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Concentration Oscillations in Three-Component Reaction Systems

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Abstract—Based on the sufficient conditions for the existence of oscillation modes in the mathematical models of biological systems, simple three-component schemes of chemical reactions with oscillatory behavior including only mono- and bimolecular steps are suggested.

Key words: oscillation, chemical systems

Considerable recent attention has been focused on biochemical oscillations in relation with the problem of biochemical clocks. Possible origin of initiation of biochemical rhythms is discussed. Most scientists consider that some auto-oscillation system of biochemical reactions can generate biological rhythms. For this viewpoint, discovery of simple mechanisms of chemical reactions with oscillatory behavior is of particular importance. However, the main features of real chemical reactions should be retained.

The goal of this work was to reveal theoretical schemes of simple chemical reaction systems with oscillatory behavior.

Chemical reaction systems are considered simple if they satisfy the following criteria: a) the reaction rate is described by the mass-action expression; b) the order of reaction does not exceed two; c) the number of reagents and steps is small.

A simple scheme can consist of two reagents, that is, it should be a two-component one. Two Lotka models can be model examples of two-component systems with oscillatory behavior [1, 2]. Simplicity and existence of periodic solutions at all positive values of parameters are the advantages of these models. A drawback is that they are conservative, whereas it is known that real systems are described by non-conservative systems of equations [3]. It is also difficult to interpret these systems in a chemical sense.

Sel'kov suggested a non-conservative two-component oscillatory model [4]; however, it included a trimolecular step highly improbable under ordinary conditions. Higgins suggested another two-component model [5]. This model was obtained as a result of reduction by small parameters and can hardly be considered as a simple one because one of its steps is not described by the mass-action expression.

This raises the question whether two-component non-conservative systems of chemical reactions with oscillatory behavior are possible? Our analysis showed that except for the Lotka reaction system [1, 2], there is no other simple two-component reaction system with oscillatory behavior [6].

Is oscillatory behavior in a three-component reaction system really possible? The question was already discussed, and only one reaction scheme with mono- and bimolecular steps was found [7, 8]. Wilhelm and coauthors stated that this scheme is unique and called it the simplest system of chemical reactions with Haupf bifurcation [7, 8].

As demonstrated in this work, not one but several schemes of reactions with oscillatory behavior are possible in three-component systems.

ABOUT THE METHOD OF ANALYSIS OF STABILITY OF STEADY STATES OF CHEMICAL SYSTEMS

First of all let us define what is called a "chemical system". A system of kinetic equations accounting for the interactions of the order not higher than two is called chemical if all u_k values mean concentrations and consequently, are positive; there are no autocatalytic terms in the system.

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$$\frac{du_k}{dt} = \sum_{i=1}^{m} \gamma_{ik} f_i(t, u) + v_k(t) \; (k = 1, 2, ..., n) \qquad (1)$$

In the framework of this definition, a system of differential equations (1) describes dynamics of chemical reactions in which the substances u_k ($k = 1, ..., n$) participate:

$$\sum_{k=1}^{n} \alpha_{ik} u_k \rightarrow \sum_{k=1}^{n} \beta_{ik} u_k \; (i = 1, 2, ..., m) . \qquad (2)$$

In Eqs. (1) and (2), β_{ik} and α_{ik} are stoichiometric coefficients (the number of the molecules of compound U formed and/or consumed in the ith reaction, respectively), $\gamma_{ik} = \beta_{ik} - \alpha_{ik}$, $f_i(t, u)$ is the rate of the ith reaction step, $v_k(t)$ is the inflow rate of reagent k, m is the number of reactions, n is the number of reagents, and u is concentration of the ith component.

It has been proved in [9] that if the system of inequalities

$$L_i(s) = \sum_{k=1}^{m} \gamma_{ik} s_k \leqslant 0 \; (i = 1, 2, ..., n) \qquad (3)$$

has non-negative solutions $s_i \geq 0$ ($i = 1, 2, ..., n$), the solutions of system (2) are limited at $t \rightarrow \infty$. Demand for existence of a positive solution of system (3) has a simple chemical meaning: in chemical kinetics it means the existence of material balance in the reaction system (1).

In correct mathematical models of real chemical reactions, the stable steady-state solutions should be limited, that is, the system of inequalities (3) should have a non-negative solution. If this condition is not met, it means that the model is incorrect and requires further improvement.

