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MATHEMATICAL ANALYSIS OF QUALITATIVE CHARACTERISTICS OF SOLUTIONS OF SYSTEMS OF DIFFERENTIAL EQUATIONS DESCRIBING BIOCHEMICAL PROCESSES RATES

The article considers mathematical modeling of biochemical processes rates in biological systems. It is given the system of differential equations which, in the general case, describes biochemical processes rates. It is noticed in which cases the system of differential equations can be solved analytically and when the exact solution can be obtained. It is shown the importance of qualitative characteristics to predict changes in the nature of the system behavior when conditions change. It is analyzed how the state of the system is represented at an arbitrary moment of time. It is shown that qualitative analysis makes it possible to determine the nature the solution of the system of differential equations by the form of phase trajectories. It is shown how the change in the state of the system over time is described by the evolution operator. Mathematical analysis of qualitative characteristics of solutions of systems of differential equations describing biochemical processes rates is performed in the article. Examples of phase portraits are considered and investigated.

Keywords: *biochemical process, system of differential equations, phase portrait.*

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МАТЕМАТИЧНИЙ АНАЛІЗ ЯКІСНИХ ХАРАКТЕРИСТИК РОЗВ'ЯЗКІВ СИСТЕМ ДИФЕРЕНЦІАЛЬНИХ РІВНЯНЬ, ЯКІ ОПИСУЮТЬ ШВИДКОСТІ БІОХІМІЧНИХ ПРОЦЕСІВ

У статті виконано математичний аналіз якісних характеристик розв'язків систем диференціальних рівнянь, які описують швидкості біохімічних процесів. Проаналізовано, як зображується стан системи в довільний момент часу. Показано, як описується зміна стану системи з плином часу за допомогою оператора еволюції. Розглянуто і досліджено приклади фазових портретів.

Ключові слова: *біохімічний процес, система диференціальних рівнянь, фазовий портрет.*

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МАТЕМАТИЧЕСКИЙ АНАЛИЗ КАЧЕСТВЕННЫХ ХАРАКТЕРИСТИК РЕШЕНИЙ СИСТЕМ ДИФФЕРЕНЦИАЛЬНЫХ УРАВНЕНИЙ, ОПИСЫВАЮЩИХ СКОРОСТИ БИОХИМИЧЕСКИХ ПРОЦЕССОВ

В статье выполнено математический анализ качественных характеристик решений систем дифференциальных уравнений, описывающих скорости биохимических процессов. Проанализировано, как изображается состояние системы в произвольный момент времени. Показано, как описывается изменение состояния системы с течением времени с помощью оператора эволюции. Рассмотрено и исследовано примеры фазовых портретов.

Ключевые слова: *биохимический процесс, система дифференциальных уравнений, фазовый портрет.*

Problem formulation. Mathematical modeling of biochemical processes rates in biological systems can mainly be reduced to the construction of the system of differential equations of the following form

$$\begin{cases} \dfrac{dc_1}{dt} = f_1(c_1, c_2, c_3, \ldots, c_N), \\ \dfrac{dc_2}{dt} = f_2(c_1, c_2, c_3, \ldots, c_N), \\ \dfrac{dc_3}{dt} = f_3(c_1, c_2, c_3, \ldots, c_N), \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \dfrac{dc_N}{dt} = f_N(c_1, c_2, c_3, \ldots, c_N) \end{cases} \tag{1}$$

where

- $f_i(c_1, c_2, c_3, \ldots, c_N)$ are generally nonlinear functions that do not explicitly depend on time *t*;
- $c_1, c_2, c_3, \ldots, c_N$ are the concentrations of substances in biochemical reactions that are functions of time and initial conditions. The concentrations of substances cannot be negative.

Since the system (1) describes changes in the concentrations of substances over time, then it is dynamic.

Mathematical analysis of qualitative characteristics of solutions of systems of differential equations of the form (1) is especially important.

Analysis of the latest research and publications. If the right-hand sides of the differential equations of the system (1) are linear functions of their arguments, then the system of equations (1) can be solved analytically [1]-[4]. If the system (1) is a system of non-linear differential equations, then the exact solution can only be obtained for some special types of functions $f_i(c_1, c_2, c_3, \ldots, c_N)$, and in the general case, this system of non-linear differential equations can only be solved by approximate numerical methods.

