

# Mechanisms of Chemical Oscillators: Conceptual Bases<sup>1</sup>

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Oscillations are familiar phenomena in mechanical systems and in electric circuits. Direction of motion of an object or an electric current may repeatedly reverse itself with or without damping of the amplitude of oscillation, and repetitive standing or traveling waves may be generated in a continuous medium. Chemical systems are less prone to oscillation, and their evolution usually leads to monotonic change of chemical parameters.

However, it is well established that oscillation does occur in some purely chemical systems. Figures 1 and 2 illustrate coupled temporal oscillation in the concentrations of intermediates in two different homogeneous (well-stirred) systems. Closely related to temporal oscillation is the development of spatial patterns of intermediate concentrations in an unstirred medium such as is illustrated in Figure 3. Both phenomena will be discussed in this Account.

Oscillations have also been observed during homogeneous gas reactions.<sup>3</sup> Living organisms exhibit many processes like heart beats or nerve impulses that generate repetitive temporal or spatial changes. The mechanisms and energy sources driving these biological processes are ultimately chemical in nature, and the dynamics of many biological and chemical oscillators are likely to contain analogous features.

Previous reviews<sup>4</sup> discuss in depth the theoretical and practical aspects of oscillation in chemical and biological systems. This Account is narrower in scope, though perhaps broader in the audience addressed.

We shall discuss general aspects of chemical oscillators using a specific model to illustrate some important concepts concerning the theory of chemical oscillators. This model seems to contain the essential

features of the switching mechanism common to the two chemical oscillators whose mechanisms are presently well understood. While we feel that this model will be found to be representative of a large and important class of chemical and biological oscillators, we do not intend to exclude the possibility that other as yet unknown chemical oscillators may have qualitatively quite different mechanisms. In a later Account<sup>5</sup> we shall discuss in detail several examples of well-characterized chemical oscillators and shall show how this model relates to known mechanisms.

Although mechanical, electrical, and chemical systems are all susceptible to oscillation, chemical oscillators differ from the others in important ways. In a frictionless (conservative) oscillating mechanical system, the sum of potential and kinetic energies remains constant while they are repeatedly interconverted. Although total energy is sufficient to define the repetitive trajectory in such a conservative system, both a coordinate and a momentum must be stated simultaneously to define the instantaneous state. Inertia repeatedly carries the system through the position of minimum potential energy to which it will eventually decay if any friction is present.

In an electrical oscillator the voltage and the current behave very much like potential and kinetic energies, respectively, and both must be specified to define the instantaneous state. If there is no external source of power, the oscillations repeatedly carry the voltage through the value to which the system eventually decays; the overshoot arises because induction associated with the current behaves very much like mechanical inertia.

In a closed chemical system at constant temperature and pressure, the Gibbs free energy is somewhat analogous to a potential energy in a mechanical or electrical system. However, both the instantaneous state and its rate of change in a homogeneous chemical system are uniquely defined by specifying the activities of all chemical species and the dynamic laws of the system. Therefore, there is no dynamic property like a momentum or current that can be specified inde-

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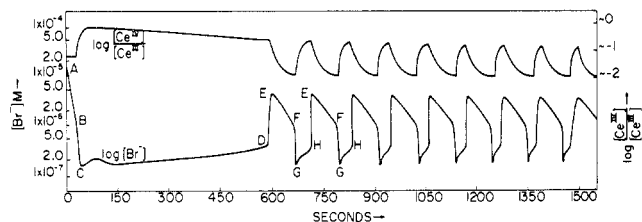
(1) Paper No. 18 in the series Oscillations in Chemical Systems. Paper No. 17 is S. Barkin, M. Bixon, R. M. Noyes, and K. Bar-Eli, *Int. J. Chem. Kinetics*, in press.

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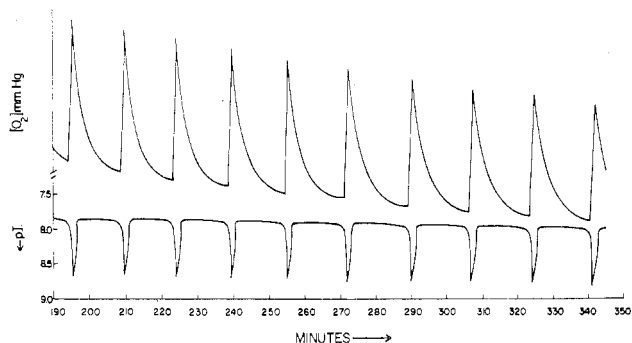
(3) P. Gray, J. F. Griffiths, and R. J. Moule, *Faraday Symp. Chem. Soc.*, 9, 103 (1974), and references therein.

(4) (a) G. Nicolis, *Adv. Chem. Phys.*, 19, 209 (1971); (b) G. Nicolis and J. Portnow, *Chem. Rev.*, 73, 365 (1973); (c) R. M. Noyes and R. J. Field, *Annu. Rev. Phys. Chem.*, 25, 95 (1974).

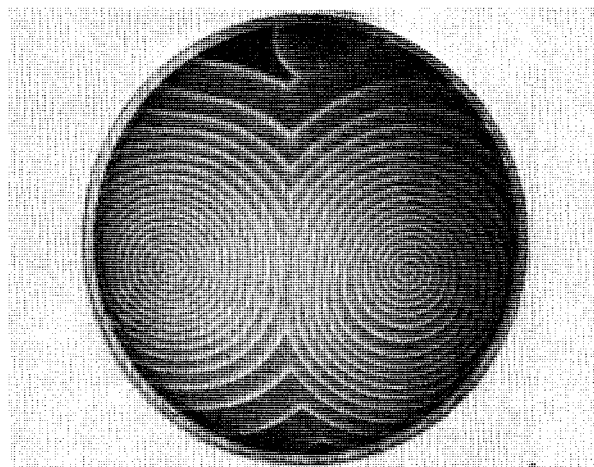
(5) R. M. Noyes and R. J. Field, *Acc. Chem. Res.*, in press.



