

Chemical Oscillations Arise Solely from Kinetic Nonlinearity and Hence Can Occur Near Equilibrium

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ABSTRACT A minimal kinetic scheme for a system displaying sustained chemical oscillations is presented. The system is isothermal, and all steps in the scheme are kinetically reversible. The oscillations are analyzed and the crucial points elucidated. Both positive and negative feedback, if properly introduced, support oscillations, provided the state responsible for feedback is optimally buffered. It is shown that the requisite nonlinearity is introduced at the kinetic level because of feedback regulation and not, as is usually assumed, by large affinities that introduce nonlinearity at the thermodynamic level. Hence, sustained oscillations may occur near equilibrium.

INTRODUCTION

Since the pioneering work of Onsager it has been well known that oscillations are not possible in linear or linearized systems in the vicinity of equilibrium states (de Groot and Mazur, 1962; Keizer, 1987). Moreover, it was originally considered (Glansdorff and Prigogine, 1971; Stucki, 1978) and is still commonly supposed (Somogyi and Stucki, 1991) that a system has to be far from equilibrium for sustained oscillations to occur. Thus back reactions were neglected in the well-known Brusselator scheme (Prigogine and Lefever, 1968). For the same reason the Oregonator scheme (Field and Noyes, 1974), although designed to be kinetically reversible, was analyzed without back reactions. It has been argued that whereas neglecting the back reactions violates the law of mass action, including them eliminates any possibility of oscillation (Gray and Morley-Buchanan, 1985). Nevertheless, we and others pointed out some years ago that, despite these arguments, back reactions can be included without eliminating oscillations (Walz and Caplan, 1988; Gray et al., 1988; Lefever et al., 1988).

In this study we establish the minimum number of components required by a chemical system for oscillation to occur, and the kinetic relations between them. It will be seen that all that is necessary for oscillation is two states connected by two transitions, the coupling of one transition to an energizing reaction, and the regulation of at least one transition by a feedback mechanism, as in the case of autocatalysis. The feedback may be introduced in any transition or even split between transitions, the only requirement being a feedback regulation coefficient (relating to all feedback mechanisms together) larger than 1. However, sustained oscillations are only possible if the state responsible for feedback is optimally buffered because of an additional transition to a third state. It will be shown that oscillations about a steady state near equilibrium can occur,

and can even take place in the range of linear flow-force relations, provided the requisite nonlinearity is present as a consequence of a sufficiently large feedback regulation. It will be further shown that such oscillations do not violate the above-mentioned stability criterion for systems near equilibrium.

A MINIMAL KINETIC SCHEME FOR AN OSCILLATING SYSTEM

Consider an isolated, isothermal system with a species that can exist in three different states denoted by A, X, and Y (see Fig. 1). These states might comprise one species in three compartments or three conformations of a species, or a mixture of both. Transitions between the states are due to either chemical reactions or transport processes or both. All processes occur both in the forward and backward directions, which, however, does not exclude the possibility that under certain circumstances the rate in one direction may become negligibly small in comparison to that in the other.

Detailed balancing

The rate parameters k_{ij} (see Fig. 1) are related to thermodynamic equilibrium constants by detailed balancing (Walz and Caplan, 1988):

$$K_1 = [c_A/c_X]_{eq} = k_{21}/k_{12} \quad (1)$$

$$K_2 = [c_Y/c_X]_{eq} = \{[c_S/c_P]_{eq} k_{23}^0/k_{32}^0\}^{1/(v+1)} = k_{23}/k_{32} \quad (2)$$

$$K_B = [c_Y c_B/c_Z]_{eq} = k_{43}/k_{34}^0 \quad (3)$$

where c_i denotes the concentration of the i th species; the subscript eq indicates equilibrium; and K_1 , K_2 , and K_B are the equilibrium constants corresponding to the transitions $A \rightleftharpoons X$, $X \rightleftharpoons Y$, and $Y \rightleftharpoons Z$, respectively. The pertinent constant for the energizing reaction is

$$K_{en} = [c_P/c_S]_{eq} \quad (4)$$

Received for publication 12 December 1994 and in final form 23 July 1995.

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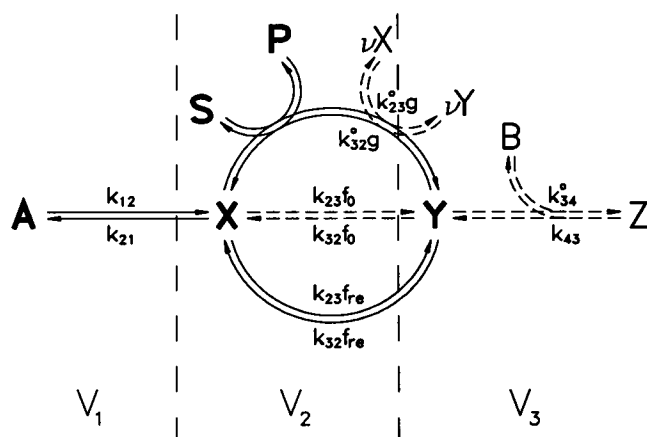


FIGURE 1 A minimal kinetic scheme for an oscillating system. Optional transitions are indicated by broken lines and included only for generality. For transport processes the compartment volumes V_i may be different, and the rate parameters $k_{ij} = k_{ji}$ are the overall permeabilities divided by V_2 . For chemical reactions at least two of the compartments coincide and the pertinent volumes are accordingly equal. In this case in general $k_{ij} \neq k_{ji}$. There are two mandatory transitions between X and Y; one is coupled to the energizing reaction $S \rightleftharpoons P$, and the other may be regulated by a feedback mechanism as indicated by the function f_{re} . The optional X to Y transition may be considered as a leak process whose relative contribution is determined by the factor f_0 . The energizing reaction may be a chemical reaction or an enzyme-catalyzed reaction and in addition may be feedback-regulated, as indicated by the function g . It may involve one ($\nu = 0$) or two species X and Y ($\nu = 1$). The optional binding of species Y to a buffering species B yielding the species Z ($= YB$) increases the chemical capacity for Y (Walz, 1990).

Let \mathcal{A}_{en} be the thermodynamic affinity of the energizing reaction. It is convenient to define a quantity A as

$$A = \exp\{\mathcal{A}_{en}/RT\} = K_{en}c_S/c_P \quad (5)$$

where the second equality follows from the definition of \mathcal{A}_{en} and the relation between K_{en} and the standard chemical potentials of the reactants (Walz, 1990).