However, all numerical methods have one significant disadvantage: in case of arbitrary change of parameters or initial conditions, all calculations must be done from the very beginning. It is still impossible to exactly predict what result we will get with each subsequent calculation. However, many problems do not require accurate quantitative calculations, and a qualitative description of the phenomena is enough, but it is important to be able to predict the change in the nature of the behavior of the system when conditions change. This is especially important in biochemical problems, where the values of parameters and initial conditions cannot usually be specified. Therefore, the mathematical description should make it possible to find out significant qualitative characteristics [5]. For instance, whether there are steady states in the system, whether these states are stable and how the nature of the stability of these states changes when changing parameters.

Thus, there is no need to solve the complicated system of differential equations (1), that is to find functions $c_i(t)$ in the explicit form, but it is enough to investigate the general laws of the behavior of the system by the form of functions $f_i(c_1, c_2, c_3, \ldots, c_N)$.

The larger the number of differential equations in the system of differential equations is, the more difficult it is to conduct research and the less clear and obvious the results are. The article [6] discusses how to reduce the number of differential equations in a system of differential equations in mathematical modeling of biochemical processes rates in biological systems. The fewer differential equations remains in the system (for example, two or three ones), the easier it is to investigate this system.

The aim of the investigation is to perform mathematical analysis of qualitative characteristics of solutions of systems of differential equations describing biochemical processes rates; to analyze how the state of the system is represented at an arbitrary moment of time; to show how the change in the state of the system over time is described by the evolution operator; to consider and investigate examples of phase portraits.

Presentation of the main material. For simplicity and greater clarity, let us consider the following system of differential equations with two unknowns

$$\begin{cases} \dfrac{dc_1}{dt} = f_1(c_1, c_2), \\ \dfrac{dc_2}{dt} = f_2(c_1, c_2). \end{cases} \tag{2}$$

In this case, in a qualitative study, we apply the method of the phase plane of a dynamic system since a phase is a quantity that characterizes the state of the system (process) at a given moment of time and is determined by the coordinates (in this case, by the concentrations) and the rates. Note, that we have the phase space in the case of three variables and we have *N*-dimensional phase space for *N* variables.

The state of the system, at an arbitrary moment of time *t*, can be depicted by the phase point on the phase plane Oc_1c_2. The state of the system changes over time and the phase point depicting this state moves along the phase plane Oc_1c_2. Thus, dynamics of the system is represented by motion of the phase point along the phase plane.

It is necessary to show how the position of the phase point $(c_1; c_2)$ changes on the phase plane.

Let one defined phase point in the position P_1 on the phase plane of coordinates c_1, c_2 correspond to some state of the system at the moment of time t_1, i.e., to the set of the values $c_1(t_1)$ and $c_2(t_1)$

(Fig. 1). Then for time Δt the coordinate c_1 will change by the value Δc_1 and the coordinate c_2 will change by the value Δc_2 and accordingly the phase point will move from the position P_1 to the position P_2. Considering infinitesimal increments of time, we can obtain all intermediate positions of the phase point on the phase trajectory. The slope θ of the tangent line at each point of the phase trajectory is determined by the value of the derivative $\frac{dc_2}{dc_1}$ at this point.

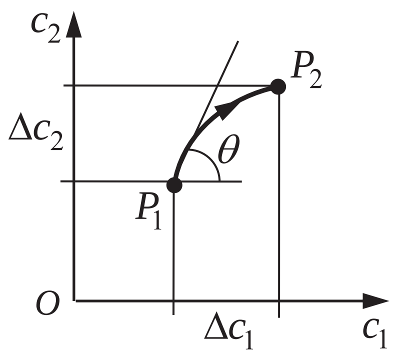


Fig. 1. **The segment of the phase trajectory**

Dividing the second differential equation of the system (2) by the first one, we obtain a new differential equation that does not contain time *t* in explicit form:

$$\frac{dc_2}{dc_1} = \frac{f_2(c_1, c_2)}{f_1(c_1, c_2)}. \quad (3)$$

The general solution of this differential equation that is usually simpler than the system (2) has the form

$$c_2 = c_2(c_1, C)$$

and is a family of phase trajectories (orbits) of the system of differential equations (2), where the arrows indicate the direction of movement along these curves with increasing time *t*, as in Fig. 2 (or is a family of integral curves of the differential equation (3), without arrows), where

