# Chemical Oscillations

G. NICOLIS and J. PORTNOW*

*Faculté des Sciences de l'Université Libre de Bruxelles, Brussells, Belgium*

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## Contents

## *I. Theoretical Background*

### A. Introduction

Theoretical and experimental studies of oscillating reactions are now being carried out at many laboratories, and the interest in this type of phenomena is increasing very rapidly. This was not always the case. First regarded as curiosities or even as artifices, oscillating reactions reached the status of a branch of laboratory chemistry only in the early 60's, thanks partly to the discovery of oscillations in biochemical pathways. Interestingly, thermodynamicists and applied mathematicians did not wait until then to work out models of such reactions and discuss the feasibility of oscillations in homogeneous chemical systems. Thus, as early as 1955,[1] general criteria were available about the type of chemical reactions that could present undamped oscillations. Later advances, especially in the last few years, have shown the generality of this type of behavior in nonlinear systems driven far from equilibrium and have established a highly interesting connection with stability theory.

The purpose of the present review is to provide a synthetic view of the mathematical, thermodynamical, and purely kinetic or experimental work on chemical oscillations. Special emphasis is given to the theoretical significance of the various experimental findings and to the integration of the results into the general frame of thermodynamics of irreversible processes. Unavoidably, this rather ambitious goal implies certain limitations in our treatment. Thus, the subjects of electrochemical and biochemical oscillations are treated selectively. The remaining chapters are more comprehensive with bibliographic references up to 1972.

Previous reviews of chemical oscillations by Higgins[2] and Degn[3] and of biochemical oscillations by Hess and Boiteux[4] are available in the literature. The presentation we follow here will be oriented differently, and also will focus special attention on a number of additional topics. Let us also mention two useful books[5] which provide an account of the recent work of Soviet scientists in this field.

After a brief historical survey, we develop in sections I.C and I.D the mathematical and physical concepts which we think are necessary for the theoretical interpretation of observations on chemical oscillations. Section II is devoted to the presentation of the experiments and of the kinetic analysis of systems showing sustained oscillations. We discuss, successively, chemical oscillations in homogeneous isothermal mixtures (II.A) and in heterogeneous systems (II.B), temperature oscillations (II.C), electrochemical oscillations (II.D), biochemical oscillations (II.E), and finally the coupling between oscillatory

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* Author to whom correspondence should be addressed at Woods Hole Oceanographic Institute, Woods Hole, Mass. 02543.

(1) I. Prigogine and R. Balescu, *Bull. Cl. Sci., Acad. Roy. Belg.*, **41**, 912 (1955). See also Th. Bak, "Contributions to the Theory of Chemical Kinetics," W. A. Benjamin, New York, N. Y., 1963.

(2) J. Higgins, *Ind. Eng. Chem.*, **59** (5), 19 (1967).

(3) H. Degn, *J. Chem. Educ.*, **49**, 302 (1972).

(4) B. Hess and A. Boiteux, *Annu. Rev. Biochem.*, **40**, 237 (1971).

(5) "Oscillatory Processes in Biological and Chemical Systems," Vol. I, G. M. Frank, Ed., Nauka, Moscow, 1967; Vol. II, E. E. Sel'kov, Ed., Puschino-na-Oka, 1971.

and spatial phenomena (II.F). In section III we try to combine the results of sections I and II and analyze some theoretical aspects of chemical oscillations, including the origin of these phenomena. The final section, IV, which is somewhat speculative, deals with the significance and the physical role of oscillations in various fields such as chemistry, biology, or ecology.

## B. Historical Survey

References to early work on chemical oscillations are given throughout the main text. In this section we want to survey briefly the historical evolution of the role that oscillations have played in chemistry and of the concepts involved in their explanation.

The few isolated examples of oscillatory processes known in chemistry before the 1920's had not modified the deep belief of scientists that the evolution of any physico-chemical system leads invariably to a steady state of maximum disorder. This property was considered to follow immediately from the second law of thermodynamics and was thought to rule out any coherent behavior such as sustained oscillations. It was only in the 1940's that Bertalanffy,[6] Schrödinger,[7] and Prigogine[8,9] insisted on the concept of *open system* and on the necessity to treat particularly biological systems as open systems. It was soon realized that this enabled one to understand, in principle, the spontaneous appearance of organization including the possibility for oscillations. Meanwhile the investigation of biological periodicities such as circadian clocks[10] and the rhythmic activity of the central nervous system[11] had shown that, at least, in large-scale biological phenomena oscillations are the rule rather than the exception. This belief was strengthened even more by the discovery, in the 1960's, of oscillatory biochemical processes *at the cellular level* like the glycolytic pathway,[12] the peroxidase-catalyzed reaction,[13] or the biosynthesis of certain proteins.[14] These accumulated observations gave rise to a multiplicity of theoretical developments. On the one hand, inspired by the pioneering work of Lotka and Volterra on the oscillatory behavior of competing biological species,[15,16] a number of scientists have worked out mathematical models to explain the observed periodicities.[17] Most of these models were nonlinear, and their analysis was based on the theory of nonlinear differential equations which had been worked out by Poincaré and later by the Andronov school.[18] On the other hand, starting from the concept of an open system, a generalized thermodynamics has been developed which gives useful criteria under which a physico-chemical system can exhibit ordered behavior.[19]

These theoretical developments, which were motivated essentially by the study of biological systems, were enriched recently by the discovery of several striking nonbiological examples of oscillatory behavior. We shall mention three of them: the Belousov–Zhabotinskii reaction,[20] the Bénard problem with two constituents,[21] and the Dupeyrat–Guastalla[22] effect. In all three cases oscillations are so unexpected that their appearance is almost a challenge to common sense.

In the Belousov–Zhabotinskii reaction, which is the oxidation of analogs of malonic acid by bromate in the presence of Ce (or Fe or Mn) ions, sustained oscillations in the concentration of chemicals appear spontaneously if the reaction is carried out in a well-stirred homogeneous medium. The periods and amplitudes are very sharp and reproducible. This reaction will be discussed in detail in section II.

The remaining two examples are nonchemical. Consider a horizontal fluid layer initially at rest heated from below. The layer consists of a two-component mixture with a *negative Soret coefficient, e.g.*, water and ethanol. For a critical value of the temperature gradient, the state at rest becomes unstable and the fluid switches to a state where regular convection patterns appear.[23] Surprisingly, for some range of values of the various parameters, these patterns, as well as the temperature field, are not stationary. Thus, Platten[21] has recently found sharp, sustained oscillations in the temperature at various points with perfectly reproducible periods of the order of minutes. At the time the experiment was made, a theory of this type of phenomenom was available.[24] Still it is surprising to see a "thermal diffusion clock" emerging in the laboratory from a system which one would tend to consider as the prototype of a dissipative, disordered system!

The Dupeyrat–Guastalla effect may be described briefly as follows.[22] An electric potential difference is applied between two immiscible liquid phases (water–nitrobenzene) in contact, containing two tensioactive salts at composition equilibrium. The aqueous phase becomes negative with respect to the organic phase. As a result, a current flows across the interface. Next, one suppresses the electric constraint and lets the system relax to equilibrium. After a few minutes, the interface starts moving spontaneously and rhythmically for a time interval of the order of hours. It has been observed that this motion is accompanied by abrupt curvature changes of the meniscus.

Concluding this short chapter, one may say that the importance and the universality of periodic phenomena in biochemistry, chemistry, or even in fluid dynamics is such that oscillations will soon become a central theme in the study of the macroscopic properties of physicochemical systems.

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(6) For a review of Bertalanffy's ideas, see L. von Bertalanffy, "General System Theory," Braziller, New York, N. Y., 1968.

(7) E. Schrödinger, "What Is Life?," Cambridge University Press, London, 1945.

(8) See, *e.g.*, I. Prigogine, "Introduction to Thermodynamics of Irreversible Processes," Interscience, New York, N. Y., 1961.

(9) I. Prigogine, "Etude Thermodynamique des Processus Irréversibles," Desoer, Liège, 1947.

(10) For a review, see F. A. Brown, J. W. Hastings, and J. D. Palmer, "The Biological Clock," Academic Press, New York, N. Y., 1970.

(11) See, *e.g.*, articles by F. Morrel and W. M. Landau in "The Neuro Sciences," Rockefeller University Press, New York, N. Y., 1967, pp 452, 469.

(12) A. Ghosh and B. Chance, *Biochem. Biophys. Res. Commun.*, **16**, 174 (1964).

(13) I. Yamazaki, K. Yokota, and R. Nakajima, *Biochem. Biophys. Res. Commun.*, **21**, 582 (1965).

(14) See, *e.g.*, W. A. Knorre, *Biochem. Biophys. Res. Commun.*, **31**, 812 (1968).

(15) A. Lotka, *J. Phys. Chem.*, **14**, 271 (1910); *Proc. Nat. Acad. Sci. U. S.*, **6**, 410 (1920).

(16) V. Volterra, "Leçons sur la théorie Mathématique de la lutte pour la vie," Gauthier-Villars, Paris, 1931.

(17) Detailed references to this work are given in section III.A.

(18) A. A. Andronov, A. A. Vitt, and S. E. Khaikin, "Theory of Oscillators," Pergamon Press, Oxford, 1966.

(19) P. Glansdorff and I. Prigogine, "Thermodynamic Theory of Structure, Stability and Fluctuations," Wiley-Interscience, New York, N. Y., 1971.

(20) B. P. Belousov, *Sb. Ref. Radiats. Med., Moscow, 1958*, 145 (1959).

(21) J. K. Platten and G. Chavepeyer, *Phys. Lett. A*, **40**, 227 (1972).

(22) H. Colson-Guastalla, M. Dupeyrat, and J. Guastalla, *J. Chim. Phys. Physicochim. Biol.*, **67**, 1508 (1970).

(23) The theoretical study of this phenomenon for a single component can be found in S. Chandrasekhar, "Hydrodynamic and Hydromagnetic Stability," Clarendon Press, Oxford, 1961.

(24) R. S. Schechter, I. Prigogine, and J. Hamm, *Phys. Fluids*, **15**, 379 (1972).

## C. Mathematical Background

### 1. Equations of Conservation

Before we go into a detailed description of known examples of various types of chemical oscillations, it will be useful to comment on the origin and some general characteristics of this phenomenon. We shall first discuss, in this chapter, the mathematical properties of reaction networks which can give rise to oscillations. Section I.D will be devoted to an analysis of oscillations from the standpoint of the thermodynamics of irreversible processes.

Most of the chemical systems studied in the laboratory can be described, as far as their *macroscopic* properties are concerned, in terms of a limited number of *local* variables, which are connected by the same relations as in the state of thermodynamic equilibrium. The conditions for the validity of this *local equilibrium* description have been investigated extensively by Prigogine and coworkers.[25] From the microscopic point of view, it has been shown that these conditions are satisfied provided that locally, the momentum distribution function of the reacting mixture does not deviate appreciably from the Maxwellian form. This implies, in turn, that the external forces and the gradients (of composition, temperature etc. . . . ) imposed on the system should not be very large. On the other hand, the local equilibrium condition seems to be compatible with quite large deviations from *chemical* equilibrium.[26] The conclusion is, therefore, that the great majority of chemical systems of interest can be treated safely within the framework of a local equilibrium description except, perhaps, when interfacial effects are important, for in this case the gradients of the local variables may become very high.

Consider now the most general reaction mixture containing $n$ species, $X_1, \ldots, X_n$, in a volume $v$, which satisfies the local equilibrium condition. The system may be open to the flow of chemicals from the outside world which react with $X_1, \ldots, X_n$ inside the reaction volume. We assume, however, that the boundary conditions remain time independent and that the system is in mechanical equilibrium. Under these conditions the instantaneous state will be described by the composition variables $X_1, \ldots, X_n$ denoting, *e.g.*, the average densities of the chemicals, and by the internal energy density $\rho e$, where

$$\rho = \sum_{i=1}^{n} X_i \tag{1}$$

and $e$ is the specific energy per unit mass. These quantities satisfy the well-known conservation equations[27]

$$\frac{\partial X_i}{\partial t} = v_i(\{X_j\},T) - \nabla\cdot\mathbf{J}_i^{\mathrm{d}} \tag{2}$$

$$\frac{\partial}{\partial t}(\rho e) = -\nabla\cdot\mathbf{J}^{\mathrm{th}} + \mathrm{i}\cdot\mathbf{E} \tag{3}$$

$$(\mathrm{i} = 1, \ldots, n)$$

$\mathbf{J}_i^{\mathrm{d}}$ and $\mathbf{J}_i^{\mathrm{th}}$ are respectively the diffusion and the heat flow vector and $T$ is the temperature. $v_i$'s describe the production of $i$ by all the chemical reactions. In a homogeneous medium they will be given by the usual phenomenological laws of chemical kinetics; *i.e.*, they will be, in general, *nonlinear* functions of $X_j$'s. Note that in an open system $\Sigma_i v_i \neq 0$. $E$ is the electric field and i the current density which is given by

$$\mathrm{i} = \sum_{i=1}^{n} z_i\mathbf{J}_i^{\mathrm{d}} \tag{4}$$

with $z_i$ the charge per unit mass of $i$. We shall assume that i and $\mathbf{E}$ vary slowly enough to neglect respectively magnetic and time-dependent polarization effects.

Now if the gradients are not too high, $\mathbf{J}_i^{\mathrm{d}}$ and $\mathbf{J}^{\mathrm{th}}$ can be expressed in terms of the unknown functions appearing in eq 2 and 3 by the phenomenological relations[27]

$$\mathbf{J}_i^{\mathrm{d}} = -D_iX_i[\nabla\mu_i(X_1, \ldots, X_n, T)]_T - D'_i\frac{\nabla T}{T^2} \tag{5}$$

$$\mathbf{J}^{\mathrm{th}} = -\lambda\nabla T - \sum_i D'_i\frac{(\nabla\mu_i)_T}{T} \tag{6}$$

assuming a diagonal diffusion coefficient matrix $\{D_i\delta_{ij}^{\mathrm{kr}}\}$. $\mu_i$ is the electrochemical potential of constituent $i$, $\lambda$ the thermal conductivity of the mixture, and $D'_i$ the thermal diffusion coefficient of $i$.

