal dimension and a large number of positive LCEs. Each unit of the spatially extended system possesses an unstable focus and a period one limit cycle if taken autonomously. The creation of the hyperchaotic attractor can thus be attributed to the addition of linear diffusive coupling between the oscillators.

In the present study we have investigated the globally disordered spatio-temporal pattern with respect to local stimulation. We found that with sinusoidal perturbation of a single unit (in the 1D case) periodic wave patterns were induced for certain frequency windows at a given amplitude of the forcing. Whereas a local single pulse is destroyed by the divergence along the attractor in phase space, a permanent stimulation of proper frequency can spread a train of waves with large amplitude over the whole system (Fig. 2). In a sense, the spreading of the periodic waves can again be attributed to the diffusive coupling between units because still each autonomous unit would be in a limit cycle state with (comparatively) small amplitude. Surprisingly, not only waves of period one but also waves of period two were observed, albeit in narrower frequency windows. This means that for a given amplitude of the sinusoidal stimulation the system can be tuned to two distinct coherent patterns apart from the incoherent (autonomous) state. Each coherent pattern is maintained as long as the stimulation is turned on, and is quickly destroyed if the stimulation is turned off. The results from the one-dimensional case can all be verified in the two-dimensional case in a straightforward manner. 2D waves are obtained by local stimulation of two neighboring units at the border [Figs. 6(c) and 7].

Unexpectedly, the ordered spatial states do not necessarily reflect the (temporal) order of the stimulation signal. Even a deterministic chaotic signal can be used to maintain a coherent pattern (Fig. 4). The important factors to achieve this are that the stimulation keeps oscillating at approximately the correct frequency and that the mean amplitude of the oscillations is above a certain threshold.

A coherent wave pattern of period one or period two can be obtained even in the absence of any oscillatory perturbation. A local change of the influx parameter suffices (Fig. 5). This exploits the fact that the influx parameter varies the frequency of the oscillator in accordance with experimental recordings of calcium oscillations.[7] Thus, altering parameter a in one unit (as exemplified in Fig. 5) can be viewed as a local change of the oscillator frequency. This way a locally altered level of a concentration (of IP_3 in the present model) can be used to switch the spatially extended system from a disordered to either one of two ordered states.

The oscillator model with the present parameters shows a feature of excitability. Namely, an isolated unit Eq. (1) can be perturbed to yield a large amplitude excursion before returning to the limit cycle. The chaos caused by diffusive coupling of the extended system, however, prevents any spreading of a singular local excitation over a considerable distance. This is in contrast to the behavior of an ordinary excitable medium. If, on the other hand, a local excitation is applied over and over again, certain stimuli are enhanced rather than destroyed by the coupling and communicated to the neighboring units. The high-dimensional chaos both prevents the spontaneous formation of an ordered structure (if unperturbed) and supports the formation of specific patterns if phase relations between neighboring units are stimulated appropriately.

Apart from (concentric) waves the 2D hyperchaotic system is capable of exhibiting spiral patterns (Fig. 8). The particular stimulation used to induce a stable spiral is artificial and was not presented to explain experimental observations. Rather it serves to demonstrate that the hyperchaotic system allows the formation of qualitatively different kinds of patterns when only a few units are stimulated. As a consequence, the experimental observation of spirals in *Xenopus* oocytes[8] does not necessarily imply that the unperturbed system has to be in an ordinary excitable state (see, e.g., Ref. 9). It could as well be hyperchaotic. As in the case of periodic waves the spiral is only found for certain frequency windows. Again, the frequency of the local excitation serves as an important pattern selection parameter.

The fact that deterministic chaos can be suppressed by weak external periodic forcing was reported for the case of nonextended systems.[10] This effect was interpreted as a parametric resonance mechanism. For an extended system it was reported that applying disorder to coupled arrays of forced, damped, nonlinear oscillators can be used to turn chaotic into regular spatiotemporal patterns.[11] The occurrence of coherence in a continuous system of coupled oscillators subject to a strongly resonant forcing was analyzed in Ref. 12, and the generation of patterns (as spiral waves or hexagonal patterns) out of turbulence by means of external forcing was demonstrated numerically. Recently, experimental data motivated by this theoretical study were reported.[13] It was shown that periodic optical forcing of the light-sensitive Belousov–Zhabotinsky (BZ) reaction transforms a rotating spiral wave into a labyrinthine standing-wave pattern. However, in all these cases external forcing had to be applied globally in order to achieve a global control of the spatio-temporal dynamics, while in our case a local stimulation suffices in order to induce long-range ordered patterns.

The present results are not an instant of ''controlling chaos''[14,15] because we did not stabilize specific unstable periodic orbits of the hyperchaotic attractor and no feedback signals using information from the system itself were used to generate the perturbation.

The fact that the frequency of a local stimulation can be used to select a specific pattern is of interest in an information theoretic context in biology. This way the reaction-diffusion system acts as a nonlinear frequency filter and it translates a local temporal signal into a robust spatial pattern. Local temporal information of biological relevance can be encoded in a meaningful (ordered) spatio-temporal pattern that creates corresponding temporal signals at distant sites. For example, in the case of calcium ion waves in biological cells the reaction-diffusion system would be a model for the spatial distribution of cytosolic calcium ions inside the cell. It is known that external hormonal information leads to local perturbations at the cell membrane where receptors are located. The presence of a strongly disordered yet deterministic state could then explain why certain local hormonal stimuli can, in principle, be spread over the whole cell with great reliability. The model also offers a means to transfer different qualitative pieces of information (via distinct patterns) by change of a single control parameter. Thereby pattern formation inside a cell would act as a biologically relevant encoding mechanism to transfer extracellular signals to targeted sites of biochemical action.

Experimental evidence for the possible relevance of such an encoding mechanism in biological cells was found by Camacho and Lechleiter.[6] They reported the experimental formation of a regular spatial calcium wave pattern following local receptor activation by applying a constant (external) concentration level of bombesin to *Xenopus* oocytes. In the model this could correspond to a local increase of parameter a at the margin of the field as in the simulations of Fig. 6. During activation of receptors a propagating wave pattern is generated with the origin in the point of activation. In this context, our model predicts that the successful transduction of information as in Ref. 6 (in terms of large-amplitude calcium waves) can only be achieved for *finite* ranges of receptor activation rather than for any suprathreshold perturbation as in an ordinary excitable medium. Also it would predict that very brief activations do not spread over the whole cell but are destroyed in the vicinity of the point of activation.

To summarize, an extended reaction-diffusion system is capable of generating high-dimensional spatio-temporal disorder and well-defined spatio-temporal order depending solely on the presence or absence of a specific local stimulation. This instance of pattern control might play a role in information encoding and transmission in biology.

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