- phase trajectory is a trajectory of movement of a phase point along the phase plane, which depicts how the state of a dynamic system changes over time *t* (the segment of the phase trajectory is shown in Fig. 1);
- *C* is a parameter that is determined by the initial conditions.

The qualitative behavior of the system is determined by the family of curves (trajectories) indicating the direction of motion along these curves with increasing time *t*.

By the Cauchy theorem (on existence and uniqueness of a solution of differential equations), only one integral curve, the slope of which at this point is determined by the equation (3), can pass through each point of a plane.

Exceptions are fixed points (stationary points, equilibrium positions) at which $f_1(c_1, c_2) = 0$ and $f_2(c_1, c_2) = 0$ simultaneously, i.e.,

$$\begin{cases} f_2(c_1, c_2) = 0, \\ f_1(c_1, c_2) = 0. \end{cases} \quad (4)$$

Thus, in the case of (4), the solution of the differential equation (3) is depicted by a fixed point, and this solution is called a fixed point.

The angle of slope of the tangents at these points is undetermined, since, in this case, the equation (3) takes the form

$$\left(\frac{dc_2}{dc_1}=\frac{0}{0}\right),$$

therefore, an infinite number of integral curves may intersect here.

In this case, taking into account the system (4), the system of differential equations (2) takes the form

$$\begin{cases}\dfrac{dc_1}{dt}=0,\\ \dfrac{dc_2}{dt}=0.\end{cases}$$

The position of fixed points does not change for all values of time *t*.

Thus, under the condition (4), the rates of change of the c_1-coordinate, $\dfrac{dc_1}{dt}$, and the c_2-coordinate, $\dfrac{dc_2}{dt}$ (the rates of change of the concentrations of substances in biochemical reactions), become zero.

This means that fixed points on the phase plane Oc_1c_2 correspond to the positions of equilibrium of the dynamic system, i.e., the concentrations of substances take stationary values.

Then the system of differential equations (2) takes the form

$$\begin{cases}f_1(\overline{c}_1,\overline{c}_2)=0,\\ f_2(\overline{c}_1,\overline{c}_2)=0.\end{cases}$$

If the differential equation (3) is solved analytically, then the family of integral curves can be constructed exactly. The solution of the differential equation (3) gives only the connection between the variables $c_1(t)$ and $c_2(t)$ at an arbitrary moment of time *t*, and we do not know $c_1(t)$ and $c_2(t)$ separately, i.e., we do not know the solution of the system of differential equations (2).

However, qualitative analysis makes it possible to determine the nature of the solution of the system of differential equations (2) by the form of integral curves (by phase portrait). For this, we do not even have to solve the differential equation (3), we just need to determine the position of fixed points and construct the phase portrait of the system approximately geometrically.

Thus, the geometric interpretation of qualitative behavior of the solutions of the system of differential equations (2) is the phase portrait of the system (2).

The phase portrait shows the direction of the phase point motion. Thus, the phase portrait shows the qualitative picture of dynamics.

We can say that the phase portrait determines "the nature" of the fixed point.

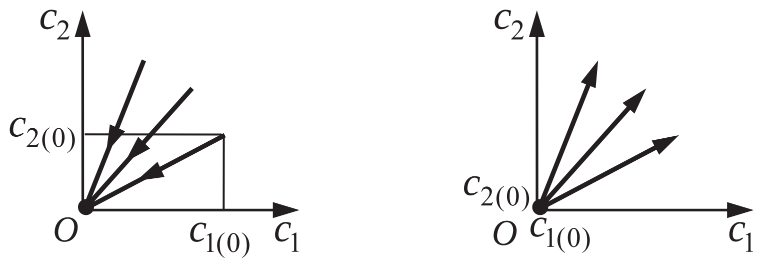
Note that different systems of differential equations can have solutions with the same qualitative behavior. This behavior is determined by the nature.