Existence of oscillatory models in dynamics of chemical reactions is related with stability of the steady states of the system. Steady-state stability is studied by linearization of nonlinear kinetic equations near the steady-state points. The eigenvalues governing behavior of the system near these steady states are the roots of characteristic equation $|\lambda \mathbf{I} - \mathbf{J}| = 0$, where λ are the eigenvalues, $\mathbf{I}$ is a unitary matrix, and $\mathbf{J}$ is the Jacobian of the system. If the Jacobian of the system of kinetic equations with the elements

$$J_{ij} = \sum_{k=1}^{m} \gamma_{ij} \, \partial v_k / \partial u_j$$

has an eigenvalue with a negative real part, the steady state is stable (v_k is the rate of the kth reaction). The eigenvalue of the Jacobian can be found using a characteristic equation

$$\lambda^n + a_1 \lambda^{n-1} + ... + a_r \lambda^{n-r} = 0 , \qquad (4)$$

where r is the rank of the matrix of stoichiometric coefficients of the reaction.

For qualitative study of the system dynamics, it is sufficient to know the signs of the roots of characteristic equation (4) which are defined by the coefficients of Eq. (4).

If at least one of the coefficients a_i of the characteristic polynomial of the reaction system changes sign from plus to minus on change in the reagent concentrations, the steady state of the system becomes unstable.

Ivanova proved that if the system of inequalities (3) has non-negative solutions, the minor coefficient of the characteristic equation, a_r, is negative, and there are no steady-state points on the border of the invariant polyhedron determined by the conservation equations of the reagent concentrations (balances) in the phase space, but there are several steady-state points within the polyhedron (multiple steady state) [10].

If $a_r > 0$ at any concentrations, the steady-state point is unique (provided that the conditions on the border of the polyhedron are met). However, if another coefficient $a_{r-k} < 0$, this unique steady-state point can be unstable. Together with this, a critical steady-state cycle, i.e., auto-oscillatory, arises near the unique unstable steady-state point. Thus, analysis of critical modes is related with the coefficients of characteristics of polynomial (4).

ABOUT THE POSSIBLE OSCILLATION MODE IN THREE-COMPONENT SYSTEM OF MONO- AND BIMOLECULAR REACTIONS

Behavior of a three-component reaction system is qualitatively described by the following characteristic equation:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 . \qquad (5)$$

For existence of the oscillatory mode it is necessary that either $a_1 < 0$, $a_3 > 0$, or $a_2 < 0$, $a_3 > 0$, or $a_1 < 0$, $a_2 < 0$, $a_3 > 0$. The coefficients a_i in Eq. (5) are determined by the contribution from subsystems consisting of i components participating in the reaction [6, 11]. Consequently, a_2 is defined as the sum of contributions from two-component subsystems. Two-component fragments of the considered system which give negative contribution will be further called critical fragments of the second order. Thus, existence of an oscillatory mode in a three-component system is related with the critical fragments of the second order. Considering this, to find possible kinetic schemes with oscillatory behavior, a search for the three-component systems was performed within the limits of the following requirements: a) critical fragments of the second order should be present; b) all reaction steps are described by the mass-action expression; c) stoichiometric coefficients of reagents do not exceed two.

One hundred various schemes satisfying these conditions were found. Analyzing stability of the steady state of these schemes, several reaction systems including autocatalytic steps were revealed. From the kinetic viewpoint, there are these autocatalytic steps which cause destabilizing effect on the stability of the steady state of the reaction system. In this regard autocatalytic steps resemble “negative friction” in non-conservative mechanical oscillatory systems.

As mentioned above, true chemical systems should not include autocatalytic steps. However, it does not mean that autocatalytic steps do not have real chemical meaning. In real chemical systems the rates of various reactions in fact differ significantly. Kinetic properties of the system as a whole are defined by the rates of the slowest reactions. The Tikhonov theorem about the minor condition can be applied here [12]; as a result, the terms corresponding to autocatalytic steps can appear in the differential equation system describing the reaction system kinetics. This can be proved more strictly using the Korzukhin theorem [13]: it is always possible to construct a chemical system of kinetic equations with behavior to any desirable extent coinciding with behavior of the given system of kinetic equations:

$$dx_j/dt = \Psi_j(x_1, x_2, ..., x_n) , \tag{6}$$

where $\Psi_j(x_1, x_2, ..., x_n)$ are any polynomials with integer non-negative powers ($j, i = 1, 2, ..., n$).