**Figure 1.** Potentiometric traces at room temperature of a bromide-sensitive electrode (lower curve) and of a tungsten electrode (upper curve) that responded to cerium(IV). The 0.8 M sulfuric acid solution contained malonic acid, potassium bromate with a small amount of bromide, and a cerium(III) catalyst (from ref 8).



**Figure 2.** Potentiometric traces at 50 °C of an iodide-sensitive electrode (lower curve) and of an oxygen-sensitive electrode (upper curve). Solution contained hydrogen peroxide, potassium iodate, and perchloric acid. Amplitude of oxygen oscillations was not calibrated exactly but corresponds to about 300 Torr in equivalent saturation pressure (from K. R. Sharma and R. M. Noyes, *J. Am. Chem. Soc.*, **97**, 202 (1975)).



**Figure 3.** Pattern of rotating spiral bands in a thin layer of solution prepared from sodium bromate, sodium bromide, malonic acid, ferrous phenanthroline, and sulfuric acid according to the composition of ref 29a (courtesy of Professor Arthur T. Winfree of Purdue University).

pendently of the free energy of a chemical system and that can be coupled to it conservatively and reversibly. Chemical change in a closed system leads irreversibly to entropy increase and/or heat evolution. A chemical system resembles a pendulum subject to such severe viscous damping that the momentum is always negligibly small; specification of a coordinate is sufficient to determine direction of change, and overshoot of the final equilibrium position is impossible.

Once a chemical system has attained exactly its equilibrium configuration, each dynamic process occurs

at the same rate in both the forward and the reverse directions, and there is no further spontaneous change. Furthermore, the Onsager relations guarantee that the equilibrium configuration is stable to small perturbations and that the final approach to equilibrium will be monotonic. Thus an oscillatory trajectory in a closed chemical system cannot pass through the point where all coordinates simultaneously have their ultimate equilibrium value the way the trajectories of mechanical and electrical oscillators may.

Because mechanical and electrical oscillators often oscillate through their ultimate equilibrium positions, and because such oscillation is absolutely forbidden to chemical systems, many chemists have tacitly assumed that chemical oscillators are impossible. However, the Onsager relations only demand that the final approach to equilibrium be monotonic. Prigogine<sup>6</sup> was one of the first to point out that oscillations are in fact possible for some chemical systems provided they are far enough from equilibrium. In far-from-equilibrium chemical systems it is intermediate or catalyst species that oscillate around pseudo-steady-state values as the free energy of the system monotonically decreases. Even for these species, however, the final approach to equilibrium is monotonic.

Innumerable hypothetical mechanisms might lead to oscillation in systems sufficiently far from equilibrium. Many features will undoubtedly be common to most or all that are chemically plausible, but theories have not yet developed enough to say that all possibilities have been considered. We shall discuss here a particularly simple model and shall then try to generalize from it concerning the probable requirements of other oscillator models.

### A Model of a Temporal Chemical Oscillator

The Oregonator model<sup>7</sup> of five irreversible chemical steps shows how a chemical system might oscillate. This model was developed to describe the mechanism of the cerium ion catalyzed oxidation of malonic acid by bromate,<sup>5,8</sup> but we believe it illustrates principles that will be applicable to other systems not yet elucidated. Tyson<sup>9</sup> has discussed the Oregonator in much more detail and from a somewhat different viewpoint than is adopted here. The model is



Because all of the steps are irreversible, the free energy of the model system is indefinitely far removed from its equilibrium value. Species A and B are irreversibly consumed, and P and Q are irreversibly produced. A stoichiometric factor is denoted by  $f$ . The species X, Y, and Z are both consumed and produced,

(6) (a) I. Prigogine and G. Nicolis, *J. Chem. Phys.*, **46**, 3542 (1967); (b) P. Glansdorff and I. Prigogine, "Thermodynamic Theory of Structure, Stability and Fluctuations", Wiley-Interscience, New York, N.Y., 1971.

(7) R. J. Field and R. M. Noyes, *J. Chem. Phys.*, **60**, 1877 (1974).

(8) R. J. Field, E. Körös, and R. M. Noyes, *J. Am. Chem. Soc.*, **94**, 8649 (1972).

(9) J. J. Tyson, "Lecture Notes in Biomathematics", Vol. 10, S. Levin, Ed, Springer-Verlag, Berlin, 1976.

and their concentrations may oscillate depending upon the relative rates of production and consumption. The differential equations describing their dynamic behavior are eq 1-3.

$$\frac{d[X]}{dt} = [\dot{X}] = k_1[A][Y] - k_2[X][Y] + k_3[B][X] - 2k_4[X]^2 \quad (1)$$

$$\frac{d[Y]}{dt} = [\dot{Y}] = -k_1[A][Y] - k_2[X][Y] + fk_5[Z] \quad (2)$$

$$\frac{d[Z]}{dt} = [\dot{Z}] = k_3[B][X] - k_5[Z] \quad (3)$$

Note that X is formed by steps that are zero (M1) and first (M3) order in its concentration and is destroyed by steps that are first (M2) and second (M4) order. Also note that [Z] has no direct effect on the rates of any processes forming or destroying X (eq 1). The model is particularly tractable if the reactions destroying X are sufficiently rapid that [X] is always much smaller than the concentrations of the other species and can be considered to be in a steady state. Then the right hand side of eq 1 can be set equal to zero, and to the validity of the steady-state approximation the resulting eq 4 couples [X] to [A], [B], and [Y].

$$[X]_{\text{coupled}} = \frac{k_3[B] - k_2[Y] + \{(k_3[B] - k_2[Y])^2 + 8k_1k_4[A][Y]\}^{1/2}}{4k_4} \quad (4)$$

Two special cases of eq 4 correspond to large and small [Y]. When [Y] is large, step M4 and perhaps also step M3 can be neglected compared to M1 and M2; eq 4 then reduces to eq 5 for  $[X]_{\text{small}}$ . When [Y] is small, step M1 and perhaps also step M2 can be neglected compared to M3 and M4; the steady state is then described by eq 6 for  $[X]_{\text{large}}$ .