When (5) and (6) are substituted into (2) and (3), one obtains a closed system of nonlinear partial differential equations for $\{X_i\}$ and $T$, provided one also uses the constitutive relation

$$e = e(X_1, \ldots, X_n, T) \tag{7}$$

Their form is

$$\frac{\partial X_i}{\partial t} = v_i(\{X_j\},T) + \nabla\cdot\left[D_iX_i(\nabla\mu_i)_T + D'_i\frac{\nabla T}{T^2}\right] \qquad (i = 1, \ldots, n) \tag{8}$$

$$C(\partial T/\partial t) = \nabla\cdot\lambda\nabla T + \text{(diffusion and thermal diffusion terms)} + i\cdot E + \sum_\rho(-\Delta H)_\rho w_\rho \tag{9}$$

where $C$ is the heat capacity of the mixture and $\Delta H_\rho$ and $w_\rho$ are respectively the heat and the velocity of reaction $\rho$. Equations 8 and 9 must of course be supplemented with appropriate boundary conditions.

### 2. The Homogeneous, Isothermal, Nonelectric Case

In order to get some feeling about the behavior of solutions of the above set of equations we shall study, in this section, the case of homogeneous isothermal systems. In this limit the equations simplify to

$$\mathrm{d}X_i/\mathrm{d}t = v_i(\{X_j\}) \quad (i = 1, \ldots, n) \tag{10}$$

They become nonlinear *ordinary* differential equations of the autonomous type (*i.e.*, with right-hand sides which do not depend explicitly on $t$). The mathematical theory of such equations has been developed extensively by several workers beginning with Poincaré, especially in the case of two dependent variables.[18] In contrast, the corresponding theory for partial differential equations is still in a rather primitive stage.[28] Mathematical convenience is not, however, the only reason for giving here rather special emphasis in the homogeneous case. As we shall see soon, several experimental examples of oscillatory reactions in homogeneous phase are now known. Moreover, biochemical oscillations as, e.g., those of the glycolytic intermediates, have also been reproduced *in vitro* under homogeneous conditions. In all these cases, oscillations can only be due to the chemical mechanism, since all additional causes such as the presence of surfaces, macroscopic inhomogeneities, electric effects, etc., have been removed. Thus the study of the

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(25) I. Prigogine, *Physica* (*Utrecht*), **14**, 272 (1949); G. Nicolis, J. Wallenborn, and M. G. Velarde, *ibid.*, **43**, 263 (1969).

(26) I. Prigogine, *Nuovo Cimento Suppl.*, **6**, 1 (1949).

(27) See, *e.g.*, S. R. De Groot and P. Mazur, "Nonequilibrium Thermodynamics," North-Holland Publishing Co., Amsterdam, 1961.

(28) For recent attempts in this direction, see D. Sattinger, "Topics in Stability and Bifurcation Theory," University of Minnesota, 1971.

system of eq 10 will reveal the conditions under which a chemical mechanism can by itself generate an oscillatory behavior.

Let $X_i(t)$ be a solution of system 10. We assume that the motion is defined in the open time interval $(0, \infty)$ and that $X_i(t)$ exists in this interval. Clearly, any function of the form $X_i(t + t_0)$, where $t_0$ is an arbitrary constant (the phase), is still a solution of this system. These infinitely many solutions define in the $n$-dimensional space of $X_j$'s a *trajectory c* (or orbit) of the system. The behavior of the trajectories is characterized by the following two key notions.[18]

*Structural Stability.* A system is structurally stable if the topological structure of its trajectories in the $X_n$ space is unaffected by small disturbances modifying the form of the equations of evolution (eq 10).

*Lyapounov Stability.* A state $X_i(t)$ is (Lyapounov) stable if, given $\epsilon > 0$, there exists an $\eta > 0$ such that any other solution $X_{i0}(t)$ within distance $\eta$ from $X_i$ at time $t_0$ remains within distance $\epsilon$ from $X_i$ for all $t > t_0$. If, moreover, the distance $|X_i(t) - X_{i0}(t) \rightarrow 0$ as $t \rightarrow \infty$, $X_i(t)$ will be *asymptotically stable.*

These two notions are related as follows. As a rule, the behavior of a chemical system described by (10) depends on the values of a set of parameters $\{A\}$ describing, *e.g.*, the rate of entry of substances from the external world or the initial composition of the mixture. The solutions of the differential equations thus become functions of $\{A\}$. We assume that at least one of these solutions belongs to an asymptotically stable trajectory. If for some range of $\{A\}$ these solutions vary smoothly without any qualitative modifications of the topology of the trajectories (the system will then be structurally stable), these values of $\{A\}$ will be called *ordinary* values. But if, after passing through the values $\{A\} = \{A_c\}$ the topological structure of the trajectories changes qualitatively (the system can then be shown to be for $\{A\} = \{A_c\}$ structurally unstable[18]), we will say that $\{A_c\}$ is a set of critical, or *bifurcation*, values. Certain solutions (*e.g.*, steady-state ones) or trajectories of solutions of (10) become at this point (Lyapounov) unstable.

Now an elementary property one should expect from a physical system which is in a well-defined state and that should be imposed on any mathematical model describing the macroscopic behavior of this system is structural stability. Indeed, a physical system is always subject to all sorts of external disturbances as well as to its own fluctuations (see also section III.C). Without structural stability, the behavior of the system would resemble a random noise, which is contrary to common observation. A simple illustration of this idea is given by the motion of a pendulum. The usual mathematical model of this system is in this case the harmonic oscillator. It belongs to the class of *conservative systems, i.e.*, systems having a (regular) constant of motion, all of which are structurally unstable.[18] In nature, however, a pendulum is never a harmonic oscillator, as it is always subject to friction. This makes the system structurally stable. The practical functioning of a dependable clock requires, therefore, a finite external driving force which compensates the effects of friction.

Coming now to the chemical case, common observation has always shown that a reacting mixture subject to time-independent boundary conditions ends up in a *stationary state*, where the concentrations $\{X_{0i}\}$ of the chemicals remain time independent. On the other hand (see section II), evidence is now accumulating very rapidly to show that chemical systems going to a steady state under certain conditions can also occur for different conditions in states where the concentrations $\{X_i(t)\}$ exhibit sustained oscillations with perfectly reproducible periods and amplitudes. In the terminology introduced before, in both cases one must have structurally stable systems, but obviously the topological structure of their trajectories in the $X_n$ space is quite different. Thus it is natural to adopt the point of view that the transition from a steady state to an oscillatory behavior is accompanied by a bifurcation phenomenom which occurs for some critical values of a set of parameters influencing the system. At this point the steady-state solution becomes (Lyapounov) unstable. The system has then to evolve to a new type of regime which under certain conditions could be a sustained oscillation.

We want to suggest, therefore, that chemical sustained oscillations are examples of *supercritical phenomena* occurring beyond an unstable transition. This shows an interesting analogy with several well-known physical phenomena such as instabilities in fluid dynamics or even phase transitions. We shall discuss this point further in section I.D.

### 3. Homogeneous Systems of Two Variables

The theory of bifurcations has been developed particularly well for systems described by two variables.[18,29] The case $n > 2$ is still studied very actively, but one is far from having a complete characterization of the phenomena that may occur at the bifurcation point. In this section we compile a few results on differential systems of two variables. The reason is not only academic. Several chemical systems showing sustained oscillations can sometimes be described by two variables. For instance, the oscillations of the glycolytic intermediates can be discussed quite satisfactorily in the ATP–ADP system which appears in a reaction step catalyzed by phosphofructokinase.

In the theory of two-dimensional bifurcations, a particularly important role is played by closed trajectories, which obviously represent periodic motions. In a structurally stable system, two closed trajectories are necessarily separated by a finite distance. Following Poicaré we shall call them *limit cycles.*[18,29] In contrast, structurally unstable systems like conservative systems may exhibit in a finite domain an infinity of closed trajectories. Their amplitudes and periods are determined by the initial conditions, whereas in the limit cycle case they are determined by the system itself.

The following important results may be established for limit cycles.

A closed trajectory surrounds at least one point representing a steady state. Hereafter we shall refer to these points as *singular points.*

Negative criterion of Bendixson. If the expression $(\partial v_1/\partial X_1 + \partial v_2/\partial X_2)$ (see eq 10) does not change sign in a domain of the $(X_1, X_2)$ space, there can be no limit cycles in this domain. This statement also proves that *limit cycles can only arise in nonlinear systems.*

Of particular interest in our discussion will be the determination of the conditions of emergence of stable limit cycles, which are the only ones to describe chemical oscillations observed in nature, from a regime where oscillations were absent. It can be shown that this bifurcation can occur in the following ways.[18,29]

(a) Stable limit cycles can be created from a singular point whose stability properties change for a critical set of values of the parameters. In particular, for the critical

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(29) A. A. Andronov, E. A. Leontovich, I. I. Gordon, and A. G. Maier, "Theory of Bifurcations of Dynamical Systems on a Plane," Israel Program for Scientific Translations, Jerusalem, 1971.

values the singular point should behave as a *multiple focus*. This means that at the critical point small perturbations around the singular point should present undamped oscillations. Clearly, case (a) is the most important for chemical oscillations.

(b) Stable limit cycles can emerge from multiple limit cycles. The latter can arise from the coalescence of a stable and an unstable limit cycle.

(c) More complicated bifurcations of limit cycles can also occur in the presence of *separatrices* joining two singular points, one of which is a *saddle point*. By definition, a saddle point is a singular point such that small perturbations around it can be decomposed into one exponentially growing and one exponentially decaying mode. A separatrix is a trajectory of the differential system passing through singular points.

In addition to the appearance of limit cycles, a bifurcation can also give rise to multiple singular points. The latter emerge from a critical state where two singular points coalesce. The simplest known case is the coalescence of a saddle point and a *node*. By definition, a node is a singular point around which small perturbations either decrease or increase exponentially with time. It is believed (see also section III.A) that multiple steady states should arise in certain classes of biochemical control reactions.

### 4. *More General Systems*

As we pointed out earlier, chemical kinetic systems are generally inhomogeneous, and they are subject, in addition, to external driving forces of, *e.g.*, electric origin. The theory of bifurcations for such systems, which are described by partial differential equations, is a much less developed subject than the theory of ordinary differential equation and is, in fact, still a subject of active research. The most common bifurcation phenomena starting from a steady state of a given spatial symmetry are[28] (a) the spontaneous breaking of symmetry of the original state at some critical point and the evolution thereafter to a new *steady* state having a different spatial symmetry; (b) the bifurcation of *periodic solutions* in the form of standing or propagating waves; (c) the bifurcation of *quasi-periodic* solutions from a periodic solution of the type (b).

As we shall see in section II, there is now chemical evidence for the phenomena (a) and (b). Case (c), which is believed to arise in certain fluid dynamical instabilities, has not yet found any chemical analog.

## D. Thermodynamic Analysis of Chemical Oscillations

### 1. *Impossibility of Oscillations in the Linear Region of Irreversible Processes*

In the preceding section we have seen that stable sustained oscillations of the limit cycle type may appear in certain nonlinear systems, usually beyond the domain of stability of a steady state. We shall now try to relate instabilities and oscillations to the thermodynamic properties of the systems, such as entropy or entropy production per unit time.

Consider an arbitrary system which may be open; *i.e.*, it may exchange energy and matter with the surroundings. The entropy change $dS$ during a time interval $dt$ may be decomposed as follows[8,27]

$$dS = d_eS + d_iS \tag{11}$$

with $d_iS \geq 0$, where $d_eS$ is the *flow of entropy* due to exchanges with the surroundings, and $d_iS$ is the *entropy production* inside the system due to irreversible processes such as chemical reactions, diffusion, heat conduction (see also (12) and (13)). The second law requires $d_iS \geq 0$. For isolated systems ($d_eS = 0$), this implies that $dS = d_iS \geq 0$, *i.e.*, that, for time-independent boundary conditions, the system will tend irreversibly to an equilibrium state $d_iS = d_eS = 0$, which will be time independent and asymptotically stable with respect to all disturbances. On the other hand, open systems can attain *steady nonequilibrium states* such that $dS = 0$, but $d_eS = -d_iS < 0$. Consider now a system far from the equilibrium state and which satisfies the local equilibrium condition described in section I.C. One can calculate explicitly $d_iS/dt$, and the result is[8,27] (where $\mathcal{V}$ = volume)

$$\mathcal{P} = \frac{d_iS}{dt} = \int d\mathcal{V} \sum_\rho J_\rho X_\rho \geq 0 \tag{12}$$

$J_\rho$'s are the rates of irreversible processes (chemical reaction velocities, diffusion, and heat flow) and X's are the corresponding forces (chemical affinities, electrochemical potential gradients, temperature gradient).

Near equilibrium, the $J_\rho$'s are *linear* functions of X's and (12) becomes quadratic in the X's. It has been shown by Prigogine[8,9,27] that in this limit, and for time-independent boundary conditions

$$d\mathcal{P}/dt \leq 0 \tag{13}$$

The equality sign refers to the steady state. For an open system this implies a minimum entropy production at the steady (nonequilibrium) state and the asymptotic stability of this state with respect to all disturbances.(30) As a result, a regime of sustained oscillations cannot bifurcate from the steady state in this domain. *Oscillations cannot be close to equilibrium phenomena.*

In an isolated system, no steady state other than equilibrium can exist. The meaning of inequality 13 in this case is that oscillations cannot take place around a *transient state*, in the course of the approach of the system to equilibrium.

### 2. *Nonlinear Thermodynamics. Oscillations Past an Instability*

Inequality 13 breaks down for states far from thermodynamic equilibrium. Moreover, one cannot derive in this domain an extended inequality which would guarantee the stability of steady or transient states. Instead, one can derive a *stability condition* for such states. It is found that stability will be ensured whenever[19]

$$\delta^2\mathcal{P} = \int d\mathcal{V} \sum_\rho \delta J_\rho \delta X_\rho \geq 0 \tag{14}$$

Here $\delta J_\rho$ and $\delta X_\rho$ are the excess flows and forces due to the deviation of the state of the system from the reference state whose stability is sought. This deviation may arise from random or systematic disturbances acting on the system. We shall come back to this point in section III.C which is devoted to study of the onset of oscillations.