From the above consideration it follows that an autocatalytic step can be presented as sufficiently fast non-autocatalytic reaction of particle production, that is, an “instant production step”.

Thus, our bifurcation analysis demonstrated that in a three-component system not a single but several reaction schemes with oscillatory behavior are possible.

Some of these reaction schemes with oscillatory behavior are given in this work. One of them includes the following steps:

$$\begin{aligned} &y + z \xrightarrow{k_1} 2y , \\ &y + x \xrightarrow{k_2} z , \\ &y \xrightarrow{k_3} A . \end{aligned} \tag{7}$$

Component A is a reservoir-like one, since its concentration does not influence kinetics of the system. As shown in the scheme, some reagents should be delivered outside to maintain the steady-state mode.

Let us analyze in details stability of the steady state of the scheme given above; its kinetic behavior is described by the following system of differential equations:

$$\begin{aligned} \frac{dx}{dt} &= v_{ox} - k_2 xy , \\ \frac{dy}{dt} &= v_{oy} + k_1 zy - k_2 xy - k_3 y , \\ \frac{dz}{dt} &= -k_1 zy + k_2 xy . \end{aligned} \tag{8}$$

Here v_{ox} and v_{oy} are the constant inflow rates of reagents x and y, respectively. The system has one steady state with the following coordinates:

$$\bar{x} = \frac{k_3 v_{ox}}{k_2 v_{oy}}, \quad \bar{y} = \frac{v_{oy}}{k_3}, \quad \bar{z} = \frac{k_3 v_{ox}}{k_1 v_{oy}} . \tag{9}$$

Together with this, there exist positive decisions of the system of inequalities:

$$\sum_{k=1}^{3} \gamma_{ik} s_k \leqslant 0 \quad (i = 1, 2, 3) , \tag{10}$$

which mean that decisions of the system (8) are limited in the phase plane. Consequently, if the system (8) is removed from the steady state, the phase trajectories cannot go to infinity. However, depending on the sign of coefficients in the characteristic equation (5), the phase point can return to the initial steady state or rotate around this steady-state point.

Coefficient of the characteristic equation (5) for the system (8) appear as follows:

$$a_1 = \frac{v_{oy}}{k_3}(k_1 + k_2) + k_3 , \tag{11}$$

$$a_2 = -k_2 v_{ox} + v_{oy}(k_1 + k_2 + k_1 k_2 \frac{v_{oy}}{k_3}), \tag{12}$$

$$a_3 = k_2 k_3 v_{ox} . \tag{13}$$

It is obvious from these formulae that a_1 and a_3 are positive at all positive values of the parameters. If additionally $a_2 > 0$, the only steady state is stable. At $a_2 < 0$ stability of the steady state is disrupted and stable oscillations arise. So, for appearance of oscillations in the considered system it is necessary that $v_{oy} < v_{ox}$. However, if the first term in Eq. (12) exceeds the second in absolute value, the a_2 value will be negative, and oscillatory behavior is possible in the system.

The negative value of the discriminant (D) of the characteristic equation (5) is sufficient for the oscillatory behavior of three-component systems:

$$D = a_1^2 a_2^2 - 4a_2^3 - 4a_1^3 a_3 + 18a_1a_2a_3 - 27a_3^2.$$

If $D < 0$, Eq. (5) will have two complex-conjugate roots. However, this condition is necessary but not sufficient for continuous oscillation, because if $D < 0$ and all the coefficients of Eq. (5) are positive, the complex-conjugate root will have negative real part and consequently, arising oscillations will relax. For continuous oscillations, Eq. (5) should have at least one negative coefficient. Actually, at $D < 0$ the "oscillatory decisions" of the characteristic equation (5) are always possible and if $a_1 < 0$ or $a_2 < 0$, according to the Cartesian sign rule [14], the real parts of the complex roots will be positive, i.e., they will destabilize the only steady state. These facts are sufficient condition for existence of critical cycles in dynamics of the considered reaction system.