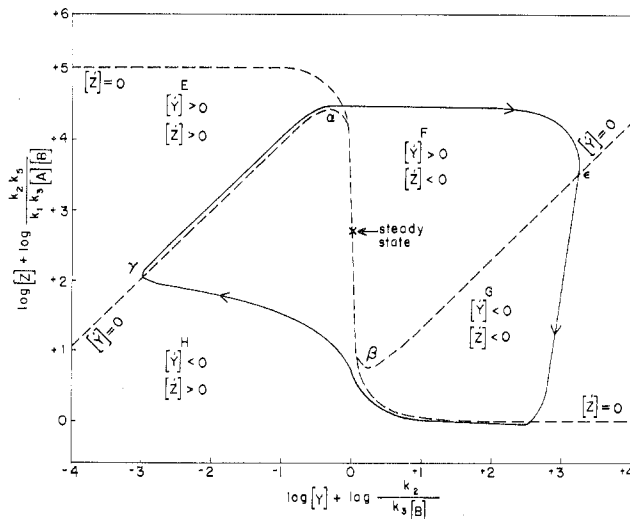
$$[X]_{\text{small}} = \frac{k_1[A][Y]}{k_2[Y] - k_3[B]} \rightarrow \frac{k_1[A]}{k_2} \quad (5)$$

$$[X]_{\text{large}} = \frac{k_3[B] - k_2[Y]}{2k_4} \rightarrow \frac{k_3[B]}{2k_4} \quad (6)$$

Whenever [Y] passes through  $[Y]_{\text{critical}}$  (eq 7) where  $k_2[X][Y] = k_3[B][X]$ , the autocatalytic nature of M3 guarantees that [X] switches very rapidly between the regions of validity of the two approximations. We therefore refer to the Oregonator as a "switching" mechanism of chemical oscillation.

$$[Y]_{\text{critical}} = k_3[B]/k_2 \quad (7)$$

If [X] is indeed much smaller than the concentrations of other species, it can be ignored when net chemical change is considered. Although steps forming and destroying X can be paired in four different ways,<sup>10</sup> the most appropriate combinations are probably (M1 + M2) and (2M3 + M4) as suggested by the approximations leading to eq 5 and 6. These combinations generate the stoichiometries of (Mi) and (Mii), respectively.



**Figure 4.** Logarithmic phase diagram showing steady-state and limit cycle for a stiffly coupled Oregonator. Calculations used:  $2k_1k_4[A]/k_2k_3[B] = [X]_{\text{small}}/[X]_{\text{large}} = 8.375 \times 10^{-6}$ ,  $k_5/k_1[A] = 12.44$ ,  $k_3[B]/k_1[A] \rightarrow \infty$  (stiff coupling approximation),  $f = 1$ .



Process Mi is dominant at  $[Y] > [Y]_{\text{critical}}$  and process Mii is dominant at  $[Y] < [Y]_{\text{critical}}$ . If the rate constants are such that [Y] and [Z] are always much smaller than [A] and [B], Mi and Mii can be combined with M5 to generate a net chemical change in terms of A, B, P, and Q only. Contrary to a previous claim,<sup>7,11</sup> the Oregonator model does not generate a unique stoichiometry for this total net change.<sup>10</sup> However, the conversion of A and B to P and Q necessarily goes almost irreversibly with a decrease in free energy.

It is always possible to define a mathematical steady state by setting the derivatives in eq 1-3 equal to zero. In this case [X], [Y], and [Z] couple to the slowly decreasing reactant concentrations, [A] and [B]. For many values of the rate constants, precisely this steady state is attained, and the reaction proceeds smoothly in the way generally familiar to chemists. However, process Mi destroys Y, process Mii produces Z, and step M5 converts Z to Y. It is conceivable that the smooth steady-state reaction might be unstable with respect to a sequential process in which [Y] and [Z] pass through repetitive maxima and minima.

Just such a situation applies<sup>7</sup> if  $[X]_{\text{large}} \gg [X]_{\text{small}}$ , if the stoichiometric factor  $f$  is not too far from unity, and if  $k_5$  is small enough that there is appreciable delay in converting Z to Y. The situation is illustrated by the logarithmic plot in Figure 4. Rate constants are chosen to resemble those needed to describe the Belousov-Zhabotinsky reaction to be discussed in a future Account.<sup>5</sup> The dashed  $[\dot{Y}] = 0$  curve is a solution of eq 2 for  $[X] = [X]_{\text{coupled}}$ . It goes through a relative maximum at point  $\alpha$  in a region where the  $[X]_{\text{large}}$  approximation is valid and through a relative minimum at point  $\beta$  where the  $[X]_{\text{small}}$  approximation is valid. The  $[\dot{Z}] = 0$  curve is a similar solution of eq 3 and crosses the  $[\dot{Y}] = 0$  curve in the region between  $\alpha$  and  $\beta$ . The crossing point is the overall steady state representing the smooth reaction that satisfies eq 1-3 simultaneously. The four regions, E, F, G, and H, in

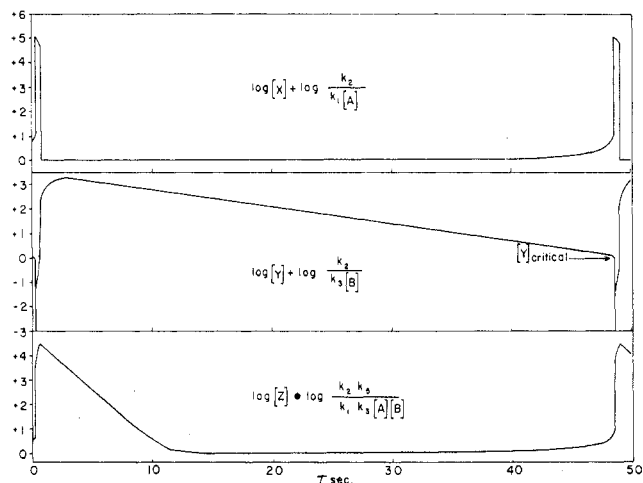


Figure 5. Logarithmic plot of limit cycle oscillations of Oregonator intermediates for situation of Figure 4 with  $k_5 = 1 \text{ s}^{-1}$ .

