

A chemical approach to designing Turing patterns in reaction-diffusion systems

(pattern formation/nonlinear dynamics)

ISTVÁN LENGYEL*[†] AND IRVING R. EPSTEIN*[‡]

*Department of Chemistry and [‡]Center for Complex Systems, Brandeis University, Waltham, MA 02254-9110; and [†]Institute of Physical Chemistry, Kossuth Lajos University, H-4010, Debrecen, Hungary

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ABSTRACT A systematic approach is suggested to design chemical systems capable of displaying stationary, symmetry-breaking reaction diffusion patterns (Turing structures). The technique utilizes the fact that reversible complexation of an activator species to form an unreactive, immobile complex reduces the effective diffusion constant of the activator, thereby facilitating the development of Turing patterns. The chlorine dioxide/iodine/malonic acid reaction is examined as an example, and it is suggested that a similar phenomenon may occur in some biological pattern formation processes.

The stable, stationary, reaction-diffusion patterns predicted by Turing (1) have served as the basis for several theories of morphogenesis (2, 3). They have recently been found experimentally in the chlorite/iodide/malonic acid (CIMA) system in a gel reactor (4). The difficulty in observing Turing patterns in other systems arises from the necessary condition that the diffusion coefficients of the activator and inhibitor species be very different. Here, we show that introduction of a reagent that reversibly forms an unreactive, immobile complex with the activator species can circumvent this requirement, making it possible to produce Turing patterns in systems that would not otherwise exhibit such structures.

The experimental difficulty of demonstrating the chemical nature of the postulated morphogens has prevented direct study of the Turing mechanism in biological systems. Chemical reactions, in which the relevant species can be identified and monitored, offer far better prospects for investigating Turing structures. The need, however, for the activator—i.e., the species responsible for the positive feedback—to diffuse significantly less rapidly than the inhibitor (3) has posed a major obstacle, since in aqueous media nearly all simple molecules and ions have diffusion coefficients within a factor of 2 of $1.5 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.[§]

A General Two-Variable Model

In the CIMA reaction, we have suggested that interactions of the activator iodine species with the polyacrylamide gel and/or with the starch indicator result in a major reduction of the effective activator diffusion coefficient (6). Here we generalize that idea to an algorithm for designing systems that exhibit Turing instability. Consider a system characterized by parameters (e.g., rate constants) p and containing an activator species X and an inhibitor species Y that react and diffuse according to Eq. 1.

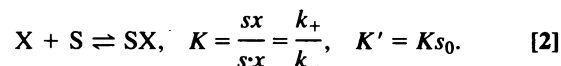
$$\frac{\partial x}{\partial t} = f(x, y, p) + D_x \frac{\partial^2 x}{\partial z^2}$$

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$$\frac{\partial y}{\partial t} = g(x, y, p) + D_y \frac{\partial^2 y}{\partial z^2} \quad [1]$$
$$a_{11} \equiv \frac{\partial f}{\partial x}, \quad a_{12} \equiv \frac{\partial f}{\partial y}, \quad a_{21} \equiv \frac{\partial g}{\partial x}, \quad a_{22} \equiv \frac{\partial g}{\partial y},$$

where D_x and D_y are the respective diffusion constants, lowercase letters represent concentrations, and the elements a_{ij} of the Jacobian matrix are evaluated at the steady state of interest. The identification of X and Y as activator and inhibitor, respectively, implies that $a_{11} > 0$ and $a_{22} < 0$.

Suppose now that X can react to form a complex with another species S , which is either bound to a gel matrix or is so large that the diffusivities of S and the complex SX are effectively zero.[¶] Suppose also that the complex is unreactive, either because of its chemical properties or because steric factors prevent Y from approaching X when it is bound to the large molecule. For simplicity we assume a large excess of S ($s \gg x$) uniformly distributed so that its concentration is always very close to its initial value s_0 . The complex formation is described by



If the spatial distribution of S is uniform, the new reaction-diffusion system is described by

$$\frac{\partial x}{\partial t} = f(x, y, p) - k_+ s_0 x + k_- s x + D_x \frac{\partial^2 x}{\partial z^2} \quad [3a]$$

$$\frac{\partial y}{\partial t} = g(x, y, p) + D_y \frac{\partial^2 y}{\partial z^2} \quad [3b]$$

$$\frac{\partial sx}{\partial t} = k_+ s_0 x - k_- s x. \quad [3c]$$

If the formation and dissociation of the complex are rapid, the concentration of SX instantaneously follows that of X , and sx can be expressed in terms of x by using the last two expressions in Eq. 2.^{||} The set of differential equations can then be simplified by adding Eqs. 3a and 3c and replacing sx by $K'x$.