Mass balances

Let N_{tot} denote the total mole number of species A, X, Y, and Z, and c_{Btot} the total concentration of the buffering species B. Then

$$V_1c_A + V_2c_X + V_3(c_Y + c_Z) = N_{tot} \quad (6)$$

$$c_B + c_Z = c_{Btot} \quad (7)$$

Using the quantities

$$c_1 = N_{tot}/V_1, \quad \phi_1 = V_2/V_1, \quad \text{and} \quad \phi_3 = V_2/V_3 \quad (8)$$

Eqs. 6 and 7 are reduced to the dimensionless forms

$$a + \phi_1[x + (y + z)/\phi_3] = 1 \quad (9)$$

$$b + z = b_{tot}. \quad (10)$$

In Eqs. 9 and 10 we make use of the reduced concentrations

defined as follows:

$$\begin{aligned} a &= c_A/c_1, \quad x = c_X/c_1, \quad y = c_Y/c_1, \\ s &= c_S/c_1, \quad p = c_P/c_1, \quad z = c_Z/c_1, \\ b &= c_B/c_1, \quad \text{and} \quad b_{tot} = c_{Btot}/c_1 \end{aligned} \quad (11)$$

As is evident from Eq. 3 the equilibrium constant K_B has to be reduced in accordance with the redefined concentrations:

$$K_b = K_B/c_1. \quad (12)$$

Rate laws

The concentrations of the reactants S and P are assumed to be constant because of the operation of appropriate homeostatic mechanisms (or clamps). We then can define a convenient time unit as

$$t_o = 1/k_{12} \quad (13)$$

which serves to define a reduced time τ given by

$$\tau = t/t_o. \quad (14)$$

The flows associated with the transitions shown in Fig. 1 are (see, e.g., Walz, 1990)

$$J_a = V_2[k_{12}c_A - k_{21}c_X] = V_2c_1[a - K_1x]/t_o \quad (15)$$

$$\begin{aligned} J_e &= V_2[k_{23}^0c_Sc_X^{\nu+1} - k_{32}^0c_Pc_Y^{\nu+1}] \\ &= V_2c_1\alpha_e g[A(K_2x)^{\nu+1} - y^{\nu+1}]/t_o \end{aligned} \quad (16)$$

$$\begin{aligned} J_r &= V_2[k_{32}(f_{re} + f_0)c_Y - k_{23}(f_{re} + f_0)c_X] \\ &= V_2c_1\alpha_r f[y - K_2x]/t_o \end{aligned} \quad (17)$$

$$J_b = V_2[k_{34}c_Bc_Y - k_{43}c_Z] = V_2c_1\alpha_b[by - K_bz]/t_o \quad (18)$$

The right-hand sides of the above equations are obtained by means of Eqs. 1–3 and 11, the relation $k_{23}^0c_S = k_{32}^0c_PAK_2^{\nu+1}$ (which stems from Eqs. 2, 4, and 5) and the following reduced rate parameters:

$$\alpha_e = k_{32}^0c_Pc_1^{\nu}t_o \quad (19)$$

$$\alpha_r = k_{32}t_o, \quad f = f(x, y) = f_{re}(x, y) + f_0 \quad (20)$$

$$\alpha_b = k_{34}c_1t_o \quad (21)$$

The flows in Eqs. 15–18 give rise to the following concentration changes:

$$dc_A/dt = -J_a/V_1 \quad (22)$$

$$dc_X/dt = [J_a - (\nu + 1)J_e + J_r]/V_2 \quad (23)$$

$$dc_Y/dt = [(\nu + 1)J_e - J_r - J_b]/V_3 \quad (24)$$

$$dc_Z/dt = -dc_B/dt = J_b/V_3 \quad (25)$$

By means of Eqs. 9, 10, 15–18, and 22–25 the rate equations for the system can be written in terms of the reduced

concentrations and the reduced time as follows:

$$\frac{da}{d\tau} = -\phi_1 \left[\frac{dx}{d\tau} + \frac{(dy/d\tau + dz/d\tau)}{\phi_3} \right] \quad (26)$$

$$\begin{aligned} \frac{dx}{d\tau} = 1 - \{K_1 + \phi_1 + K_2[\alpha_r f + (\nu + 1)\alpha_e g A(K_2 x)^\nu]\}x \\ + \left[\alpha_r f + (\nu + 1)\alpha_e g y^\nu - \frac{\phi_1}{\phi_3} \right] y - \left(\frac{\phi_1}{\phi_3} \right) z \end{aligned} \quad (27)$$

$$\begin{aligned} \frac{dy}{d\tau} = \phi_3 \{K_2[\alpha_r f + (\nu + 1)\alpha_e g A(K_2 x)^\nu]x \\ - [\alpha_r f + (\nu + 1)\alpha_e g y^\nu + \alpha_b(b_{\text{tot}} - z)]y \\ + \alpha_b K_b z\} \end{aligned} \quad (28)$$

$$\frac{dz}{d\tau} = -\frac{db}{dt} = \phi_3 [\alpha_b(b_{\text{tot}} - z)y - \alpha_b K_b z] \quad (29)$$

In the absence of the optional binding of Y to B (see Fig. 1) Eqs. 18, 21, 25, and 29 do not apply. In this case $\alpha_b = b_{\text{tot}} = 0$, and $z(\tau) = b(\tau) \equiv 0$.

A general form of the function g characterizing the energizing reaction that comprises most cases of interest is

$$\begin{aligned} g(x, y) = \left[1 + \left(\frac{x}{K_{mX}} \right)^{\nu+1} + \left(\frac{y}{K_{mY}} \right)^{\nu+1} + \left(\frac{xy}{K_{mXY}} \right)^{\nu+1} \right]^{-1} \\ \times \left[1 + \left(\frac{x}{K_g} \right)^m \right]^{-1} \end{aligned} \quad (30)$$

The first term in Eq. 30 describes an enzyme-catalyzed reaction. It is valid if the binding of the reactants to the enzyme is ordered and if the enzyme does not display a slip (Walz, 1990), in which case the Michaelis-Menten rate law for reversible reactions applies. The "Michaelis constants" K_{mX} , K_{mY} , and K_{mXY} (as well as the rate parameter α_e) depend on the enzyme concentration and the sum $c_s + c_p$. If X is bound to the enzyme before S, and P is released from the enzyme before Y, the quantity K_{mXY} is absent or $K_{mXY} = \infty$. If the energizing reaction is purely chemical, all Michaelis constants are set to infinity. The second term in Eq. 30 represents a negative feedback regulation exerted by X on the energizing reaction. In the case of enzyme catalysis this is a substrate inhibition of the noncompetitive type. If no such regulation occurs, $K_g = \infty$.

STABILITY ANALYSIS

Steady states

Steady states of the system are of considerable interest with regard to stability. Starting from any arbitrary initial conditions the system will either relax into a steady state or oscillate around it. Alternatively, the system in a steady state either returns to that state after a perturbation or starts to oscillate. The following relations between the steady state reduced concentrations (indicated by a

subscript s) are readily obtained from the above rate equations:

$$x_s(a_s) = a_s/K_1 \quad (31)$$

$$y_s(x_s) = \begin{cases} h_2 x_s/h_1 & \text{if } \nu = 0 \\ -h_3 + [h_3^2 + h_4]^{1/2} & \text{if } \nu = 1 \end{cases} \quad (32)$$

$$z_s(y_s) = b_{\text{tot}} y_s / (y_s + K_b) \quad (33)$$

with the abbreviations

$$h_1 = \alpha_r f_s + \alpha_e g_s \quad (34a)$$

$$h_2 = K_2 [\alpha_r f_s + \alpha_e g_s A] \quad (34b)$$

$$h_3 = \alpha_r f_s / (4\alpha_e g_s) \quad (34c)$$

$$h_4 = K_2 x_s [\alpha_r f_s / 2 + \alpha_e g_s A x_s] / (\alpha_e g_s) \quad (34d)$$

Here f_s and g_s mean that the functions have to be taken at the steady state values of the reduced concentrations. To obtain explicit expressions for these concentrations Eqs. 31–33 must be introduced into Eq. 9, giving in general higher order polynomials or transcendental equations that can only be solved numerically. At equilibrium $A = 1$, and hence for the cases $\alpha_b = b_{\text{tot}} = 0$ and either $\nu = 0$ or $\nu = K_2 = 1$, it follows from Eqs. 9, 31, and 32 that $a_{\text{eq}} = K_1/Q$, $x_{\text{eq}} = 1/Q$, and $y_{\text{eq}} = K_2/Q$, where $Q = \phi_1 + K_1 + \phi_1 K_2 / \phi_3$. In other cases the relations are more complex but always yield one unique set of equilibrium values. The present system thus differs from the system discussed by Chu and Ross (1990), which has multiple equilibrium states.

