ON THE "SIMPLEST" OSCILLATING CHEMICAL SYSTEM

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Abstract

It is pointed out that the linear system which makes conservative oscillations along elliptic trajectories can be considered reasonable in chemistry as long as the concentrations of the two intermediates are not too close to zero. As examples, two biochemical systems are discussed.

1. Introduction

Lotka in 1920 discovered a very simple two-dimensional chemical system showing conservative oscillations. This system has a reasonable interpretation in ecology and nowadays the Lotka–Volterra system is very often cited as a simple model for structure formation (see e.g. Nicolis and Prigogine, 1977 or Ebeling, 1976). Noszticzius, Farkas and Schelly (1984) used the Lotka–Volterra model as a basis to construct models of the Belousov–Zhabotinsky reaction. As an example for the construction of simple oscillating chemical systems we mention here the paper by Tyson & Light (1974) and that of Gray & Scott (1985). Nowadays attention is focused on oscillations in biological systems as well (e.g. Rowe, 1987).

Sometimes it is stated that the Lotka–Volterra model is the simplest chemical system showing oscillations (e.g. Noszticzius 1980, 1982).

The equation of the integral curves of the Lotka–Volterra model is given by the first integral:

$$V(x, y)=x-\ln x+(y-\ln y)/C \tag{1}$$

after a proper scaling (e.g. Farkas & Noszticzius, 1985). From a mathematical point of view, these integral curves are not simple and the time dependence cannot be given in closed analytical form. Note that Escher (1979) constructed reasonable models which show limit cycle oscillations along elliptic integral

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curves. On the other hand, his model is not simple from a chemical point of view because it contains trimolecular reactions, too.

From a mathematical point of view, there is no doubt that the simplest system showing oscillations is:

$$\dot{x} = -y \qquad \dot{y} = x \tag{2}$$

The integral curves of this system are circles, centered at the origin. In a chemical system x and y denote concentrations and therefore they should be positive. To fulfill this condition, we have to move the center into the positive quadrant. The general linear form of this type reads:

$$\dot{x} = K_1 - K_2 y \tag{3a}$$

$$\dot{y} = K_3 x - K_4 \tag{3b}$$

which has the ellipses

$$\frac{(x-x_0)^2}{a^2} + \frac{(y-y_0)^2}{b^2} = 1 \tag{4}$$

as integral curves where a is an integration constant, and

$$x_0 = K_4/K_3 \qquad \omega = \sqrt{K_2 K_3} \tag{5}$$

$$y_0 = K_1/K_2 \qquad b = a\sqrt{K_3/K_2}$$

With the initial condition

$$x(0) = x_0 + a \qquad y(0) = y_0 \tag{6}$$

the time dependence is:

$$x = x_0 + a \cdot \cos \omega t \tag{7}$$

$$y = y_0 + b \cdot \sin \omega t$$

Obviously, the following conditions should be valid:

$$a < x_0, \qquad b < y_0 \tag{8}$$

in order for the trajectories to remain in the positive quadrant.

2. A simple kinetic interpretation

The first term on the right-hand side of equation (3a), K_1 represent a constant production of X. This may be easily realized by a constant input of X or by an in situ production of X from some starting materials, the concentrations of which are kept constant. The term $K_3 x$ in (3b) represents the production of Y from some starting materials of constant concentration

catalyzed by X. This step may be realized without any trouble as well. The difficulty due to which the model (3) was not thought to be a realistic one by chemists is that the term $-K_2y$ in (3a) means a zero-order decay of X, catalyzed by Y, and the term $-K_4$ in (3b) means a constant zero-order decay of Y. The former is a so-called negative cross-effect term which, according to Tóth and Hárs (1986), should not be involved in a kinetic differential equation of a chemical reaction.

In fact, zero-order reactions are rare, but not unknown in chemistry, there are several examples in the literature. Especially in biochemistry zero-order reactions are quite common, the velocity of enzyme catalyzed reactions with increasing substrate concentrations tends to a maximum constant value (see Michaelis & Menten, 1913, Monod et al., 1965, and Plowman, 1972). Predators feed on prey according to the Michaelis–Menten–Monod kinetics, too (e.g. Legović, 1987, and M. Farkas, 1984).