Systems of differential equations are qualitatively equivalent if they have an equal number of fixed points of the same nature arranged in the same order on the phase plane.

Let us give the example of the phase portrait (Fig. 2a). Given the system of differential equations

$$\begin{cases}\dfrac{dc_1}{dt}=-c_1,\\ \dfrac{dc_2}{dt}=-c_2.\end{cases} \tag{5}$$

Hence, $\dfrac{dc_2}{dc_1}=\dfrac{c_2}{c_1}$. Therefore, the system of differential equations (5) has the fixed point *O* with the coordinates $c_1=0,\ c_2=0$. On the phase plane Oc_1c_2, the family of phase trajectories is determined by the equation $c_2 = Cc_1$, where a constant C becomes different depending on the initial data $c_{1(0)}, c_{2(0)}$, $C = \frac{c_{2(0)}}{c_{1(0)}}$ (Fig. 2a). The arrows on the trajectories indicate the direction of motion of the phase point.



a) b)

Fig. 2. **Phase trajectories on the phase plane (phase portraits): a) the system is stable; b) the system is unstable**

Since c_1, c_2 are the concentrations of substances, they cannot be negative.

Note, that the system of differential equations (5), in addition to the fixed point $(0;0)$, has the general solution

$$c_1(t) = A_1 e^{-t}, \quad c_2(t) = A_2 e^{-t}$$

which for all *t*, satisfies the equation $\frac{c_2(t)}{c_1(t)} = \frac{A_2}{A_1}$ or the equation $c_2(t) = \frac{A_2}{A_1} c_1(t)$ where A_1, A_2 are some real constants. We can see from the solution that when $A_1 \neq 0, A_2 \neq 0$, then $c_1(t) \to 0$ and $c_2(t) \to 0$ as $t \to \infty$ that corresponds to Fig. 2a.

We can see from Fig. 2a that with negative signs in the right-hand side of the system (5), over time *t*, all the phase trajectories tend to the fixed point $(0;0)$ which is stable (stable node), i.e., the equilibrium position of such a system is stable. Therefore, in this case, the phase point moves in the direction of a fixed point (to the origin) from arbitrary initial conditions over time *t* (when time increases).

If we take positive signs in the right-hand side of the system (5), then from arbitrary initial conditions, the phase point tends to infinity over time *t*, since the system (5) taking the form

$$\begin{cases} \frac{dc_1}{dt} = c_1, \\ \frac{dc_2}{dt} = c_2 \end{cases}$$

also has the fixed point $(0;0)$, but another general solution of the form

$$c_1(t) = A_1 e^{t}, \quad c_2(t) = A_2 e^{t}.$$

We can see from this solution that when $A_1 > 0, A_2 > 0$, the $c_1(t) \to \infty$ and $c_2(t) \to \infty$ as $t \to \infty$ what corresponds to Fig. 2b.

However, when initial data $c_{1(0)}, c_{2(0)}$ correspond to the equilibrium position, i.e., $c_{1(0)} = \overline{c}_1$, $c_{2(0)} = \overline{c}_2$ (in this case, to the point $(0;0)$), then the system will remain at this point, but arbitrary random deviations Δc_1 or Δc_2 from zero will bring the system on the trajectory that goes to infinity. Such a fixed point is unstable (an unstable node) (the phase portrait in Fig. 2b).

Let us give another example of the phase portrait (Fig. 3). Given the system of differential equations

$$\begin{cases} \dfrac{d(\Delta c_1)}{dt} = \Delta c_2, \\ \dfrac{d(\Delta c_2)}{dt} = -\Delta c_1 \end{cases} \qquad (6)$$

where Δc_1 and Δc_2 are small deviations from stationary concentrations of substances, i.e., $c_1 = \overline{c}_1 + \Delta c_1$, $c_2 = \overline{c}_2 + \Delta c_2$.