Eigenvalues of the Jacobian matrix

The local stability of a system can be examined by looking at the eigenvalues λ_i of the Jacobian matrix whose i, j th element is $\partial[du_i/d\tau]/\partial u_j$ ($u_i, u_j = x, y, z$). The system displays sustained oscillations if at least one real λ_i or the real part of an imaginary λ_i is positive. The system displays damped oscillations if imaginary values of λ with negative real parts exist, whereas it is stable if all values of λ are real and negative (Stucki, 1978). Considering the stability of the present system in the vicinity of a steady state, the eigenvalues are the roots of the characteristic polynomial

$$P(\lambda) = \lambda^3 + \lambda^2 P_1 + \lambda P_2 + P_3 \quad (35)$$

where the coefficients are

$$P_1 = \phi_1 + K_1 + p_1 + \phi_3(p_2 + p_4) \quad (36a)$$

$$P_2 = \phi_1 p_1 \quad (36b)$$

$$+ \phi_3 [p_2(\phi_1 + K_1) + p_4(\phi_1 + K_1 + p_1) + \phi_3 p_2 p_3]$$

$$P_3 = \phi_3 [\phi_1 p_1 p_4 + \phi_3 p_2 p_3 (\phi_1 + K_1)] \quad (36c)$$

The abbreviations used in Eqs. 36 are

$$p_1 = K_2[\alpha_r f_s + \alpha_e g_s A(\nu + 1)^2 (K_2 x_s)^\nu] + (\partial f / \partial x)_s \alpha_r (K_2 x_s - y_s) \quad (37a)$$

$$+ (\partial g / \partial x)_s \alpha_e (\nu + 1) [A (K_2 x_s)^{\nu+1} - y_s^{\nu+1}]$$

$$p_2 = \alpha_r f_s + \alpha_e g_s (\nu + 1)^2 y_s^\nu - (\partial f / \partial y)_s \alpha_r (K_2 x_s - y_s) - (\partial g / \partial y)_s \alpha_e (\nu + 1) [A (K_2 x_s)^{\nu+1} - y_s^{\nu+1}] \quad (37b)$$

$$p_3 = \alpha_b (K_b + y_s) \quad (37c)$$

$$p_4 = p_3 + \alpha_b (b_{\text{tot}} - z_s). \quad (37d)$$

The case without optional binding of Y to B corresponds to the minimal system necessary for oscillations. It involves only three concentration parameters of which two vary independently, i.e., there are two degrees of freedom. The characteristic polynomial is then of second order, and the eigenvalues are given by

$$\lambda_{1,2} = -P_1/2 \pm [P_1^2/4 - P_2]^{1/2} \quad (38)$$

with coefficients P_1 and P_2 according to Eqs. 36, with $p_3 = p_4 = 0$.

EXPLORING THE STABILITY OF THE SYSTEM

In the case that $b_{\text{tot}} = 0$ and $\nu = 0$ the eigenvalues in Eq. 38 can be analyzed further. For the real part of $\lambda_{1,2}$ to become positive it is sufficient that $P_1 < 0$. Using Eqs. 32, 36a, and 37, it can be shown that

$$P_1 = H_1 - \alpha_e K_2 H_2 \quad (39)$$

Because

$$H_1 = \phi_1 + K_1 + \alpha_r f_s (K_2 + \phi_3) + \phi_3 \alpha_e g_s > 0 \quad (40)$$

a necessary condition for $P_1 < 0$ is (see also Eq. 32)

$$H_2 = (A - 1) \alpha_r [g_s D_f - f_s D_g] x_s / h_1 - A g_s = (A - 1) \alpha_r [g_s D_f - f_s D_g] y_s / h_2 - A g_s > 0 \quad (41)$$

where

$$D_f = \left[\frac{\partial f}{\partial x} - \phi_3 \frac{\partial f}{\partial y} \right]_s \quad \text{and} \quad D_g = \left[\frac{\partial g}{\partial x} - \phi_3 \frac{\partial g}{\partial y} \right]_s \quad (42)$$

It is seen that, to satisfy the inequality in Eq. 41,

$$D_f \geq 0 \quad \text{and} \quad D_g \leq 0 \quad \text{if} \quad A > 1 \quad (43a)$$

$$D_f \leq 0 \quad \text{and} \quad D_g \geq 0 \quad \text{if} \quad A < 1 \quad (43b)$$

Furthermore, it is evident that the quantity A has to be only just large enough if $A > 1$ or small enough if $A < 1$ that the first term overrides the second in Eq. 41. If in addition $\alpha_e K_2 H_2 > H_1$ (cf. Eq. 39), then Eq. 41 is also a sufficient condition. Note that at equilibrium ($A = 1$) H_2 is always negative and hence, as expected, no oscillations are possible.

The conditions in Eq. 43a can be fulfilled by an energizing reaction described by g according to Eq. 30, and a positive feedback exerted by X on the regulated transition according to

$$f(x) = x^n [1 + (x/K_f)^n]^{-1} + f_0. \quad (44)$$

Note that Eq. 44 applies to autocatalysis if K_f is set to infinity. When introducing Eqs. 30 and 44 into Eq. 41 it is found that the inequality holds if

$$\rho = \frac{n}{W_1} + \left(1 + \frac{f_0 W_1}{x_s^n} \right) \left[\frac{m (x_s/K_g)^m}{W_2} + \frac{x_s [1/K_{mX} - \phi_3/K_{mY} + (y_s - \phi_3 x_s)/K_{mXY}]}{W_3} \right] \quad (45)$$

$$> \frac{A [1 + (W_1/x_s^n) [f_0 + \alpha_e / (\alpha_r W_2 W_3)]]}{A - 1}$$

with the abbreviations

$$W_1 = 1 + (x_s/K_f)^n, \quad W_2 = 1 + (x_s/K_g)^m,$$

and

$$W_3 = 1 + x_s/K_{mX} + y_s/K_{mY} + x_s y_s/K_{mXY} \quad (46)$$

The quantity ρ can be interpreted as a feedback regulation coefficient that comprises all feedback mechanisms in the system. It must be larger than 1 for sustained oscillations, as has been recognized previously for special cases (Stucki, 1978), but otherwise may be composed of any combination of feedback mechanisms with parameter values properly chosen so that the inequality in Eq. 45 is satisfied.

