New Theoretical Schemes of the Simplest Chemical Oscillators

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Abstract—Based on the sufficient conditions for existence of concentration oscillations of the components of bicomponent reaction, all possible chemical reactions with two, three, or four intermediate stages proceeding via the mass-action expression are considered. About forty new schemes of chemical/biochemical oscillators are developed.

Key words: chemical/biochemical oscillations, oscillator

It is known that many biochemical systems are able to function in an oscillatory mode. However, the role of such oscillations is not completely elucidated. Oscillator types not yet studied may exist in living cell. That is why it is necessary to reveal simple theoretical reaction schemes in complex networks of various biological processes that may result in concentration oscillations of reagents and to estimate under what conditions oscillations arise and are maintained.

In mathematical modeling of biochemical oscillators, terms taken from technical sciences (regulation, negative/positive feedback) are used. The concepts of feedback and direct relation suggest participation of an inhibitor in regulation of some enzyme. However, oscillations may be induced by other mechanisms. Empirical dependences of steady-state activity of enzyme on various ligands (activators/inhibitors) are often used in modeling enzymatic reactions. Besides this, the standard formulae and analogies with the technical concepts often do not allow revealing a true mechanism of initiation and maintenance of oscillations.

The goal of this study was to describe the simplest kinetic models (critical fragments), which can be responsible for critical phenomena in a network of biochemical reactions, and to analyze conditions under which these critical fragments induce concentration oscillations of the system participants.

METHODS OF INVESTIGATION

To study critical phenomena in chemical/biochemical system, we used Lyapunov’s stability theory. In order to use the theory of steady-state stability in a dynamic chemical system, let us consider the main terms of chemical kinetics.

**Main terms. Equations of chemical kinetics.** Let us designate participants of a complex chemical/biochemical reaction consisting of \( R \) elementary reactions as \( X_1, X_2, ..., X_n \) (reagents, intermediates, and products). Hereafter we shall consider a reversible complex reaction as two elementary reactions: direct \( v_i \) and reverse \( v_{-i} \). In this case, the stoichiometric equation of a complex reaction is as follows:

\[
\sum_{i=1}^{n} \alpha_{ri} x_i \xrightarrow{v_i} \sum_{j=1}^{n} \beta_{rj} x_j \quad (r = 1, 2, ..., R),
\]

where \( v_r \) is the rate of \( r \)th elementary stage and \( \alpha_{ri} \) and \( \beta_{rj} \) are stoichiometric coefficients—non-negative integer values indicating how many molecules of reagent \( X_i \) and the product \( X_j \), respectively, are consumed and formed as a result of one reaction stage \( v_r \). According to the mass-action expression, for mechanism (1), the rate of \( r \)th reaction can be written as follows:

\[
v_r = k_r x_1^{\alpha_{r1}} x_2^{\alpha_{r2}} \cdots x_n^{\alpha_{rn}},
\]

where \( k_r \), \( x_i \), and \( \alpha_{ri} \) are the reaction rate constant, concentration, and stoichiometric coefficient of the substance \( X_i \), respectively.

By definition, the reaction rate for component \( X_i \) is an algebraic sum of the rates of consumption (\( l \) reactions) and formation (\( p \) reactions) of substance \( X_i \) in all elementary reactions \( v_r (r = 1, 2, ..., S) \), where \( S = l + p \) with participation of \( X_i \), multiplied by the corresponding stoichiometric coefficient:
Thus, when a number of physicochemical conditions (homogeneous medium, the absence of flows, etc.) are fulfilled, any complex chemical/biochemical reaction with participation of substance $X_i$ ($i = 1, 2, ..., n$) uniquely corresponds with a system of ordinary differential equations of $m$ order ($m < n$) provided that $n$ variables are not all independent and there exist $(n - m)$ balance ratios.