Relation 14 provides a universal thermodynamic stability criterion for nonequilibrium states. In the neighborhood of equilibrium, the inequality is always satisfied, in agreement with the results of the previous section. Moreover, for systems obeying linear kinetic laws one can show that the sign of the inequality cannot be inverted as the distance from equilibrium increases.(31) In contrast, in

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(30) Assuming that the equilibrium state itself is stable, that is, that the system is far from a phase transition.

(31) J. Z. Hearon, *Bull. Math. Biophys.*, **15**, 121 (1953), had already shown that a closed isothermal system of first-order reactions will approach to equilibrium without oscillations; see also K. G. Denbigh, M. Hicks, and F. M. Page, *Trans. Faraday Soc.*, **44**, 479 (1948).

*nonlinear systems* driven *far from equilibrium* the inequality 14 can be violated beyond a critical set of values of the parameters. In an open system, this will result in deviations from the branch of steady states which is the extrapolation of the close-to-equilibrium behavior and which will become unstable. We shall refer to this branch of states as *the thermodynamic branch.*[19] According to the previous section, beyond instability one can have a stable sustained oscillation of the limit cycle type bifurcating from the (unstable) steady state. Notice that the premise of nonlinearity for the appearance of limit cycles, which was stressed in section I.C.3, is also found, independently, in the thermodynamic analysis of this section. In conclusion, sustained oscillations in an open system can be understood as *supercritical phenomena* arising beyond the domain of stability of steady states on the thermodynamic branch. In this respect, they belong to the class of *dissipative structures,*[19] which have been defined by Prigogine as spatially or temporally organized states which are created and maintained by the flow of matter from the outside world, *i.e.*, ultimately by the dissipation arising from the irreversible processes inside the system. Surprisingly, dissipation seems to become an organizing factor under certain conditions, contrarily to what common intuition would suggest.

Several model reaction schemes analyzed by various authors (see also section III.A) confirm the validity of this conclusion. We are confident that the oscillations observed in the laboratory (see section II) will be explained in these terms.

In an isolated system, or in a system which is closed to mass transfer, the notion of stability of the thermodynamic branch becomes less obvious. Oscillations around a transient state which is far from equilibrium are possible, and in fact they have been observed experimentally (see section II). However, these oscillations are necessarily damped since, by the second law, the system will eventually go to equilibrium. Strictly speaking, they do not arise beyond an instability of a time-dependent state. They belong, as transient states do, to the thermodynamic branch. Nevertheless, in some cases they can be treated as the oscillations in open systems. Imagine a reaction mixture where some substances are put initially in a large excess and let the reaction rates be not too fast, say of the same order of magnitude as the inverse characteristic times for diffusion or heat conduction. One can then consider for an extended interval of time the intermediate products as an open system subject to a quasi-steady flow of the initial excess chemicals. Such systems can exhibit nearly sustained oscillations, similar in nature and in origin to the oscillations observed in strictly open systems.

### 3. *Mathematical and Physical Prerequisites for Chemical Oscillations*

In concluding the theoretical part of our discussion, it would be desirable to give some kind of classification of the types of chemical systems that may give rise to sustained oscillations. From the discussion of sections I.C.3 and I.D.2 it is obvious that these systems must be nonlinear, but one would like to be more specific about the types of nonlinearities that can be involved.

From the purely mathematical viewpoint, a partial answer to this question can be given only in the case of homogeneous systems of two variables. Let us write the chemical kinetic equations in the form

$$\begin{aligned} dX_1/dt &= v_1(X_1,X_2) \\ dX_2/dt &= v_2(X_1,X_2) \end{aligned} \tag{15}$$

A straightforward application of the results of section I.C.3 leads to the following criteria for $v_1$, $v_2$.

**C1**. The expression div $\mathbf{v} \equiv (\partial v_1/\partial X_1) + (\partial v_2/\partial X_2)$ must change sign in the $(X_1, X_2)$ plane.

**C2**. In the most common case of a limit cycle bifurcating from a multiple focus[32] (case (a) of section I.C.3), the Jacobian determinant

$$\begin{vmatrix} (\partial v_1/\partial X_1)_0 & (\partial v_1/\partial X_2)_0 \\ (\partial v_2/\partial X_1)_0 & (\partial v_2/\partial X_2)_0 \end{vmatrix} \tag{16}$$

evaluated at the steady state should remain positive at and beyond the critical set of values of the parameters for which div $\mathbf{v}$ vanishes.

$$\Delta = (\partial v_1/\partial X_1)_0(\partial v_2/\partial X_2)_0 - (\partial v_1/\partial X_2)_0(\partial v_2/\partial X_1)_0 > 0 \tag{17}$$

In this way small perturbations around the steady state will present undamped oscillations at the critical point.

The requirement about div $\mathbf{v}$ implies that at least one of the $(\partial v_i/\partial X_i)_0$'s should remain positive around the critical point.[33] The most obvious physical way to fulfill this property is the following.

**C3**. At least one of $X_1$, $X_2$ catalyzes its own production, either directly through an *autocatalytic reaction step* or indirectly by *activating* one substance which produces it.

As an example of **C3**, consider the sequence of autocatalytic steps

$$\begin{aligned} A + X_1 &\xrightarrow{k_1} 2X_1 \\ X_1 + X_2 &\xrightarrow{k_2} 2X_2 \end{aligned} \tag{18}$$

The contributions of these steps to $dX_1/dt$, $dX_2/dt$ are

$$\begin{aligned} v_1 &= k_1AX_1 - k_2X_1X_2 \\ v_2 &= k_2X_1X_2 \end{aligned} \tag{19}$$

We see that

$$\text{div } \mathbf{v} = k_1A - k_2X_2 + k_2X_1$$

which may indeed change sign for sufficiently large $X_2$. Notice that eq 18 by itself cannot exhibit limit cycle behavior but needs to be coupled with additional steps.

An example of activation giving rise to a limit cycle in a two-variable system is provided by Sel'kov's model of glycolytic oscillations which is discussed in section III.A.

Combining **C1** and (17), we also conclude that $(\partial v_1/\partial X_2)_0(\partial v_2/\partial X_1)_0$ should remain negative in some neighborhood. This condition is equivalent to the following.

**C4**. Either $X_1$ (or $X_2$) takes part in the autocatalytic process producing $X_2$ (or $X_1$) according to **C3** or the reaction step involves at least one cross-catalytic step wherein $X_1$ acts as catalyst to produce $X_2$; then $X_2$ is converted (directly or through another catalyst) to $X_1$.

An example of the first possibility is provided again by (16). The second possibility may be illustrated by the example

$$\begin{aligned} A + X_1 &\xrightarrow{k_1} X_1 + X_2 \\ X_2 &\xrightarrow{k_2} X_1 \end{aligned} \tag{20}$$

with partial rates (see also section III.A.3)

$$\begin{aligned} v_1 &= \frac{k_2x_2}{1 + \sigma x_2{}^p} \\ v_2 &= k_1AX_1 - \frac{k_2x_2}{1 + \sigma x_2{}^p} \end{aligned} \tag{21}$$

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(32) P. Hanusse, *C. R. Acad. Sci., Ser. C*, **274**, 1245 (1972), has shown that a two-variable system with mono- and bimolecular steps only cannot have a limit cycle encircling a multiple focus.

(33) In principle, the particular case $\partial v_1/\partial X_1 = \partial v_2/\partial X_2 = 0$ at the critical point is possible.

We see that

$$\partial v_2/\partial X_1 = k_1 A > 0$$

$$\frac{\partial v_1}{\partial X_2} = \frac{k_2 + k_2 \sigma X_2{}^{\rho}(1 - \rho)}{(1 + \sigma X_2{}^{\rho})^2} \tag{22}$$

$\partial v_1/\partial X_2$ may become negative for $\rho > 1$. This shows at the same time that the second reaction (eq 20) should be inhibited by the substrate. Examples of this type have been worked out by Sel'kov.

For more than two variables the situation changes considerably. It has been shown on models (see also section III.A) that inhibition alone, without additional catalytic steps, can give rise to sustained oscillations.

In addition to the criteria formulated here, useful information can often be obtained by analyzing the bilinear form (eq 14) appearing in the thermodynamic stability condition. We see immediately the following.

**C5**. The bifurcation of a limit cycle from the steady state necessitates steps contributing negative amounts to the excess entropy production $\delta^2 \mathcal{P}$.

This criterion may be satisfied by autocatalytic steps (see also section I.C.3) but is much more general. It would be very interesting to analyze the sign of the bilinear form (eq 14) in the most general case and find the conditions imposed on the kinetics by a change of sign of the inequality.[34]

In conclusion, *positive or negative feedback, sometimes combined with cross-catalysis, is a necessary prerequisite for the existence of stable, sustained oscillations.*

## *II. Experimental Results*

### A. Homogeneous Oscillations

The earliest reported periodic chemical reaction in homogeneous solution is the catalytic decomposition of hydrogen peroxide by the iodic acid–iodine oxidation reduction couple.

Caukins and Bray[35] discovered the periodic nature of the reaction while investigating the dual role of $H_2O_2$ as an oxidizing and reducing agent. The reaction mixture which was studied consisted of $H_2O_2$, $KIO_3$, and $H_2SO_4$, and the experiments were performed at 60° (though oscillations were obtained at 25° as well). $H_2O_2$ oxidizes $I_2$ to $HIO_3$

$$5H_2O_2 + I_2 = 2HIO_3 + 4H_2O \tag{23}$$

and reduces $HIO_3$ to $I_2$.

$$5H_2O_2 + 2HIO_3 = 5O_2 + I_2 + 6H_2O \tag{24}$$

Thus $H_2O_2$ apparently dismutates

$$H_2O_2 = H_2O + 0.5O_2 \tag{25}$$

After an initial induction period the rate of oxygen evolution and the concentration of iodine oscillate, with the maximum rate of $O_2$ evolution occurring during the phase of decreasing $I_2$ concentration. The period of oscillation is especially sensitive to the initial concentration of $H_2SO_4$. Bray offered no explanation for the oscillation other than referring to Lotka's theoretical work (see section III.A) and suggesting that autocatalysis was involved in the mechanism.

Rice and Reiff[36] reported that the periodicities disappeared when $H_2O_2$ was distilled, thus implicating commercially added inhibitors in the mechanism. They further suggested that the periodicities resulted from a heterogeneous reaction on the surface of dust particles. Peard and Cullis[37] performed experiments in the temperature range 57–77°. They pointed out that $I_2$ is autocatalytically formed in reaction 24 and suggested that the physical removal of iodine by the evolving oxygen could account for the oscillations: as $[I_2]$ increases, the rate of $O_2$ evolution increases; eventually the rate of removal of $I_2$ by the evolving $O_2$ overtakes the rate of formation by the chemical reaction and $[I_2]$ decreases, thereby decreasing the rate of $O_2$ evolution; the $[I_2]$ again increases and the process repeats itself. Shaw and Pritchard[38] observed that the exclusion of daylight suppressed the oscillation and suggested that photochemical and heterogeneous effects were the source of the oscillation. In a later paper,[39] they indicated that the formation and evolution of oxygen bubbles were probably responsible for the oscillation. Bray himself had already eliminated this possibility by observing oscillations at 25° without the formation of bubbles.

Degn, in a very interesting paper,[40] challenged most earlier interpretations of the oscillations and also advanced his own theory. By obtaining oscillations in the dark, he ruled out the importance of photochemical effects and by obtaining oscillations with $Na_2O_2$ and distilled $H_2O_2$ the importance of the inhibitor was eliminated. In addition, the oscillations were unaffected by stirring, thus eliminating the importance of hetereogeneous (gradient) effects.

Degn proposed that reactions 23 and 25 took place *via* a free radical chain reaction and that the oscillations were due to a quadratic branching of the chain. The free radical intermediates were not identified experimentally and no detailed mechanism was proposed. In a separate paper[41] a formal reaction scheme representing a quadratically branched chain reaction was shown to give rise to oscillations similar to the experimental results.

The most recent work on this reaction has been carried out by Vavilin and Zhabotinskii,[42] Woodson and Liebhafsky,[43] and Liebhafsky, Matsuzaki, and Woodson.[44] Woodson and coworkers have shown that in addition to the oscillations in the $O_2$ evolution rate and iodine concentration there are also oscillations in the iodide concentration and the hydrogen ion concentration, as well as oscillations in the temperature.

In spite of the many experimental studies of the reaction, the detailed mechanism of the oscillation is still an open question. In fact, the cause of the oscillation itself remains a matter of controversy.

Belousov[20] reported a second case of an oscillatory chemical reaction in homogeneous solution: the oxidation of citric acid by potassium bromate catalyzed by the ceric–cerous ion couple. Zhabotinskii[45,46] continued to study the reaction and demonstrated that the cerium cat-

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(34) An attempt in this direction has already been made by J. Perdang, Ph.D. dissertation, University of Liège, 1970.

(35) W. C. Bray, *J. Amer. Chem. Soc.*, **43**, 1262 (1921); see also, W. C. Bray, and H. A. Liebhafsky, *ibid.*, **53**, 38 (1931).

(36) F. O. Rice and M. Reiff, *J. Phys. Chem.*, **31**, 1352 (1927).

(37) M. G. Peard and C. F. Cullis, *Trans. Faraday Soc.*, **47**, 616 (1951).

(38) D. M. Shaw and M. O. Pritchard, *J. Phys. Chem.*, **72**, 1403 (1968).

(39) D. M. Shaw and M. O. Pritchard, *J. Phys. Chem.*, **72**, 2693 (1968).

(40) H. Degn, *Acta Chem. Scand.*, **21**, 1057 (1967); see also H. Degn and J. Higgins, *J. Phys. Chem.*, **72**, 2692 (1968).

(41) P. Lindblad and H. Degn, *Acta Chem. Scand.*, **21**, 791 (1967).

(42) V. A. Vavilin and A. M. Zhabotinskii, ref 5, Vol. I, p 220.

(43) J. H. Woodson and H. A. Liebhafsky, *Nature (London)*, **224**, 690 (1969).

(44) H. A. Liebhafsky, I. Matsuzaki, and J. H. Woodson, *Bull. Chem. Soc. Jap.*, **43**, 3317 (1970).

(45) A. M. Zhabotinskii, *Dokl. Akad. Nauk SSSR*, **157**, 392 (1964).