Except for A values close to unity, the term $A - 1$ can be approximated by A . Hence the limit for ρ is essentially independent of A , whereas H_2 is essentially proportional to A . Therefore, an A value can in principle be found such that $P_1 < 0$ is also fulfilled. Moreover, the larger the value of ρ , the larger becomes the term in square brackets in Eq. 41, and the closer A comes to unity. This is demonstrated by the examples listed in columns 2–4 of Table 1, where f_{re} represents positive feedback and g an unregulated chemical reaction (i.e., $g = W_2 = W_3 = 1$ because $K_g = K_{mX} = K_{mY} = K_{mXY} = \infty$). In this case it follows from Eq. 45 that $n = W_1$ ρ has to be larger than 1. Similar features are observed if the optional binding of Y to B is included. This increases the chemical capacity for Y as compared to the case without binding (Walz, 1990); hence V_3 can be decreased accordingly. As is evident from columns 5–7 of Table 1, the limits for sustained oscillations are then shifted to larger \mathcal{A}_{en} values and the ranges are broadened. The quantity f_0 has little or no effect if $f_0 \ll 1$, but progressively increasing f_0 values shift the lower limits to larger \mathcal{A}_{en} values and narrow the ranges (not shown).

Fig. 2 presents by way of example the time course of x , y , and a in the system with binding of Y to B. The about fourfold increase in chemical capacity for Y arising in this case from binding was compensated by a fourfold smaller

TABLE 1 Ranges of $\mathcal{A}_{en}/RT = \ln A$ in which sustained oscillations occur when $f(x) = x^n[1 + (x/K_f)^n]^{-1} + f_0$ and $g = 1$

n^*	Without binding of Y to B			With binding of Y to B		
	$\phi_1 = 0$	$\phi_1 = 0.01$	$\phi_1 = 0.02$	$\phi_1 = 0$	$\phi_1 = 0.01$	$\phi_1 = 0.02$
1	n.o.*	n.o.	n.o.	n.o.	n.o.	n.o.
2	3.61–	n.o.	n.o.	4.73–	n.o.	n.o.
3	1.82–	1.96–3.22	n.o.	2.29–	2.40–4.75	n.o.
4	1.35–	1.40–3.25	1.53–2.37	1.73–	1.77–4.80	1.85–3.45
5	1.09–	1.12–3.15	1.20–2.32	1.42–	1.44–4.68	1.50–3.37
6	0.92–	0.94–3.04	1.01–2.22	1.22–	1.23–4.53	1.28–3.24
7	0.80–	0.82–2.94	0.88–2.12	1.07–	1.08–4.39	1.12–3.11
8	0.71–	0.72–2.85	0.78–2.02	0.96–	0.97–4.25	1.00–2.99
9	0.64–	0.65–2.76	0.71–1.93	0.87–	0.87–4.12	0.91–2.87
10	0.58–	0.59–2.68	0.65–1.84	0.79–	0.80–4.00	0.83–2.77

*Values of other parameters are $K_1 = K_2 = 1$, $\alpha_e = 5$, $\nu = 0$, $\alpha_r = 7$, $K_f = 5$, $f_0 = 10^{-5}$, and either $\phi_3 = 0.5$, $\alpha_b = b_{tot} = 0$, or $\phi_3 = 5$, $b_{tot} = 100$, $\alpha_b = 0.02$, $K_b = 20$ in the case without or with binding of Y to B, respectively. The case $n = 1$ is included only for reasons of completeness.

*No sustained oscillations occur.

volume V_3 . The value of α_b was chosen such that the rate of binding cannot fully cope with the changes in y . This causes the spikes in the y curve and the smooth maxima in the x curve. With a 100-fold larger α_b value, binding is always at a pseudo-equilibrium and the spikes in the y curve disappear, and the maxima of the x curve become spiky. With a tenfold smaller α_b value, binding is too sluggish and the oscillations are damped out.

An enzyme-catalyzed energizing reaction introduces a negative feedback with a coefficient on the order of 1 (cf. Eq. 45). In this case the coefficient n for the positive feedback of the regulated transition can be reduced to 1. If, in addition, X acts as a noncompetitive inhibitor of the enzyme, n can even be set to zero, as demonstrated by the example shown in Fig. 3. Note that enzyme catalysis also introduces a negative feedback exerted by Y, which tends to

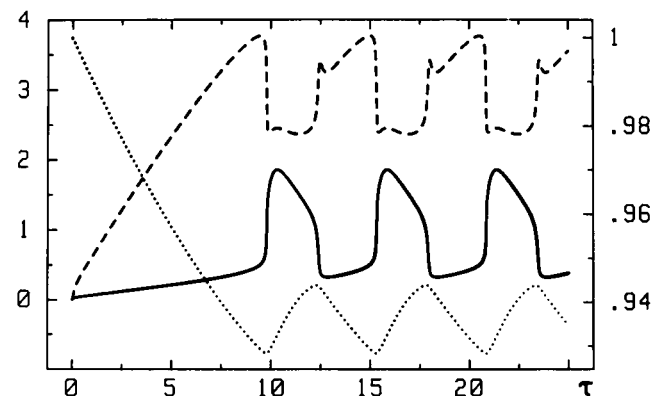


FIGURE 2 Dependence of the reduced concentrations x (—), y (---), and a (·····) on the reduced time, τ , in a system with feedback exerted by X and binding of Y to B. The function $f(x, y)$ is according to Eq. 44, and $g = 1$. The left ordinate is for x and y , the right one for a ; initial values $a(0) = 1$, $x(0) = y(0) = z(0) = 0$. Values of parameters are $\mathcal{A}_{en} = 2.5 RT$, $K_1 = K_2 = 1$, $\alpha_e = 5$, $\nu = 0$, $\alpha_r = 28$, $n = 3$, $K_f = 5$, $f_0 = 10^{-5}$, $b_{tot} = 60$, $K_b = 20$, $\alpha_b = 0.05$, $\phi_1 = 0.01$, and $\phi_3 = 2$.

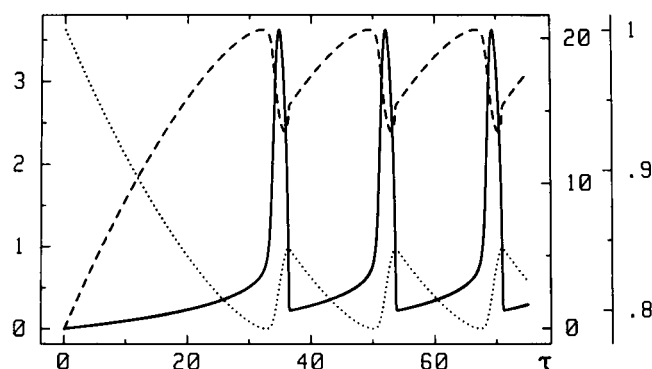


FIGURE 3 Dependence of the reduced concentrations x (—), y (---), and a (·····) on the reduced time, τ , in a system with an enzyme-catalyzed energizing reaction. X is a noncompetitive inhibitor of the enzyme according to Eq. 30, whereas $f = 1$. Ordinates from left to right pertain to x , y , and a ; initial values $a(0) = 1$, $x(0) = y(0) = 0$. Values of parameters are $\mathcal{A}_{en} = 5.5 RT$, $K_1 = K_2 = 1$, $\alpha_e = 1$, $\nu = 0$, $K_{mX} = 0.4$, $K_{mY} = 1000$, $K_{mXY} = \infty$, $m = 1$, $K_g = 0.4$, $\alpha_r = 1$, $\alpha_b = b_{tot} = 0$, $\phi_1 = 0.01$, and $\phi_3 = 1$.

stabilize the system (cf. Eq. 45). Thus, if K_{mY} is given progressively smaller values than that used in Fig. 3, the period and the amplitude of the oscillations decrease, and the system eventually enters the regime of damped oscillations if $K_{mY} < 39$.