However, there is a simple and general method to construct a reaction with apparent zero-order kinetics. Let us introduce a new component W and consider a two-step process. The first step is a slow constant production of W, the second one is a fast reaction between Y and W. The second reaction results in an indifferent product and the kinetic orders of this step with respect to both reactants are one. The steady-state approximation $\dot{w}=0$ leads to the zero order decay of Y. Korzukhin (1967) on the basis of this idea constructed a rather complicated model. Here we present a simpler kinetic interpretation for the "simplest" chemical oscillator (3):

$$\rightarrow X \tag{K1}$$

$$\xrightarrow{Y} Z \tag{K2a}$$

$$X+Z\rightarrow \tag{K2b}$$

$$\xrightarrow{X} Y \tag{K3}$$

$$\rightarrow W \tag{K4a}$$

$$W+Y\rightarrow \tag{K4b}$$

The corresponding kinetic equations are:

$$\dot{x}=k_1-k_{2b}xz \tag{9}$$

$$\dot{y}=k_3x-k_{4b}yw \tag{10}$$

$$\dot{z}=k_{2a}y-k_{2b}xz \tag{11}$$

$$\dot{w}=k_{4a}-k_{4b}yw \tag{12}$$

Now the steady-state approximations

$$\dot{z}=0 \qquad k_{2a}y=k_{2b}xz \tag{13}$$

$$\dot{w}=0 \qquad k_{4a}=k_{4b}yw \tag{14}$$

transform (9–12) into (3) with the notations

$$K_1=k_1, \qquad K_2=k_{2a}, \qquad K_3=k_3, \qquad K_4=k_{4a} \tag{15}$$

The steady-state approximations (13–14) are valid for the limit case

$$k_{2b}\to\infty \qquad k_{4b}\to\infty \tag{16}$$

What we want to stress is that the system (3) can be considered as a realistic scheme except for the vicinity of the axes x and y (see later, conditions (29–30)).

In the following sections we discuss two biochemical examples for the systems (9–12) and (3).

3. Cascade catalysis

Let us first consider the scheme (K) introducing starting materials and products of reasonable biochemical meaning:

$$S_1+\ \ldots\ +S_n\to X \tag{CA 1}$$

$$\tilde{Y}\xrightarrow{X} Y \tag{CA 2}$$

$$S_{n+1}\xrightarrow{Y} Z \tag{CA 3}$$

$$X+Z\to\tilde{X} \tag{CA 4}$$

$$S_{n+2}+\ \ldots\ S_m\to W \tag{CA 5}$$

$$W+Y\to\tilde{Y}' \tag{CA 6}$$

CA 1: production of an activating enzyme X; $S_1 \ldots S_n$ denote amino acids, nucleic acids, and enzymatic factors necessary for protein synthesis

CA 2: X activates the enzyme Y from the inactive form $\tilde{Y}$

CA 3: the metabolite Z is produced by the action of Y from the substrate S_{n+1}

CA 4: Z desactivates X, the product is the inactive $\tilde{X}$

CA 5: the inhibitor W is produced; $S_{n+2} \ldots S_m$ denote the necessary starting materials and enzymes; alternatively this step may be realized by a constant input of W

CA 6: W desactivates Y, the product is the inactive $\tilde{Y}'$

Let us assume that the reaction rates are of the form

$$I_1 = f_1(s_i); \quad i = 1, \ldots n; \quad s_i = \text{const.} \tag{17}$$

$$I_2 = f_2(\tilde{y})x; \quad \tilde{y} = \text{const.} \tag{18}$$

$$I_3 = f_3(s_{n+1})y; \quad s_{n+1} = \text{const.} \tag{19}$$

$$I_4 = k_4 xz \tag{20}$$

$$I_5 = f_5(s_i); \quad i = n+2, \ldots m; \quad s_i = \text{const.} \tag{21}$$

$$I_6 = k_6 wy \tag{22}$$

where the f_i-s are positive definite functions, k_i-s are positive constants. If the conditions

$$I_4 \gg I_3, \qquad I_6 \gg I_5 \tag{23}$$

hold, this system, in the same way as (9–12), gives (3) with the notations

$$K_1 = f_1(s_i), \qquad K_2 = f_3(s_{n+1}), \qquad K_3 = f_2(\tilde{y}),$$
$$K_4 = f_5(s_i) \tag{24}$$

It is noteworthy that Kaufman & Thomas (1987) proposed a model for the humoral immune response, which has some analogy with this system.

