

Limit cycle oscillations in compartmental chemical systems

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The dynamics of a chemical system which is localized in two compartments between which mass transport occurs at a rate proportional to the difference in chemical concentrations between the two compartments have been studied. Pursuing a problem posed by Smale, we have tried to find a set of reactions such that when the cells are uncoupled there is a single unique stable steady state in each compartment, but when the cells are coupled there is a single unique global limit cycle oscillator in the combined system. We have analyzed open systems far from equilibrium in which there are two reacting chemicals. A linear stability analysis in the region of the homogeneous steady state has been performed for the case in which identical reactions are occurring in both compartments. We have also studied, using both local and global techniques, a class of systems in which different reactions are occurring in each compartment. For this latter class of systems we have been able to find evidence that there can be limit cycle oscillations which require transport in order to be sustained.

I. INTRODUCTION

In recent years there has been a rebirth of interest in periodic processes in chemical systems.¹ This interest has been partially sparked by new demonstrations of oscillations in chemical systems, for example, the periodic bromination of malonic acid in an acid medium,^{2,3} a phenomenon reminiscent of the periodic oxidation of phosphorous⁴ and the Bray reaction.⁵ Also, the physical chemical basis of biochemical oscillations are being intensively studied, using both *in vivo* and *in vitro* preparations.⁶ A fundamental and still poorly understood problem is to determine the way in which diffusion interacts with reactions to generate and sustain oscillations in spatially homogeneous and heterogeneous chemical systems. In the following, we analyze one way in which diffusion can act to destabilize steady states and generate limit cycle oscillations in chemical systems localized in two compartments between which there is diffusive coupling.

A large theoretical literature analyzing periodic chemical systems has been developed. This work stems from an early demonstration by Lotka of the possibility of temporal oscillations in autocatalytic chemical reactions,⁷ and a study by Turing of the properties of chemical systems in which both reaction and diffusion are simultaneously occurring.⁸ Turing demonstrated that homogenous chemical systems can become unstable with respect to concentration fluctuations of finite wavelength and evolve into spatially periodic patterns. This analysis has been extended from the cyclic one-dimensional system considered by Turing, to a number of other geometries.⁹ Since diffusion normally brings about homogeneity there is an element to Turing's result which might appear at first paradoxical. However, Prigogine and co-workers have analyzed these instabilities using nonequilibrium statistical mechanics and developed thermodynamic stability criteria corresponding to the criteria found by Turing.¹⁰⁻¹² In recent work, conditions needed for wave propagation in reaction diffusion systems have also been analyzed.^{13,14} Turing assumed homogeneous reaction kinetics. If this condition is relaxed and the possibility of localized (heterogeneous) catalysis is admitted, then a whole new class of

dynamic phenomena can be predicted. For example, catalysts can act as pacemakers generating propagating waves,^{14,15} and the qualitative dynamics of reacting systems can depend on the geometrical arrangement of the localized catalysts.^{16,17}

In the theoretical work cited, the stability properties of reacting systems in the region of a homogeneous steady state are usually analyzed by linearizing the equations in the neighborhood of the steady state. Such techniques are intrinsically insufficient to give information about the global properties of the dynamics for all regions of concentration space where the complete nonlinear kinetic equations must be considered. The comparative lack of mathematical techniques for analyzing the qualitative properties of these nonlinear systems necessitates doing computer simulation of specific chemical reactions on a digital or analogue computer, and one such scheme, "the Brusselator" has been intensively studied.^{10,12}

The formidable mathematical difficulties encountered in the study of nonlinear reaction-diffusion systems, has lead to the formulation by Smale of the following intriguing problem.¹⁸ Consider two compartments which are open to mass and energy flow and in which chemical reactions are occurring. Let us designate the nonlinear kinetics of N chemical species

$$\begin{aligned} dz_{i1}/dt &= R_{i1}\{\mathbf{z}_1\}, \\ dz_{i2}/dt &= R_{i2}\{\mathbf{z}_2\}, \quad i=1, N \end{aligned} \quad (1.1)$$

where \mathbf{z}_1 and \mathbf{z}_2 are the vectors of concentration in compartments 1 and 2, respectively. If the two compartments are coupled so that mass transport by diffusion occurs at a rate proportional to the concentration differences between the two compartments the resulting system is given by

$$\begin{aligned} dz_{i1}/dt &= R_{i1}\{\mathbf{z}_1\} + D_i(z_{i2} - z_{i1}), \\ dz_{i2}/dt &= R_{i2}\{\mathbf{z}_2\} + D_i(z_{i1} - z_{i2}), \quad i=1, N \end{aligned} \quad (1.2)$$

where D_i is the effective diffusion coefficient for the i th species.¹⁹ It is required to find a set of R_{ij} so that:

- (1) When the two compartments are uncoupled [Eq.

(1.1)] there is a single steady state attractor in each compartment to which all trajectories tend as $t \rightarrow \infty$.

(2) When the two compartments are coupled [Eq. (1.2)] there is a limit cycle attractor to which all trajectories tend as $t \rightarrow \infty$.

(3) Concentrations of chemicals are bounded in a finite positive region of concentration space.

Smale constructed an example in which $R_{i1} = R_{i2}$, $i = 1, N$ where $N = 4$ which displays these properties.¹⁸ The paradoxical nature of the diffusional coupling here is again apparent. Instead of tending to stabilize the dynamics of the coupled system, the effect is to destabilize the system and lead to oscillations. No attempt was made to find a realistic chemical system displaying the proposed kinetics, and no other system for which $R_{i1} = R_{i2}$ displaying these properties is known.