To find the solution of this system of differential equations, we pass to polar coordinates on the plane:

$$\Delta c_1 = r\cos\theta, \quad \Delta c_2 = r\sin\theta. \qquad (7)$$

Hence, $r^2 = (\Delta c_1)^2 + (\Delta c_2)^2, \quad \mathrm{tg}\theta = \dfrac{\Delta c_2}{\Delta c_1}, \quad \Delta c_1 \neq 0.$

Differentiating these expressions with respect to *t*, we obtain

$$2r\frac{dr}{dt} = 2\Delta c_1 \frac{d(\Delta c_1)}{dt} + 2\Delta c_2 \frac{d(\Delta c_2)}{dt}, \quad \sec^2\theta\cdot\frac{d\theta}{dt} = \frac{\Delta c_1 \dfrac{d(\Delta c_2)}{dt} - \Delta c_2 \dfrac{d(\Delta c_1)}{dt}}{(\Delta c_1)^2}.$$

Substituting the values $\dfrac{d(\Delta c_1)}{dt}$ and $\dfrac{d(\Delta c_2)}{dt}$ from the system of differential equations (6) into the expressions obtained, we have

$$r\frac{dr}{dt} = \Delta c_1\cdot\Delta c_2 + \Delta c_2\cdot(-\Delta c_1) \quad \text{or} \quad r\frac{dr}{dt} = 0,$$

$$\sec^2\theta\cdot\frac{d\theta}{dt} = \frac{-(\Delta c_1)^2 - (\Delta c_2)^2}{(\Delta c_1)^2} = -1 - \left(\frac{\Delta c_2}{\Delta c_1}\right)^2 = -1 - \mathrm{tg}^2\theta \quad \text{or} \quad \sec^2\theta\cdot\frac{d\theta}{dt} = -\sec^2\theta,$$

whence

$$\frac{dr}{dt} = 0 \quad \text{and} \quad \frac{d\theta}{dt} = -1.$$

From these equations we obtain

$$r(t) \equiv A_1 \quad \text{and} \quad \theta(t) = -t + A_2 \qquad (8)$$

where A_1 and A_2 are some real constants.

Substituting (8) into (7), we obtain the general solution of the system of differential equations (6):

$$\Delta c_1(t) = A_1\cos(-t + A_2), \quad \Delta c_2(t) = A_1\sin(-t + A_2)$$

from which it follows that $(\Delta c_1)^2 + (\Delta c_2)^2 = A_1^2$.

In this case, the phase trajectories are the family of concentric circles centered at the fixed point $(0;0)$ (Fig. 3). This is another type of quality system behavior. The fact that the phase trajectories are closed reflects the fact that $\Delta c_1(t)$ and $\Delta c_2(t)$ are periodic functions with the same period.

In Fig. 3, the phase trajectories are closed, so the phase point passes through the same points of the phase plane again and again over time *t*.

Note, that, for example, for $A_1 > 0, A_2 = 0$ when t is increasing from $t = 0$ to $t = \dfrac{\pi}{2}$, $\Delta c_1(t) = A_1\cos(-t + A_2)$ decreases and $\Delta c_2(t) = \left|A_1\sin(-t + A_2)\right|$ increases. This makes it possible to set the direction of all trajectories (see the *IV*-th quadrant in Fig. 3).

These examples show that qualitatively different solutions lead to the phase trajectories with different geometric properties.

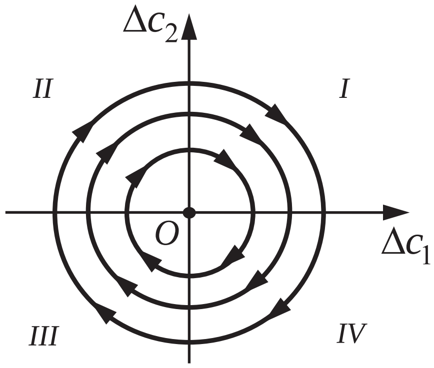


Fig. 3. **Closed phase trajectories on the phase plane (phase portrait)**

We can assume that the system of differential equations (2) defines the flow of the phase points on the phase plane Oc_1c_2. Functions $f_1(c_1,c_2)$ and $f_2(c_1,c_2)$ define the rate of this flow at each value c_1, c_2.