Abbreviation: CIMA, chlorite/iodide/malonic acid.

[§]This is paper no. 76 in the series "Systematic Design of Chemical Oscillations." Paper no. 75 is ref. 5.

[¶]Hunding and Sorensen (7) have suggested a similar approach to describe size adaptation of Turing patterns in developing embryos.

^{||}This reduction can be made rigorous using singular perturbation theory by letting $k_+ = k'_+/\epsilon$, $k_- = k'_-/\epsilon$, where k_+ and k_- are $O(1)$, and then letting $\epsilon \rightarrow 0$.

$$\frac{\partial(x + sx)}{\partial t} = (1 + K') \frac{\partial x}{\partial t} = f(x, y, p) + D_x \frac{\partial^2 x}{\partial z^2}$$

$$\frac{\partial y}{\partial t} = g(x, y, p) + D_y \frac{\partial^2 y}{\partial z^2} \quad [4]$$

This two-variable reaction-diffusion system is more easily analyzed if one rescales the time and length variables by setting $t = t'/(1 + K')$, $z = D_x^{1/2} z'$. The differential Eq. 4 then takes the form

$$\frac{\partial x}{\partial t'} = f(x, y, p) + \frac{\partial^2 x}{\partial z'^2}$$

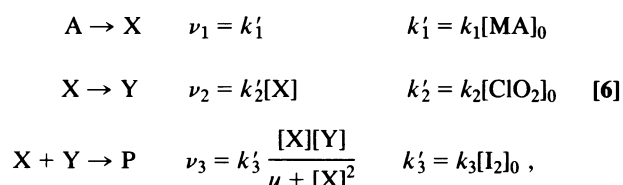
$$\frac{\partial y}{\partial t'} = \sigma \left[g(x, y, p) + c \frac{\partial^2 y}{\partial z'^2} \right], \quad [5]$$

where $\sigma = 1 + K'$ and $c = D_y/D_x$. Observe that f , g , and p retain the same form. Whether or not the original differential equation system (Eq. 4) is in dimensionless form, the complex formation (Eq. 2) and the subsequent transformation change neither the scaling of the dependent (concentration) variables nor the kinetic parameters of the system.** Physically, formation of the complex separates the time scales for changes in the activator and inhibitor concentrations by a factor of σ . In particular, the more stable the complex, the greater the difference between the time scales for the diffusion of the two components.

Complex formation does not change the steady-state composition of the system. It may, however, modify the stability of the steady state. If the system has a unique unstable steady state and hence shows oscillatory behavior in the absence of S ($\sigma = 1$), then complex formation ($\sigma > 1$) can stabilize the homogeneous steady state at this same set of parameters. Introduction of S thus broadens the range of steady-state stability as illustrated in Fig. 1, making it possible for diffusion-induced instability to occur at parameter values that were inside the oscillatory region of the complex-free system. Equivalently, complex formation may be viewed as shifting the homogeneous Hopf bifurcation to larger parameter values, so that the Turing bifurcation occurs before the Hopf point and is therefore observable. The wavelength of the Turing patterns and the stability of the inhomogeneous steady state are independent of the concentration of complexing agent, a result in agreement with observations (P. De Kepper, personal communication) on the CIMA/starch system with varying concentrations of starch.

The CIMA System

We illustrate these ideas with reference to the CIMA reaction (4). More general and detailed treatments of the Turing bifurcation can be found in refs. 3 and 8. The system is well described by three overall stoichiometric processes whose rate laws have been experimentally determined. After some simplifications, the dynamics can be summarized in a two-variable model (9):



**Note that if one does not change to dimensionless variables at this stage, the "length" variable z' in Eq. 5 has dimensions of (time)^{1/2}.

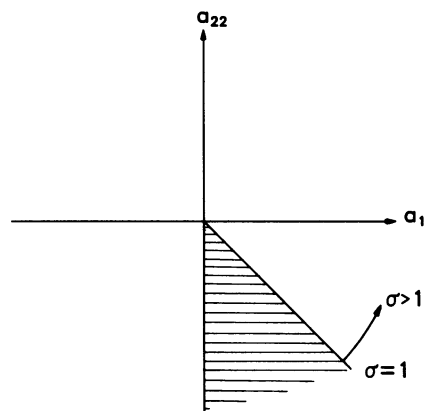
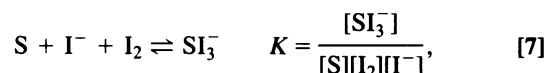


FIG. 1. Stability boundary for a general activator-inhibitor model in the a_{11} vs. a_{22} space. The hatched area indicates the stable steady state.

where X and Y denote iodide and chlorite ions, the activator and inhibitor, respectively, and MA denotes malonic acid.