(46) A. M. Zhabotinskii, *Biofizika*, **9**, 306 (1964).

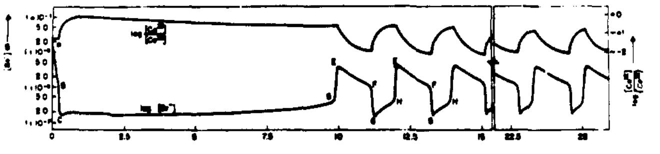

**Figure 1.** Potentiometric traces at 25° of log [$Br^-$] and log [$Ce^{III}$] *vs.* time during the Belousov reaction: [malonic acid] = 0.032 *M*, [$KBrO_3$] = 0.063 *M*, [$Ce(NH_4)_2(NO_3)_5]_0$ = 0.001 *M*, [$H_2SO_4$] = 0.8 *M*, and [$KBr]_0$ = 1.5 × $10^{-5}$ *M* (from R. J. Field, *J. Chem. Educ.*, **49**, 308 (1972)).

alyst could be replaced by manganese or ferroin and that the citric acid reducing agent could be replaced by a variety of organic compounds either possessing a methylene group or easily forming such a group during oxidation (*e.g.*, malonic acid, bromomalonic acid, acetoacetic acid, oxalacetic acid, acetonedicarboxylic acid). Zhabotinskii reported experimental studies of the reaction mixture consisting of potassium bromate, ceric sulfate, and malonic acid or bromomalonic acid dissolved in dilute sulfuric acid. With bromomalonic acid, oscillations in the ceric-cerous concentration begin immediately, whereas with malonic acid there is an induction period. Zhabotinskii qualitatively explained the oscillations and the induction period in the following way. In the case of bromomalonic acid, potassium bromate oxidizes the cerous ion

$$Ce^{3+} \xrightarrow{BrO_3^-} Ce^{4+} \qquad (26)$$

and bromomalonic acid reduces the ceric ion

$$Ce^{4+} \xrightarrow{C_3H_3BrO_4} Ce^{3+} + Br^- \qquad (27)$$

Reaction 26 is a chain reaction competitively inhibited by a low concentration of the bromide ion formed during reaction 27. Consequently, reaction 26 does not proceed while $Ce^{4+}$ remains in the system. $Ce^{3+}$ accumulates while reaction 27 proceeds. Then, with reaction 27 complete, $Ce^{3+}$ is rapidly depleted by reaction 26, an autoaccelerating reaction, and the process repeats itself.

The induction period encountered when malonic acid is used as the reducing agent is a measure of the time necessary for bromomalonic acid to accumulate (through the bromination of malonic acid by the reduction products of reaction 26) and reaction 27 to begin. Since malonic acid also reduces the ceric ion

$$Ce^{4+} \xrightarrow{CH_2(COOH)_2} Ce^{3+} \qquad (28)$$

during the induction period, reactions 26 and 28 maintain, relatively constant, the concentrations of ceric and cerous ions.

Zhabotinskii demonstrated that $Br^-$ is indeed an inhibitor by suppressing oscillations with a continuous addition of $Br^-$ to the mixture. In addition, Vavilin, Zhabotinskii, and Zaikin[47] suppressed oscillations by irradiating the reaction system with ultraviolet light. Apparently, the radiation decomposes bromine-containing compounds, releasing bromide ions which then inhibit the reaction.

In addition to further studies by Zhabotinskii and his collaborators,[48] important investigations of the reaction have also been carried out by Degn[49] who suggests that dibromomalonic acid, and not bromide, is the important inhibitor. Kasperek and Bruice[50] suggested that colloidal complexes were necessary for the oscillation. Most recently, Field, Körös, and Noyes[51-53] completed an extensive series of experiments on the malonic acid reaction and proposed a detailed kinetic mechanism of the reaction. Potentiometric traces of log [$Ce^{4+}$]/[$Ce^{3+}$] and log [$Br^-$] are shown in Figure 1.

The stoichiometry of the overall reaction is

$$3BrO_3^- + 5CH_2(COOH)_2 + 3H^+ \rightarrow 3BrCH(COOH)_2 + HCOOH + 4CO_2 + 5H_2O \qquad (29)$$

There are four principal reactions whose stoichiometry is given by the following processes.

$$BrO_3^- + 2Br^- + 3CH_2(COOH)_2 + 3H^+ \rightarrow 3BrCH(COOH)_2 + 3H_2O \qquad (30)$$

$$BrO_3^- + 4Ce^{3+} + CH_2(COOH)_2 + 5H^+ \rightarrow BrCH(COOH)_2 + 4Ce^{4+} + 3H_2O \qquad (31)$$

$$6Ce^{4+} + CH_2(COOH)_2 + 2H_2O \rightarrow 6Ce^{3+} + HCOOH + 2CO_2 + 6H^+ \qquad (32)$$

$$4Ce^{4+} + BrCH(COOH)_2 + 2H_2O \rightarrow 2CO_2 + 5H^+ + Br^- + 4Ce^{3+} + HCOOH \qquad (33)$$

The essential nonlinearity in the problem arises in connection with reaction 31 whose underlying steps involve a first-order autocatalytic production of $HBrO_2$ along with its second-order decomposition. In addition, $HBrO_2$ participates in reaction 30, and its concentration depends critically on [$Br^-$]: when [$Br^-$] is small, [$HBrO_2$] is large and reaction 31 is significant; when [$Br^-$] is large [$HBrO_2$] is small and reaction 31 is slow. Thus, bromide inhibits reaction 31 and, in fact, there exists a well-defined threshold concentration turning reaction 31 on and off. Using these facts the oscillations in [$Ce^{4+}$]/[$Ce^{3+}$] can be accounted for in the following very simple qualitative manner.[54] The reader should consult the papers of Noyes and coworkers[52] for a complete discussion of the oscillatory mechanism including a detailed *kinetic* description of the individual processes and experimental evidence in support of the mechanism. Initially all the cerium is in the trivalent state, reaction 31 is inhibited, and [$Br^-$] is depleted by reaction 30. When the bromide concentration is low enough reaction 31 begins and [$Ce^{4+}$] accumulates until its production by reaction 31 is balanced by its destruction through reaction 32; the induction period begins and [$Ce^{4+}$]/[$Ce^{3+}$] remains relatively constant. During the induction period reaction 31 produces bromomalonic acid and reaction 33 begins to produce $Br^-$. $Br^-$ does not immediately accumulate but eventually its concentration is high enough to inhibit reaction 31: [$Ce^{4+}$] falls as a result of reaction 32 and [$Br^-$] falls as a result of reaction 30. When [$Br^-$] reaches a critical value, reaction 31 begins again and [$Ce^{4+}$] increases. Once again [$Br^-$] accumulates, reaction 31 shuts off, [$Ce^{4+}$] falls, and the process repeats itself. There is no further induction period because the concentration of bromomalonic acid is such that the critical bromide concentration necessary to shut off reaction 31 is quickly attained.

Franck and Geiseler,[55] and more recently Busse,[56] have reported temperature oscillations during the reaction of the order of 1°. It is unlikely that the heat of reac-

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(47) V. A. Vavilin, A. M. Zhabotinskii, and A. N. Zaikin, *Russ. J. Phys. Chem.*, **42**, 1649 (1968).

(48) See ref 5, various communications by A. M. Zhabotinskii, *et al.*

(49) H. Degn, *Nature (London)*, **213**, 589 (1967).

(50) G. J. Kasperek and T. C. Bruice, *Inorg. Chem.*, **10**, 382 (1971).

(51) R. M. Noyes, R. J. Field, and E. Körös, *J. Amer. Chem. Soc.*, **94**, 1394 (1972).

(52) R. J. Field, E. Körös, and R. M. Noyes, preprint.

(53) See also R. M. Noyes, R. J. Field, and R. C. Thompson, *J. Amer. Chem. Soc.*, **93**, 7315 (1971).

(54) For further discussion, see R. J. Field, *J. Chem. Educ.*, **49**, 308 (1972).

(55) U. Franck and W. Geiseler, *Naturwissenschaften*, **58**, 52 (1970).

(56) H. G. Busse, *Nature (London)*, *Phys. Sci.*, **233**, 137 (1971).

tion is involved in the oscillatory mechanism. The work of Field, Körös, and Noyes establishes with fair certainty that the oscillations are a purely kinetic phenomenon.[57]

Recently, Bowers, *et al.*,[58] reported oscillations in the oxidation of 2,4-pentanedione by bromate catalyzed by manganese. Bowers, *et al.*, observed that the oscillatory behavior damped away faster with stirring than without, and concluded that a heterogeneous step[59] is essential to the reaction mechanism.

Concentration oscillations occurring during the isothermal decomposition of sodium dithionite in aqueous solution have been reported by Lynn,[60] Rinker,[61] and Rinker, Lynn, Mason, and Corcoran.[62] The dithionite decomposition follows the stoichiometry

$$2S_2O_4^{2-} + H_2O \rightarrow S_2O_3^{2-} + 2HSO_4^{-}$$

Rinker, *et al.*, reported oscillations in the dithionite ion concentration in buffered solution (pH range 4–7) and oscillations in the hydrogen ion concentration as well in unbuffered solutions. At 60° the oscillations are marked, while at 80° they have practically disappeared. Further investigations[63] of the reaction are needed to identify the intermediates and satisfactorily elucidate the oscillatory mechanism.

## B. Heterogeneous and Inhomogeneous Oscillations

Often, chemical reactions by themselves will not lead to oscillatory behavior, but, when coupled to physical processes such as film formation or diffusion, oscillatory behavior appears. Representative examples of such phenomena are presented below.

Numerous investigators[64-66] have observed a periodic luminescence during the vapor-phase oxidation of phosphorus. Weiser and Garrison[67] attributed the phenomena to a periodic breakdown and re-formation of a protective oxide film. Rayleigh[68] observed travelling pulses of luminosity in a cylindrical reaction vessel with phosphorus at one end and an oxygen inlet at the other. Waran[69] assumed that for luminous oxidation to occur the partial pressure ratio of oxygen and phosphorus vapors must reach a certain minimum value. He attributed the periodic flashes to the existence of such a critical ratio which is alternately being destroyed by the oxidation and reestablished by diffusion. Semenov[70] determined that phosphorus oxidation is a branched-chain reaction. Nevertheless, the mechanism of oscillation is still unknown.

Bredig and Weinmayr[71] discovered that the catalytic decomposition of hydrogen peroxide by mercury in slightly alkaline solution is periodic (alkali concentration range: $10^{-3}$–$10^{-4}$ $N$). Further work on the reaction was carried out by Bredig and Wilke,[72] Bredig and Kerb,[73] and Lemoine.[74] Fredenhagen[75] and Antropoff[76] attributed the oscillation to the observed periodic breakdown and formation of a protective oxide film on the mercury surface. The nature of the interfacial processes and the coupling of these processes to the kinetics of the decomposition were not accounted for.

Ostwald[77] observed periodicities in the rate of hydrogen evolution during the dissolution of chromium in hydrochloric acid. Hedges and Myers[78] found similar periodicities in a variety of systems, for example, zinc and hydrochloric acid, sodium amalgam and water, and aluminum and potassium carbonate. They suggested that oscillations occur in such systems only in the presence of a third component (a colloid or a second, properly prepared metal), often contaminating the reaction vessel and apparently acting as a catalyst. No mechanism for the oscillation was proposed.

Investigations of the periodic evolution of carbon monoxide during the dehydration of formic acid by sulfuric

$$HCOOH = CO + H_2O$$

acid were carried out by Morgan.[79] He attributed the oscillation to a supersaturation effect. Hedges and Myers[78] pointed out that a simple supersaturation phenomenon could not account for the fact that the purest acids suppressed oscillations, while alcohols induced oscillations.

## C. Thermochemical Oscillations

Chemical oscillations that are driven by temperature changes and which would not occur in isothermal systems have been of considerable interest to chemical engineers in the design and stability control of chemical reactors.[80-82] Recently, Bush[83] reported a detailed theoretical and experimental investigation of the occurrence of such oscillations during the vapor-phase chlorination of methyl chloride.

Periodicities, apparently originating in temperature changes, have also been reported by various workers[84-86] in the combustion of hydrocarbon fuels.

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(57) See J. F. Lefelhocz, *J. Chem. Educ.*, **49**, 312 (1972), for a discussion of an undergraduate kinetics experiment.

(58) P. G. Bowers, K. E. Caldwell, and D. F. Prendergast, *J. Phys. Chem.*, **76**, 2185 (1972).

(59) See Kasperek and Bruice[50] for a discussion of this idea in connection with the Belousov–Zhabotinskii reaction.

(60) S. Lynn, Ph.D. Thesis, California Institute of Technology, 1954.

(61) R. G. Rinker, Ph.D. Thesis, California Institute of Technology, 1959.

(62) R. G. Rinker, S. Lynn, D. M. Mason, and W. H. Corcoran, *Ind. Eng. Chem. Fundam.*, **4**, 282 (1965).

(63) For a mathematical model, see J. R. Bischoff and D. M. Mason, *Chem. Eng. Sci.*, **23**, 447 (1968).

(64) P. S. Munck af Rosenschöld, *Pogg. Ann. Phys. Chem.*, **32**, 216 (1834).

(65) Joubert, Thèse sur la phosphorescence du phosphore, Paris, 1874.

(66) E. Gilchrist, *Proc. Roy. Soc. Edinburgh*, **43**, 197 (1923).

(67) H. B. Weiser and A. Garrison, *J. Phys. Chem.*, **25**, 61 (1921).

(68) Lord Rayleigh, *Proc. Roy. Soc., Ser. A*, **99**, 372 (1921).

(69) H. P. Waran, *Phil. Mag.*, **45**, 1132 (1923).

(70) N. N. Semenov, "Some Problems in Chemical Kinetics," Princeton University Press, Princeton, N. J., 1959.

(71) G. Bredig and J. Weinmayr, *Z. Phys. Chem.*, **42**, 601 (1903).

(72) G. Bredig and E. Wilke, *Chem. Zentr.*, 64 (1905); *Biochem. Z.*, 11, 67 (1908).

(73) G. Bredig and J. W. Kerb, *Verh. Naturhist. Med. Vereins. Heidelberg*, **10**, 23 (1909).