A number of other workers have previously studied the properties of Eq. (1.2) for particular cases of R_{ij} . Turing gave an example of a linear system in which $R_{i1} = R_{i2}$, $i = 1, 2$ which is destabilized by diffusion.⁸ Further, the effects of localization of the "Brusselator" in two compartments coupled by diffusion was studied and the stability properties of the resulting homogeneous and inhomogeneous steady states were analyzed.^{12,20} This work has recently been extended, with particular emphasis on the biological problem of coupling oscillators regulating mitosis.²¹ In other work, Glass and Kauffman gave a system in which $R_{i1} \neq R_{i2}$, $i = 1, 2$ and gave numerical evidence that this system satisfies the three properties cited above.²² The system was based on a mechanism proposed by Jacob and Monod to account for metabolic oscillations.²³

In the following, we study the properties of Eqs. (1.1)–(1.2) when $N = 2$, with particular emphasis on finding oscillatory behavior induced by diffusive coupling in this system. In Sec. II we analyze the qualitative dynamics of Eq. (1.2) for homogeneous reactions, $R_{i1} = R_{i2}$, $i = 1, 2$ in the region of a homogeneous steady state. In Sec. III we relax the condition of identical kinetics in the two compartments and consider the equations proposed by Glass and Kauffman. The steady states for this system with and without diffusive coupling are found, and a linear stability analysis is performed. In Sec. IV a global analysis of a special case of these equations is given and limit cycles are shown. The results are discussed in Sec. V.

II. IDENTICAL KINETICS IN BOTH COMPARTMENTS

In this section we investigate the stability properties of Eq. (1.2) in the region of a homogeneous steady state for identical kinetics in each compartment, $R_{i1} = R_{i2}$, $i = 1, 2$. We employ the methods of linear stability theory which can be used to analyze and classify the dynamic behavior of nonlinear chemical systems in the region of steady states provided the kinetic equations have non-vanishing first order terms in the series expansion around the steady state. The linearized kinetic equations can be represented

$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} \quad (2.1)$$

where \mathbf{x} is a column vector giving the displacement of concentrations from steady state and \mathbf{A} is a matrix giving the linearized equations. The qualitative dynamics are determined by the eigenvalues of the characteristic equation²⁴

$$\det |\mathbf{A} - p\mathbf{I}| = 0 \quad (2.2)$$

where \mathbf{I} is the identity matrix (see Appendix A).

We assume the linearized equations in the region of the steady state for Eq. (1.1) are

$$\begin{aligned} \dot{x} &= ax + by \\ \dot{y} &= cx + dy \end{aligned} \quad (2.3)$$

where we have called the reacting chemicals x and y . The characteristic equation

$$\det \begin{vmatrix} a-p & b \\ c & d-p \end{vmatrix} = 0 \quad (2.4)$$

is solved to give

$$p_{1,2} = \frac{1}{2} \{a + d \pm [(a-d)^2 + 4bc]^{1/2}\} \quad (2.5)$$

For the case in which the two compartments are coupled by diffusion in the neighborhood of the homogeneous steady state corresponding to the steady state of the uncoupled system, the linearized equations for Eq. (1.2) are given by

$$\begin{aligned} \dot{x}_1 &= ax_1 + by_1 + D_x(x_2 - x_1) \\ \dot{y}_1 &= cx_1 + dy_1 + D_y(y_2 - y_1) \\ \dot{x}_2 &= ax_2 + by_2 + D_x(x_1 - x_2) \\ \dot{y}_2 &= cx_2 + dy_2 + D_y(y_1 - y_2) \end{aligned} \quad (2.6)$$

If we introduce the change of variables

$$\begin{aligned} x_+ &= x_1 + x_2 & x_- &= x_1 - x_2 \\ y_+ &= y_1 + y_2 & y_- &= y_1 - y_2 \end{aligned} \quad (2.7)$$

the characteristic equation for this system can be written

$$\det \begin{vmatrix} a-p & b & 0 & 0 \\ c & d-p & 0 & 0 \\ 0 & 0 & a-2D_x-p & b \\ 0 & 0 & c & d-2D_y-p \end{vmatrix} = 0 \quad (2.8)$$

Two of the eigenvalues of this equation are identical to those in the uncoupled system and are given by $p_{1,2}$ in Eq. (2.5). The other two eigenvalues are

$$p_{3,4} = \frac{1}{2} (a + d - 2(D_x + D_y)) \pm \{[(a-d) - 2(D_x - D_y)]^2 + 4bc\}^{1/2} \quad (2.9)$$

We are interested in determining the cases in which diffusion can act to destabilize a steady state in a compartmentalized system. In the present case, we wish to determine if there are any cases in which the real parts of $p_{1,2}$ are both negative and the real parts of at least one of the roots $p_{3,4}$ are positive. If $\text{Re } p_{1,2} < 0$ then $a + d < 0$. Since D_x, D_y are positive definite, if $p_{3,4}$ are complex conjugates, $\text{Re } p_{3,4} < 0$. It is therefore impossible for a Hopf bifurcation (see Appendix A) to occur

for this system. If $p_{3,4}$ are not complex conjugates, there will be a single positive root provided

$$\left\{ [(a-d) - 2(D_x - D_y)]^2 + 4bc \right\}^{1/2} > |a+d - 2(D_x + D_y)| \quad (2.10)$$

Turing gave an example⁸ in which $a=5$, $b=-6$, $c=6$, $d=-7$, $D_x=0.5$, $D_y=4.5$, for which $p_{1,2}=-1$, -1 and $p_{3,4}=2$, -14 . When the two compartments of this system are uncoupled, both reach a single unique steady state. However, if the two compartments are coupled, the homogeneous steady state is unstable. In order to study the dynamics of the system away from the instability, the complete nonlinear kinetics would have to be analyzed.

III. LINEAR ANALYSIS OF A TWO COMPARTMENT OSCILLATOR

In the preceding analysis we have shown that for chemical systems with two chemicals there is no Hopf bifurcation in the region of the homogeneous steady state of Eq. (1.2) if the kinetics are identical in both compartments and if there is a single stable steady state for each compartment when the compartments are uncoupled. However, when the kinetics differ in the compartments, oscillations driven by diffusive transport between the two compartments can be demonstrated. In the remainder of this paper we discuss a class of reaction-diffusion systems based on (but not limited to) a mechanism for feedback regulation of cellular metabolism which was initially posed by Jacob and Monod.^{22,23} The equations we adopt are discrete analogs of the equations proposed previously^{15,16} to describe localized catalysis in continuous systems.