The conditions in Eq. 43b can be fulfilled by a negative and a positive feedback exerted by X on the regulated transition and the energizing reaction, respectively,

$$f(x) = [1 + (x/K_f)^n]^{-1} + f_0 \quad (47)$$

and

$$g(x) = x^m[1 + (x/K_g)^m]^{-1}$$

The feedback regulation coefficient then becomes

$$\rho = \frac{n(x_s/K_f)^n}{W_1} + \frac{(1 + f_0 W_1)m}{W_2} > \frac{A[1 + W_1[f_0 + \alpha_e x_s^n/\alpha_r W_2]]}{1 - A} \quad (48)$$

with W_1 and W_2 given by Eq. 46. Except for A values close to unity, the term $1 - A$ can be approximated by 1. It seems that in this case ρ can be smaller than 1 and even approach zero for small enough A values. However, because the first term in Eq. 41 is then essentially independent of A whereas the second decreases with decreasing values of A , ρ has to be chosen such that $\alpha_e K_2 H_2 > H_1$ (cf. Eq. 39), which again requires ρ values larger than 1.

In terms of the quantities D_f and D_g a feedback exerted by Y is entirely equivalent to one exerted by X. Indeed, when using the second equality in Eq. 41 and appropriately chosen feedback mechanisms, relations for ρ can be derived that are analogous to those in Eqs. 45 and 48 and readily satisfiable. But the first term of H_2 is now inversely proportional to h_2 , which itself depends on A (cf. second equality in Eq. 41 and Eq. 34b). As a consequence, the

positive term of H_2 is only weakly dependent on A , whereas the negative term is proportional to A . Hence under no circumstances can values for A and ρ be found such that $P_1 < 0$. It thus appears that the minimal kinetic scheme without the optional binding of Y to B (see Fig. 1) is incapable of producing sustained oscillations if feedback is exerted only by Y . However, if the optional binding of Y to B is included sustained oscillations do occur, as demonstrated by the example shown in Fig. 4. This was to be expected, because such a scheme is formally the "mirror image" of a corresponding scheme with feedback exerted by X and binding of Y to B .

STABILITY CRITERIA IN TERMS OF THERMODYNAMIC PARAMETERS

According to Lefever et al. (1988), "oscillatory behavior is restricted to the far from thermodynamic equilibrium domain, i.e., in this case to values $(\mathcal{A}_{II}/RT) > 1$, where linear relations between thermodynamic fluxes and forces no longer hold." Note that \mathcal{A}_{II} in this statement is identical to our \mathcal{A}_{en} . The flows in the present system are given by Eqs. 15–18; they can be converted to reduced flows according to

$$j_i = J_i t_o / (V_2 c_1) = d\xi_i / d\tau \quad (49)$$

Here ξ_i denotes the progress variable (or degree of advancement) of the i th process, which will serve later as a state variable. The conjugate forces, when written in the reduced form $x_i = X_i/RT$, are

$$x_a = \ln\{a/(K_1 x)\} \quad (50)$$

$$x_e = \ln\{A(K_2 x/y)^{\nu+1}\} = \mathcal{A}_{en}/RT - (\nu+1)x_r \quad (51)$$

$$x_r = \ln\{y/(K_2 x)\} \quad (52)$$

$$x_b = \ln\{(b_{tot} - z)y/(K_b z)\} \quad (53)$$

As is evident from Eqs. 15–18 flows are governed by differences in concentrations of reactants, whereas forces are governed by ratios of concentrations (see Eqs. 50–53). As a consequence, with the exception of the case $x_i \ll 1$, which holds only in the immediate vicinity of equilibrium, flow-force relations are in general ambiguous (see Fig. 5), because a given value of the force is not associated a priori with a unique set of values for the concentrations and hence for the flow. In view of this the meaning of "linear relations between thermodynamic fluxes and forces" is not clear.

If certain constraints apply, the flow-force relations do become unambiguous over certain restricted ranges of values (Walz, 1990). Nevertheless, as shown in Fig. 6 by means of the system introduced in Table 1, oscillations are then possible in the linear domain of the flow-force relations and can occur even if $\mathcal{A}_{en} < RT$. This is due to the feedback regulation that converts the essentially single-valued function $j_0(x_r)$ (broken line in Fig. 6 C) into the multivalued function $j_{re}(x_r)$ (solid line in Fig. 6 C).

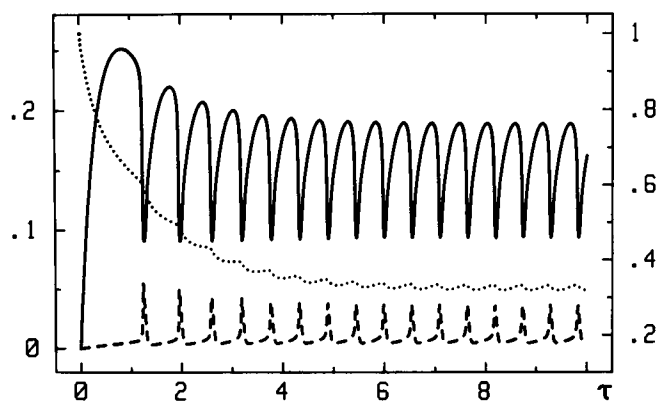


FIGURE 4 Dependence of the reduced concentrations x (—), y (---), and a (····) on the reduced time, τ , in a system with feedback exerted by Y . The function $f(y) = y^n$ (autocatalysis) and $g = 1$. The left ordinate is for x and y , the right one for a ; initial values $a(0) = 1$, $x(0) = y(0) = z(0) = 0$. Values of parameters are $\mathcal{A}_{en} = -4.5 RT$, $K_1 = 2$, $K_2 = 1$, $\alpha_e = 200$, $\nu = 0$, $\alpha_r = 10^5$, $n = 2$, $b_{tot} = 25$, $K_b = 1$, $\alpha_b = 2$, $\varphi_1 = 1$, and $\varphi_3 = 0.5$.