(74) G. Lemoine, *C. R. Acad. Sci.*, **162**, 580 (1916).

(75) K. Fredenhagen, *Z. Elektrochem.*, 11, 859 (1907).

(76) A. v. Antropoff, *Z. Phys. Chem.*, **62**, 513 (1908).

(77) W. Ostwald, *Z. Phys. Chem.*, **35**, 33, 204 (1900); *Phys. Z.*, 1, 88 (1900).

(78) E. S. Hedges and J. E. Myers, *J. Chem. Soc., London, Trans.*, 604 (1924). These authors have also written a book, "The Problem of Physicochemical Periodicity," Arnold, London, 1926, which is an interesting source of early investigations of chemical periodicity. Two additional surveys of chemical periodicity are: Kreman, *Samm. Chem. Vort.*, **19**, 298 (1913); Veil, Actualités Scientifiques et Industriels, Noisy, 1934.

(79) J. S. Morgan, *J. Chem. Soc., London, Trans.*, **109**, 274 (1916).

(80) R. Aris and N. R. Amundson, *Chem. Eng. Sci.*, **7**, 121 (1957).

(81) J. M. Douglas and D. W. T. Rippon, *Chem. Eng. Sci.*, **21**, 305 (1966).

(82) E. D. Gilles and H. Hoffman, *Chem. Eng. Sci.*, **15**, 328 (1961).

(83) S. F. Bush, *Proc. Roy. Soc., Ser. A*, **309**, 1 (1964).

(84) H. A. Beatty and G. Edgar, *J. Amer. Chem. Soc.*, **56**, 112 (1934).

(85) D. M. Newitt and L. S. Thornes, *J. Chem. Soc.*, 1656, 1665, 1669 (1937).

At low temperatures ($\leq 400°$) the incomplete combustion of alkanes and related substances (*e.g.*, propane, butane, heptane, butanone) gives rise to the periodic appearance of pale blue, slowly travelling flames which are accompanied by only small temperature and pressure rises, so-called cool flames.[87,88] Walsh[89] and Frank-Kamenetzkii[90-92] attributed the periodicity to the reaction mechanism which they described symbolically in terms of a Volterra-Lotka model.[93] On the other hand, Pease[86,94] argued that the oscillation originated in the exothermicity of the reaction. Pointing to a region of negative temperature coefficient for propane oxidation, he reasoned that self-heating brought the reaction system into this region causing a reduction in the rate and a consequent temperature drop, whereupon, the process would repeat itself. Sal'nikov[95] discussed the oscillation in terms of a homogeneous exothermic reaction

$$A \xrightarrow{1} X \xrightarrow{2} B$$

If step 2 is highly exothermic and its temperature coefficient much greater than the temperature coefficient of step 1, the reaction begins, the temperature rises, X is consumed by step 2, the temperature drops, X is replenished, and the process repeats itself.

At first sight this intuitive argument appears to contradict the conclusions of part I (see especially section I.D.3). It should be pointed out, however, that most of the theoretical results of section I.D.3 refer to *isothermal* situations. When the effect of temperature is taken into account, a new element favoring oscillations is added owing to the highly nonlinear dependence of the reaction rate constants on the temperature.

Bardwell and Hinshelwood[88] extended these ideas in their discussion of butanone oxidation. They suggested that the oxidation rate was proportional to the concentration of a labile intermediate (a peroxide) which participated in a degenerate branching reaction. Self-heating of the overall reaction and a branching factor that can change sign (due to different temperature coefficients of the destructive and regenerative chain processes) will then lead to oscillatory behavior in a manner similar to Pease's original suggestion.

Periodicities have also been noted in the oxidation of hydrogen sulfide

$$2H_2S + 3O_2 = 2H_2O + 2SO_2$$

giving rise to a succession of incomplete explosions.[96,97] No mechanism for the oscillations has been proposed.

## D. Electrochemical Oscillations

The earliest reported examples of chemical oscillations were found in electrochemical systems. As early as 1828 Fechner[98] reported oscillations in passivating electrodes. Today there are countless examples of current oscillations under potentiostatic conditions[99,100] and potential oscillations under galvanostatic conditions.[101,102] Potential oscillations under zero current conditions have also been reported[103] and are of especial interest to corrosion scientists.[104]

Most studies have examined oscillations associated with anodic processes at passivating electrodes, as, for example, Fe in $HNO_3$,[105,106] but anodic oscillations at nonpassivating electrodes are also well known, as in the case of $H_2$ oxidation on Pt.[107-109] In addition, cathodic oscillations have been reported in many systems, for example, in the reduction of $HCrO_4^-$ on Hg.[110-112] Cathodic and anodic oscillations can be further distinguished by the importance of diffusion; for example, ethylene oxidation is diffusion controlled,[113] whereas oscillations in formate oxidation persist in the absence of diffusion.[114] It is generally assumed that oscillations accompanying anodic processes involve the periodic breakdown and formation of an oxide film on the electrode. But the existence of cathodic oscillations indicates that film formation is not essential for electrochemical oscillation.[110,115]

Bonhoeffer[116,117] as well as Franck[118] have discussed the conditions for instability of the steady-state in electrochemical systems. Franck has also discussed a mathematical model of oscillations at passivating electrodes.[119]

Indira, Rangarajan, and Doss[120] have discussed the solid-state effects involved in the passivation process and responsible for potential oscillations. Degn[121] has formu-

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lated a simple mathematical model to account for relaxation-type oscillations in passivating systems. Essential for the occurrence of oscillations in this theory are an external series resistance (*e.g.*, the solution resistance), concentration polarization, and a region of negative Tafel slope. Initially the current is high; it decreases because of concentration polarization, driving up the electrode potential (to compensate the *iR* drop across the external resistance). The electrode potential reaches the passivation threshold, whereupon the current abruptly drops; the concentration polarization decreases and the electrode potential falls. It reaches the Flade potential and becomes active, the current increases, and the process repeats itself. De Levie and coworkers[115,122-124] have reported current oscillations in the electrocatalytic reduction of In(III) in aqueous thiocyanate solution and have discussed the oscillations in terms of the electrical properties of the circuit;[125] in particular, they relate the oscillation to a negative charge-transfer resistance, a negative diffusion impedance, and a positive solution resistance and double layer capacitance.

Conway and coworkers[113,114,126] have investigated the occurrence of oscillations in ethylene oxidation and have ascribed the oscillations to a coupling between diffusion and an autocatalytic stripping reaction of an oxide film. Oscillations not under diffusion control, as, for example, in formate oxidation (oscillatory behavior is obtained with both stationary and rotating electrodes), are accounted for in terms of cross-coupling between chemisorption and electrochemical oxidation steps and an autocatalytic surface stripping reaction.

Most of the theoretical work on electrochemical oscillations has involved the description of a simplified model and the subsequent determination of instability (stability) criteria. A complete mathematical treatment of the oscillatory behavior starting from the relevant mass transport and rate equations is still to be done.

## E. Biochemical Oscillations

### *1. Metabolic Level*

Oscillations in biochemical systems are perhaps the most intriguing of all chemical oscillations. Indeed, as we have already mentioned, the present interest in chemical oscillations is due largely to the discovery of oscillating biochemical phenomena.

Such phenomena have been observed on both the genetic (*e.g.*, enzyme synthesis) and metabolic level. The most completely investigated and well-understood instance of oscillatory behavior at the metabolic level involves the glycolytic system.[127] Oscillations of NADH were first reported by Duysens and Amesz.[128] Subsequently Ghosh and Chance[12,129] reported damped oscillations in the NADH level in suspensions of intact yeast cells, and, later, damped and sustained oscillations were obtained in cell free extracts.[130,131] In fact, all glycolytic metabolites have been observed to oscillate.[132] pH and $CO_2$ production oscillate as well[133,134] (see Figure 2). Glycolytic oscillations have also been observed in suspensions of tumor cells[135] and beef heart extracts,[136] but the determination of the oscillatory mechanism has been carried out only in the yeast system.

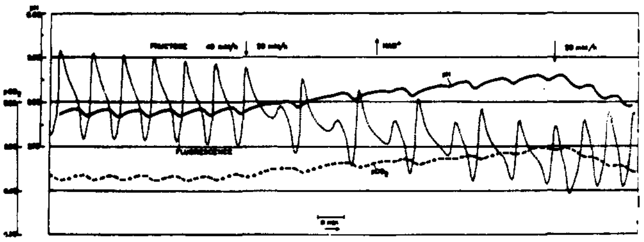

**Figure 2.** Recording of NADH by fluorimetry in an extract of *S. carlsbergensis*. NADH scale in arbitrary units. $pCO_2$ scale corresponds to pH meter readings. The arrows indicate change in input rate (from B. Hess and A. Boiteux, "Regulatory Functions of Biological Membranes," Elsevier, Amsterdam, 1968)).

Extensive experimental investigations have revealed that the source of the oscillation lies in the action of phosphofructokinase (PFK).[4,132,134,137] Apparently, PFK, an allosteric enzyme, is activated by both its products, fructose diphosphate (FDP) and ADP (*via* AMP), and also by one of its substrates, fructose 6-phosphate (F6P). Oscillatory behavior is propagated along the glycolytic pathway by the coupling of the ATP system with all control points along the pathway. The various theoretical models of oscillating glycolysis are discussed in section III.A.

Oscillatory phenomena in soluble enzyme systems were first observed by Yamazaki, *et al.*,[13,138] in the aerobic oxidation of NADH by horseradish peroxidase. Subsequently, oscillations in the concentrations of oxygen and compound III were also reported for the lactoperoxidase system.[139] Degn[140,141] obtained oscillations with dehydroxyfumarate and indole-3-acetic acid in place of NADH. Yamazaki[138] attributed the oscillatory behavior to the regulatory properties of compound III, but Degn[142] has disputed the importance of compound III and favors a branched-chain reaction control of the oscillations in which compound III has no essential role.

Oscillatory behavior in the dark cycle of photosynthesis was first observed by Calvin and Wilson[143] in the form of

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$CO_2$-dependent oscillatory transients. Chernavskaya and Chernavskii[144] subsequently proposed a kinetic model to account for photosynthetic oscillations. van der Veen[145] observed oscillations in the $CO_2$ consumption in green leaves, and recently Bannister[146] induced oscillations in the $O_2$ evolution with changes in white illumination. Changes in white illumination have also been reported to induce oscillation in the trans-membrane potential difference in the alga *Hydrodictyon reticulatum.*[147]

### 2. *Mitochondria, Membranes, and Muscles*

Mitochondrial oscillations of various types have been reported by several investigators.[148-150] Oscillations in ion movements[151,152] and respiratory rate[153] have been noted, as well as volume changes[154] and cyclic variations in the redox state of flavoproteins,[155] cytochromes,[155] and pyridine nucleotides.[155,156] Oscillations have been induced with antibiotics such as valinomycin[148] and various nonaction homologs,[157] as well as chelating agents like EDTA,[153] all of which are known to increase mitochondrial permeability to monovalent cations.[158] In addition $Mg^{2+}$, an inhibitor of cation permeability, has been shown to inhibit oscillatory behavior.[159] Thus, while the oscillatory mechanisms are still unknown, a very close coupling between respiratory control and ion permeability is undoubtedly essential.

Periodic membrane processes not directly coupled to chemical reactions have been observed in both natural and artificial membrane systems.[160] For example, Kishimoto observed repetitive action potentials in the alga *Nitella.*[161] Further oscillations in *Nitella* were induced by variations in the ionic concentration of the surrounding medium.[162] Also, Teorell reported the induction of potential oscillations in isolated frog skin by Li ions.[163] In addition, Teorell demonstrated pressure, electrical resistance, and potential oscillations across a porous glass membrane separating NaCl solutions of different concentrations and under constant current conditions.[164,165] Mueller and Rudin[166] found potential oscillations in bimolecular lipid membranes, and Shashua[167] observed oscillations across a thin polyelectrolyte double membrane, also under constant current conditions. Finally, Huxley,[168] Fitzhugh,[169] and Nagumo, *et al.*,[170] have indicated that oscillatory solutions can exist for the Hodgkin–Huxley equation. And Teorell[165,171] as well as Kobatake and Fujita[172] have presented theories of oscillatory behavior in membranes.

Oscillatory phenomena in muscles are also well known.[4] For example, Golenhofen has reported oscillations of the spontaneous activity of tonicity of guinea pig *Taenia coli.*[173] And of particular importance are the mechanically induced oscillations, *e.g.*, forced fiber length changes, that have helped elucidate the mechanochemical coupling in muscular contraction.[174,175] In addition, Shnoll[176] has recently reported spontaneous oscillations in the amount of titratable SH groups, ATPase activity and the absorption properties of concentrated actomyosin preparations.

### 3. *Genetic Level and Oscillations in Continuous Cell Culture*

Oscillations in enzyme synthesis have been observed by many investigators.[177,178] Knorre[14] reported oscillations in the rate of $\beta$-galactosidase synthesis in asynchronously growing cultures of *E. coli* with a period comparable to the generation time.

Also, oscillations in pyruvate synthesis in a continuous culture of *E. coli* B have been reported by Sikyta and Slezák.[179] Masters, Kuempel, and Pardee,[180,181] Donachi,[182] and Masters and Pardee[183] have all reported periodic enzyme synthesis in synchronous populations of *Bacillus subtilis:* usually a single burst of enzyme activity per cell cycle. Masters and Donachie[184] further demonstrated such periodicity in aspartate transcarbamylase and ornithine transcarbamylase activity in the absence of DNA synthesis, thus indicating autonomous control pro-

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cesses. Goodwin[185] has proposed an entrainment model coupling DNA replication with the enzyme control circuit to account for the fact that the cell cycle period corresponds to the period of the enzyme activity oscillation. Such a coupling is, of course, related to the Jacob–Monod model of induction and repression (see section III.A). Oscillatory behavior in mammalian cells was observed by Klevecz[186] in the periodic synthesis of lactate dehydrogenase in Chinese hamster cells: cell cycle time, 11.5–12 hr; enzyme synthesis period, 3.5 hr.

Mention should also be made of the recently discovered periodicities in transcription initiation. Baker and Yanofsky[187] and Imamoto[188] observed oscillations in the initiation of transcription of the tryptophan operon in *E. coli*, and Contesse, Crépin, and Gros[189] have recently reported similar oscillations for the lactose operon. The mechanism of the phenomenon is not yet understood.

