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The role of trans-membrane signal transduction in turing-type cellular pattern formation

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Abstract

The Turing mechanism (Phil. Trans. R. Soc. B 237 (1952) 37) for the production of a broken spatial symmetry in an initially homogeneous system of reacting and diffusing substances has attracted much interest as a potential model for certain aspects of morphogenesis (Models of Biological Pattern Formation, Academic Press, London, 1982; Nature 376 (1995) 765) such as pre-patterning in the embryo. The two features necessary for the formation of Turing patterns are short-range autocatalysis and long-range inhibition (Kybernetik 12 (1972) 30) which usually only occur when the diffusion rate of the inhibitor is significantly greater than that of the activator. This observation has sometimes been used to cast doubt on applicability of the Turing mechanism to cellular patterning since many messenger molecules that diffuse between cells do so at more-or-less similar rates. Here we show that Turing-type patterns will be able to robustly form under a wide variety of realistic physiological conditions though plausible mechanisms of intra-cellular chemical communication without relying on differences in diffusion rates. In the mechanism we propose, reactions occur within cells. Signal transduction leads to the production of messenger molecules, which diffuse between cells at approximately equal rates, coupling the reactions occurring in different cells. These mechanisms also suggest how this process can be controlled in a rather precise way by the genetic machinery of the cell.

Keywords: Turing pattern; Signal transduction; Morphogen; Pattern formation; Morphogenesis; Reaction-diffusion

1. Introduction

Each cell in an organism contains an identical copy of the full set of genetic material for that organism, yet a brain cell is very different from a kidney cell. The vast functional differences between cell types in a multi-cellular organism are due to differences of gene expression: some of the genes are turned on in every cell, while others are turned on only in cells of a given type. Other genes are designed to turn on and off throughout the life of the cell, and do this in response to specific internal signals or external stimuli. Most genes in a cell are probably turned off most or all of the time. Through modulation of the genetic "switches" occurring at the transcriptional level, or further downstream at the translational level, the genetic program can also modulate the rates of many processes. For all of the above reasons it is wrong to view the genetic information as a mere list of proteins—it is also a detailed program for how to use these proteins, when to start and stop their production, and which genes get turned on and off together. In an embryo there is initially only one genetic program since there is only one copy of genetic material. As the cells in the embryo divide, more identical copies of the genes are made, but how does the cell "know" where and when to switch different genes on and off? In this context what could possibly constitute a genetic blueprint for the developments of a complicated multicellular organism?

This is a fundamental problem in biology, the problem of cellular morphogenesis in the embryo. It is a problem that ultimately requires much more than a list of genes for its full solution. While insight into this problem may be applicable to many types of biological pattern formation, here we are particularly interested in the early stages of morphogenesis. This process is initiated by a cascade of gene switching events that

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occur, seemingly magically, at the right times and places within an embryo leading to the development of a complex multicellular organism. The principal problem in this case is the determination of a mechanism by which complex order may set in an initially homogeneous system. That is, if the initial state of each cell (the set of active genes) and the laws of development (the genetic information *in toto*) are the same in every cell, how is the symmetry of the fertilized egg broken? How does the initial symmetry breaking occur within the rather constrained arena of the genetic regulatory processes and biochemistry of the cell? So far no one has provided a convincing answer to this important problem.

This question was partially addressed by Alan Turing in 1952 in his seminal paper on chemical morphogenesis (Turing, 1952) where he showed that a system of reacting and diffusing chemical species could spontaneously form stationary spatial patterns given a certain set of *chemically* plausible mechanisms. This requires that there be at least two reacting chemical species that diffuse at very different rates. The system is an intrinsically non-equilibrium one; both substances are continuously created (by the cells) at every point in space, and also decay or are removed at specified rates. The slowly diffusing substance (the activator) is autocatalytic, meaning it participates in its own production. In another reaction some of the activator is transformed into the fast-diffusing substance (the inhibitor). Lastly, the inhibitor causes the activator to be removed from the system at a rate proportional to the concentration of the inhibitor at that point in space. Thus in these reactions the activator makes more activator and inhibitor, and the inhibitor destroys the activator.