Figure 4, represent different combinations of signs for  $[Y]$  and  $[Z]$ .

If changes in  $Z$  take place slowly, the steady state ( $[Y] = [Z] = 0$ ) in Figure 4 is clearly unstable to fluctuations in  $[Y]$ . Any perturbation that makes  $[Y]$  greater than the steady-state value will enter a region where  $[Y] > 0$ , and the perturbation to  $[Y]$  will grow. Any perturbation that makes  $[Y]$  less than the steady-state value will cause  $[Y]$  to decrease still more, and this perturbation will also grow. Fluctuations even at the molecular level will be sufficient to cause a real system to leave the steady state and to evolve to the trajectory of the solid curve which necessarily passes outside of points  $\alpha$  and  $\beta$  and never comes near the steady-state point.

Figure 5 illustrates the actual behavior of  $[X]$ ,  $[Y]$ , and  $[Z]$  with time as determined by numerical integration of eq 1-3 for the stiffly coupled situation of Figure 4. During most of a cycle,  $[Y]$  is large enough that the  $[X]_{\text{small}}$  approximation is valid and process Mi is dominant. However,  $Y$  is irreversibly consumed by that process, and its concentration eventually falls to  $[Y]_{\text{critical}}$ . At that point, process Mii becomes dominant, and most of the remaining  $Y$  is destroyed by step M2 while  $[X]$  is described by the  $[X]_{\text{large}}$  approximation. Process Mii is now faster than Mi, and  $[Z]$  builds up. If  $f$  is near unity and  $k_5$  is sufficiently small, as in Figure 5, there is an appreciable delay as  $[Z]$  increases to the point where process Mii can generate  $Y$  rapidly enough to overcome its destruction by step M2 and to return the system to dominance by process Mi. During this delay  $[Y]$  is driven to very low values by step M2 only to be driven to very high values as the pool of  $Z$  produced during the delay is converted to  $Y$ . This *delayed feedback* associated with a small value of  $k_5$  is a very important feature of the oscillatory behavior.

Oscillations do not merely require a sufficiently small value of  $k_5$ . If the stoichiometric factor  $f$  is below about 0.5,  $Z$  will produce insufficient  $Y$  to overcome the destruction by step M2, and the system will go to a steady state, satisfying the  $[X]_{\text{large}}$  approximation regardless of the value of  $k_5$ . Similarly, if  $f$  is above about 2.4, step M5 produces  $Y$  so efficiently that the system goes to a stable steady state, satisfying the  $[X]_{\text{small}}$  approximation.<sup>12</sup>

## Generalized Requirements for Temporal Oscillators

The Oregonator model discussed above exhibits features that are common to those homogeneous temporal oscillators whose mechanisms are well known. The species in a closed chemical system can usually be characterized cleanly as reactants, products, intermediates, and catalysts. Because the total free energy must monotonically decrease during any spontaneous process in an isothermal closed chemical system, even oscillatory processes must include some species (reactants such as  $A$  and  $B$  in the Oregonator) whose amounts decrease monotonically and other species (products such as  $P$  and  $Q$ ) whose amounts increase. Catalysts may exist in two or more forms that are interconverted during the reaction. Those catalyst forms and other intermediate species are created and destroyed by different steps. *Chemical oscillations are confined to intermediate and catalyst species.*

All chemical oscillator systems are so complicated that a full representation would require a multidimensional phase space. Often the reactants and products change so slowly that their concentrations are virtually constant during a single period; a semi-quantitative treatment of the oscillations can then ignore the monotonic change of reactant concentrations. To this level of approximation, the  $X$ - $Y$  coupled irreversible Oregonator will exhibit repetitive oscillation traversing a trajectory located in the  $[Y]$ - $[Z]$  plane but determined only by  $[A]$  and  $[B]$  and the values of the rate constants. Such a trajectory is stable to perturbation and is called a *limit cycle*.<sup>13</sup>

Even though the oscillatory trajectory is uniquely determined by the barely changing concentrations of reactants, a position along that trajectory is not so determined. We define as *phase-determining intermediates* (PDI) those species (like  $Y$  and  $Z$  in the coupled Oregonator) whose concentrations must be stated independently in order to define a position along the oscillatory trajectory. Because a chemical system does not have an analogue of a momentum independent of coordinate, two states having the same  $[Y]$  must differ otherwise in composition if  $[Y]$  is increasing in one state and decreasing in the other. Therefore, *at least two phase-determining intermediates are needed to describe the trajectory of any homogeneous chemical oscillator.* The system will be particularly easy to handle if there are only two such intermediates.

We believe that at least a third intermediate species will be necessary to describe the detailed chemistry of a real chemical oscillator. Its concentration may be great enough that it also must be considered phase determining, but the system can be treated more easily when it (like  $X$  in Figures 4 and 5) is present at concentrations so much less than those of the two PDI that it can be treated as stiffly coupled to at least one of these species. The oscillatory effects may be particularly dramatic when this third species is both formed and destroyed by processes first order in its concentration; that concentration may then switch by a large

(12) R. J. Field and R. M. Noyes, *Faraday Symp. Chem. Soc.*, 9, 21 (1974).

(13) N. Minorsky, "Nonlinear Oscillations", Van Nostrand, Princeton, N.J., 1962.

factor whenever conditions change between even mild dominance by one or the other of these processes.

The curves  $[\dot{Y}] = 0$  and  $[\dot{Z}] = 0$  in Figure 4 cross at a steady-state point, and the oscillatory limit cycle trajectory passes around that point just as the trajectory of a mechanical oscillator in coordinate-momentum space passes around the point defining minimum potential and kinetic energy. A steady state like that in Figure 4 is *unstable* if an infinitesimal perturbation causes the system to leave that region of phase space permanently. In general, *chemical systems oscillate around an unstable steady state* and the oscillatory trajectory never passes through the point at which all species have equilibrium or steady state values simultaneously.