In addition to the periodic pyruvate synthesis reported by Sikyta and Slezák,[179] oscillations in continuous cell cultures have been reported by Maxon[190] in cell concentration and by Harrison[191] and Harrison and Pirt[192] in NADH concentration and respiratory rate. Degn and Harrison[193] have proposed a mathematical model to account for the respiratory rate oscillations. And recently, Degn and Harrison[194] reported flavin oscillations in respiring, nongrowing samples of *Klebsiella aerogenes* harvested from a continuous culture. No significant NADH oscillations were observed, thus indicating that glycolytic oscillations are not responsible for the phenomenon.

## F. Spatial Periodicities

The appearance of periodic spatial structures[195,196] in purely chemical systems fascinates all but the most somber observer. The varied colored Liesegang rings[197,198] are a well-known example of such structures: a crystal of $AgNO_3$ is placed in the center of a thin layer of gelatin gel containing $KrCrO_4$, and after several days concentric rings of $Ag_2CrO_4$ crystals have encircled the original $AgNO_3$ crystal.[199] These rings are static; they are merely the record of a diffusion process. Recently, Flicker and Ross[200] proposed a model of coupled autocatalytic nucleation and diffusion to account for the rings. Thiéry[201] has discussed an alternative model. An intriguing example of periodic bulk motion induced by chemical reaction is the mercury heart:[202] mercury is placed in the center of a watch glass into which sulfuric acid and potassium dichromate are added and an iron nail is put into the solution close to the mercury. The mercury begins to oscillate and one of the oscillatory modes indeed resembles the beating of a heart.

Travelling waves have already been mentioned in connection with the travelling waves of luminosity[68] encountered in phosphorus oxidation. A one-dimensional pattern of layers of alternating oxidation and reduction character can be found in the Belousov–Zhabotinskii reaction. Busse[203] first reported the formation of such a pattern subject to an initial concentration gradient. Subsequently, Herschkowitz-Kaufman[204] reported similar patterns without initial concentration gradients. Furthermore, Zaikin and Zhabotinskii[205,206] have reported travelling two-dimensional waves, and Winfree[207] and Zaikin and Zhabotinskii[208] have reported spiral waves as well. The waves are generated at pacemaker centers; moreover, the centers of highest frequency eventually destroy all other centers and synchronize the entire space.[209] Field and Noyes[210] have recently proposed a qualitative explanation of the travelling waves.

# III. *Theoretical Aspects and the Origin of Chemical Oscillations*

## A. Mathematical Models and Related Problems

### 1. *Conservative Oscillations*

The first theoretical model predicting sustained oscillations was reported by Lotka in 1920[15] and may be described as follows.

$$\begin{aligned} A + X_1 &\xrightarrow{k_1} 2X_1 \\ X_1 + X_2 &\xrightarrow{k_2} 2X_2 \\ X_2 &\xrightarrow{k_3} B \end{aligned} \qquad (34)$$

The concentration of substance A is maintained constant inside the reaction volume. Thus the system is open. Because of the two autocatalytic steps, the overall reaction rates $v_1$, $v_2$ are quadratic in $X_1$, $X_2$. An analysis of the kinetic equations shows that the system admits one nontrivial steady state and an *infinity* of (undamped) periodic solutions whose periods and amplitudes depend on the initial conditions. This degeneracy is due to the existence of a constant of motion for system 34 whose expression is[16]

$$V = X_1 + X_2 - \frac{k_3}{k_2} \ln X_1 - \frac{k_1 A}{k_2} \ln X_2 = \text{constant} \qquad (35)$$

As we mentioned in sections I.C.2 and I.C.3, oscillations in conservative systems like the Lotka system *cannot* satisfy the fundamental requirement of structural sta-

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(206) See also M. T. Beck and Z. B. Váradi, *Nature (London), Phys. Sci.*, **235**, 15 (1972).

(207) A. T. Winfree, *Science*, **175**, 634 (1972).

(208) A. M. Zhabotinskii and A. N. Zaikin, ref 5, Vol. II, p 279.

(209) See sections III.A and IV.B for detailed references and for a discussion of nonlinear entrainment and synchronization.

(210) R. J. Field and R. M. Noyes, *Nature (London)*, **237**, 390 (1972).

bility and therefore must be ruled out as models for chemical oscillations observed in the laboratory.

Further examples of conservative oscillations have been given by Goodwin[211,212] and Cowan[213] in connection with models describing respectively the control of protein biosynthesis and the rhythmic activity of the nervous system.

### 2. *Simple Autocatalytic and Cross-Catalytic Models*

The first example of instability in the homogeneous steady state of a model catalytic chemical system is due to Turing.[214,215] Moore[214] had previously analyzed chains of simple autocatalytic reactions and found damped oscillations in the concentrations. Turing's model, which describes a cross-catalytic reaction chain, was dealing with the problem of morphogenetic patterns during the embryonic development. It gave rise to a space-dependent steady state of the type mentioned in sections I.C.4 and II.F. Since then, several models giving rise to sustained oscillations have also been elaborated. An exhaustive study of the autocatalytic model of an open system

$$\begin{aligned} &A \xrightarrow{k_1} X_1 \\ &2X_1 + X_2 \xrightarrow{k_2} 3X_1 \\ &B + X_1 \xrightarrow{k_3} D + X_2 \\ &X_1 \xrightarrow{k_4} E \end{aligned} \tag{36}$$

has been performed by the Brussels group. Depending on the values of the concentrations of A, B, etc., and on the diffusion coefficients of $X_1$, $X_2$, A, and B, they find that a limit cycle,[216] a spatial structure,[217,218] or even a propagating composition wave[219] may bifurcate from the steady state belonging to the thermodynamic branch. Further simple models giving rise to limit cycles as well as to multiple steady states have been worked out by several authors. For a review of these models, see ref 220.

An interesting property of nonlinear oscillators, which is also shared by chemical oscillators of the limit cycle type, is entrainment, *i.e.*, the ability to synchronize to an external (periodic) action.[18] Moreover, nonlinear oscillators can generate subharmonics of the driving frequency, *i.e.*, submultiples of this frequency. Both these phenomena can also be expected in coupled nonlinear oscillators without external influences. The mutual entrainment of populations of model nonlinear oscillators of biochemical interest has been studied by Winfree and Pavlidis in the context of the circadian clock problem (see section IV.B for references). More recently, Tyson[221] has studied the coupling "in series" of two nonlinear reactions described by reactions 36. He finds several rather unexpected effects, the most interesting of which is the appearance of quasi-periodic oscillations of one of the reaction schemes arising from the influence of the first reaction which acts like a periodic input on the second.

### 3. *End Product Inhibition*

It is well established that certain biochemical reaction chains regulate the concentration of the metabolites involved through various feedback devices. One of the most common ones is that in which the product of a chain diminishes the activity of an enzyme synthesizing some distant precursor of the inhibitory substance. Walter[222-225] has proposed models for this type of feedback which may be summarized as follows

$$\begin{aligned} dX_1/dt &= F(X_{n+1}) - k_1X_1 \\ dX_i/dt &= k_{i-1}X_{i-1} - k_iX_i \;\; (i = 1, \ldots, n + 1) \end{aligned} \tag{37}$$

where $X_i$ are the metabolite concentration and $F(X_{n+1})$ is a decreasing function of $X_{n+1}$ which describes the effect of inhibition. The most widely used form for F is

$$F(X_{n+1}) = \frac{C}{1 + \alpha X^{\rho}{}_{n+1}} \tag{38}$$

Walter finds limit cycle behavior for this type of system provided $n \geq 2$ and $\rho > 2$.

An alternative type of feedback in biochemical reactions is repression by the product of an enzymatic reaction of the genetic mechanism responsible for the synthesis of the enzyme. Goodwin and Griffith have devised models for this process, which are inspired by the Jacob–Monod theory[226,227] of repression. Thus, Griffith[228] considers a protein, E, encoded by the mRNA, M, and a metabolite, P, acting as repressor

$$\begin{aligned} dM/dt &= (1/P^m + 1) - \alpha M \\ dE/dt &= M - \beta E \\ dP/dt &= E - \gamma P \end{aligned} \tag{39}$$

He finds strong evidence for sustained oscillations as long as $m > 8$. More promising is the possibility of oscillations for lower values of $m$ in systems in which two or more genes are coupled. Sel'kov has recently investigated the case where the enzyme synthesized has several subunits and has found that the probability for sustained oscillations increases rapidly with the number of subunits.

Early studies on eq 37 have been reported by Sel'kov[229] and Morales and McKay.[230] One of the first theoretical models treating the effect of inhibition on the oscillatory behavior is due to Spangler and Snell.[231,232]

### 4. *End Product Inhibition and/or Substrate Inhibition*

Sel'kov, *et al.*, have studied models[233,234] where both

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(211) B. C. Goodwin, "Temporal Organization in Cells," Academic Press, New York, N. Y., 1963.

(212) B. C. Goodwin, *Advan. Enzyme Regul.*, **3**, 425 (1965).

(213) E. R. Caianiello, Ed., "Neural Networks," Springer-Verlag, Berlin, 1968.

(214) A. M. Turing, *Phil. Trans. Roy. Soc. London, Ser. B*, **237**, 37 (1952); M. J. Moore, *Trans. Faraday Soc.*, **45**, 1098 (1949).

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

(216) R. Lefever and G. Nicolis, *J. Theor. Biol.*, **30**, 267 (1971); B. Lavenda, G. Nicolis, and M. Herschkowitz-Kaufman, *ibid.*, **32**, 283 (1971).

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

(218) R. Lefever, *J. Chem. Phys.*, **48**, 4977 (1968); *Bull. Cl. Sci. Acad. Roy. Belg.*, **54**, 712 (1968).

(219) M. Herschkowitz-Kaufman and G. Nicolis, *J. Chem. Phys.*, **56**, 1890 (1972).

(220) G. Nicolis, *Advan. Chem. Phys.*, **19**, 209 (1971).

(221) J. J. Tyson, "Some Further Studies of Nonlinear Oscillations in Chemical Systems," Preprint, University of Chicago, 1972.

(222) C. F. Walter, *Biophys. J.*, **9**, 863 (1969).

(223) C. F. Walter, *J. Theor. Biol.*, **23**, 23 (1969); **23**, 39 (1969).

(224) C. F. Walter, *Proc. Biophys. Soc.*, **13**, A-211 (1969).

(225) C. F. Walter, *J. Theor. Biol.*, **27**, 259 (1970).

(226) J. Monod and F. Jacob, *Cold Spring Harbor Symp. Quant. Biol.*, **26**, 389 (1961).

(227) J. R. Beckwith and D. Zipser, Ed., "The Lactose Operon," Cold Spring Harbor Laboratory, New York, N. Y., 1970.

(228) J. S. Griffith, *J. Theor. Biol.*, **20**, 202, 209 (1968).

(229) E. E. Sel'kov, ref 5, Vol. I, p 81.

(230) M. F. Morales and D. McKay, *Biophys. J.*, **7**, 621 (1967).

(231) R. A. Spangler and F. M. Snell, *Nature (London)*, **191**, 457 (1961).

(232) R. A. Spangler and F. M. Snell, *J. Theor. Biol.*, **16**, 381 (1967).

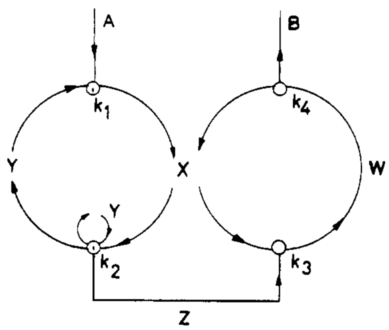

**Figure 3.** A branched autocatalytic reaction model.

substrate and product repress the enzyme activity, on the basis of the equations

$$\mu\frac{dX_1}{dt} = \beta_1(X_0 - X_1) - \nu(X_1,X_2)$$
$$\frac{dX_2}{dt} = \nu(X_1,X_2) - \beta_2X_2 \qquad (40)$$

where $\mu$ is a small parameter and $\nu(X_1,X_2)$ a decreasing function of both $X_1$ and $X_2$. He finds domains of existence of multiple steady states as well as of limit cycles encircling the unstable steady state. Degn[141] has studied a model with substrate inhibition only and found multiple steady states. He suggests that this type of model could explain certain properties of biochemical oxidation reactions, like, *e.g.*, the peroxidase-catalyzed reaction (see section II.E.1).

### 5. Activation by the Product

As we mentioned in the discussion of the glycolytic oscillations, the enzyme phosphofructokinase, which catalyzes one of the steps of the glycolytic chain, is *activated* by ADP, which is one of the products of this step. Sel'kov[235-237] and Higgins[238] have worked out mathematical models for this type of process. Sel'kov considers equations of the form

$$\frac{dX_1}{dt} = V_1 - \nu(X_1,X_2)$$
$$\frac{dX_2}{dt} = \mu[\nu(X_1,X_2) - \beta X_2] \qquad (41)$$

$X_1$ is the substrate and $X_2$ the product concentration. $\nu$ is an increasing function of $X_2$, $\mu$ is the ratio of the Michaelis constant for $X_1$ to the activation constant for $X_2$, $v_1$ is the rate of $X_1$ entry, and $\beta$ is the rate of $X_2$ consumption. Sel'kov finds that sustained oscillations may arise provided the degree of product activation is higher than one.

More recently, Goldbeter and Lefever[239] have studied the influence of the allosteric nature of the enzyme on the properties of the oscillations. Further comments are made in section III.B.

### 6. Models Involving Branchings

Tomita and Kitahara[240] have studied a fairly general class of model mechanisms wherein an otherwise closed reaction pathway gives rise to one nonlinear branching according to the scheme in Figure 3. A and B are the initial and sink reactants. The intermediate X is converted into Y, with one autocatalytic step, according to the left part of the diagram. At $k_3$ the reaction is branched and a new pathway involving Z and W appears. The two chains are coupled through X as shown in Figure 3. A simplified version of this model has been independently proposed by Zhabotinskii[241] to explain certain features of the bromate reaction discussed in section II.A. Tomita and Kitahara have also pointed out the possibility of the following analogy (see also section II.A).