The Turing mechanism has often been put forward, as was Turing's original intent, as a model for certain aspects of morphogenesis (Meinhardt, 1982; Koch and Meinhardt, 1994; Kondo and Asai, 1995; Sawai et al., 2000) such as pre-patterning in the embryo. It has also served as a model for self-organization in more generic systems (Glansdorff and Prigogine, 1971). With the first verifiable observation of Turing pattern formation in a real chemical system (Castets et al., 1990) the subject now finally has an experimental basis (Lengyel and Epstein, 1992). The specific model proposed by Turing is not the only possibility that will support pattern formation of the type Turing was specifically interested in. The two features of the reaction necessary for the formation of Turing patterns are short-range autocatalysis and long-range inhibition (Gierer and Meinhardt, 1972), and there are a number of ways this can be brought about. However, under most conditions it has been found that pattern formation can only occur when the diffusion rate of the inhibitor is significantly greater than that of the activator.

Therein lies, as is often noted by researchers familiar with real biological mechanisms, a big problem: fairly small molecules usually do the diffusing, but most small molecules diffuse at approximately the same rates in aqueous solutions. Even molecules of substantially different size will diffuse at fairly similar rates. (A least-squares fit of the diffusion coefficients of 146 proteins in Sober (1970) reveals that they scale roughly as $D \propto M^{-0.37}$.) While some patterns can form in systems where the ratio of the diffusion coefficients is greater than 2, in practice it has been found that the diffusion rates usually need to be even more different that this for stable and robust patterns to form. Not only is it difficult to imagine molecules that have the appropriate properties, it is also difficult to imagine how any kind of sensitive cellular control of the pattern forming process can be achieved since it would probably be nearly impossible for the cell to directly modulate intrinsic properties like the diffusion rates of chemical morphogens. These caveats have been more than enough to cause some to seriously doubt the applicability of the Turing mechanism to cellular patterning of any kind.

Turing's original model is also completely linear. The original intent was to illustrate the *onset* of an instability leading to pattern formation. The model is not realistic in regard to the subsequent development of the pattern, since the patterns would have to be restablized far from equilibrium by nonlinearities not included in the original model. Even subsequent nonlinear studies have in most cases focused on mathematically interesting improvements rather than chemically or biologically realistic mechanisms. What is needed is a realistic model for pattern formation that is robustly able to produce patterns out of the basic biochemical machinery of the cell. Because of the above-mentioned problems it is not obvious how this is to be accomplished. In the past, most or all of the focus has been placed on reactional aspects, while the more difficult problems of the chemicals behind the reactions, and especially the biological mechanisms behind these reactions, have been largely ignored.

In this paper we aim to deal with these neglected aspects of the problem. We show that stationary, symmetry-breaking Turing-type patterns can form in physiologically realistic systems, even when the extracellular diffusion coefficients are equal. Strictly speaking then, these are not "Turing" patterns since the mechanism is different. However "Turing-type" patterns do occur for the same reasons as "Turing" patterns. The physiologically realistic models we consider are ones that make use of the basic kinetic properties of the receiver and transmitter proteins responsible for signal transduction through the cell membrane. The proposed pattern-forming mechanism is not only capable of explaining pattern formation when the diffusion rates of the morphogens are very similar, but also shows how details of the mechanism might be sensitively controlled by the genetic machinery of the cell.

2. The signal-transduction and reaction–diffusion mechanisms

In the class of mechanisms we examine, schematized in Fig. 1, we make a sharp distinction between reactants, which participate in reactions inside the cell, and messenger molecules, which diffuse between cells. No transport of molecules across cell membranes takes place. Rather, signal transduction across the cell membrane, mediated by membrane proteins, connects the genetically controlled biochemical reactions in the cytosol to the production of messenger molecules that diffuse through the aqueous extracellular matrix. The messenger molecules diffuse outside the cells at approximately equal rates, coupling the reactions taking place inside cells at different points in space. Importantly, the cell essentially has nearly complete freedom to control the signal transduction kinetics, whose associated rates could quite easily vary by many orders of magnitude. This is to be strongly contrasted with the situation where the diffusion coefficients themselves are required to differ by a large amount—the standard route to Turing patterns—since it is difficult to imagine realistic situations where this holds true.

The specific model we use as an example below makes use of reactions and reaction kinetics of a type which can be found in every living cell. The chemical equations we use are derived from catalysed chemical reactions.