We assume that there are two chemicals, called x and y . Synthesis of x occurs only in compartment 1, and synthesis of y occurs only in compartment 2. The synthesis of each chemical will be assumed to be regulated by the concentration of the other chemical so that the production is given by

$$\begin{aligned} dx_1/dt &= \lambda_x [1 - S_x(y_1)] \\ dy_2/dt &= \lambda_y S_y(x_2) \end{aligned} \quad (3.1)$$

where λ_x , λ_y are production constants and S_x , S_y are non-linear monotonic functions such that

$$\begin{aligned} S_{x,y}(0) &= 0 \quad , \\ S_{x,y}(\infty) &= 1 \quad , \\ dS_{x,y}(z)/dz &> 0 \quad . \end{aligned} \quad (3.2)$$

For example, in many experiments, dependence of synthetic rates is well fit by the phenomenological Hill function (belonging to the class S),

$$f_{\text{Hill}}(z) = z^n / (z^n + \theta^n) \quad , \quad (3.3)$$

where n and θ are positive, definite numbers.^{25,26} In both compartments both x and y decay at rates γ_x , γ_y , respectively, proportional to their concentrations. We assume the system is open and far from equilibrium. The resulting kinetics for this compartmentalized system are then given by²²

$$dx_1/dt = \lambda_x [1 - S_x(y_1)] - \gamma_x x_1 + D_x(x_2 - x_1) \quad ,$$

$$\begin{aligned} dx_2/dt &= -\gamma_x x_2 + D_x(x_1 - x_2) \quad , \\ dy_1/dt &= -\gamma_y y_1 + D_y(y_2 - y_1) \quad , \\ dy_2/dt &= \lambda_y S_y(x_2) - \gamma_y y_2 + D_y(y_1 - y_2) \quad . \end{aligned} \quad (3.4)$$

Since we are interested in displaying oscillatory behavior, we choose a special case of the parameters which facilitate algebraic computations. Assuming

$$\gamma = \gamma_x = \gamma_y, \quad D = D_x = D_y \quad (3.5)$$

and defining

$$\beta = D/\gamma, \quad \tau = \gamma t \quad (3.6)$$

Eq. (3.4) can be rewritten in terms of reduced variables

$$\begin{aligned} \bar{x}_1 &= \frac{x_1}{(\lambda_x/\gamma)}, \quad \bar{y}_1 = \frac{y_1}{(\lambda_y/\gamma)}, \\ \bar{x}_2 &= \frac{x_2}{(\lambda_x/\gamma)}, \quad \bar{y}_2 = \frac{y_2}{(\lambda_y/\gamma)}, \end{aligned} \quad (3.7)$$

to give

$$\begin{aligned} d\bar{x}_1/d\tau &= 1 - S_x[(\lambda_y/\gamma)\bar{y}_1] - \bar{x}_1 + \beta(\bar{x}_2 - \bar{x}_1) \\ d\bar{x}_2/d\tau &= -\bar{x}_2 + \beta(\bar{x}_1 - \bar{x}_2) \\ d\bar{y}_1/d\tau &= -\bar{y}_1 + \beta(\bar{y}_2 - \bar{y}_1) \\ d\bar{y}_2/d\tau &= S_y[(\lambda_x/\gamma)\bar{x}_2] - \bar{y}_2 + \beta(\bar{y}_1 - \bar{y}_2) \quad . \end{aligned} \quad (3.8)$$

When the two compartments are separated, $D=0$, we find the steady state concentrations

$$\bar{y}_2 = \bar{y}_1 = \bar{x}_2 = 0, \quad \bar{x}_1 = 1 \quad (3.9)$$

to which all trajectories tend as $t \rightarrow \infty$. For $D \neq 0$ the equations can be solved for the steady state by setting all derivatives equal to zero. After some algebra we find the steady state is given by the solution of the simultaneous nonlinear equations

$$\begin{aligned} \bar{x}_2 &= [\beta/(1+2\beta)] \{1 - S_x[(\lambda_y/\gamma)\bar{y}_1]\} \\ \bar{y}_1 &= [\beta/(1+2\beta)] \{S_y[(\lambda_x/\gamma)\bar{x}_2]\} \end{aligned} \quad (3.10)$$

from which \bar{x}_1 and \bar{y}_2 can be found from the relations

$$\begin{aligned} \bar{x}_1 &= [(\beta+1)/\beta] \bar{x}_2 \\ \bar{y}_2 &= [(\beta+1)/\beta] \bar{y}_1 \quad . \end{aligned} \quad (3.11)$$

From the conditions of monotonicity on S_x and S_y we find there is one and only one steady state for this system.

The linearized stability criteria in the neighborhood of this steady state can now be evaluated. Defining

$$\left. \frac{\partial S_x}{\partial y_1} \right|_{s.s.} = \omega_x, \quad \left. \frac{\partial S_y}{\partial x_2} \right|_{s.s.} = \omega_y \quad (3.12)$$

we find the characteristic equation of the linearized system

$$\det \begin{vmatrix} -1 - \beta - p & \beta & -\omega_x & 0 \\ \beta & -1 - \beta - p & 0 & 0 \\ 0 & 0 & -1 - \beta - p & \beta \\ 0 & \omega_y & \beta & -1 - \beta - p \end{vmatrix} = 0 \quad . \quad (3.13)$$

Expanding the determinant we compute

$$(1 + \beta + p)^4 - 2\beta^2(1 + \beta + p)^2 + \beta^4 + \beta^2\omega_x\omega_y = 0. \quad (3.14)$$

Equation (3.14) can be solved for the four roots

$$\begin{aligned} p_{1,2} &= -(\beta + 1) - [\beta(\omega_x\omega_y)^{1/2}/2\phi] \pm i\phi \\ p_{3,4} &= -(\beta + 1) + [\beta(\omega_x\omega_y)^{1/2}/2\phi] \pm i\phi, \end{aligned} \quad (3.15)$$

where

$$\phi = (\beta/\sqrt{2}) \{-1 + [1 + (\omega_x\omega_y/\beta^2)]^{1/2}\}^{1/2}. \quad (3.16)$$