4. Cross catalysis

Making use of the biochemical zero-order processes one can construct a scheme directly according to (3) as follows:

$$S_1 + \ldots S_n \rightarrow X \tag{CR 1}$$

$$S_{n+1} + \ldots + S_m \xrightarrow{X} Y \tag{CR 2}$$

$$X \xrightarrow{Y} P_1 + \ldots + P_e \tag{CR 3}$$

$$Y \xrightarrow{U} \tilde{Y} \tag{CR 4}$$

CR 1: production of mRNA chains X coding ribonuclease, i.e. transscription; $S_1 \ldots S_n$ denote DNA, nucleotides, and enzymatic factors

CR 2: the synthesis of ribonuclease, $S_{n+1} \ldots S_m$ denote amino acids, tRNA, and enzymatic factors

CR 3: hydrolysis of the mRNA X by the ribonuclease Y to the products $P_1 \ldots P_e$

CR 4: desactivation of Y by the action of another enzyme U, this may be some specific one or a general protein hydrolase

Let us assume that the reaction rates are of the form:

$$I_1 = f_1(s_i); \qquad i = 1 \ldots n; \quad s_i = \text{const.} \tag{25}$$

$$I_2 = f_2(s_i)x; \qquad i = n+1 \ldots m; \quad s_i = \text{const.} \tag{26}$$

$$I_3 = k_3 y \tag{27}$$

$$I_4 = k_4 u; \qquad u = \text{const.} \tag{28}$$

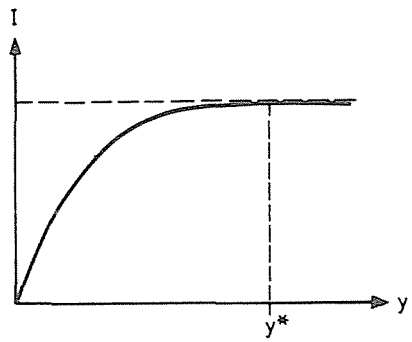

Fig. 1. Rate of an enzyme reaction depending on substrate concentration

Here the functions f_1 and f_2 are positive and definite, k_3 and k_4 are positive constants, (27) and (28) mean enzyme catalysed zero-order decay for X and Y, respectively. This requires the conditions (29–30) to be held (Fig. 1):

$$y > y^* \tag{29}$$

$$x > x^* \tag{30}$$

In other words, in the domain of concentrations characterized by (29–30) zero-order kinetics is valid to a good approximation. The system (25–28) is equivalent to (3) with the notations

$$K_1 = f_1(s_i), \qquad K_2 = k_3, \qquad K_3 = f_2(s_i), \qquad K_4 = k_4 u \tag{31}$$

Some similar biochemical oscillators were reviewed by Nicolis (1971). It should be noted that model (3) does not contain any autocatalytic reaction or other nonlinearities which are often stated in the literature as necessary for oscillatory systems.

(24) and (31) contain a lot of adjustable parameters and therefore we hope that experimental biochemists will realize these models some day in vitro or in vivo.

5. Stability analysis and numerical examples

To investigate the (9–12) system, we should transform it into a simpler form. By scaling one has:

$$\dot{X} = 1 - XZ \tag{32}$$

$$\dot{Y} = A(X - YW) \tag{33}$$

$$\dot{Z} = B(Y - XZ) \tag{34}$$

$$\dot{W} = C(1 - YW) \tag{35}$$

which results in a unique steady state (1, 1, 1, 1).