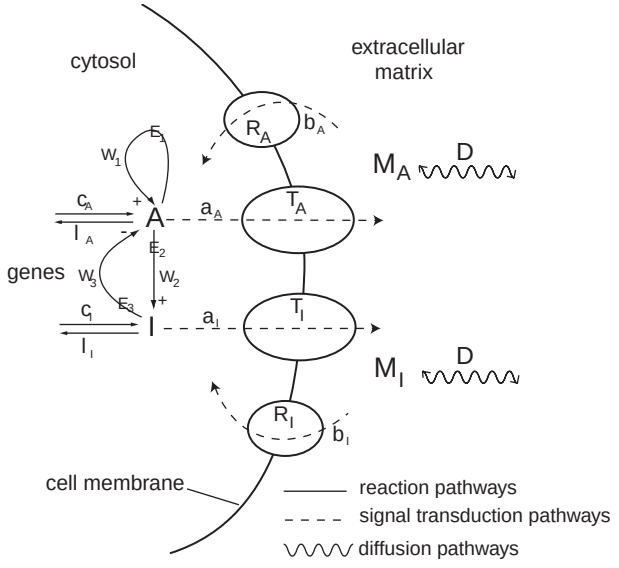

Fig. 1. General kinetic schematic for model. The three basic kinetic elements of our model are shown. The simplified reactions in the cytosol involve an activator substance A and inactivator I which are created at constant rates by the cell and likewise broken down at the rates λ_A and λ_I. In this case trans-membrane signal transduction takes the form of transformation of A and I in the cytosol (mediated by the membrane proteins T_A and T_I) into corresponding messenger molecules M_A and M_I in the extracellular matrix. Likewise R_A and R_I mediate the reverse transformation. Both of the messenger substances diffuse at rate D through the extracellular matrix.

The genetic machinery of the cell controls the rates of these reactions by controlling the production of the catalysts. The chemical reactions and other properties incorporated in this class of models are rather generic, and similar results can be realized in many possible systems.

We purposely do not specify the details of this signal transduction mechanism any more than is absolutely necessary, and virtually any type of signal transduction kinetics will do. We will show that the coupling via signal transduction between reactions occurring in cells is enough to allow Turing-type patterns to spontaneously form in collections of cells, even if the messenger diffusion rates (D) are identical or very similar in the aqueous extracellular environment. Because of this we believe the mechanisms described here could be of some relevance to understanding many aspects of cellular morphogenesis.

The simplified set of reactions taking place in the cytosol involves an "activator" substance A and an "inhibitor" substance I that are synthesized by the cell at the rates c_A and c_I respectively, and in turn are broken down by the cell at the rates λ_A and λ_I as diagrammed in Fig. 1, where

$$\mathrm{d}[A]/\mathrm{d}t = c_A - \lambda_A[A], \quad \mathrm{d}[I]/\mathrm{d}t = c_I - \lambda_I[I]. \tag{1}$$

Activator is also produced by the autocatalytic process

$$A + E_1 \rightleftharpoons E_1A \ (K_1 = [E_1][A]/[E_1A]),$$
$$\psi + E_1A \xrightarrow{k_1} E_1A + A, \tag{2}$$
$$\mathrm{d}[A]/\mathrm{d}t = V_1[A]/(K_1 + [A]), \quad V_1 = [E_1]_c k_1,$$

where we will use ψ as a shorthand for substances from the large and constant concentration of assorted biochemical building blocks present in the cell that are used to synthesize A and I. The activator also catalyzes the production of more inhibitor through the set of reactions

$$A + E_2 \rightleftharpoons E_2A \ (K_2 = [E_2][A]/[E_2A]),$$
$$\psi + E_2A \xrightarrow{k_2} E_2A + I, \tag{3}$$
$$\mathrm{d}[I]/\mathrm{d}t \simeq V_2[A]/K_2, \quad V_2 = [E_2]_c k_2,$$

where for simplicity we have assumed that this reactions operates well below saturation, with $[A] \ll K_2$. Lastly, the inhibitor suppresses the activator through the set of reactions

$$A + E_3 \rightleftharpoons E_3A \ (K_3 = [E_3][A]/[E_3A]),$$
$$I + E_3A \xrightarrow{k_3} E_3AI \to E_3\psi I \to E_3 + \psi + I, \tag{4}$$
$$-\mathrm{d}[A]/\mathrm{d}t = V_3[A][I]/(K_3 + [A]), \quad V_3 = [E_3]_c k_3.$$

The rates of the catalytic process are given by the Michaelis–Menten (Fersht, 1984) kinetics, where K_i are the Michaelis constants, k_i the catalytic rates and V_i the

limiting rates for the catalytic processes. The E_i's are catalysts of the reactions where $[E_i]_c$ are the total concentrations of these catalysts produced by the genetic machinery of the cell. Because of the need for enzymes, we assume these reactions, including the breakdown of A and I, can only occur inside the cell.