The real parts of $p_{1,2}$ are always less than zero. However, the real parts of $p_{3,4}$ can either be positive or negative, and the locus along which the values change is found by solving

$$2(\beta + 1)\phi = \beta(\omega_x\omega_y)^{1/2}. \quad (3.17)$$

Calling

$$\eta^2 = \beta^2 + \omega_x\omega_y \quad (3.18)$$

and substituting in Eq. (3.17) we find after some simplification

$$(2/\beta)^{1/2}(1 + \beta) = (\beta + \eta)^{1/2}. \quad (3.19)$$

From this we can compute the curve that separates the stable from the unstable region

$$\omega_x\omega_y = (4/\beta^2) + (16/\beta) + 20 + 8\beta. \quad (3.20)$$

The two stability regimes are indicated in Fig. 1.²⁷ We note that although our initial problem Eq. (3.8) is given in terms of four parameters $\lambda_x, \lambda_y, \gamma, D$ and two nonlin-

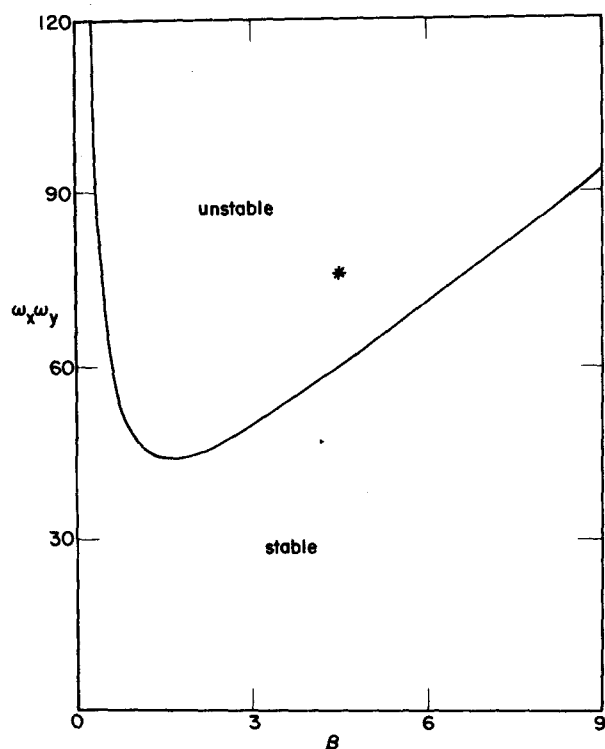


FIG. 1. The two stability regions found when Eq. (3.4) is linearized at the steady state. The curve which separates the stable and unstable regions is given in Eq. (3.20). The asterisk gives the value of $\omega_x\omega_y$ at steady state when the parameters in Eq. (4.1), are substituted in Eq. (3.4).

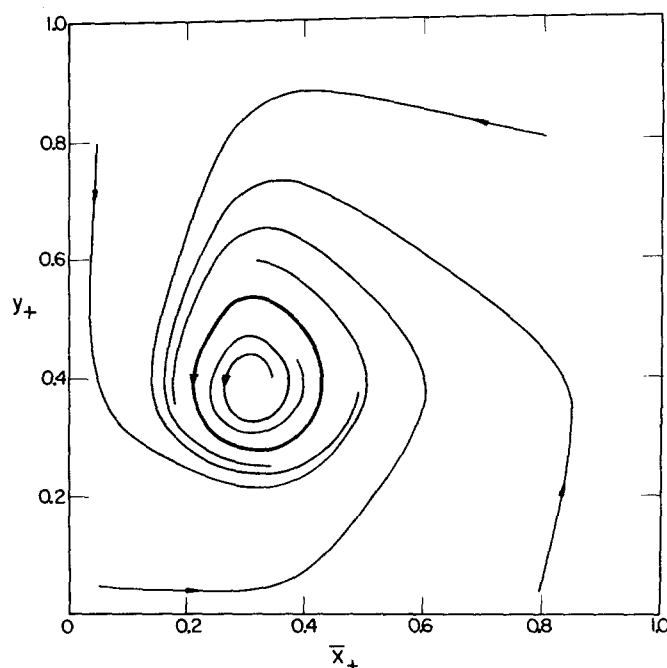


FIG. 2. A two dimensional representation of Eq. (3.4) found by numerically integrating the equation using the parameters of Eq. (4.1). Each trajectory starts from an initially homogeneous state.

ear functions, S_x, S_y , the stability criteria of the linearized equation in the neighborhood of the steady state can be given in a two dimensional space. For any value of β , the steady state can be destabilized by arbitrarily increasing the slope of either S_x or S_y in the region of the steady state.

IV. GLOBAL ANALYSIS OF A TWO COMPARTMENT OSCILLATOR

In the preceding section we have given local results. Nothing has yet been said about the dynamics in the non-linear regime away from the steady state. However, computer simulation shows global limit cycle oscillations in this regime. In Fig. 2 we display the kinetics found by numerically integrating Eq. (3.4) for the parameters

$$\begin{aligned} \beta &= 4.5 \quad (\lambda_x/\gamma) = (\lambda_y/\gamma) = 5 \\ S_x(z) &= S_y(z) = [z^6/(\theta^6 + z^6)] \quad \theta = 0.75. \end{aligned} \quad (4.1)$$

The linearized steady state for this system falls well inside the region of instability shown in Fig. 1, and is indicated by an asterisk. No general technique for global analysis was found for Eq. (3.4). However, by selecting a special case of these equations limit cycle behavior can be shown. For convenience, we assume $\lambda_x = \lambda_y = \lambda$ and $\lambda/\gamma = \alpha$.