Tyson<sup>14</sup> has identified the types of interreaction that may destabilize a steady state. They are direct autocatalysis, indirect autocatalysis by competition, by symbiosis, or by positive feedback loop, and negative feedback loop. All of these interactions involve feedback, which means that formation of a product affects the rate of its further formation in some way other than by simple mass action reversibility. In general, *some feedback interaction is necessary to destabilize a steady state*.

Destabilizing interactions can be identified by generating the Jacobian matrix of the dynamic equations at the steady state. That matrix is defined as  $[\partial[\dot{I}_i]/\partial[I_j]]_{[I_k]}$  where  $I_i$  and  $I_j$  are intermediate species and  $I_k$  refers to all intermediates other than  $I_j$ . The signs of various sums and products of elements in this matrix determine stability. A detailed discussion is provided by Tyson,<sup>14</sup> and an equivalent treatment in terms of graph theory is given by Clarke.<sup>15</sup> We shall not provide a full discussion here but shall use the Oregonator model to illustrate various types of destabilization.

Figure 4 reveals that  $(\partial[\dot{Y}]/\partial[Y])_{[Z]} > 0$ , so that to the stiffly coupled approximation a perturbation of  $[Y]$  is reinforced rather than damped. Such behavior is called *direct autocatalysis*. If the system can be described with only two PDI, oscillations around the steady state are not possible unless autocatalysis is severe enough that eq 8 is satisfied.

$$(\partial[\dot{Y}]/\partial[Y])_{[Z]} + (\partial[\dot{Z}]/\partial[Z])_{[Y]} > 0 \quad (8)$$

If the stiffly coupled approximation is removed so that all three variables are considered,  $(\partial[\dot{X}]/\partial[X])_{[Y],[Z]}$ ,  $(\partial[\dot{Y}]/\partial[Y])_{[X],[Z]}$ , and  $(\partial[\dot{Z}]/\partial[Z])_{[X],[Y]}$  are all negative. Therefore, none of the three species of the full model exhibits direct autocatalysis at the steady state even though step M3 implies that  $[X]$  may exhibit autocatalytic behavior under some conditions.

Despite this lack of direct autocatalysis for the full model,  $(\partial[\dot{X}]/\partial[Y])_{[X],[Z]}$  and  $(\partial[\dot{Y}]/\partial[X])_{[Y],[Z]}$  are both negative. Therefore, a change in  $[Y]$  will change  $[X]$  in a direction so the resulting change in  $[X]$  will cause reaction to accentuate the initial change in  $[Y]$ . Such an indirect autocatalysis is called *competition* because  $[X]$  and  $[Y]$  change in opposite directions from their steady-state values. If the same derivatives were both positive,  $[X]$  and  $[Y]$  would leave the steady state in the same direction, and the indirect autocatalysis would be *symbiotic*. If the two derivatives were of opposite

sign, their influence would be in the direction of stabilizing the steady state. If the system can be described by only two PDI, neither competition nor symbiosis can generate oscillations, but they may make the steady state unstable with respect to motion to another region of the phase plane.

The three derivatives  $(\partial[\dot{X}]/\partial[Y])_{[X],[Z]}$ ,  $(\partial[\dot{Y}]/\partial[Z])_{[X],[Y]}$ , and  $(\partial[\dot{Z}]/\partial[X])_{[Y],[Z]}$  are all nonzero, the first being negative and the other two positive. Tyson<sup>14</sup> calls such a sequence a feedback loop. If the product of all derivatives in such a loop is positive, the net effect is an indirect autocatalysis much like symbiosis or competition in a two variable system. A negative feedback loop like that in the Oregonator can also serve to destabilize a steady state.

The above discussion indicates the types of interactions that can destabilize a steady state, but quantitative calculations are necessary to determine whether or not the state is unstable for a particular set of rate constants. Clarke<sup>16</sup> has developed graph-theoretic methods of analyzing the stability matrix so that dominant interactions are identified quantitatively and absolute stability properties of the steady state can be calculated.

An unstable steady state does not guarantee the system is an oscillator. It may simply leave the steady state while intermediate concentrations change monotonically until reactants are consumed. *An oscillating system also exhibits delayed feedback at positions far from the steady state*. By delayed feedback we mean that a process that would be expected to counteract movement from the steady state is delayed so that this state may be grossly overshoot before the counteracting force becomes effective. Thus for the trajectory in Figure 4,  $[Y]$  becomes much less than the steady-state value but does not begin to increase until the system passes from region H to E at point  $\gamma$ . Similarly, it becomes much more than the steady-state value before it passes from region F to G at point  $\epsilon$ . Points  $\gamma$  and  $\epsilon$  have  $[Y]$  values very different from that at the steady state, so there is a great overshoot in each case before  $[Y]$  starts to move toward the steady-state value.

Even if the dynamic behavior of a closed chemical system can be described by only two phase-determining intermediates, *the necessity for delayed feedback requires there to be at least three net dynamic processes each involving at least one of those species*. The stiffly coupled Oregonator can be described by processes M1, Mii, and M5, but still another process is necessary for a full description.<sup>10</sup>

The italicized statements above seem to define necessary conditions at least for the nonbiochemical oscillators whose mechanisms are now known. They may not be universally valid, and other oscillatory mechanisms can certainly be devised. However, these features are probably useful to look for during efforts to elucidate other mechanisms.

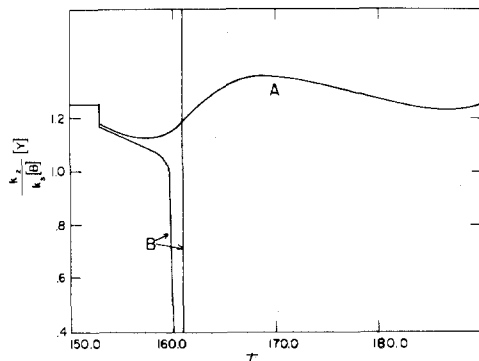
#### Additional Characteristics of Steady States

The discussion of the preceding section was concerned with whether or not a steady state was stable and was restored after an infinitesimal perturbation. Even when the steady state is stable by this definition,

(14) J. J. Tyson, *J. Chem. Phys.*, **62**, 1010 (1975).