In addition to being biologically reasonable, our model differs from the classical Turing model in two important respects. First, it takes into account the fact that genetically regulated biochemical processes will take place inside the cell, while cell-to-cell interaction must involve some form of trans-membrane signaling, since most biomolecules are highly insoluble in the lipid matrix of the cell membrane. Secondly, the diffusion of the two messenger molecules through the extracellular matrix can take place at identical rates D.

Since pre-patterning is likely to involve switching on different sets of genes in different cells, some mechanisms must exist for signaling between the genes. Our model makes use of signal transduction kinetics diagrammed in Fig. 1, where α_A and α_I are the rates of production of the messenger molecules M_A and M_I. This process is mediated by *transmitter* proteins T_A and T_I in the membrane. In the figure, signal transduction is viewed as the transformation of A and I into M_A and M_I respectively (though transformation into messenger molecules is not a requirement of the model). Conversely, the β_A and β_I are the rates of transformation of M_A and M_I into A and I, a process mediated by R_A and R_I, the *receiver* proteins. Since the basic features responsible for the self-organization of the system are generic, this simplified picture can stand for more complex signal transduction mechanisms. For example, the signal transduction could involve the binding of A or I to specific receptor proteins on the intracellular side of the membrane, triggering the release of messenger molecules on the extracellular side of the membrane which then carry the signal to other cells.

One could view the coupling of the reactions occurring within cells as a process analogous to diffusion. Viewed in this general way, it relies on the same basic mechanism of short-range activation and long-range inhibition as Turing patterns. However, we stress that the pattern formation is not enabled by differing rates of diffusion in the true sense. Another important distinction is that in our model the parameters that control pattern formation are determined by the rates of production of the proteins that serve as the catlysts inside the cell. As a result it is clear how, in this case, pattern formation could be be switched on and off or from one mode to another by the genetic machinery, possibly on the scale of minutes.

The biological mechanism we propose here is analogous to the mechanism proposed as an explanation for the chlorite-iodide-malonic acid-starch reaction system, which was the first chemical system in which Turing patterns were observed experimentally (Castets et al., 1990). Lengyel and Epstein (1991, 1992) showed that the existence of Turing patterns in this system, despite the similar diffusion coefficients of the reactants, is a consequence of the binding and unbinding of iodine to starch molecules that have been immobilized by the gel, which serves as an "inert" medium of the reaction. What we are proposing here is a biologically realistic and necessary mechanism that is able to provide just this type of effect in living cells. In this analogy, the role of the starch is played by the cell membrane.

3. Discrete model

Since cells are discrete, we consider the case where reactions take place at discrete locations, but where the extracellular matrix in which cell-to-cell diffusion takes place is continuous. Taking an array of cells, where $A_j(t)$ and $I_j(t)$ represent the concentrations $[A]$ and $[I]$ of activator and inhibitor in the cell at location (x_j, y_j), we have the ordinary differential equations

$$\frac{\mathrm{d}A_j}{\mathrm{d}t} = c_A - \lambda_A A_j + \frac{V_1 A_j}{K_1 + A_j} - \frac{V_3 A_j I_j}{K_3 + A_j} - \alpha_A A_j + \beta_A M_A(x_j, y_j), \tag{5}$$

$$\frac{\mathrm{d}I_j}{\mathrm{d}t} = c_I - \lambda_I I_j + \frac{V_2 A_j}{K_2} - \alpha_I I_j + \beta_I M_I(x_j, y_j). \tag{6}$$

In the extracellular matrix, each cell is a point source and sink (represented with delta functions). Letting $M_A(x, y) = [M_A]$ and $M_I(x, y) = [M_I]$ be the concentrations of messenger molecules at position (x, y) we have

$$\partial_t M_A(x, y) = \alpha_A \sum\nolimits_j \delta_j A_j - \beta_A \sum\nolimits_j \delta_j M_A - D\nabla^2 M_A, \tag{7}$$

$$\partial_t M_I(x, y) = \alpha_I \sum\nolimits_j \delta_j I_j - \beta_I \sum\nolimits_j \delta_j M_I - D\nabla^2 M_I, \tag{8}$$

where $\delta_j = \delta(x - x_j)\delta(y - y_j)$ is equal to 1 when $x = x_j$ and $y = y_j$ and 0 otherwise.