In similar fashion to Sec. II, we define the new variables

$$\begin{aligned} \bar{x}_+ &= \bar{x}_1 + \bar{x}_2, \quad \bar{x}_- = \bar{x}_1 - \bar{x}_2, \\ \bar{y}_+ &= \bar{y}_1 + \bar{y}_2, \quad \bar{y}_- = \bar{y}_2 - \bar{y}_1. \end{aligned}$$

Equation (3.8) can now be rewritten in terms of these

new variables. We designate the plus and negative variables by the subscript i and write

$$\begin{aligned}\frac{d\bar{x}_i}{d\tau} &= 1 - S_x \left[\alpha \left(\frac{\bar{y}_+ - \bar{y}_-}{2} \right) - \bar{x}_i \right] - \tau_i \\ \frac{d\bar{y}_i}{d\tau} &= S_y \left[\alpha \left(\frac{\bar{x}_+ - \bar{x}_-}{2} \right) - \bar{y}_i \right] - \tau_i\end{aligned}\quad (4.3)$$

$$\tau_+ = 1, \quad \tau_- = 1/(1 + 2\beta) .$$

In a previous study, the dependence of the qualitative properties of Eq. (4.3) was studied as a function of S .²² By numerically integrating this equation it was found that, in at least a limited region of parameter space, the existence, phase relations, and period of the limit cycle oscillation found for this equation were not sensitive to changes in the control function S , from the Hill function, to the error function, to the discontinuous Heaviside function

$$\begin{aligned}S(w) &= H(w - \theta) = 1 \quad w \geq \theta \\ S(w) &= H(w - \theta) = 0 \quad w < \theta\end{aligned}\quad (4.4)$$

We choose to consider the special case of step function control [Eq. (4.4)] where we require

$$\theta < \alpha\beta/(1 + 2\beta) . \quad (4.5)$$

With these assumptions, Eq. (4.3) becomes piecewise linear, and starting from any initial condition can be integrated exactly. The solutions can be written as

$$\begin{aligned}\bar{x}_i(\tau) &= \bar{x}_i(0) e^{-\tau/\tau_i} + \tau_i \left(1 - H \left\{ \alpha \left[\frac{\bar{y}_+(\tau) - \bar{y}_-(\tau)}{2} \right] - \theta \right\} \right) (1 - e^{-\tau/\tau_i}) \\ \bar{y}_i(\tau) &= \bar{y}_i(0) e^{-\tau/\tau_i} + \tau_i H \left\{ \alpha \left[\frac{\bar{x}_+(\tau) - \bar{x}_-(\tau)}{2} \right] - \theta \right\} \\ &\quad \times (1 - e^{-\tau/\tau_i}) \quad i = +, -\end{aligned}\quad (4.6)$$

Here the initial values are first assumed. The concentrations of each variable is then given in terms of these values until the step function of one of the variables crosses a threshold for production. This determines a new set of initial values. This process is iterated until a steady state or cycle is reached. We have been unable to find any analytic techniques which can be used to study the qualitative properties of the solutions of Eq. (4.6). We therefore make the additional assumption, $\beta \gg 1$.

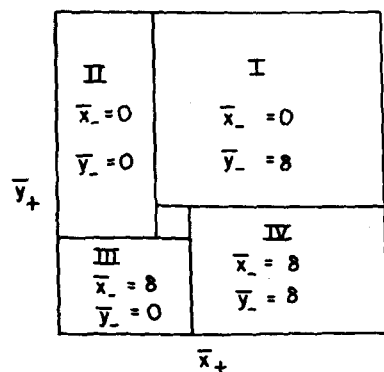


FIG. 3. The four regions of phase space found when $\beta \gg 1$ and there is discontinuous Heaviside step function modulation of production (see text).

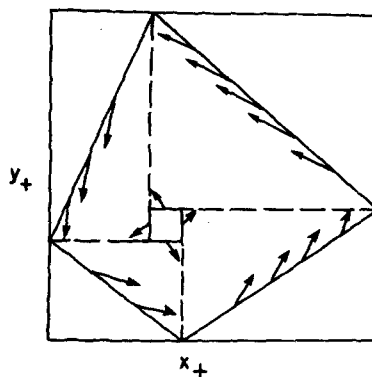


FIG. 4. Figure 3 redrawn with diagonal bisectors included in each region. All trajectories defined by Eq. (4.7) enter the region bounded by the central square and the diagonal bisectors.

This assumption introduces two distinct time scales in the solution of Eq. (4.3). The variables \bar{x}_+ , \bar{y}_+ change at a rate which is rapid in comparison to changes in \bar{x}_- , \bar{y}_- . Physically this corresponds to a fast diffusion limit in comparison with the slower synthetic processes and should be applicable to systems of the size of cellular systems in biology (10^{-6} m).

The solutions can now be considered in the two dimensional \bar{x}_+ , \bar{y}_+ phase plane. The $\beta \gg 1$ limit allows relaxation of the \bar{x}_- , \bar{y}_- variables to their constant limits before \bar{x}_+ , \bar{y}_+ have changed. We can consider in the phase space, a two dimensional surface which is decomposed into four regions, where the trajectory in each region is the straight line found by simultaneously solving Eq. (4.6) for \bar{x}_+ , \bar{y}_+ . In each region the trajectory is given by

$$\frac{\bar{y}_+(0) - \bar{y}_+(\infty)}{\bar{x}_+(0) - \bar{x}_+(\infty)} = \frac{\bar{y}_+(\tau) - \bar{y}_+(\infty)}{\bar{x}_+(\tau) - \bar{x}_+(\infty)} , \quad (4.7)$$

where the asymptotic values $\bar{x}_+(\infty)$, $\bar{y}_+(\infty)$ differ in each region. Calling $\bar{\theta} = \theta/\alpha$ and $\delta = 1/(1 + 2\beta)$, the four regions can then be given:

Region I. $\bar{x}_- = 0, \bar{y}_- = \delta; 1 \geq \bar{x}_+ \geq 2\bar{\theta}, 1 \geq \bar{y}_+ \geq 2\bar{\theta} + \delta;$
 $\bar{x}_+(\infty) = 0, \bar{y}_+(\infty) = 1.$

Region II. $\bar{x}_- = 0, \bar{y}_- = 0; 2\bar{\theta} > \bar{x}_+ > 0, 1 > \bar{y}_+ \geq 2\bar{\theta};$
 $\bar{x}_+(\infty) = 0, \bar{y}_+(\infty) = 0.$

Region III. $\bar{x}_- = \delta, \bar{y}_- = 0; 2\bar{\theta} + \delta > \bar{x}_+ > 0, 2\bar{\theta} > \bar{y}_+ > 0;$
 $\bar{x}_+(\infty) = 1, \bar{y}_+(\infty) = 0.$