(15) B. L. Clarke, *J. Chem. Phys.*, **62**, 773 (1975).

(16) B. L. Clarke, *J. Chem. Phys.*, **60**, 1481, 1493 (1974); **62**, 773, 3726 (1975); **64**, 4165, 4179 (1976).



**Figure 6.** Effects of perturbations on an Oregonator in a stable steady state satisfying the  $[X]_{\text{small}}$  approximation. (Specific parameters differed from Figure 4 in that  $k_5/k_1[A] = 24.88$ ,  $k_3[B]/k_1[A] = 5970$ ,  $f = 1.5$ .) In curve A,  $[Y]$  was reduced 6.0% at a time of 153 units, and the system returned to the steady state with damped oscillations. In curve B,  $[Y]$  was reduced 6.5% at the same time. This perturbation grew until  $[Y]$  dropped below  $[Y]_{\text{critical}}$  to about 0.01 in the units of this plot. It then rose to about 1000 in the same units and ultimately returned to the steady state with damped oscillations at about 450 units in the time scale (from ref 12).

it may exhibit excitability or metastability when subjected to a finite perturbation.

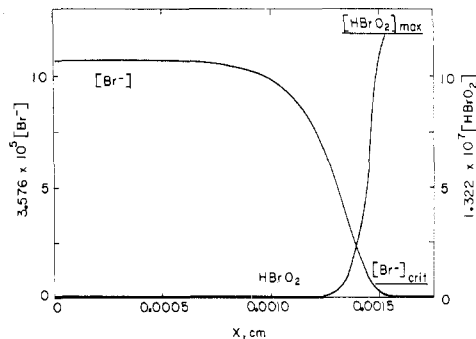
*Excitability* of the Oregonator model is illustrated in Figure 6 for a particular combination of  $f$  and  $k_5$ . If  $[Y]$  is decreased by 6% from the steady-state value, the perturbation grows to about 10% and then decays to the stable steady state. However, a perturbation of 6.5% in the same direction initiates a major excursion in which  $[Y]$  ranges between 0.01 and 1000 times the value at the stable steady state to which it eventually returns! The ability to excite such an excursion is important to the spatial effects illustrated in Figure 3.

Excitability in the Oregonator has also been investigated by Tyson<sup>17</sup> and by Troy and Field.<sup>18</sup> Troy<sup>19</sup> has demonstrated analytically the existence of a true threshold to excitability in the Oregonator.

As was mentioned above, the Oregonator steady state is unstable only if  $0.5 < f < 2.414$  and if  $k_5$  is less than some critical amount. For somewhat larger values of  $k_5$  a state that is stable to infinitesimal perturbations may still be *metastable* so that a larger perturbation may move the system to a limit cycle trajectory like that in Figure 4 moving around points  $\alpha$  and  $\beta$ . Such a transition from smooth reaction to limit cycle oscillation is called *hard excitation*. A sufficient perturbation from the oscillatory trajectory may throw the system back to smooth reaction. Clarke<sup>16</sup> has used graph theory to examine systems removed from the steady state and has shown how to extract more information than is derivable from a linear stability analysis of the region immediately adjacent to the steady state. Tyson<sup>17</sup> has qualitatively demonstrated the existence of limit cycle solutions to the Oregonator dynamic equations even when the steady state is stable.

### Models of Spatial Chemical Oscillators

Chemical oscillators can also develop spatial patterns of great intrinsic interest.<sup>4a,c</sup> These spatial patterns develop in an unstirred reagent. The traveling waves



**Figure 7.** Calculated instantaneous concentration profiles of bromide ion and of bromous acid for a trigger wave moving at constant velocity from right to left (from ref 20b).

exhibited by the Belousov-Zhabotinsky reaction are by far the best example of this phenomenon.<sup>20</sup> These spatial effects may serve as heuristic models for processes such as morphogenesis<sup>21</sup> and nerve impulse transmission.<sup>18,22</sup>

Traveling waves can be divided into two general classes depending upon the importance of diffusion to their properties. If an unstirred oscillating system is subject to a gradient of oscillatory phase in space, then waves of different composition will appear to traverse the solution as areas sequentially enter a particular point in their cycle. Nothing really moves in such a system, although motion is apparent just as the on-off cycle of lights can make apparent motion on a theater marquee. Motion of this sort is called a *phase wave*. The motion is independent of diffusive propagation, and it will continue across an impenetrable barrier placed in the oscillating medium. There is no theoretical maximum rate of propagation of a phase wave, but the frequency of passage of waves through a point is the frequency of temporal oscillation there. If the system exhibits a gradient in oscillatory frequency as well as phase, then waves will appear to pile up at the lower frequency end of the system. If the behavior of homogeneous systems is understood as a function of the key variables, analysis of phase waves offers no additional conceptual complications. The mathematics has been developed by Kopell and Howard.<sup>23</sup>

An alternative type of wave could be generated in a medium like that modeled by the Oregonator with a stable but excitable steady state such that the  $[X]_{\text{small}}$  approximation is valid, as in Figure 6. If  $[Y]$  in a small region were perturbed sufficiently below the steady state, the  $[X]_{\text{large}}$  approximation would become applicable in that region and  $[Y]$  would be reduced even further by feedback. The region of large  $[X]$  and small  $[Y]$  would then expand outward by a combination of diffusion and reaction that destroyed  $[Y]$  and produced  $[X]$  autocatalytically.<sup>20b</sup> Thus a circular wave would develop around the point at which the initial perturbation occurred. Figure 7 shows the calculated profile for the transition of a system based on the first four steps of the Oregonator. The bulk  $[Y]$  ahead of the

(20) (a) A. N. Zaikin and A. M. Zhabotinsky, *Nature (London)*, **225**, 535 (1970); (b) R. J. Field and R. M. Noyes, *J. Am. Chem. Soc.*, **96**, 2001 (1974).