Fig. 2 shows a simulation using arrays of individual cells in one and two dimensions, demonstrating patterns in which the pattern wavelength is close to the size of a cell.

4. Linear stability analysis of the system

We now consider a fully continuous version in order to examine the analytic structure of the stability of the model.

Setting $A(\mathrm{x}, t) = [A], I(\mathrm{x}, t) = [I], M_A(\mathrm{x}, t) = [M_A]$ and $M_I(\mathrm{x}, t) = [M_I]$ to be the concentration at a given time t

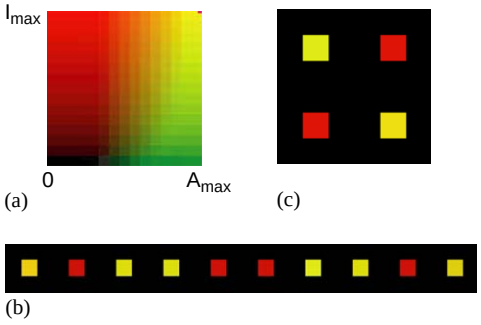

Fig. 2. Stable patterns in small arrays of cells. Concentrations were set to zero at $t = 0$ and allowed to build up naturally, the situation that would arise if the genes for the production of A and I were suddenly switched on at $t = 0$. The activator is shown as shades of green (black indicating 0 and green the maximum value A_{max}), and the inhibitor as shades of red (red indicating the maximum value I_{max}) as shown in the legend (a). The two are superimposed so that yellow indicates the presence of both activator and inhibitor. (b) A one-dimensional array of ten cells. $A_{max} = 24.2$, $I_{max} = 14.0$(c). A 2×2 array cells. $A_{max} = 28.5$, $I_{max} = 13.0$, $A_{in} = A_{out} = 4$, $I_{in} = I_{out} = 170$ and $D = 300$; there is no diffusion of reactants through the cell membrane. Numerical method: The reaction component of the equations was integrated using a forward-Euler method. For the purpose of simulation, the extracellular matrix was treated as discrete. The Laplacian (diffusion) term was implemented using the following conservative method: for each pair of locations $\{i,j\}$, $A_i(t+1) = A(t) + \Delta A$; $A_j(t+1) = A_j(t) - \Delta A$ where $\Delta A = M_{ij} D(A_i(t+1) f(i,t) - A_j(t+1) f(j,t))\Delta t$ and M_{ij} is the connectivity matrix. The noise function f is a uniformly distributed random variable, ranging from 0 to 10^{-5}, and models the effect of very weak fluctuations of the type that are require to initiate the initial instability. A von Neumann neighborhood and toroidal boundary conditions were used.

and position x, we can derive the following set of four reaction–diffusion equations:

$$\partial_t A = c_A - \lambda_A A + \frac{V_1 A}{K_1 + A} - \frac{V_3 A I}{K_3 + A} - \alpha_A A + \beta_A M_A - \varepsilon \nabla^2 A, \tag{9}$$

$$\partial_t I = c_I - \lambda_I I + \frac{V_2 A}{K_2} - \alpha_I I + \beta_I M_I - \varepsilon \nabla^2 I, \tag{10}$$

$$\partial_t M_A = \alpha_A A - \beta_A M_A - D \nabla^2 M_A, \tag{11}$$

$$\partial_t M_I = \alpha_I I - \beta_I M_I - D \nabla^2 M_I. \tag{12}$$

Here ε is a rate of diffusion arising from "leakage" though the cell membrane which occurs very rarely, and hence is very small (or negligible) in comparison to D. We introduce this small quantity for mathematical reasons in order to give the first two equations a spatial scale (which, in the discrete case, is set by the size of a cell) and to remove the singular nature of the limit where $\varepsilon = 0$. The smallness of ε is related to the smallness of the (relative) size of the cells in comparison to typical spatial scales in this continuum model. Another way to introduce a cell spatial scale is to model the cell as discrete points in space as we have done in the previous section. In this case the $\varepsilon \to 0$ limit represents the case where the ratio of the spatial scale associated with the cell dimension to the spatial scale associated with the morphogen diffusion goes to zero.