Region IV. $\bar{x}_- = \delta, \bar{y}_- = \delta; 1 \geq \bar{x}_+ \geq 2\bar{\theta} + \delta, 2\bar{\theta} + \delta > \bar{y}_+ > 0.$
 $\bar{x}_+(\infty) = 1, \bar{y}_+(\infty) = 1.$

The four regions are indicated in Fig. 3. For any point in each region there passes a single trajectory that is a straight line directed from this point to $\bar{x}_+(\infty)$, $\bar{y}_+(\infty)$. There are consequently no steady states in any of these regions. In Fig. 4 we have redrawn Fig. 3 but included diagonal bisectors in each of the regions. Consider the trajectories on the border of the planar region bounded by the central square and the diagonal bisectors. By the construction described, the trajectories along this

border can be drawn and are shown in Fig. 4. Since all trajectories enter the planar region, there is a limit cycle attractor in this region by application of the Poincaré-Bendixson theorem.²⁸ Starting from any initial point in the planar region, the trajectory can be traced out as a sequence of straight lines in the \bar{x}_+ , \bar{y}_+ phase plane. In Fig. 5 we show this construction for the parameters in Eq. (4.1). With the exception of the central point, the same initial values used in Fig. 2 are assumed. Comparison of Figs. 2 and 5 gives an indication of the comparative insensitivity of the qualitative dynamics of Eq. (4.3) to the strong assumptions used to compute Fig. 5. An algebraic demonstration that there is a unique limit cycle attractor in the piecewise linear system is given in Appendix B.

V. DISCUSSION

In the preceding we have studied the kinetics of systems of two reacting chemicals localized in two compartments between which diffusion can take place. Our purpose has been to determine conditions of the reaction kinetics such that oscillations occur when the two compartments are coupled by diffusion, but do not occur when the compartments are not coupled. We have shown that for identical reaction kinetics in each compartment, there is no Hopf bifurcation in the region of the homogeneous steady state. However, if the kinetics are different in both compartments, it is possible to find chemical systems which are destabilized by diffusion and evolve to asymptotic limit cycles, and a large class of kinetic equations which display this behavior have been presented. Although the kinetic equations we have analyzed were based on a hypothetical mechanism proposed by Jacob and Monod as a basis of cellular oscillations,²³ to our knowledge, no natural or synthetic chemical system displaying the kinetics of Eq. (3.4) have yet been analyzed. It is our hope that the present analysis will facilitate the identification of natural systems whose kinetics correspond to these equations.

It is possible that the mechanism we have analyzed will provide at least a partial basis for understanding diverse biological oscillations. Compartmentalization of functions and metabolites is a ubiquitous phenomenon in biological systems. For example, at a cellular level there are nuclei, mitochondria, ribosomes, golgi bodies, and cells themselves. Further, the monotonic cooperative response to metabolites which we have assumed, the Hill function, has been observed in a large number of enzyme and gene systems.^{25,26} A mechanism similar to the one described here has been proposed as a possible basis for glycolysis in mitochondria.²⁹ It is interesting to note that there is a formal similarity between Eq. (3.4) and kinetic equations proposed to study ecological systems in which species migrate between geographically separated islands.³⁰

In Lotka's early study of oscillations,⁷ an autocatalytic step $A + X \rightarrow 2X$, played a key role in generating the oscillations. In recent studies, the importance of autocatalysis (or cross catalysis, in which two chemical species mutually catalyze each other's synthesis) as a basis for generating oscillations has been stressed.^{11,12}

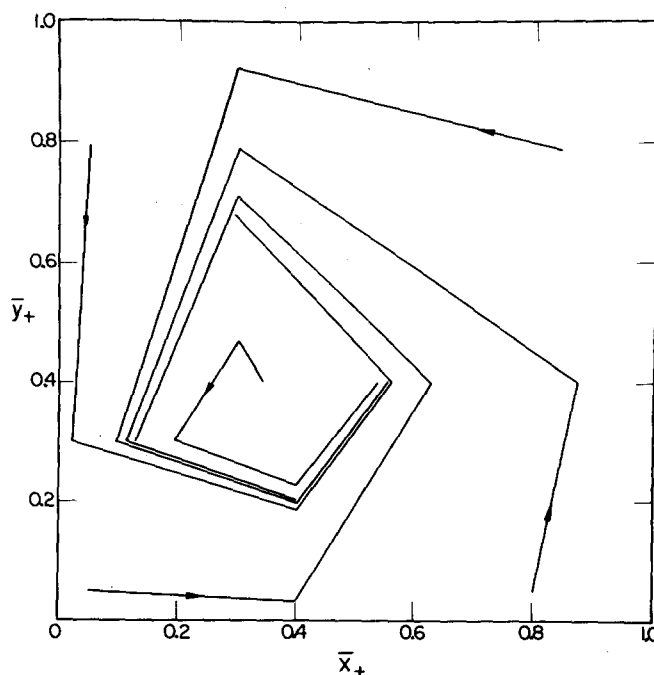


FIG. 5. The construction of the trajectories in the \bar{x}_+ , \bar{y}_+ plane for the piecewise linear approximation to Eq. (3.4). All parameters used are the same as Eq. (4.1).

In our compartmentalized system [Eq. (3.4)] there are no auto- or cross-catalytic steps. The feedback and time delays introduced by diffusion are sufficient to generate oscillations in this system.³¹ Further, although it is necessary that the diffusion coefficients of chemical species be unequal to generate the sorts of instabilities considered by Turing and Prigogine, for our system the diffusion coefficients of both chemical species are equal.

Although we have limited ourselves to the study of oscillations induced by diffusional coupling in an idealized compartmental model, there are experimental systems in which it has been shown that both reaction and transport processes must be considered to determine the stability of oscillations. In a study of electrochemical oscillations examples were given in which stable oscillations were found only when the electrochemical cell was not stirred.³² If the cell was rapidly stirred the oscillations damped out. Further in his recent studies of oscillation in the Zhabotinsky-Belousov reaction, Winfree has shown that for one set of initial conditions (the "Z" reagent) the reaction will not oscillate spontaneously but is excitable and is capable of supporting travelling waves of concentration. A consequence of this is that if no pacemaker heterogeneities are initially present there are at least two stable modes for reactions in two dimensional simply connected systems, a homogeneous nonoscillatory reaction and a rotating spiral reaction.³ Theoretical analysis of the stability of the latter behavior requires consideration of both reaction and diffusion.