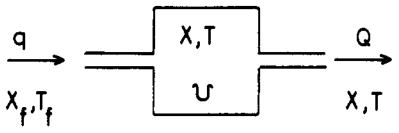

**Figure 4.** The adiabatic stirred tank reactor.

A malonic acid
X $Ce^{3+}$
Y $Ce^{4+}$
Z $Br^-$ (or bromomalonic acid, which however seems to be ruled out by the investigations of Noyes, *et al.*)
W some intermediate complex
B the product of the decomposition of W

The analytic study of the conservation of mass equations has shown that there exists a finite domain of values of the parameters *A*, *B*, and $k_1$ to $k_4$, for which the intermediates oscillate. Moreover, if the step $k_2$ is *simply autocatalytic*, the phase difference between X and Y is *always* $\pi/2$. Higher order autocatalytic feedbacks tend to reduce this phase difference. Thus, for a doubly autocatalytic step, the phase shift $\lambda$ is restricted by the inequality $0 < |\tan \eta| < 0.8$. We believe that the investigation of phase shifts will become an indispensable part of the work on chemical oscillations, as these quantities are related to the qualitative, rather than the quantitative, features of a reaction mechanism.

A linearly branched chain reaction model has also been studied by Degn and Mayer[142] in connection with the theoretical interpretation of the oscillations observed in peroxidase-catalyzed oxidation reactions.

### 7. Temperature Oscillations. The Adiabatic Stirred Tank Reactor

The role of temperature as a source of oscillations in chemical reactions is illustrated dramatically in the so-called adiabatic stirred tank reactor problem (Figure 4). The reaction volume $\upsilon$ is fed by a stream of volume rate $q$, in which the concentration of the reactant is $X_f$ and the temperature $T_f$. The reactant disappears inside $\upsilon$ by an irreversible first-order reaction at a rate $k(T)X$ per unit volume, with

$$k(T) = A\exp(-E/RT) \qquad (42)$$

Adequate stirring maintains the contents uniform in X and T. Of course, $X = X(t)$, $T = T(t)$, but $q$ is maintained constant. The mass and energy balance equations in the tank give

$$\frac{dX}{dt} = \frac{q}{\upsilon}(X_f - X) - k(T)X \qquad (43)$$

$$(C_p + C)\frac{dT}{dt} = qC_p(T_f - T) + (-\Delta H)\upsilon k(T)X \qquad (44)$$

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(233) V. A. Samoilenko and E. E. Sel'kov, ref 5, Vol. II, p 50.

(234) Yu. M. Aponin and E. E. Sel'kov, ref 5, Vol. II, p 80.

(235) E. E. Sel'kov, *Eur. J. Biochem.*, **4**, 79 (1968).

(236) E. E. Sel'kov, *Mol. Biol. (USSR)*, **2**, 252 (1968).

(237) V. A. Samoilenko, E. E. Sel'kov, and V. C. Savchuk, ref 5, Vol. II, p 54.

(238) J. Higgins, *Proc. Nat. Acad. Sci. U. S.*, **51**, 989 (1964).

(239) A. Goldbeter and R. Lefever, *Biophys. J.*, **12**, 1302 (1972); Proceedings of the 8th Federation of European Biochemical Societies Meeting, Amsterdam, 1972.

(240) K. Tomita and K. Kitahara, private communication.

(241) A. M. Zhabotinskii, A. N. Zaikin, M. D. Korzoohin, and H. P. Kreizer, ref 5, Vol. II, p 269.

where $C_p$ = heat capacity of reactant, $C$ = heat capacity of the walls, and $\Delta H$ = heat of reaction.

These equations have been studied in great detail both analytically and numerically.[242] It has been shown that, depending on the values of the parameters $q$, $X_f$, $T_f$, $\Delta H$, $C$, $C_p$, the system may exhibit multiple steady states with hysteresis, oscillations of the limit cycle type around an unstable branch of steady states, or even multiple limit cycles.

## B. Molecular Aspects of Chemical Oscillations

Structural cooperativity appears to play an essential role in biochemical oscillations. Indeed, in glycolysis the allosteric transition of phosphofructokinase is the basis of the finally tuned control circuit that leads to oscillatory behavior. Recently, Goldbeter and Lefever,[239] investigating an allosteric dimer model, elucidated the role of the allosteric transition in the substrate and product control of glycolysis. Moreover, oscillatory phenomena in muscles and membranes undoubtedly involve cooperative structure changes. And, it is not unlikely that induction and repression interactions involving structural changes contribute to genetic level periodicities. One is tempted to say the structural cooperativity at the molecular level induces, under nonequilibrium conditions, dynamic cooperativity at the cellular level.

Noyes,[52] *et al.*, have suggested that a separation of one-equivalent and two-equivalent processes similar to that found in the Belousov–Zhabotinskii reaction will also be found in the hydrogen peroxide reaction. In addition, they have suggested that second-order destruction of autocatalytically produced species (which is a characteristic of the Belousov–Zhabotinskii reaction) will be a common mechanistic feature of oscillating chemical reactions. Too few nonbiochemical oscillating reactions are understood well enough at the kinetic level for any common or necessary molecular property of the reacting species to have emerged. It is worthwhile to note though that all oscillating chemical systems involve oxidation–reduction reactions and that charged or free radical species invariably participate in the reactions.

## C. The Onset of Oscillations

In the preceding chapters we have referred to sustained chemical oscillations as supercritical phenomena arising beyond an unstable transition. Now there are at least two aspects in these chemical instabilities which are rather mysterious from the molecular standpoint.

(i) Except for a few gross properties like cooperativity, they do not seem to be related to the details of intermolecular forces. Thus, models of chemical instabilities refer, typically, to ideal systems in which the effect of interactions is weak. Experimentally also, phenomena such as glycolytic oscillations are produced *in vitro* with very low concentrations of the various chemicals.

(ii) As a rule, systems exhibiting chemical instabilities are, locally, quite close to equilibrium in the sense that the momentum distribution function of the particles is nearly maxwellian.

To summarize, we have systems which are purely disordered and dissipative on the molecular scale, and which therefore tend to damp the *thermal* fluctuations that are always present in any system of many particles. Yet these systems undergo instabilities which change completely their large scale behavior. For instance, in the Belousov reaction, a macroscopic number of Ce ions within a macroscopic volume switch in phase from the $Ce^{3+}$ to the $Ce^{4+}$ state.

What is the molecular basis for these phenomena, and, in particular, how is the system driven to the new regime beyond the instability? For a long time chemists tended to bypass this question by the claim that various types of (macroscopic) heterogeneities in the form of dust particles or gaseous bubbles are necessary to start the oscillation,[36-38] although the precise way they would act was never explained. This attitude, which moreover seems to be contradicted by the abundant new experimental data on chemical oscillations produced in homogeneous phase, simply masks the real problem. Suppose one sets up the experiment very carefully in order to avoid external influences and then approaches gradually the transition threshold for oscillation. Is this system going to evolve to the oscillatory regime? The question is comparable to what will happen to a liquid at the crystallization point. By analogy to phase transitions one would like to say that the chemical system will evolve to the oscillatory state because of *internal fluctuations.* But then how can one understand the emergence of ordered behavior extending over macroscopic distances, starting from thermal fluctuations which vary in a molecular scale?

Clearly, an answer to these questions requires an analysis of fluctuations in nonlinear systems around states driven far from thermodynamic equilibrium. Such a study was undertaken recently on a large class of model systems by Prigogine and Nicolis,[243-246] in an approach based on the stochastic theory of chemical kinetics.[247] The results of these investigations may be summarized as follows.

(a) Small thermal fluctuations are *always damped*, even when the system is near the threshold for a chemical instability. Moreover, the distribution of these fluctuations has a universal form similar to the classical Einstein formula describing fluctuations around equilibrium.

(b) In systems undergoing an unstable transition, finite thermal fluctuations of the *macroscopic* variables, *e.g.*, fluctuations of the composition of the reacting mixture (which may be small in a macroscopic scale), behave abnormally. For instance, in the Volterra–Lotka model (see section III.A.1) which lacks structural stability, the mean quadratic fluctuations of $X_1$ and $X_2$ around the steady state *increase* in time and eventually trigger the average values themselves to a new state. Prigogine and Nicolis[244] proposed the term of *generalized turbulence* for these peculiar situations.

The results we have just described shed some light on the question of how a system undergoing a chemical instability is driven to the oscillatory regime by fluctuations. We have shown that such a system can never evolve by small thermal fluctuations, which are damped. One has to wait for the formation of a thermal fluctuation whose size is beyond some critical value. We seem to have therefore an interesting phenomenon of *nucleation* of a new type, which suggests an analogy between chemical

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(242) For a recent review, see, *e.g.*, G. R. Gavalos, "Nonlinear Differential Equations of Chemically Reacting Systems," Springer-Verlag, Berlin, 1968.

(243) G. Nicolis and A. Babloyantz, *J. Chem. Phys.*, **51**, 2632 (1969).

(244) G. Nicolis and I. Prigogine, *Proc. Nat. Acad. Sci. U. S.*, **68**, 2102 (1971).

(245) G. Nicolis, *J. Stat. Phys.*, **6**, 195 (1972).

(246) R. Hawkins and S. A. Rice, *J. Theor. Biol.*, **30**, 579 (1971).

(247) A very clear presentation of the stochastic approach to chemical kinetics can be found in D. McQuarrie, "Supplementary Series in Applied Probability," Methuen and Co., London; see also A. T. Bharucha-Reid, "Elements of the Theory of Markov Processes and Their Application," McGraw-Hill, New York, N. Y., 1960.

instabilities and first-order phase transitions. Work aiming at the calculation of this critical size and of the time of formation of this evolving mode is pursued by Portnow and Kitahara.[248,249] Let us also notice that, most certainly, a finite fluctuation will arise locally rather than everywhere in the system. As a result, a system evolving beyond a chemical instability will tend to break spontaneously its spatial homogeneity.

In principle, this interpretation of the onset of oscillations could be tested experimentally by studying the light scattering cross-section from a reacting mixture in the neighborhood of a chemical instability. In this context, it is worth mentioning that a similar experiment from a turbulent fluid[250] does indicate an abnormal behavior of fluctuations.

## *IV. The Physical Significance of Oscillations*

The types of chemical oscillations analyzed in the preceding sections are "elementary," in the sense that they refer to the behavior of a single chemical pathway. It is the purpose of this final part of the review to discuss the role of oscillations in certain *large-scale phenomena* of special biological, ecological, or even social interest. We shall deal, successively, with neural oscillations, circadian clocks, the problem of development and morphogenesis, and the interaction between competing species.

### A. Rhythmic Activity of the Nervous System

It has been shown that certain parts of the mammalian brain respond electrically to an external impulse-like stimulation, in the form of damped or even sustained oscillations.[251-253] An elegant theoretical model for this type of phenomena has been worked out by Wilson and Cowan.[254] More intriguing, however, is the fact that *self-oscillations* arise in certain parts of the brain at characteristic frequencies not related to external stimuli.[11,255] This is shown most dramatically by a Fourier analysis of electroencephalograms, which reveals the existence of several periodic (electric) oscillations known as $\alpha$, $\beta$, $\delta$, and $\vartheta$ rhythms. Particularly interesting is the fact that the $\alpha$ rhythm in man, which has a fundamental frequency of about 10 Hz, predominates when the eyes are closed. On the basis of this observation, Wiener[256] submitted the hypothesis that the brain can be regarded as a set of nonlinear coupled oscillators (with the frequencies close to 10 Hz for the $\alpha$ rhythm) and that these oscillators can entrain each other. Later, Dewan[257] and Boyarsky[258] proposed models for the brain waves in terms of limit cycles. Unfortunately their equations as well as Wiener's conjecture are not related to any known physiological data. Alternative approaches to the collective behavior of neural nets have been worked out, among others, by Caianiello,[213] Taylor,[259] and Harth, *et al.*[260] More promising is the Wilson-Cowan model,[254] but presumably it needs some modifications before it could be applied to study, *e.g.*, the $\alpha$ rhythm. Indeed, in this model the limit cycle frequency goes to zero as the intensity of the external stimulus vanishes, a property which does not seem to be shared by the $\alpha$ rhythm.

The physiological role of sustained self-oscillations in the brain is not completely elucidated. It has been suggested that coding through phase relations provides a very efficient way for information storage and retrieval. This is also supported by the fact that *short-term memory* and *learning* processes seem to be related to the electric activity of the brain.[261] An additional advantage might be that an external signal couples with a preexisting temporal organization and is therefore added vectorially rather than scalarly to the signal arising from the background activity.

### B. Circadian Clocks and the Problem of Development

The literature on innate rhythms in living systems[262-265] and on various developmental processes[266,267] is so extensive that it cannot possibly be reviewed here. We shall focus exclusively on certain general classes of biochemical models that have been proposed to explain the *origin* and the *control* of these phenomena.

One of the characteristic features of the circadian rhythms is the relative independence of the period with respect to the temperature changes.[268,269] Another key property is the existence of a spectrum of rhythms for the same vital function. Thus, subharmonic components have been observed in *Acetabularia* for the circadian rhythm determining the ATP content of chloroplasts.[270] Further examples involving rhythm splitting have been observed by Pittendrigh.[271,272] Finally, circadian rhythms are characterized by a reproducible phase-shifting response to pulses of light[273-276] and by the ability to be entrained by

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(248) K. Kitahara and J. Portnow, in preparation.

(249) One should expect that the formation time of the critical mode would have a macroscopic order of magnitude. As a result, in practice, an equally efficient mechanism to trigger the instability could be a macroscopic *external* disturbance.

(250) R. J. Goldstein and W. F. Hagen, *Phys. Fluids*, **10**, 1349 (1967); H. L. Frisch, *Phys. Rev. Lett.*, **19**, 1278 (1967); E. W. Montroll in "Contemporary Physics," Vol. 1, International Atomic Energy Agency, Vienna, 1969.

(251) W. J. Freeman, *J. Neurophysiol.*, **31**, 337 (1968).

(252) W. J. Freeman, "Annual Review of Biophysics and Bioengineering," Vol. 1, Palo Alto, Calif., 1972.

(253) W. J. Freeman, *Progr. Theor. Biol.*, **2** (1971).