For the purposes of keeping our illustration as simple as possible we will specifically consider only the case where $c_A = c_I = 1$, $\alpha_A = \beta_A = 1$ and $\alpha_I = \beta_I = \rho$. We further set limiting velocities of the catalyzed reactions to $V_1 = 600$, $V_2 = 1$, and $V_3 = 6$, and the parameters $\lambda_A = 1/100$, $\lambda_I = 7$, $K_1 = 100$, $K_2 = 1$, and $K_3 = 1/10$. For this model the stationary homogeneous state is $A(\mathrm{x}) = M_A(\mathrm{x}) \simeq 2.46$ and $I(\mathrm{x}) = M_I(\mathrm{x}) \simeq 2.25$. A standard linear stability analysis (Meinhardt, 1982) of Eqs. (1–4) about this state tells us that an initial perturbation of the uniform state with a given wave vector k will have an amplitude that grows (or shrinks) in proportion to the factor $e^{\lambda_k t}$, where λ_k are eigenvalues of the stability matrix

$$\tilde{\mathrm{S}} = \begin{bmatrix} 3.55 - \varepsilon k^2 - 1 & -5.77 & 1 & 0 \\ 6 & -7 - \rho - \varepsilon k^2 & 0 & \rho \\ 1 & 0 & -1 - k^2 & 0 \\ 0 & \rho & 0 & -\rho - k^2 \end{bmatrix}, \tag{13}$$

and can be real or come in complex conjugate pairs. Each value of k corresponds to a spatial mode with wavelength $L = 2\pi\sqrt{D/k}$. The real parts of the eigenvalues corresponding to this mode, $\Re(\lambda_k)$, determine the stability of perturbations away from the homogeneous state with the corresponding wavelength: $\Re(\lambda_k) < 0$ indicates the mode is stable, and $\Re(\lambda_k) > 0$ indicates an unstable mode which will grow when a small random fluctuation displaces it from equilibrium. Thus the existence of a wave number k such that $\lambda_k > 0$ means patterns will form. Turing patterns occur when the largest eigenvalue is real ($\Im(\lambda_k) = 0$) which is the case for the parameters we have chosen here. The largest eigenvalue has a negative real part ($\Re(\lambda_k) < 0$) when $D \to 0$ showing that the system is globally stable in the absence of diffusion. Fig. 3 shows the linear stability spectrum of the model.

The type of patterns that form will depend to a large degree on the spectrum of unstable k modes; it especially depends on the mode with the greatest λ_k, but also on the range of other unstable modes. As was mentioned above, we included a small diffusion effect *through* the membrane with diffusion coefficient ε for mathematical reasons in order to remove the singular nature of the equations when the diffusion vanishes. In Fig. 3b we show the effect of varying ε on the frequency spectrum. As $\varepsilon \to 0$ the spectrum of unstable modes is broadened towards the higher frequency modes until at $\varepsilon = 0$, the maximum k value in the spectrum goes to infinity.

Physically, this means that shorter and shorter wavelengths will come to dominate, and at some point the wavelength of the patterning will be limited by the finite dimension of the cells.

Fig. 4 shows patterns in a system in which the pattern wavelength is larger than the size of a cell, simulated according to the continuous model. The figure shows some of the ordered patterns that emerge spontaneously in the system for varying values of ρ. Patterns can range from (a) a "honeycomb" pattern ($\rho = 6$) to (b) stripes ($\rho = 11.5$) to (c) spots ($\rho = 100$).