However, we should like to relate the four-dimensional system to the two-dimensional approximate form. For this, we use another scaling:

$$\begin{aligned} x/X = z/Z = k_{4a}/k_3, \qquad & y/Y = w/W = k_{4a}/k_{2a}^{1/2}k_3^{1/2}, \\ t/T = 1/k_{2a}^{1/2}k_3^{1/2}, \qquad & U = k_1 k_3^{1/2}/k_{2a}^{1/2}k_{4a}, \\ U_2 = k_{2b}(k_{4a}/k_{2a}^{1/2}k_3^{3/2}), \qquad & U_4 = k_{4a}(k_{4a}/k_{2a}k_3) \end{aligned} \tag{36}$$

which transforms the system (9–12) into the form:

$$\dot{X} = U - U_2 XZ \tag{37}$$

$$\dot{Y} = X - U_4 YW \tag{38}$$

$$\dot{Z} = Y - U_2 XZ \tag{39}$$

$$\dot{W} = 1 - U_4 YW \tag{40}$$

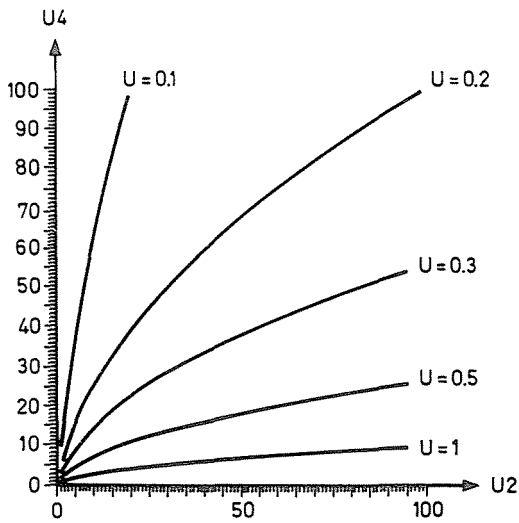

Fig. 2. Bifurcation curves $g = 0$ of system (37–40)

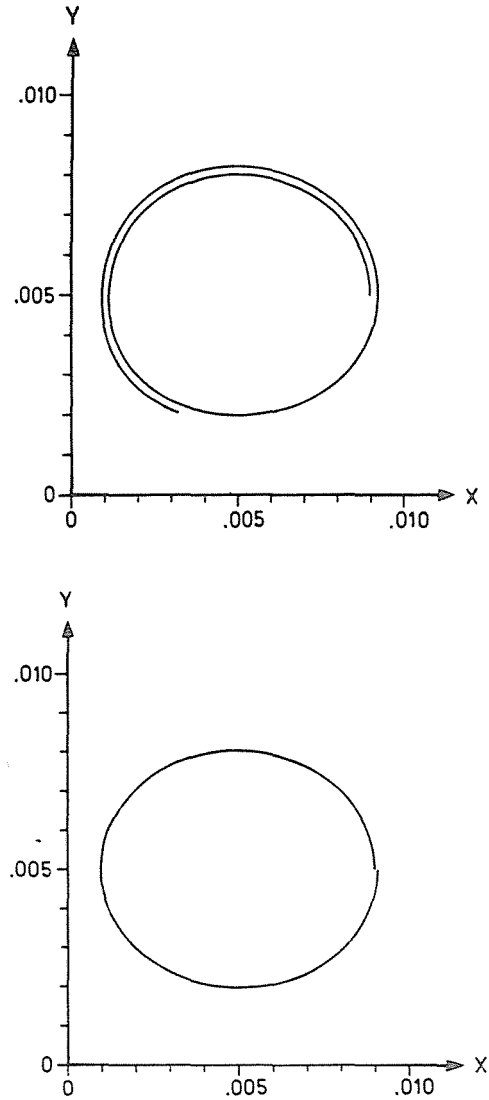

Fig. 3. Trajectories of systems (9–12) (a) and (3) (b) for a one-minute oscillator
Parameter values: a) $k_1 = 6.98 \cdot 10^{-4}$, $k_{2a} = 0.140$, $k_{2b} = 1400$,
$k_3 = 7.85 \cdot 10^{-2}$, $k_{4a} = 3.93 \cdot 10^{-4}$, $k_{4b} = 785$; b) $K_1 = k_1$,
$K_2 = k_{2a}$, $K_3 = k_3$, $K_4 = k_{4a}$

Note that the limiting process (16) for the system (37–40) takes the form:

$$U_2 \to \infty \qquad U_4 \to \infty \tag{41}$$

while the parameter U is not affected.