It is known that from a minor disturbance of system (3) around the steady state $\bar{x}_1, \bar{x}_2, ..., \bar{x}_n$, its behavior in time is defined by the values of $\lambda_1, \lambda_2, ..., \lambda_m$ roots of characteristic polynomial

$$p(\lambda) = \lambda^m + \lambda^{m-1}a_1 + ... + \lambda^{m-k}a_k + ... + a_m = 0 \quad (4)$$

of matrix $B$ (the Jacobian), whose elements by definition are given by equation:

$$b_{ij} = \frac{\partial x'_i}{\partial x_j} \bigg|_{\bar{x}_1,...,\bar{x}_n} (i, j = 1, 2, ..., m). \quad (5)$$

Substituting expression (3) for derivative $x'$ with the rate $v$, written according to definition (2) into Eq. (5), we obtained the equation for calculation of the values of the Jacobian elements in an explicit form:

$$b_{ij} = \sum_{r=1}^{s} (\beta_{ir} - \alpha_{ir}) \alpha_r \frac{v_r}{x_j} = \sum_{r=1}^{s} \gamma_r \alpha_r \frac{v_r}{x_j}, \quad (6)$$

where $\gamma_r = \beta_{ir} - \alpha_{ir} (i, j = 1, 2, ..., m)$.

As known from linear algebra, coefficient $a_i$ of the characteristic polynomial (4) is equal to the sum of all diagonal elements of matrix $B$, but with the opposite sign:

$$a_1 = (-1)^{i-1} \sum_{i=1}^{m} b_{ii}. \quad (7)$$

Coefficients $a_2, a_3, ..., a_{m-1}$ with corresponding sign are equal to the sums of determinants of all diagonal minors of the second order ($M_i = M_{i,i}^{(2)}$), third order ($M_i = M_{i,j,i}^{(3)}$), ..., $(m - 1)$ order of the Jacobian $(m \times m)$:

$$a_k = (-1)^{k-1} \sum_{j=1}^{i} M_j \quad (k = 2, 3, ..., m-1), \quad (8)$$

where $i$ is the number of all diagonal minors of $k$ order in the Jacobian and is equal to the number of combinations $k$ of $m$. Coefficient $a_m$ is equal to the determinant of matrix $B$ with the corresponding sign:

$$a_m = (-1)^{m} \det B. \quad (9)$$

Equations (6)-(9) are the main relationships for search for the necessary and sufficient conditions for existence of critical phenomena in complex chemical or biochemical systems. Criteria for existence of periodic solutions (oscillations) in mathematical models of biochemical systems. A number of criteria and indications of the absence or existence of periodic solutions of a system of differential equations were obtained in the context of qualitative theory of differential equations. Criteria are based on studies of either the properties of coefficients $a_i (i = 1, 2, ..., m)$ of characteristic polynomial (the Rauss–Gurvits criterion, Clark method [1]), or the properties of matrix elements of the Jacobian [2, 3], or the properties and topology of phase space (the Poincare–Bendickson–Dulakue criteria [4] and others). As shown in [5, 6], the positive value of the senior coefficient $a_m$ and the negative value of any of $a_k (k = 1, 2, ..., m - 1)$ coefficients of characteristic polynomial of $m$ order, that is, conditions $a_k < 0$ and $a_m > 0$ are the sufficient conditions for the existence of a periodic solution of a corresponding system of differential equations. And to the contrary, if all coefficients $a_i (i = 1, 2, ..., m)$ are strictly positive at any values of the system parameters and variables, that is, are a sign-determining function, then the single steady-state point is stable, and this excludes periodic solutions.

As proved in [7], if a system of inequalities

$$L_i(s) = \sum_{k=1}^{m} \gamma_i \alpha_k s_k \leq 0 \quad (i = 1, 2, ..., n) \quad (10)$$

has non-negative solutions $s \geq 0 (i = 1, 2, ..., n)$, solutions of system (3) are limited at $t \to \infty$. A requirement for existence of a positive solution of system (10) has a simple physical meaning. In chemical kinetics, it means material balance in the reaction system (1).

In correct mathematical models of real chemical reactions, stable steady-state solutions should be limited, that is, a system of inequalities (10) should have a non-negative solution. A break of this condition means that a model is incorrect and further improvements are needed.

RESULTS AND DISCUSSION

Since there is a great interest in the simplest schemes of chemical/biochemical oscillators, in this work we consider a possibility for initiation of oscillations in a bicomponent system.