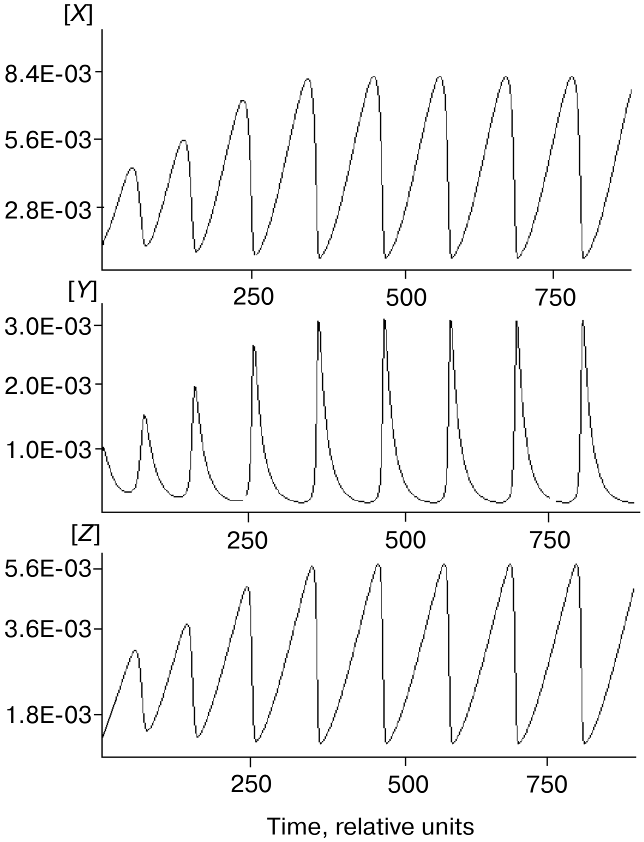

Fig. 1. Concentration oscillations of reagents in reaction system (8); X, Y, Z are concentrations of intermediates. The curves were obtained for the following steady-state concentrations: $[x] = 2.0\cdot10^{-3}$; $[y] = 1.0\cdot10^{-3}$; $[z] = 1.4\cdot10^{-3}$ M at the rate constants $k_1 = 300$, $k_2 = 250$, $k_3 = 0.1$ and inflow rates $v_{ox} = 5.0\cdot10^{-4}$ and $v_{oy} = 1.0\cdot10^{-4}$. Time is measured in arbitrary units: seconds normalized by characteristic time of the reaction system (8).

Concentration oscillations of the reagents in this system which result from the numerical solution of system (8) are shown in Fig. 1.

Another three-component reaction system with oscillatory behavior looks as follows:

$$\begin{aligned} y + z &\xrightarrow{k_1} 2y\,, \\ x + y &\xrightarrow{k_2}\,, \qquad (14) \\ x &\xrightarrow{k_3}\,. \end{aligned}$$

This scheme is described by the system of differential equations:

$$\frac{dx}{dt} = v_{ox} - k_2xy - k_3x\,,$$

$$\frac{dy}{dt} = k_1zy - k_2xy\,,$$

$$\frac{dz}{dt} = -k_1zy + v_{oz}\,.$$

Here v_{ox} and v_{oz} are the constant inflow rates of reagents X and Z, respectively. This system has only one steady state with coordinates:

$$\bar{x} = \frac{\Delta v}{k_3}\,, \qquad \bar{y} = \frac{k_3v_{oz}}{k_2\Delta v}\,, \qquad \bar{z} = \frac{k_2\Delta v}{k_1k_3}\,,$$

where $\Delta v = v_{ox} - v_{oz}$. It is obvious that for positive reagent concentrations $v_{ox} > v_{oz}$. In this case positive solutions of the inequality system also exist:

$$\sum_{k=1}^{3} \gamma_{ik}\, s_k \leqslant 0 \quad (i = 1, 2, 3)\,. \qquad (15)$$

Coefficients of the characteristic polynomial of Eq. (5) for this reaction system are as follows:

$$a_1 = \frac{k_3v_{oz}}{\Delta v}(1 + \frac{k_1}{k_2}) + k_3\,, \qquad (16)$$

$$a_2 = (k_1 - k_2)v_{oz} + \frac{k_1k_3^2\,v_{oz}}{k_2\Delta v}(1 + \frac{v_{oz}}{\Delta v})\,, \qquad (17)$$