Furthermore, the feedback regulation coefficient has to be sufficiently large; as is evident from Table 1, reducing this coefficient by unity eliminates oscillations. On the other hand, nonlinearity in the flow-force relations does not guarantee oscillatory behavior, as is seen in Fig. 7. In this case feedback regulation, although present, does not convert the single-valued function $j_0(x_r)$ into a multivalued function $j_{re}(x_r)$ because the feedback regulation coefficient has too low a value. Increasing this coefficient by unity evokes oscillations (see Table 1) and gives rise to a multivalued function $j_{re}(x_r)$. However, such a function per se does not suffice for oscillations to occur,

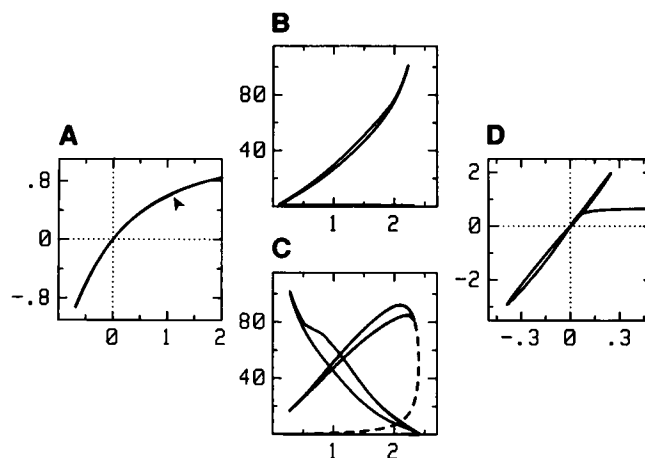


FIGURE 5 Flow-force relations for the system presented in Fig. 2. The reduced flows j_i (Eqs. 15–18 and 49) are plotted as functions of the reduced forces x_i (Eqs. 50–53) for $i = a$ (A), e (B), and b (D). The arrowhead in (A) indicates the limit of the oscillations. In (C) the two components of j_r , j_{re} (—), and j_0 ($\times 10^5$, ---) arising, respectively, from f_{re} and f_0 , are plotted separately. Note that initial forces may approach $\pm\infty$ because of the initial conditions $x(0) = y(0) = z(0) = 0$. For parameter values see legend to Fig. 2.

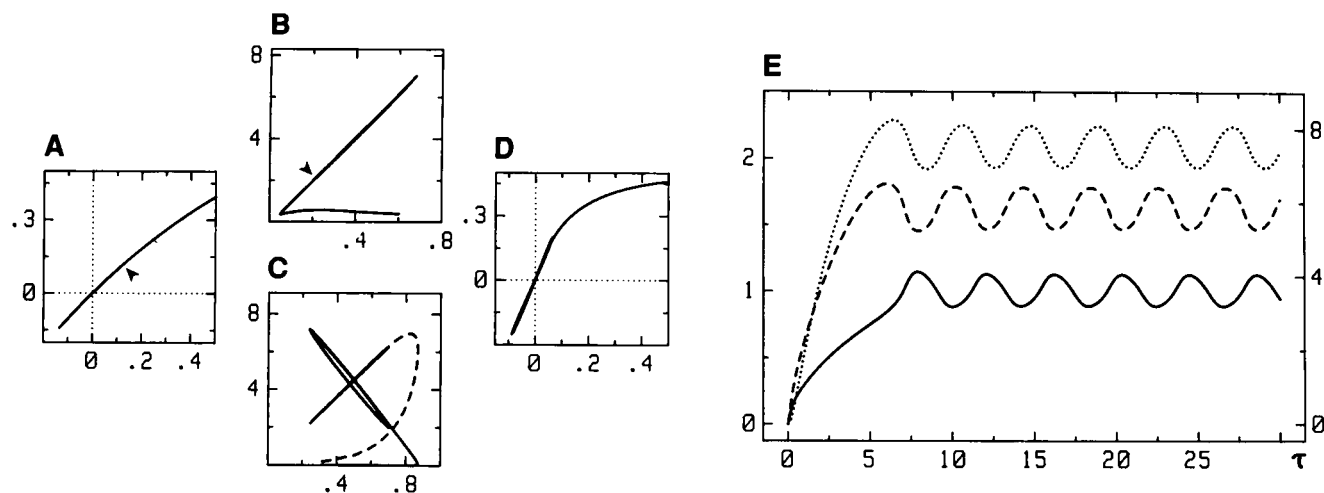


FIGURE 6 Flow-force relations for the system presented in Table 1 exhibiting sustained oscillations in the linear domain. The reduced flows j_i (Eqs. 15–18 and 49) are plotted as functions of the reduced forces x_i (Eqs. 50–53) for $i = a$ (A), e (B), and b (D). The arrowheads in (A) and (B) indicate the limits of the oscillations. In (C) the two components of j_e , j_{re} (—) and j_0 ($\times 10^5$, ---) arising, respectively, from f_{re} and f_0 , are plotted separately. The dependence of the reduced concentrations x (—), y (---), and z (····) on the reduced time, τ , is shown in (E). Initial values are $a(0) = 1$, $x(0) = y(0) = z(0) = 0$, which causes initial forces to approach $\pm\infty$. Values of parameters are $\mathcal{A}_{en} = 0.92 RT$, $K_1 = K_2 = 1$, $\alpha_e = 5$, $\nu = 0$, $\alpha_t = 7$, $n = 9$, $K_f = 5$, $f_0 = 10^{-5}$, $b_{tot} = 100$, $K_b = 20$, $\alpha_b = 0.02$, $\varphi_1 = 0$, and $\varphi_3 = 5$.

because it is also observed in the case of ambiguous flow-force relations under nonoscillatory conditions. Note that exactly the same features are found in the absence of binding of Y to B. Therefore, the stability of a chemical system can only be evaluated in terms of its feedback regulation coefficient but not in terms of its affinities or the lack of linearity of its flow-force relations.

It may appear that these findings contradict the general law that systems in the near-equilibrium domain (de Groot and Mazur, 1962) or in a steady state close to equilibrium (Keizer, 1987) cannot oscillate. However, this general law

was proved and hence is valid only under the following condition. The entropy of the system is approximated by a Taylor expansion about the equilibrium state in terms of the state variables, and the series comprises only the first nonvanishing partial derivatives of the entropy with respect to the state variables. Because entropy is maximal at equilibrium the first partial derivatives are zero, whereas the second partial derivatives, i.e., the first nonvanishing ones, are negative. It is this condition which defines what “close to equilibrium” means.

The change in entropy of a system with time is given by the dissipation function Φ , which reads, in terms of

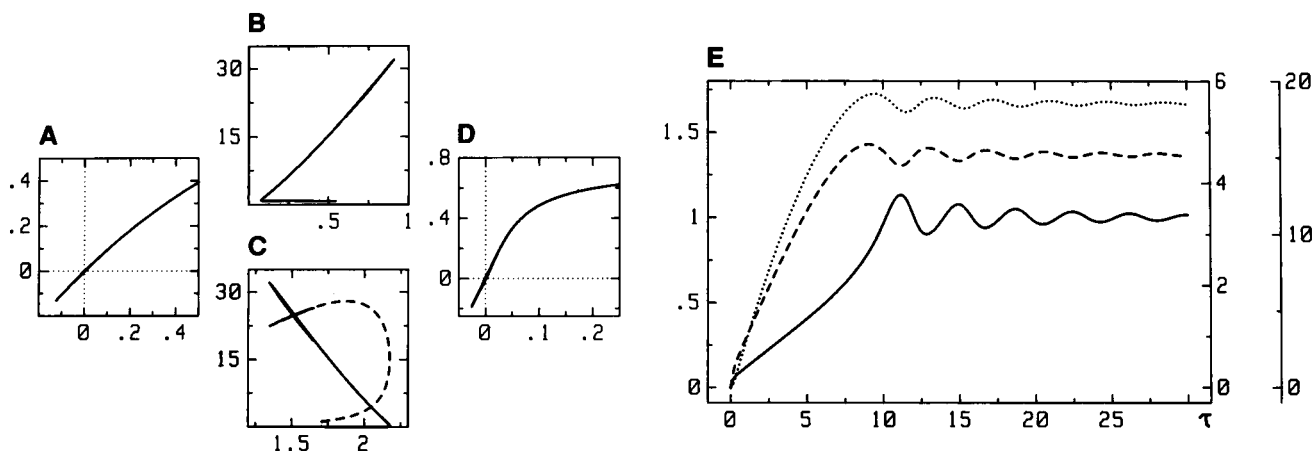


FIGURE 7 Flow-force relations for the system presented in Table 1 exhibiting damped oscillations in the nonlinear domain. The reduced flows j_i (Eqs. 15–18 and 49) are plotted as functions of the reduced forces x_i (Eqs. 50–53) for $i = a$ (A), e (B), and b (D). In (C) the two components of j_e , j_{re} (—) and j_0 ($\times 10^5$, ---) arising, respectively, from f_{re} and f_0 , are plotted separately. The dependence of the reduced concentrations x (—), y (---), and z (····) on the reduced time, τ , is shown in (E). Initial values are $a(0) = 1$, $x(0) = y(0) = z(0) = 0$, which causes initial forces to approach $\pm\infty$. Values of parameters are the same as in Fig. 6 except for $\mathcal{A}_{en} = 2.25 RT$ and $n = 3$.