In Sec. IV we have made stringent assumptions concerning the parameters in Eq. (3.4) in order to demonstrate limit cycle oscillations in the resulting systems. These assumptions were motivated by our desire to find

a suitable approximation which is tractable for analysis but which appears to preserve the important qualitative features of the original system. We have found no technique which can be used to analyze the qualitative dynamics of the original system. Although our computations for the model system, taken in conjunction with the numerical analysis give convincing evidence that the equations support global limit cycle oscillations, no proof of this conclusion has been found. In the analysis, the continuous nonlinear Hill functions were approximated by discontinuous Heaviside functions. The resulting oscillations strongly resemble the sort of dynamic behavior which is found in discrete networks.³³ Indeed, it is common for molecular biologists to speak of genes being "switched on" or "switched off" and evidence of switchlike behavior has recently been found for the oscillating Zhabotinsky-Belousov reaction.³⁴ The observation of switchlike behavior in natural systems, should allow chemists to synthesize systems displaying the kinetics proposed here, or even more complex kinetics in which reactions between chemicals synthesized at several localized sites can occur.

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APPENDIX A: THE HOPF BIFURCATION

Let $\dot{\mathbf{x}} = f^\mu(\mathbf{x})$ be an autonomous system of differential equations depending on a parameter μ and let \mathbf{x}_0 be a stationary or critical point, defined by

$$F^\mu(\mathbf{x}_0) = 0 \quad (\text{A1})$$

The matrix of the linearization of the system in the region of the critical point is given by

$$a_{ij}^\mu = \left. \frac{\partial f_i^\mu}{\partial x_j} \right|_{\mathbf{x}=\mathbf{x}_0} \quad (\text{A2})$$

The eigenvalues of this matrix, which depend on the parameter μ , will characterize the solutions in a neighborhood of the singularity. If all the real parts of the eigenvalues are negative, the critical point is stable, and if one or more of them are positive, the critical point is unstable. If for some values of μ , say $\mu < \mu_n$, the critical point is stable, and if a pair of complex conjugate eigenvalues $p_1(\mu)$, $p_2(\mu)$ crosses the imaginary axis transversely when $\mu = \mu_n$,

$$\left. \frac{d \operatorname{Re} p_1(\mu)}{d\mu} \right|_{\mu=\mu_n} \neq 0,$$

we say that a Hopf bifurcation takes place at the value $\mu = \mu_n$. If a Hopf bifurcation occurs in a system of autonomous differential equations, then there exists a family of periodic solutions of the system in a neighborhood of the critical point. This important theorem, first stated by Hopf has recently been applied in a number of studies of oscillations and instability in chemical and physical systems.^{13,35,36} It is a local result, and says nothing about the dynamics away from the Hopf bi-

furcation.

APPENDIX B: CONTRACTION MAPPING ANALYSIS OF THE TWO CELL OSCILLATOR

An analytical proof that the phase plane trajectories defined by Eq. (4.7) give a unique stable limit limit cycle oscillation can be given. A map f of a closed subset E of a Banach space into itself is called a contraction map if there exists a real number $0 \leq k < 1$, such that for any two points $p, q \in E$ the inequality

$$d[f(p), f(q)] < kd[p, q] \quad (\text{B1})$$

is satisfied where $d[a, b]$ designates the distance between a and b .³⁷ If f is a contraction map, then it can be shown

(1) There exists a unique fixed point $P \in E$ such that $f(P) = P$.

(2) If p_0 is any point of E and $p_1 = f(p_0)$, $p_2 = f(p_1) \dots p_n = f(p_{n-1})$, then $\lim_{n \rightarrow \infty} p_n = P$.

In the present case we consider the mapping f , which takes a point, initially on the border of regions I and II, Fig. 3, and generates the position of the point on the borders of regions I and II after one complete circuit around the four regions of the phase space. If f is a contraction map, then starting from any initial point on the border of regions I and II, a unique trajectory will be reached which passes through the fixed point of the mapping on the border between regions I and II. This trajectory is the limit cycle.

Consider any two points p, q , where $d[p, q] = l$, on the border between regions I and II. By applying Eq. (4.7) in region II, it is readily shown that the distance between the images of these points on the border between regions II and III is smaller than $4\theta^2 l / (2\theta + \delta)^2$. Similarly, after iteration of the equation through the remaining regions we find

$$d[f(p), f(q)] < \frac{(2\theta)^4 (1 - 2\theta - \delta)^4}{(2\theta + \delta)^4 (1 - 2\theta)^4} l \quad (\text{B2})$$

Since δ is a positive definite finite number, the inequality (B1) holds and f is a contraction map. This proves that a unique limit cycle attractor exists, and is a stronger result than was found in Sec. IV.

It is possible to compute analytically the fixed point on one of the boundaries by iterating the equations through the four regions, and requiring that the coordinates of the initial point are the same as the coordinates of the point generated after one cycle. Since the computations for arbitrary θ, δ are involved algebraically we consider a special case which clearly illustrates the geometric properties involved. Assume $\theta = 0.4$, $\delta = 0.2$. For this case the vector field is invariant to rotations about the point $(0.5, 0.5)$ of $n\pi/2$ radians where n is an integer. Assume that the coordinates of the point on the border between regions I and II are $(0.4, 1 - \epsilon)$ and that the coordinates of the point generated after iteration through region II are $(x_1, 0.4)$. If there exists an ϵ in the range $0 \leq \epsilon \leq 0.4$ such that $x_1 = \epsilon$, then by the symmetry of the vector field, $(0.4, 1 - \epsilon)$ will be the fixed point of the map after one cycle and the limit cycle at-

tractor will pass through it. By applying Eq. (4.7) in region II we find $\epsilon^2 - \epsilon + 0.16 = 0$ which has the solution $\epsilon = 0.2$. The reader can confirm by construction that the sequence of points (0.4, 0.8), (0.2, 0.4), (0.6, 0.2), (0.8, 0.6), (0.4, 0.8)... which are generated by the procedure described fall on the limit cycle attractor for this system.