The starch reacts with iodine and iodide to form a blue helical complex. Because of its high molecular weight, the starch is essentially immobile either in the gel or in aqueous solution. In a water solution, formation of the complex is a very fast process, though it may be somewhat slower in a medium like the polyacrylamide gel.

We assume rapid formation of a starch/triiodide complex SI_3^- according to



where [S] represents the concentration of starch per six monomer units needed to form a complete helix (10, 11). The dimensionless rate Eq. 4 for the system allowing for complex formation (Eq. 7) takes the form (cf. Eq. 5):

$$\frac{\partial x}{\partial \tau} = a - x - 4 \frac{xy}{1 + x^2} + \frac{\partial^2 x}{\partial z^2}$$

$$\frac{\partial y}{\partial \tau} = \sigma \left[b \left(x - \frac{xy}{1 + x^2} \right) + c \frac{\partial^2 y}{\partial z^2} \right]. \quad [8]$$

Fig. 2 shows, for realistic values of the rate parameters and concentrations, the range of diffusion-induced instability at various values of σ . In the absence of starch, c_{\min} is ≈ 10 , while with sufficient starch to give $\sigma = 8$, roughly the conditions employed by Castets *et al.* (4), c_{\min} is reduced to 1.5, a plausible value for the ratio of two small inorganic ions. Even in the absence of starch, the polyacrylamide gel may act as a complexing agent with similar effect.

A Design Algorithm

The above analysis suggests a path toward the elusive goal of designing new systems that exhibit Turing patterns, a path that may already have been followed by many biological systems. By complexing an activator molecule either with a macromolecule or with a membrane-bound species, it becomes possible to obtain Turing structures even when the ratio c of diffusivities of inhibitor and free activator does not exceed unity, if the effective complexation strength K' in Eq. 2 is sufficiently large. Such complexation almost certainly occurs in many living systems, though identification of the activator and inhibitor species is a formidable task.

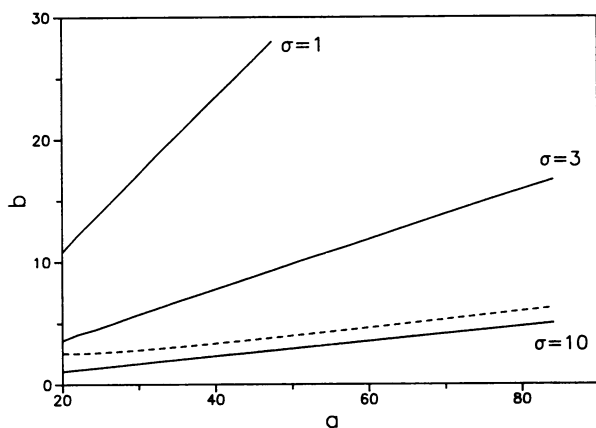


FIG. 2. Stability boundaries at several values of σ for the model of the chlorine dioxide/iodine/malonic acid/starch reaction in the range of chemically accessible parameters. Above the solid Hopf bifurcation curve, $\sigma b = 3a/5 - 25/a$, there is a stable steady state. The region of diffusion-induced instability lies above the solid line and below the dashed Turing bifurcation curve, given by $(3ca^2 - 5ab - 125c)^2 = 100abc(25 + a^2)$. $c = 1.5$.

If one wishes to study Turing patterns, chemical systems with strongly nonlinear dynamics provide more favorable opportunities, since in many cases mechanisms have been worked out and the activator and inhibitor species are reliably known. A simple design (or search) algorithm would start from a system that shows oscillation and in which the activator species, often an autocatalyst, is capable of reversible complex formation. The reaction would be run in a flow reactor with increasing amounts of complexing agent until the oscillatory state gives way to a stable steady state. The

resulting concentrations would then serve as a guide for carrying out experiments in a gel reactor (4).

The situation with respect to the study of Turing structures is similar in many ways to that of oscillating chemical reactions about a decade ago. There is a significant body of theory, but only a very small number of experimental examples, and those have been discovered largely by chance. The introduction of a systematic approach to designing chemical oscillators (12) has yielded several dozen additional experimental examples and many important insights in a relatively short time. The approach outlined above should facilitate similar rapid progress in the study of Turing structures.

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