reduced flows and forces, and the reduced time τ (cf. Eq. 51),

$$\begin{aligned}\Phi &= (T/t_0)dS/d\tau = (V_2c_1RT/t_0)\sum j_i x_i \\ &= j_a x_a + j_e x_e + j_r x_r + j_b x_b \\ &= j_a x_a + j_e \mathcal{A}_{en}/RT + [j_r - (\nu + 1)j_e]x_r + j_b x_b\end{aligned}\quad (54)$$

Note that $j_b = 0$ in the absence of the optional binding of Y to B. Integration of Eq. 54 yields the system's entropy $S(\tau)$ up to an integration constant, and the entropy at equilibrium $S_{eq} = S(\infty)$ if the integration is performed over a sufficiently (infinitely) long time period so that the homeostatic mechanisms for S and P are exhausted. A difference in reduced entropy with respect to equilibrium, $\Delta\hat{S}$, can then be defined and calculated as

$$\Delta\hat{S}(\tau) = \frac{S(\tau) - S_{eq}}{V_2c_1R} = \int_0^\tau \sum j_i x_i d\tau' - \int_0^\infty \sum j_i x_i d\tau' \quad (55)$$

In a system with only chemical processes the appropriate state variables are the progress variables ξ_i . When introducing Eq. 49 rewritten for the different processes into Eqs. 22–25, and the relation $dc_p/dt = J_e$ for the now exhaustible species P, one obtains by means of Eqs. 8 and 11 differential equations that relate the reduced concentrations to the

progress variables. Following the integration procedure outlined above yields

$$\begin{aligned}\xi_a(\tau) &= x(\tau) - x_{eq} + \frac{y(\tau) - y_{eq}}{\phi_3} + \xi_b(\tau) \\ &= -\frac{a(\tau) - a_{eq}}{\phi_1}\end{aligned}\quad (56a)$$

$$\begin{aligned}\xi_r(\tau) &= x(\tau) - x_{eq} + (\nu + 1)\xi_e(\tau) - \xi_a(\tau) \\ &= (\nu + 1)\xi_e(\tau) - \xi_b(\tau) - \frac{y(\tau) - y_{eq}}{\phi_3}\end{aligned}\quad (56b)$$

$$\xi_e(\tau) = p(\tau) - p_{eq} \quad (56c)$$

$$\xi_b(\tau) = \frac{z(\tau) - z_{eq}}{\phi_3}. \quad (56d)$$

Eqs. 55 and 56 define the function $\Delta\hat{S}(\xi_i)$ along the trajectory followed by a system when starting from given initial conditions. Fig. 8 shows examples of this function for the system presented in Table 1 without binding of Y to B but with an exhaustible capacity for S and P. Such a system has three degrees of freedom and hence can be described by three state variables. Because $\xi_e(\tau)$ and $\xi_r(\tau)$ are rather similar in value the variables ξ_a , ξ_e , and $\xi_r - \xi_e$ are used,