(254) H. R. Wilson and J. D. Cowan, *Biophys. J.*, **12**, 1 (1972).

(255) This property is *collective* in the sense that it involves large groups of neural cells.

(256) N. Wiener, "Cybernetics," MIT Press, Cambridge, Mass., 1948.

(257) E. M. Dewan, *J. Theor. Biol.*, **7**, 141 (1964).

(258) L. L. Boyarsky, *Curr. Mod. Biol.*, **1**, 39 (1967).

(259) J. G. Taylor, *J. Theor. Biol.*, **36**, 513 (1972).

(260) E. M. Harth, *et al.*, *J. Theor. Biol.*, **26**, 93, 121 (1970).

(261) See, *e.g.*, J. L. McGaugh, *Science*, **153**, 1351 (1966).

(262) Cold Spring Harbor Symposium on Quantitative Biology, Vol. 25, 1960.

(263) J. Aschoff, Ed., "Circadian Clocks," North-Holland Publishing Co., Amsterdam, 1965.

(264) E. Bünning, "The Physiological Clock," Springer-Verlag, New York, N. Y., 1964.

(265) B. M. Sweeney, "Rhythmic Phenomena in Plants," Academic Press, London, 1969.

(266) E. H. Davidson, "Gene Activity in Early Development," Academic Press, New York, N. Y., 1968.

(267) R. Harris and D. Viza, Ed., Proceedings of the 1st International Conference on Cell Differentiation, Munksgaard Publication, Copenhagen, 1972.

(268) C. S. Pittendrigh, *Proc. Nat. Acad. Sci. U. S.*, **40**, 1018 (1954).

(269) C. S. Pittendrigh, V. Bruce, and P. Kaus, *Proc. Nat. Acad. Sci. U. S.*, **44**, 965 (1958).

(270) T. Vanden Driessche, *Biochim. Biophys. Acta*, **205**, 526 (1970).

(271) C. S. Pittendrigh, ref 262, p 159.

(272) C. S. Pittendrigh in "Life Sciences and Space Research," A. H. Brown and F. G. Favorite, Ed., North-Holland Publishing Co., Amsterdam, 1967.

(273) W. Engelmann and H. W. Honneger, *Z. Naturforsch.*, **226**, 200 (1967).

(274) W. Engelmann, *Z. Vergl. Physiol.*, **64**, 111 (1969).

(275) H. W. Honneger, *Z. Vergl. Physiol.*, **57**, 244 (1967).

(276) S. D. Skopik and C. S. Pittendrigh, *Proc. Nat. Acad. Sci. U. S.*, **58**, 1862 (1967).

light-dark cycles having a period close to their "natural" period.[277,278]

In the reviewers' opinion, the most successful theoretical explanation of these phenomena is in terms of populations of coupled biochemical oscillators. Pavlidis[279-285] and Winfree[286-289] have worked out general classes of such models assuming the following.

(i) The individual oscillators are nonlinear of the limit cycle type. The reason for this choice is stability considerations (see also section I.C).

(ii) The distribution of oscillators is homogeneous in space. This might be a rather severe restriction in some cases, and it would certainly be very interesting to relax it. It may be recalled that a collection of delocalized nonlinear oscillators has already been studied on the basis of model system 36.

(iii) The coupling between oscillators is weak.

Oscillator populations having these properties do exhibit rhythm splitting, entrainment, and phase resetting. The relative insensitivity in temperature changes, as compared with the temperature dependence of individual biochemical oscillators, can also be seen by assuming particular forms of coupling. Thus, Pavlidis[285] has derived the following expression for one of the collective oscillation frequencies of the population

$$\omega = \omega_0\sqrt{1-(n-1)r} \qquad (45)$$

where $\omega_0$ is the fundamental frequency of each oscillator, $n$ the size of the population, and $r$ the coupling strength. As the temperature increases, *both* $\omega_0$ and $n$ increase, but their effect on $\omega$ is opposite. For small $r$, this can result in a quasi-constant value for $\omega$.

At present there is little doubt that the control of circadian rhythms is genetic. A particularly important role seems to be played by the various RNA's, although the precise mechanism for this dependence is still unknown.[290-293]

Populations of coupled oscillators have also been considered recently by Goodwin, Cohen, and Robertson[294-299] as a model for the spatio-temporal control of various developmental processes. They suppose that each cell in the "morphogenetic field" acts as an autonomous oscillator of period $T$. During a refractory interval $T_r$, a brief signalling state at $t = 0_+, T_+, 2T_+, \ldots,$ occurs, which is followed by a sensitive state for the remainder of the period. Finally, when a cell signals and its neighbor is sensitive, the neighbor signals after a time delay $\Delta t_s$. The "signal" may be a characteristic substance, known in embryology as a morphogen, which is produced by each cell. Provided the initial phases are suitably related, the cell with the highest frequency will entrain the others, and an *organizing wave* will propagate from that region. Although it is still too early to judge the generality of this type of control, it does seem that propagating waves appear during certain primitive developmental processes such as the aggregation of the unicellular organisms known as slime molds.[300-302] An interesting comparison between the Goodwin-Cohen-Robertson ideas and the concept of dissipative structures was attempted recently by Martinez[303] using the autocatalytic model system 36.

So far we have only discussed a possible control mechanism for development. The physico-chemical basis for the phenomenon itself, including differentiation, is still largely unknown.[266,267] What is certain is that any reasonable model must include at some stage the switching on and off of genes (see also sections II.E and III.A), although the precise mechanism of this can be different from the one proposed by Jacob and Monod.

## C. Competing Populations

The competition between populations is a very general phenomenon, whether one deals with the biosphere, human societies, or even economics. It takes place as soon as the resources necessary for the survival are limited or are exhausted. Sometimes, this constraint acts as a "selection pressure" which gives rise to an evolution of the competing entities. It is believed that both prebiological and Darwinian evolution are based, in part, on a mechanism of this kind. In other cases, however, it is not uncommon to observe some kind of "dynamical" equilibrium attained by the species. Several examples of this phenomenon are known in the biosphere, both for natural and for artificial ecosystems.

In the first class are D'Ancona's observations[304] on the fish populations of the upper Adriatic. He observed that the populations of two groups of species of fish, one of which was more voracious (presumably a predator of the small fish), varied rhythmically with the same period but different phase. A further example is provided by the fox catch data in Labrador.[305] If the annual catches are plotted against time (data are available for 40 years), one finds an oscillatory behavior with a mean period of the order of 5 years, together with random, nonperiodic fluctuations. One cannot exclude the influence of environmental factors to these fluctuations, but it is also tempting to expect that interactions with other coexisting species contribute appreciably to these fluctuations.

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Strong fluctuations of the populations have also been found on host parasite populations[306] as well as on cultures of two *Drosophila* species feeding from the same sources.[307]

Finally, an analysis of the catches of Canadian lynx and its principal food, the varying hare,[308] reveal oscillations with periods of the order of 10 years.

Among the experiments in artificial ecosystems, we mention the work of Huffaker,[309] who used a prey mite feeding on oranges along with another species of mite as predator. He found very pronounced temporal oscillations lasting several periods. The experiment was devised to permit migration of the interacting species within the vital space. In contrast, experiments conducted by Gause[310-312] have shown that one obtains invariably extinction of one or another species, sometimes with damped oscillations, unless small frequent additions of the interacting species are made.

Volterra[16] and Lotka[15] were the first to try a theoretical interpretation of the behavior of interacting species. Lotka's model was not based on direct experimental observation but was motivated by his studies on autocatalytic chemical reactions, which are described briefly in section III.A.1. He considered exclusively one prey-predator pair and proposed the equations

$$\begin{aligned}\frac{dX_1}{dt} &= k_1X_1 - \frac{k}{\beta_1}X_1X_2\\ \frac{dX_2}{dt} &= -k_2X_2 + \frac{k}{\beta_2}X_1X_2\end{aligned} \qquad (46)$$

where $X_1$ is the number of prey and $X_2$ the number of predator individuals. The quadratic term $kX_1X_2$ represents the interaction between the species, in the absence of which the prey would grow and the predator would decay exponentially. The quantities $\beta_i$ ($\beta_i > 0$) are known as "equivalence numbers" and serve to convert to a common basis the loss or gains of various species. Volterra proposed an identical pair of equations to interpret D'Ancona's observations which are described earlier in this section. He also devised a highly interesting generalization to $n$ species in the form

$$\frac{dX_i}{dt} = k_iX_i + \frac{1}{\beta_i}\sum_j a_{ij}X_iX_j \qquad (47)$$
$$(i = 1, \ldots, n)$$

By analogy to eq 47, he postulated the relation

$$a_{ij} = -a_{ji} \qquad (48)$$

Using this condition, Volterra showed that both systems of eq 46 and 47 are conservative. The constant of motion in the two species case is given by eq 35. Its existence implies that, in this case, either $X_1$ and $X_2$ will settle in a steady state or they will exhibit sustained oscillations whose periods and amplitudes depend on the initial conditions. Volterra was able to derive general theorems about the steady state and the oscillatory behavior for $n > 2$ as well.

The lack of structural stability which characterizes conservative systems implies that the average behavior described by eq 47 will be accompanied by nonnegligible fluctuations. Kerner[313-318] adopted an ensemble theoretical interpretation of these fluctuations and devised (for $n$ even) a statistical mechanical theory of competing species wherein (47) plays the role of the "microscopic" equations of motion. He was able in this way to provide a qualitatively satisfactory interpretation of the previously described fox catch data. An alternative description of the fluctuations in predator-prey populations, based on a stochastic birth and death type model, was developed by Prigogine and Nicolis.[244,245]

The Volterra-Lotka model was criticized very early for various reasons. The most common objection is the absence of an autoregulation term (known as the Verhulst term) in the growth rate. Gause[312] and several others[319-323] extended the original model to include such terms and found that, as a rule, they tend to stabilize the steady state, in agreement with certain ecological situations like the host-parasite system. An alternative generalization of the Volterra-Lotka model was proposed by Kolmogorov[324] and several others[325-328] who considered two (and more recently three) competing species obeying rate equations of the form

$$\begin{aligned}\frac{dX_1}{dt} &= X_1F_1(X_1,X_2)\\ \frac{dX_2}{dt} &= X_2F_2(X_1,X_2)\end{aligned} \qquad (49)$$

They found the necessary conditions on F1 and F2 for the existence of periodic *nonconservative* oscillations of the limit cycle type and argued that this type of oscillation reflects better the stability one expects to find in the biosphere. The necessity for models producing stable, limit cycle type oscillations was also pointed out by Samuelson[329] in connection with economic problems. An objection against limit cycle behavior is that fluctuations are then small, contrary to what seems to be established by the analysis of fox catch data. An intermediate position between the Volterra and Kolmogorov pictures has been proposed independently by Ruelle[330] and Tyson.[221] They suggest that a quasi-periodic behavior would exhibit both stability and fluctuations

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around some mean period. The most natural realization of this behavior, however, would require coupling between more than two species.

We conclude this section by the following remark. Both Gause's and Huffaker's data indicate that competition and migration are two unseparable aspects of population dynamics. It would be very interesting to work out models where the motion of individuals is taken into account and see to what extent one could obtain the formation of spatial domains, corresponding to some sort of ecological niches. Work in this direction is being pursued by Nicolis and Rodeyns.

## D. Concluding Remarks

In the preceding chapters we discussed oscillations at successively higher levels of complexity: the chemical oscillations at the level of a single reaction chain; biochemical oscillations at the intracellular level; circadian or brain rhythms at the inter- or supercellular level; and some aspects of collective behavior of interacting populations.

The physiological role of supercellular or other collective forms of oscillations is fairly obvious. The basic properties of entrainment, phase resetting, etc., of circadian rhythms permit the organism to adapt in a flexible way to the external conditions and to keep, through suitable phase relations, an identical succession of various vital processes during a cycle of the order of 24 hr. Similarly, oscillations at the genetic level and during the process of development of the adult organism are essential for cellular division and for the temporal organization of the different functions during development. Moreover, their ability to couple with diffusion provides a very efficient mechanism for spatio-temporal control.

The role of *metabolic* oscillations at the cellular level is much less clear. At first sight one might even argue that they may simply be evolutionary accidents without any selective advantage. For instance, glycolysis, which is oscillatory in yeast, is not oscillating in *Dictyostelium discoideum* which belongs to the family of slime molds.[331] It is not impossible that the very complexity of biochemical control circuits and the cooperative properties of certain enzymes involved therein make oscillations *inevitable*, although not purposeful.

There is of course a second, and perhaps more tempting, viewpoint. In the first place, the "inevitability" of oscillations in a complex control circuit is not quite obvious. Kaufman[332,333] has studied systematically *random* networks with binary elements. He finds that in the presence of $N$ connections there will be on the average $\sqrt{N}$ oscillatory modes. Thus, even if the design of metabolic pathways were random (which is certainly not the case), oscillations would constitute the exception rather than the rule.

What is then the functional advantage gained by metabolic oscillations? First, one might argue that they constitute necessary elements for genetic and circadian oscillations. Sel'kov has recently tried to systematize this viewpoint.[334] He imagines a self-oscillating biochemical system generating circadian oscillations. He argues that the long oscillation period of this system (in contrast to, *e.g.*, glycolytic oscillations whose period *in vivo* is of the order of seconds) may be explained by the presence of certain buffer chemicals which enhance the "capacitance" of the oscillator. The relative independence on the substrate level in the medium is also explained by a large buffer "capacitance" of the source feeding the self-generator. Further work is certainly necessary to elucidate the coupling between metabolic and circadian or genetic oscillators.

A biochemical oscillator can be more than a cellular clock: the sensitivity of the period and phase relationships to the cellular environment make the oscillator at once a thermometer, a pH meter, a galvanometer, etc. Moreover, if there are $n$ chemicals, then at the steady state there are simply $n$ variables that can be used to measure and control cellular activity, but the presence of an oscillation means that there are now twice the number of variables ($n$ chemicals $+ (n - 1)$ phases $+ 1$ period) thus enhancing the sensitivity and reliability of any control network and creating greater plasticity in cellular responses to environmental change.

Finally, it is difficult to comment, at this time, on the possible practical applications (comparable, say, to the applications of electronic oscillating circuits) of chemical oscillations.

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