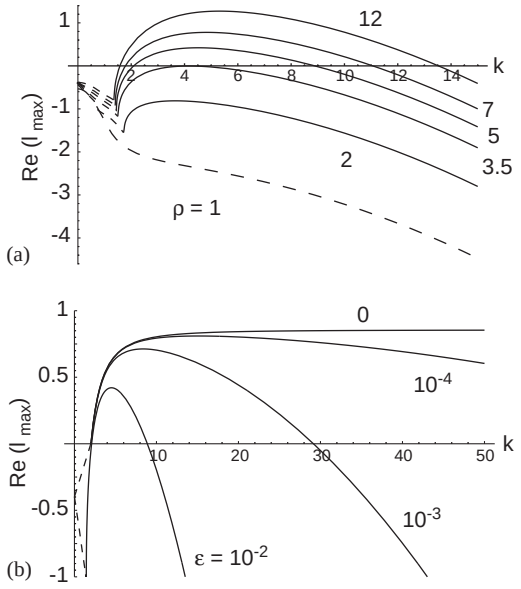

Fig. 3. Linear stability spectrum of the model. The dotted lines indicate regions where the eigenvalue with the largest real part is complex. Parameters are given in the text. Plot (a) shows the spectrum of stability eigenvalues for several values of the critical parameter ρ. For $\rho < 3.5$ all the eigenvalues have negative real parts, and the homogeneous distribution of reactants is stable. Turing patterns set in when $\rho > 3.5$, and a range of frequency modes become unstable, giving rise to spontaneous ordering. Plot (b) shows the effect on the spectrum when $\rho = 5$ as ε is varied. As $\varepsilon \to 0$, the most unstable mode shifts to higher and higher frequencies, but ordering will still take place.

5. Discussion

The proposed system is capable of supporting more or less the same patterns as an ordinary Turing mechanism that uses widely differing diffusion coefficients. The principal difference is that our mechanism provides a physiologically and chemically feasible route by which a wide range of patterns could arise.

Previous work has shown that pattern formation can occur in some systems with equal diffusion coefficients, but only if there is some kind of initial asymmetry such as a finite size perturbation (Vastano et al., 1987; Andresen et al., 1999; Henry and Wearne, 2002), an external advective flow (Rovinsky and Menzinger, 1992, 1993), or an already established gradient (Kerszberg and Wolpert 1998). These mechanisms might provide useful models for subsequent morphogenetic events in the embryo where some spatial genetic patterning or chemical gradients have already been set up, but still does not provide an adequate explanation of initial pre-patterning events which may start from a completely homogeneous initial state. The existence of an organizing center begs the question of how the center itself formed.

Our model provides a possible, physiologically realistic route to symmetry-*breaking* instabilities in cellular systems, and we hope that it will provide a useful context in which to explore the possible relevance of Turing mechanisms to cellular morphogenesis. For instance, our model makes a clear distinction between reacting and diffusing entities and thus provided somewhat different expectations for making experimental observations. The messengers could be almost any type of molecule, and are not required to have any complex reactive chemical properties. Rather, it is the properties of the transmitter and receiver proteins in the signal transduction pathway that will control the pattern formation. As a consequence it may be unproductive to search for specific "morphogens" since the biochemical substances that differentiate spatial patterns in a

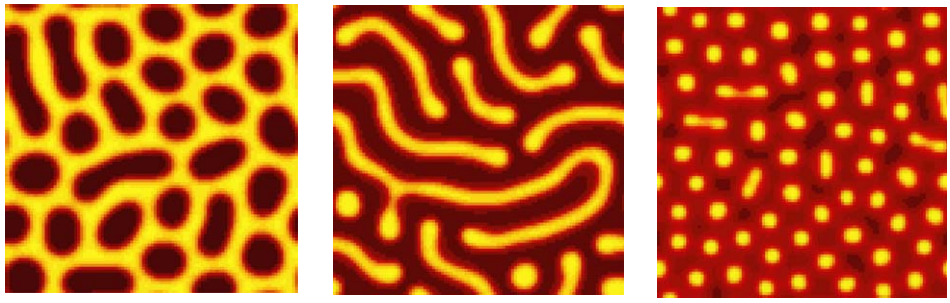

Fig. 4. Two-dimensional Turing patterns. (a) Stable concentrations of activator and inhibitor in a two-dimensional array of cells for $\rho = 6$. The extracellular diffusion rate $D = 600$ and $\varepsilon = D/100$; the grid size is 100. $A_{max} = 32.0$ and $I_{max} = 21.3$. (b) Concentrations of A and I for $\rho = 11.5$ and other parameters as above. $A_{max} = 53.8$ and $I_{max} = 28.4$. (c) Concentrations of A and I for $\rho = 100$. $A_{max} = 117.6$ and $I_{max} = 35.3$.

collection of cells may be unrelated to the substances that actually mediate the cell-to-cell communication.

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