$$a_3 = k_1k_3v_{oz}\,. \qquad (18)$$

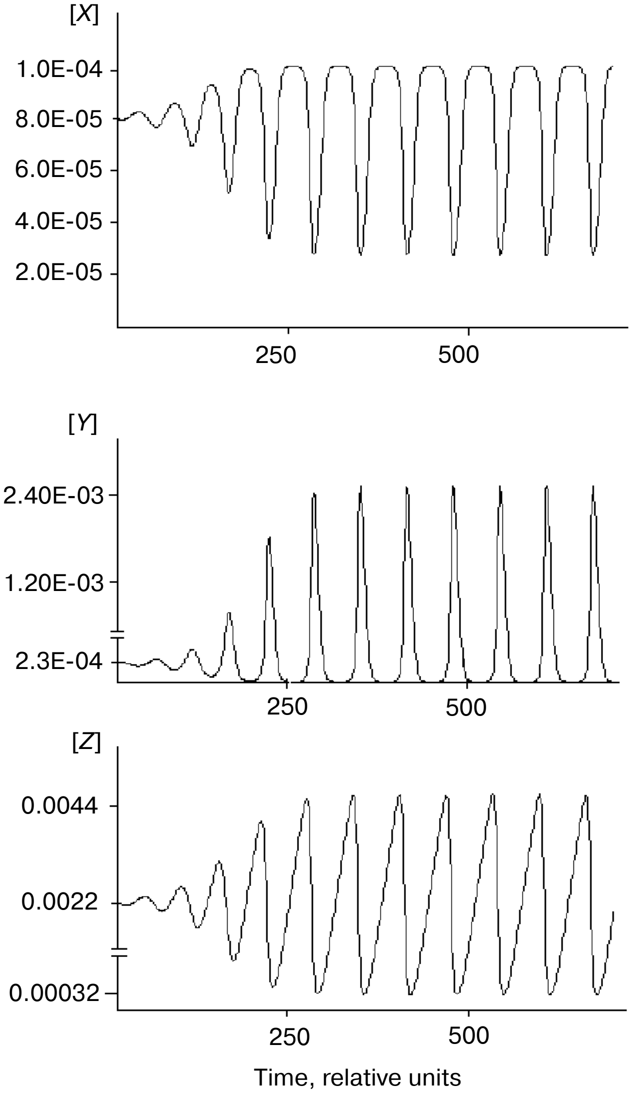

Fig. 2. Concentration oscillations of reagents in reaction system (14). The curves were obtained for the following steady-state concentrations: $[x] = 8.0 \cdot 10^{-5}$; $[y] = 2.3 \cdot 10^{-4}$; $[z] = 2.2 \cdot 10^{-3}$ M at the rate constants $k_1 = 200$, $k_2 = 5500$, $k_3 = 5$, and the inflow rates $v_{ox} = 5.0 \cdot 10^{-4}$ and $v_{oz} = 1.0 \cdot 10^{-4}$. Time is measured in relative units—seconds normalized by characteristic time of the reaction system (14).

As can be seen, a_1 and a_3 are positive at any positive values of the kinetic parameters. At $a_2 < 0$, which is possible at $k_1 < k_2$, the only steady state is unstable, and that is why continuous oscillations of reagent concentrations can occur in the considered system. Time dependences of the reagent concentrations, which were obtained as numerical solutions of the system of differential equations, are presented in Fig. 2.

So, possible initiation of the oscillatory mode in the system of simple chemical reactions with the minimal number of reagents is considered in this paper. Simplicity of reactions is defined by a set of requirements presented above. Impossibility of bifurcation in two-component reactions with mono- and bimolecular steps was shown earlier [15]. Our analysis indicates that a non-conservative minimal three-component reaction system is possible. Earlier only a model of reactions in three-component systems was found; as was demonstrated, oscillation in this single three-component system arises due to Haupf bifurcation [7, 8]. Detailed analysis of stability of the steady state of three-component reaction systems revealed several schemes with mono- and bimolecular steps in which concentration oscillations are possible. Oscillation dynamics of these reaction systems differ from the system found by Wilhelm and Heinrich: first, our systems have only one steady state; second, oscillations in our systems arise due to instability of the only steady state.

The presence of autocatalytic step is a general feature of all three-component systems with oscillatory behavior. Autocatalytic steps are destabilizing factors for the steady states. In this sense autocatalysis resembles "negative friction" in mechanical oscillation systems.

The suggested reaction systems are also interesting in a biological sense. It is well known that autocatalytic steps describe autoreproduction of biological systems in population genetics. From this viewpoint, the schemes considered above are not exclusive.

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