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¹For an early review, see E. S. Hedges and J. E. Myers, *The Problem of Physicochemical Periodicity* (Arnold, London, 1926) and for a recent review see G. Nicolis and J. Portnow, *Chem. Rev.* **73**, 365 (1973).

²A. N. Zaikin and A. M. Zhabotinsky, *Nature* **225**, 535 (1970).

³A. T. Winfree, *Science* **175**, 634 (1972); **181**, 137 (1973);

"Rotating Solutions to Reaction/Diffusion Equations in Simply Connected Media," to appear in SIAM-AMS Proceedings, Vol. 8, *Chemical and Biochemical Problems and Quantum Chemistry*, edited by D. S. Cohen (American Mathematical Society, Providence, RI, 1974).

⁴R. J. S. Rayleigh, *Proc. R. Soc. A* **99**, 372 (1921).

⁵W. C. Bray, *J. Am. Chem. Soc.* **43**, 1262 (1921).

⁶*Biochemical Oscillators*, Proceedings of the 1968 Prague Symposium, edited by E. K. Pye and B. Chance (Academic, New York, 1973).

⁷A. J. Lotka, *J. Am. Chem. Soc.* **42**, 1595 (1920).

⁸A. M. Turing, *Philos. Trans. R. Soc. Lond. B* **237**, 37 (1952).

⁹J. I. Gmitro and L. E. Scriven in *Intracellular Transport*, edited by K. B. Warren (Academic, New York, 1966); H. Othmer and L. Scriven, *J. Theor. Biol.* **32**, 507 (1971).

¹⁰P. Glansdorff and I. Prigogine, *Thermodynamics of Structure, Stability and Fluctuations* (Interscience, New York, 1971).

¹¹I. Prigogine and G. Nicolis, *J. Chem. Phys.* **46**, 3542 (1967).

¹²I. Prigogine and R. Lefever, *J. Chem. Phys.* **48**, 1695 (1968).

¹³N. Kopell and L. N. Howard, *Stud. Appl. Math.* **52**, 291 (1973).

¹⁴P. Ortoleva and J. Ross, *J. Chem. Phys.* **60**, 5090 (1974).

¹⁵P. Ortoleva and J. Ross, *J. Chem. Phys.* **58**, 5673 (1973).

¹⁶R. M. Shymko and L. Glass, *J. Chem. Phys.* **60**, 835 (1974).

¹⁷K. Bimpong-Rota, P. Ortoleva, and J. Ross, *J. Chem. Phys.* **60**, 3124 (1974).

¹⁸S. Smale, "A Mathematical Model of Two Cells via Turing's

Equation," in *Some Mathematical Questions in Biology*, Vol. 6, edited by J. Cowan (American Mathematical Society, Providence, RI, to be published).

¹⁹These are the equations for the "box diffusion model" first used by Turing⁸ and Prigogine and Lefever¹². The concentrations in boxes 1 and 2 are assumed homogeneous so that the net flux, $J(\text{gm}/l^2\tau^{-1})$ from box 2 to box 1 is given by $J = D_i'(z_{i2} - z_{i1})$, where $D_i'(l\tau^{-1})$ is a constant which must be experimentally measured. The rate of change in concentration in box 1 is therefore $JA/V_1 = D_i'(z_{i2} - z_{i1})$, where A is the area between the boxes and V_1 is the volume of box 1. We call $D_i(\tau^{-1})$ the effective diffusion coefficient and we assume $V_2 = V_1$ (also see Refs. 20, 21).

²⁰R. Lefever, *Bull. Cl. Sci. Acad. R. Belg.* **54**, 712 (1968); *J. Chem. Phys.* **49**, 4977 (1968).

²¹J. J. Tyson and S. A. Kauffman, "Control of Mitosis by a Continuous Biochemical Oscillation: Synchronization; Inhomogeneous Oscillation," *J. Math. Biol.*, (to be published).

²²L. Glass and S. A. Kauffman, *J. Theor. Biol.* **34**, 219 (1972).

²³J. Monod and F. Jacob, *Cold Spring Harbor Symp. Quant. Biol.* **25**, 389 (1961).

²⁴See, for example, R. Bellman, *Stability Theory of Differential Equations* (McGraw Hill, New York, 1953).

²⁵J. Monod, J. Wyman, and J. Changeux, *J. Mol. Biol.* **12**, 88 (1965).

²⁶G. Yagil and E. Yagil, *Biophys. J.* **11**, 11 (1971).

²⁷Similar results have been obtained by Professor N. Kazarinoff and co-workers, N. Kazarinoff (private communication).

²⁸See, for example, S. Lefshetz, *Differential Equations: Geometric Theory* (Interscience, New York, 1963), 2nd ed.

²⁹H. D. Thames, *J. Theor. Biol.* **41**, 331 (1973); unpublished results.

³⁰S. A. Levin, *Am. Naturalist* **108**, 207 (1974).

³¹For examples of oscillations in negative feedback systems with homogeneous reaction kinetics see B. Goodwin, *The Temporal Organization in Cells* (Academic, London, 1963); C. F. Walter, *J. Theor. Biol.* **27**, 259 (1970); G. Nicolis and J. Portnow, Ref. 1.

³²J. Wojtowicz and B. E. Conway, *J. Chem. Phys.* **52**, 1407 (1970).

³³L. Glass and S. A. Kauffman, *J. Theor. Biol.* **39**, 103 (1973).
³⁴R. J. Field and R. M. Noyes, *J. Chem. Phys.* **60**, 1877 (1974).

³⁵D. Ruelle and F. Takens, *Commun. Math. Phys.* **20**, 167 (1971).

³⁶D. Ruelle, *Ann. N.Y. Acad. Sci.* **35**, 66 (1973).

³⁷See, for example, M. Rosenlicht, *Introduction to Analysis* (Scott Foresman, Glenview, IL, 1968), p. 171.