The solution $c_1(t), c_2(t)$ of the system of differential equations (2) that satisfies the condition $c_1(t) = c_{1(0)}$, $c_2(t) = c_{2(0)}$ defines the evolution of the phase point which occupied the position $(c_{1(0)}; c_{2(0)})$ at the moment of time $t = t_0$, i.e., its past (at $t < t_0$) and future (at $t > t_0$) positions.

Let us introduce a function ψ_t that is a phase flow or an evolution operator, e.g., the operator ψ_t that describes some flow on the plane.

The term "evolution operator" is usually used when ψ_t describes a change in the state of the system over time. The term «flow» (for example, the phase flow on the plane or the flow on the phase plane) is more often used in the case when the dynamics is generally studied rather than the evolution of a given point.

Consider the role played by the evolution operator on the plane.

For the system of differential equations (2), solutions can be obtained from each other by shifting along the *t*-axis; the operator $\psi_t(c_1,c_2)$ converts the point $(c_1; c_2)$ into the point obtained by moving along the trajectories of the system of differential equations (2) for time *t*, i.e., $\psi_t : \mathbb{R}^2 \to \mathbb{R}^2$. Thus, the trajectory that passes though the point $(c_1; c_2)$ is the set of points $\{\psi_t(c_1,c_2) : t \in \mathbb{R}\}$, oriented in ascending *t*.

The trajectories of a linear system on a plane can be described using an evolution matrix.

Let in the system of differential equations (2)

$$f_1(c_1,c_2) = a_{11}c_1 + a_{12}c_2, \quad f_2(c_1,c_2) = a_{21}c_1 + a_{22}c_2.$$

Then we obtain the system of differential equations

$$\begin{cases} \dfrac{dc_1}{dt} = a_{11}c_1 + a_{12}c_2, \\ \dfrac{dc_2}{dt} = a_{21}c_1 + a_{22}c_2. \end{cases}$$

In matrix form, this system can be written as follows

$$\frac{d\mathbf{c}(t)}{dt} = \mathbf{Ac}(t).$$

If the initial value $\mathbf{c}(t_0) = \mathbf{c}_0$ and eigenvalues $\lambda_1 = \lambda_2 = \lambda_0$ of the matrix $\mathbf{A}$ are given, then the solution of the system of differential equations has the form

$$\mathbf{c}(t) = e^{\mathbf{A}(t-t_0)}\mathbf{c}_0 = \psi_{t-t_0}(\mathbf{c}_0)$$

where

$$e^{\mathbf{A}(t-t_0)} = e^{\lambda_0(t-t_0)}(\mathbf{E} + (t-t_0)(\mathbf{A} - \lambda_0\mathbf{E})),$$

$$\mathbf{E} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

Thus, the evolution operator for the system $\frac{d\mathbf{c}(t)}{dt} = \mathbf{A}\mathbf{c}(t)$ is given by the matrix $e^{\mathbf{A}(t-t_0)}$.

Consider the system of differential equations (6). We write the general solution of this system in matrix form:

$$\begin{pmatrix} \Delta c_1(t) \\ \Delta c_2(t) \end{pmatrix} = \begin{pmatrix} \cos(-t + A_2) & 0 \\ 0 & \sin(-t + A_2) \end{pmatrix} \begin{pmatrix} A_1 \\ A_1 \end{pmatrix}$$

whence

$$\psi_t = \begin{pmatrix} \cos(-t + A_2) & 0 \\ 0 & \sin(-t + A_2) \end{pmatrix} \tag{9}$$

is the evolution operator for this system.

Thus, the evolution of the point $(c_1; c_2)$ is described (defined) by the formula (9).

Conclusions and prospects for further research. Mathematical analysis of qualitative characteristics of solutions of systems of differential equations describing biochemical processes rates is performed in the article. It is analyzed how the state of the system is represented at an arbitrary moment of time. It is shown how the change in the state of the system over time is described by the evolution operator. Examples of phase portraits are considered and investigated.

A promising area of further research is to determine the nature of the stability of a fixed point in general cases.

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