(21) A. M. Turing, *Philos. Trans. R. Soc. London, Ser. B*, **237**, 37 (1952).

(22) W. C. Troy in "Theoretical Chemistry: Advances and Perspectives (Periodicities in Chemistry and Biology)", H. Eyring, Ed., Academic Press, New York, N.Y., 1977.

(23) (a) N. Kopell and L. N. Howard, *Science*, **180**, 1171 (1973); (b) *Studies Appl. Math.*, **52**, 291 (1973); (c) *SIAM-AMS Proc.*, **8**, 1 (1974).

(17) J. J. Tyson, *J. Chem. Phys.*, **66**, 905 (1977).

(18) W. C. Troy and R. J. Field, *SIAM J. Appl. Math.*, in press.

(19) W. C. Troy, "Threshold Phenomena in the Field-Noyes Model of the Belousov-Zhabotinskii Reaction", *J. Math. Anal. Appl.*, in press.

wavefront is 21.45 times  $[Y]_{\text{crit}}$ , and the diffusion coefficients assigned to both X and Y are  $1.8 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ . Almost all chemical change takes place in a region of a few micrometers across, and the calculated rate of motion of that region is  $0.114 \text{ cm s}^{-1}$ . If step M5 is added to the mechanism, at some finite distance behind the moving front [Y] will rise again to  $[Y]_{\text{crit}}$ , [X] will fall to the region of validity of the  $[X]_{\text{small}}$  approximation, and [Z] will decrease as all concentrations approach steady-state values.

A disturbance like this moves undamped at constant velocity through a uniform medium and is called a *trigger wave* by Winfree.<sup>24</sup> Unlike a phase wave, propagation of a trigger wave can be blocked by the introduction of a physical barrier that separates regions of the solution. Passage of a trigger wave is unidirectional and is closely followed by a region of high [Y] in which no new trigger wave could be initiated. When [Y] falls near the steady-state value, a finite negative perturbation could initiate another wave. The importance of the excitability properties of the Oregonator discussed earlier is apparent.

A trigger wave must be initiated by a localized excitation such as on the surface of a dust particle. Showalter<sup>25</sup> has shown that a silver or nichrome wire that slowly depletes bromide ion (Y in the Oregonator) can act as a "pacemaker" to initiate successive trigger waves. A sufficient negative bias can suppress this pacemaker activity, and a positive pulse of a few millisecond duration can then initiate a trigger wave just as a signal could be applied to a nerve.

The situation can be even further complicated if a trigger wave is initiated in a medium that is oscillating homogeneously. This can occur in an oscillatory Belousov-Zhabotinsky reagent where Winfree<sup>26</sup> has experimentally demonstrated the simultaneous existence of both types of waves. Passage of a trigger wave establishes a continuous phase gradient and initiates a set of phase waves traveling behind and at the velocity of the initial trigger wave and appearing at each point with the period of the temporal oscillation. Thus a set of concentric rings will develop around the point of the initial disturbance, but only the first is a true trigger wave. The velocity of a trigger wave is a unique characteristic of the medium through which it moves. The velocity of a phase wave depends upon the steepness of the phase gradient in the medium, but a phase wave cannot move through a medium slower than a trigger wave would propagate, because the phase wave would initiate a trigger wave. Reusser and Field<sup>27</sup> have investigated wave behavior in the Oregonator model by numerically integrating eq 1-3 with diffusion terms for X, Y, and Z included and with values of  $f$  and  $k_5$  such that temporal oscillations would appear in a homogeneous system. They found that the velocity of the observed phase wave decreased as the steepness of the phase gradient increased until the phase wave moved so slowly that diffusion became important. After a transition period, a trigger wave appeared whose velocity was independent of the initial phase gradient.

The velocity calculated for this trigger wave agreed with the experimentally observed velocity to within the accuracy anticipated from the uncertainties of individual rate constants. Field and Troy<sup>28</sup> proved analytically and found numerically the existence of trigger waves in a somewhat simplified Oregonator model. They used values of  $f$  and  $k_5$  such that the steady state of a homogeneous system would be stable.

Even more diverse spatial structures can be generated by trigger waves in the Belousov-Zhabotinsky system with ferroin as both indicator and catalyst. Winfree<sup>29</sup> describes phenomenologically many complicated situations such as two-dimensional spirals (Figure 3) and three-dimensional "scrolls" that can develop around certain foci. Winfree<sup>30</sup> also has demonstrated numerically the existence of rotating spiral solutions to a simple set of reaction-diffusion equations. The intriguing thing about these structures is that they are stable and self-sustaining in a medium in which temporal oscillations are not observed. Tyson<sup>17</sup> has treated the Oregonator equations including diffusion analytically and demonstrated the existence of rotating spiral solutions.

## Conclusion

Although unambiguous examples of chemical oscillators were discovered over a half a century ago, even a decade ago most chemists including ourselves were unaware of the phenomenon existed. In this Account we have discussed some fundamental concepts underlying oscillation in chemical systems. In a later Account<sup>5</sup> we shall discuss the detailed mechanisms of some real chemical oscillators within the context of the principles presented here.

Unlike mechanical and electrical oscillators, chemical oscillators never pass through their final equilibrium configuration in the course of an oscillatory cycle. Oscillations take place in the concentrations of intermediate or catalyst species. These oscillations are driven by the overall decrease in free energy as reactants are converted into products in a far-from-equilibrium system.

The minimum kinetic requirement for chemical oscillation is that the steady-state solution to the dynamic equations is unstable to small fluctuations. Such a system may then evolve to another state which is sometimes oscillatory in nature. We have used here a model mechanism to illustrate some requirements for such steady-state instability in terms of the number and sorts of chemical reactions necessary for it to occur. The dynamic equations describing chemical systems that exhibit oscillation are always nonlinear. Beyond steady-state instability, a further fundamental property of oscillatory chemical systems seems to be *delayed feedback* such that the effect of processes expected to counteract movement away from the steady state is delayed until the steady state has been grossly overshoot. Autocatalytic processes can be very important in assuring movement away from a steady state is so rapid that oscillation occurs even though feedback is not greatly delayed.