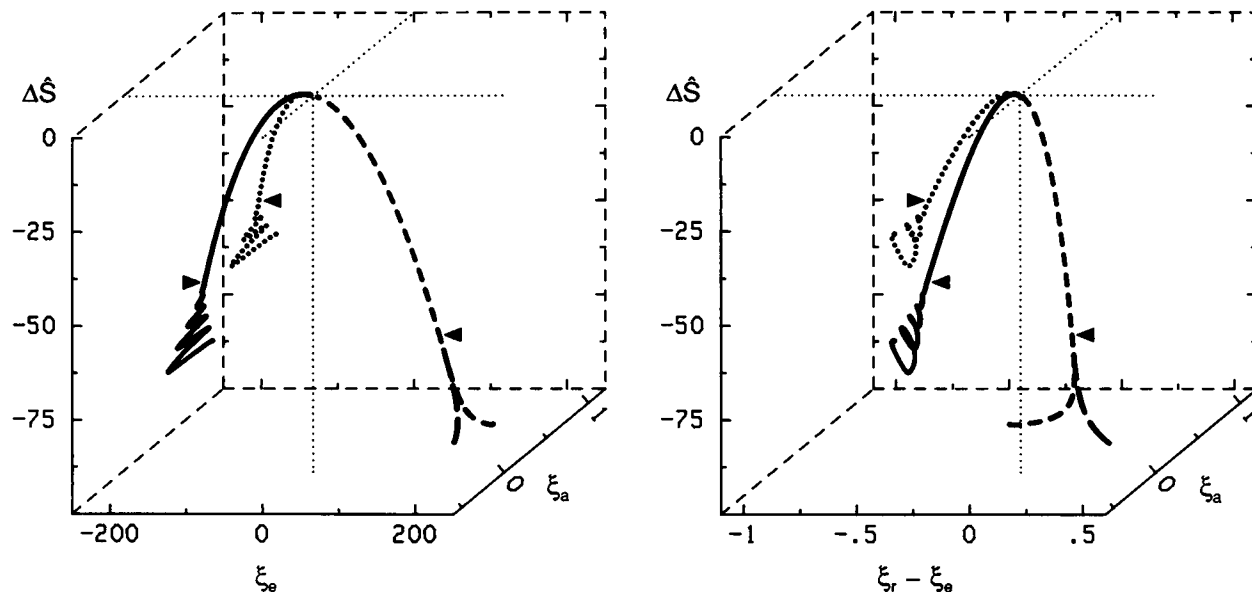


FIGURE 8 Dependence of entropy on state variables for the system presented in Table 1. The change in reduced entropy with respect to equilibrium $\Delta\hat{S}$ and the progress variables ξ_i were calculated by means of Eqs. 55 and 56, respectively, for the system without binding of Y to B but with an exhaustible capacity for S and P. The arrowheads indicate where oscillations cease ($\xi_a = 0.646$, $\xi_e = -213$, $\xi_r - \xi_e = -0.656$, $\Delta\hat{S} = -61.5$, —; $\xi_a = 0.620$, $\xi_e = -139$, $\xi_r - \xi_e = -0.634$, $\Delta\hat{S} = -39.3$, ···) or where the two broken lines join ($\xi_a = -0.362$, $\xi_e = 205$, $\xi_r - \xi_e = 0.364$, $\Delta\hat{S} = -56.8$). For the sake of clarity only the short broken line is drawn where short and long broken lines coincide. The straight dotted lines represent coordinate axes through the origin. Values of parameters are $K_1 = K_2 = 1$, $\alpha_e = 5$, $\nu = 0$, $\alpha_r = 7$, $n = 6$ (short broken line) or $n = 9$ (other cases), $K_f = 5$, $f_0 = 10^{-5}$, $\alpha_b = b_{tot} = 0$, $\phi_1 = 0$, and $\phi_3 = 0.5$. The sum $s(\tau) + p(\tau)$ is constant and equal to 1000 (····) or 1500 (other cases); initial values $s(0)$ and $p(0)$ are chosen such that initially $\mathcal{A}_{en} = 0.69 RT$ (solid and dotted line), $\mathcal{A}_{en} = -0.69 RT$ (short broken line), or $\mathcal{A}_{en} = -0.68 RT$ (long broken line); $K_{en} = 1$ (cf. Eq. 5). Other initial values are $a(0) = 1$, $z(0) = 0$ for all cases; $x(0) = 0.886$, $y(0) = 1.48$ (solid and dotted line), $x(0) = 1.13$, $y(0) = 1$ (short broken line), and $x(0) = 0.952$, $y(0) = 0.7$ (long broken line).

which correspond to the second set of flows and forces in Eq. 54. As is evident from Fig. 8, $\Delta\hat{S}(\xi_i)$ indeed follows a paraboloidal surface near equilibrium. However, the value where $\Delta\hat{S}(\xi_i)$ deviates from this surface is not a constant but depends on the kinetic parameters and initial conditions.

In conclusion, then, the sustained oscillations about a steady state close to equilibrium observed in systems with sufficiently large feedback regulation coefficients do not violate the stability criterion valid near equilibrium. Instead, they clearly demonstrate that it is in general impossible to delineate the "near-equilibrium domain" based on model-free thermodynamic considerations alone. Some knowledge of the kinetic mechanisms involved, and of at least some of the kinetic parameters such as the feedback regulation coefficient in the present examples, is indispensable to answer this question.

DISCUSSION

The minimal scheme shown in Fig. 1 (which one might call the "Baselator") provides considerable insight into the mechanics of oscillatory behavior in physicochemical and biochemical systems. This is best seen when following the evolution of the system shown in Fig. 2. The species A is converted into X, which in turn is converted into Y by the energizing reaction. Hence the concentration of X rises much slower than that of Y, and the conversion of Y to X is slow because of the positive feedback of X exerted on the regulated transition. Y, together with Z if B is present, constitutes a store of material that accumulates on the way to the static head of the energized transition. As a consequence the store is rapidly discharged when the concentration of X reaches values which, because of the positive feedback, speed up the conversion of Y to X. This causes the fast rise of the concentration of X and the fast decrease in the concentration of Y. Concomitantly, the energizing reaction increases in rate, thus tending to decrease the concentration of X, which in turn tends to decrease the rate of the regulated Y to X reaction. With these processes alone the system would eventually reach a steady state, possibly after a few damped oscillations. However, the concentration of X at this steady state is higher than the equilibrium concentration that would be attained if only the A to X reaction occurred. Hence the conversion of X to A sets in, and the concentration of X falls below the steady-state value for the isolated X to Y transitions, further slowing down the regulated reaction. This enables the energizing reaction to charge up the store beyond the level of Y, which would have been attained in the absence of the A to X conversion. Consequently, a new cycle is initiated.

This picture, with appropriate modifications, also applies to other conditions, including the cases of $\nu = 1$. Thus, in the system presented in Fig. 3, the discharge of the store through the unregulated Y to X conversion occurs when the concentration of X reaches values which, because of the negative feedback, substantially slow down the energized X

to Y conversion. If $A < 1$, the store is depleted rather than accumulated. It is then filled up (see Fig. 4) or further depleted (not shown) when the concentration of the species involved in feedback (Y or X, respectively) enters the range where feedback becomes effective. Sustained oscillations persist until the chemical capacities of S and P or those of the homeostatic devices are exhausted.

The *buffering function* of the A to X transition is of key importance for sustained oscillations because it prevents the system from attaining the stable steady state pertaining to the isolated X to Y conversions. This is the reason why a system with feedback exerted by Y does not oscillate unless the Y to Z transition is included (see Fig. 4). It thus can be stated that sustained oscillations are only possible if the species involved in feedback are appropriately buffered. Both too strong and too weak buffering prevent oscillations; hence the equilibrium constants K_1 and/or K_b as well as the chemical capacity of the buffering species (A and/or B) have to be appropriate. The role of the chemical capacity for A, which is equal to V_1 (Walz, 1990), is evident from the effect of ϕ_1 on the ranges for \mathcal{A}_{en}/RT listed in Table 1. The transition A to X is also responsible for the only constant term in the rate equations (see term 1 in Eq. 27), which is the "zeroth order, i.e., constant term in the differential equations" referred to by Stucki and Somogyi (1994) as an essential requirement for sustained oscillations. In the case of the Brusselator the role of the A to X transition is taken over by the reaction sequence $A \rightarrow X \rightarrow E$. Note that $X \rightarrow E$ is a substitute for the back reaction $X \rightarrow A$ in the transition $A \rightleftharpoons X$. It had to be included because all back reactions were omitted in the original Brusselator scheme.

The *feedback mechanisms* characterized by the feedback regulation coefficient ρ represent a second key feature for sustained oscillations because they introduce the necessary kinetic nonlinearity. As mentioned earlier, it has been claimed that nonlinearity is introduced by sufficiently large affinities \mathcal{A}_{en} (Lefever et al., 1988). In contrast, the present study demonstrates that systems with small affinities and linear flow-force relations can oscillate if kinetic nonlinearity is present because of feedback regulation. Although, as claimed by Lefever et al. (1988), a lower limit for the affinities with respect to sustained oscillations does exist, this limit is not related to thermodynamic linearity but depends on the values of the rate constants, on the feedback mechanisms chosen, and most crucially on ρ . Therefore, the limit can be moved close to equilibrium by appropriate values of ρ (cf. Table 1). However, the feasibility of extremely high feedback regulation coefficients is doubtful, besides which the amplitudes of the oscillations markedly decrease with increasing ρ and eventually become comparable to the thermal noise level, so that the oscillations are no longer detectable. This is the real limit to oscillations about steady states close to equilibrium.

The Baselator, although written in a general form, relates to biochemical systems, particularly when read in terms of the partitioning of a species between compartments that is catalyzed by membrane-bound enzymes such as pumps and

regulated pores. Thus, it comprises the scheme proposed by Chay (1981), which displays H^+ oscillations and was intended as a model for substrate oscillations in cells. With a slight extension, the Baselator also includes the model proposed by Somogyi and Stucki (1991) for Ca^{2+} oscillations in hepatocytes. The single passive transition A to X has merely to be supplemented by an additional X to A transition that is energized by an additional reaction. In this case the A to X transitions oscillate about the static head instead of equilibrium, as in the case of the Baselator with only a passive A to X transition.

We would like to thank Professor John Ross for his clarifying comments and Clemens Wagner for many helpful discussions.

D.W. acknowledges financial support by the Swiss National Science Foundation. S.R.C. was supported by the Basic Research Foundation administered by the Israel Academy of Sciences and Humanities.

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