A lengthy, but straightforward calculation proves that the condition of Hopf bifurcation is:

$$g(U, U_2, U_4)=0 \tag{42}$$

where

$$g(U, U_2, U_4)\equiv U_2^2+U_2(U+1/U-U^3U_4^2)+$$
$$+(1+U^2-U_4-2U^2U_4^2-U^4U_4^2-U^4U_4^3) \tag{43}$$

The curves of Hopf bifurcation in the U_2-U_4 plane for different values of U are plotted in Fig. 2. It can be shown that at parameter values satisfying condition (42), two of the eigenvalues of the Jacobian have negative real parts and the other two eigenvalues are imaginary. The stationary point $(1, U, U/U_2, 1/UU_4)$ is stable if $g>0$ and unstable if $g<0$, at least near the bifurcation curve.

Fig. 3 demonstrates the validity of the approximation (13–14): a) refers to the four-dimensional system (9–12), b) refers to the approximate two-dimensional system (3). The numerical values of the parameters were chosen to be adequate to have biochemical meaning. We remark that all cyclic or spirallizing curves in the phase-plane are counter-clockwise.

Fig. 4 shows an interesting effect: the amplitude of the oscillation at first gradually decreases, and then grows higher than its original value. This behaviour resembles an experimentally found phenomenon: chemical oscillation

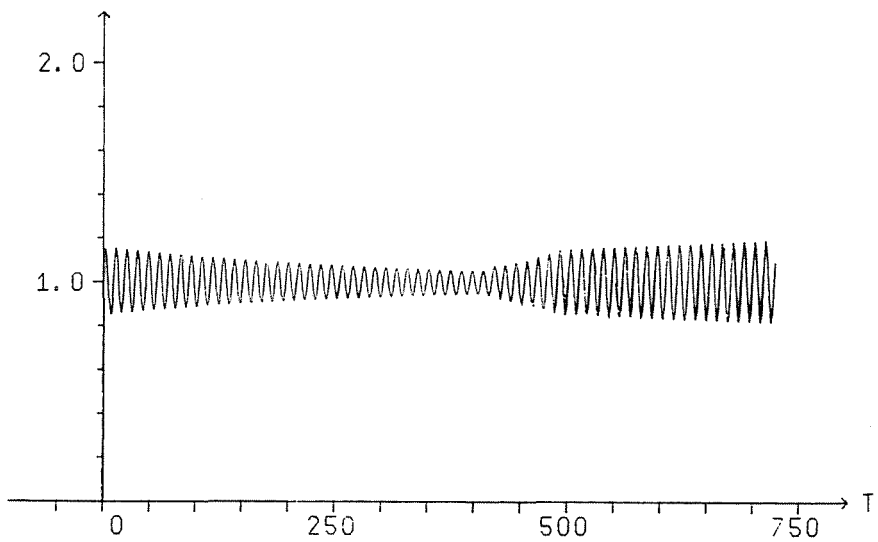

Fig. 4. "Pause"-like behaviour under the bifurcation curve $g=0$, $U=1$, $U_2=1.3$, $U_4=0.9$. The other three variables show a similar time depends dependence. System (37–40)

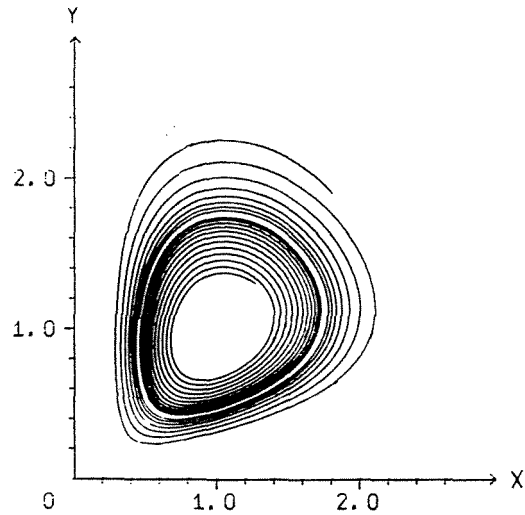

Fig. 5. Stable limit cycle over the bifurcation curve $g=0$, $U=1$. System (37–40), $U_2=1.3$, $U_4=1.1$

in a special Belousov–Zhabotinsky system has a pause (Wittmann et al., 1987). So far there is no mathematical model for that pause.

Fig. 5 demonstrates that our system (37–40) has a stable limit cycle. The parameters were chosen in the region above the bifurcation curve $U=1$ of Fig. 2.

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