(24) A. T. Winfree in "Lecture Notes in Biomathematics", P. van den Dreische, Ed., Springer-Verlag, New York, N.Y., 1974.

(25) K. Showalter and R. M. Noyes, *J. Am. Chem. Soc.*, **98**, 3730 (1976).

(26) A. T. Winfree, *Faraday Symp. Chem. Soc.*, **9**, 38 (1974).

(27) E. Reusser and R. J. Field, University of Montana, report in preparation.

(28) R. J. Field and W. C. Troy, *Arch. Rat. Mech. Anal.*, submitted for publication.

(29) (a) A. T. Winfree, *Science*, **175**, 634 (1972); (b) *ibid.*, **181**, 937 (1973); (c) *Sci. Am.*, **230**, 82 (1974).

(30) A. T. Winfree, *SIAM-AMS Proc.*, **8**, 13 (1974).

The phenomenon of excitability may be more important than oscillatory behavior per se. A steady state may be stable to infinitesimal fluctuations due to random molecular motion, but very minor external perturbations may still generate pulses of large chemical change. These pulses may then migrate to transmit signals.

These unusual events in purely chemical systems

suggest obvious analogies to events in living organisms, and we believe the greatest significance of this work will be to suggest models useful for interpreting some of the basic processes of life itself.

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## Interstellar Chemistry

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The interstellar medium (ISM) of our galaxy lies mainly in the galactic disk and has a characteristic thickness of about 600 light years perpendicular to the galactic plane. Its mean density is roughly 1 H atom  $\text{cm}^{-3}$ , though large density variations occur. The ISM is composed of "clouds" of mainly neutral gas and an "intercloud" region of gas that is at least partly ionized. The latter type of gas is hot ( $\approx 10^3$ – $10^5$  K) and of low density ( $\lesssim 0.1$  particle  $\text{cm}^{-3}$ ).

Clouds are cool ( $\lesssim 100$  K) and dense ( $\sim 10$ – $10^6$  particles  $\text{cm}^{-3}$ ) and contain the interstellar molecules. Characteristic dimensions for clouds are 30 light years. The lower density clouds ( $\lesssim$  few hundred particles  $\text{cm}^{-3}$ ) typically attenuate even ultraviolet starlight by less than an order of magnitude and can thus be observed with optical instruments. Other clouds (typically with  $\gtrsim 10^4$  particles  $\text{cm}^{-3}$ ) are completely opaque and can only be studied with radio telescopes.

For convenience, I will discuss interstellar molecule reactions in terms of these two extreme cases—the "diffuse" and the "dense" clouds. Their chemistry seems to be qualitatively different in that starlight is present in diffuse clouds, but not in dense clouds, to ionize atoms and dissociate molecules. Except for hydrogen, the gas is mainly atomic. The interstellar starlight spectrum is cut off at 13.6 eV due to absorption by hydrogen, so that the atoms with ionization potentials above that of hydrogen are mostly neutral and those with lower ionization potentials exist mainly in ionized form in diffuse clouds. Electron densities are about  $10^{-4}$  of the gas density.

In the dense clouds which exclude starlight, dissociation is slow and collisions are more rapid so that most elements are bound into molecules. Ionization to initiate the proposed chemical reactions in the gas phase and to maintain at least a low-level electron density ( $\lesssim 10^{-6}$  of the particle density) is presumably supplied by the higher energy ( $\gtrsim 100$  MeV/nucleon) cosmic ray

protons. The intensity of these cosmic rays is measured directly for our neighborhood and indirectly throughout the galaxy from observation of  $\gamma$  rays produced in collisions between the cosmic rays and the interstellar gas.

Element abundances throughout the ISM are thought to be essentially the same as in young stars. Relative abundances by number are:<sup>1</sup> H, 1; He, 0.1; C,  $4 \times 10^{-4}$ ; N,  $9 \times 10^{-5}$ ; O,  $6 \times 10^{-4}$ ; Ne,  $5 \times 10^{-5}$ ; all other elements near or less than  $10^{-5}$ .

Besides the gas of the ISM, there also exist dust grains. The presence of dust grains is indicated by the continuous attenuation of starlight as a function of wavelength, and their dimensions ( $\approx 10^{-5}$  cm) are determined from the wavelength dependence of this attenuation. Except close to bright stars, the temperatures of these grains are maintained by absorption of starlight from the galactic background and are  $\approx 10$  to 20 K. From cloud to cloud, the relative abundance of dust grains is approximately constant and expressed as a surface area per H atom in the gas is  $5 \times 10^{-22}$   $\text{cm}^2$ . The mass of material in grains is roughly 0.01 of the gas and requires a considerable fraction (perhaps most) of the available "heavy" elements (C, N, O, etc.).

A major uncertainty in studying reactions in the ISM is the degree to which the heavy elements have been depleted in the gas by freezing onto the cold grains or by incorporation into the refractory grain material in the atmospheres of cool stars.

### Observation of Molecules in the Interstellar Gas

In Table I we list the observed interstellar molecules along with the type cloud in which they are detected and a rough estimate of their abundance. Although  $\text{H}_2$  and HD are not directly detectable in dense clouds, essentially all the hydrogen and deuterium is expected to be in this form. After  $\text{H}_2$ , carbon monoxide is the most abundant molecule in dense clouds and thus has special importance. The deuterated forms DCN ( $\text{DCN}/\text{HCN} \approx 1/200$ ) and  $\text{DCO}^+$  ( $\text{DCO}^+/\text{HCO}^+ \approx 10^{-2}$ – $1$ ) have been found in several dense clouds as well

(1) C. W. Allen, "Astrophysical Quantities", 3rd ed, P. Athlone, London, 1973, p 30.

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