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CONSTRUCTION AND STUDY OF THE SYSTEM OF DIFFERENTIAL EQUATIONS THAT DESCRIBES SELF-OSCILLATIONS IN GLYCOLYSIS

Губаль Г. М. Побудова та дослідження системи диференціальних рівнянь, яка описує автоколивання у гліколізі. У статті побудовано та досліджено систему диференціальних рівнянь, яка описує автоколивання в гліколізі.
Ключові слова: гліколіз, концентрація, система диференціальних рівнянь, автоколивання.
Літ. 3.

Губаль Г. Н. Построение и исследование системы дифференциальных уравнений, описывающей автоколебания в гликолизе. В статье построено и исследовано систему дифференциальных уравнений, описывающей автоколебания в гликолизе.
Ключевые слова: гликолиз, концентрация, система дифференциальных уравнений, автоколебания.
Лит. 3.

Hubal H. M. Construction and study of the system of differential equations that describes self-oscillations in glycolysis. In the article, the system of differential equations describing self-oscillations in glycolysis is constructed and investigated.
Keywords: glycolysis, concentration, system of differential equations, self-oscillations.
Bibl. 3.

Introduction. Consider self-oscillating system which means periodic changes of glycolysis intensity, that is the process by which a cell can replenish energy by oxidation of sugar.

Glycolysis is a complex enzymatic process of anaerobic unhydrolyte decomposition of carbohydrates in the human and animals organism [1-3]. Glycolysis is one of the oldest processes of energy supply of a cell. It arose in the early stages of evolution when the World Ocean was inhabited by simple organisms incapable of either photosynthesis or respiration. There was almost no oxygen in the atmosphere (it appeared later as a result of the activities of photosynthetic organisms), and the main source of food where organic products (carbohydrates) which randomly appeared from inorganic compounds. These carbohydrates (or sugars) containing 6 carbon molecules, during the process of glycolysis, become three-carbonic acids containing three carbon molecules (for example, pyruvic acid that is pyruvate or lactic acid that is lactate). Thus, due to the excess of free energy which is contained in sugars compared to three-carbonic acids, adenosine three-phosphate (ATF) that is a universal energy currency (UEC) is formed in the cell during the process of glycolysis.

From the point of view of efficiency of forming of UEC, glycolysis is inferior respiration: in glycolysis, in the processing one six-carbon sugar molecule, two UEC molecules are formed while breathing the same amount of organic substances gives thirty-eight UEC molecules. It is natural since when breathing, the oxidation of organic substances goes to the limit, i.e. to the formation of carbon dioxide and water, which is only possible with the participation of oxygen. Glycolysis goes without oxygen (in anaerobic conditions) and its products are not very oxidized. Pyruvate which is the end product for glycolysis represents the initial product of the respiratory cycle of reactions where it goes to the end, that is to carbon dioxide and water.

Main part. Glycolysis has survived in the evolution and has used by nature for several reasons by now.

Many organisms that are able to breath getting in anaerobic conditions switch to glycolysis because there is no other way in the absence of osygen. Getting back into the oxygen atmosphere, the organism switches back: intensive respiration begins and glecolysis is inhibited.

The mankind specifically cultivates many of these microorganisms under anaerobic conditions. There is the goal to get not energy and those exidized products which are of greater value than the original carbohydrates, for example getting alcohol from sugar or starch.

Glycolysis apparatus is stored not only in the cells of microorganisms but also in the cells of higher ones including mammalians. However, in the cells of an adult organism under normal conditions, energy supply takes place by means of breathing and there are specific respiratory mechanisms that inhibit glycolysis. If there is a need for rapid growth and reproduction of cells, for example injuries, wounds and so on, then when it is required rapid regeneration of cells, glycolysis is more beneficial than breathing. In terms of regeneration, there is a need not only for energy, but also for "construction materials" which are mediocine products of glycolysis. The cell that is incapable of photosynthesis can not use the product of the respiratory cycle, i.e. carbon dioxide as a building material.

Thus, in higher organisms, glycolysis remained as reserve: it is inhibited under normal conditions but it is activated in the case of an accident. However, this stock is dangerous to hold. If the regulatory mechanisms that maintain glycolysis at a reasonable low level deteriorate for any reason, then glycolysis becomes intense and the cells begin to grow out of control quickly. The nutrients, i.e. sugars are rapidly absorbed and neighbouring normal cells begin to starve. This process is the formation of malignant tumors.

Let us investigate the role of oscillations in the regulatory mechanism of glycolysis.

Biochemical processes in glycolysis are schematicly depicted in Fig.1.

We denote six-carbon compounds by the symbol C_6 and three-carbon compounds by the symbol C_3.

The original substance (substrate) is glucose, which can replaced by more complex sugar; the 1st stage of glycolysis runs noticeably slower. The final product that is pyruvite acid (pyruvate) which is later used as a substrate in other processes. The main function of glycolysis is to form a universal energy currency adenosine three-phosphate (ATF) from adenosine diphosphate (ADF) and inorganic phosphorus F_{in}.

Note, that in the 1st stages of glycolysis, this "currency" is not synthesized, but rather spent. The currency is "borrowed" to make it easier to implement the process and in the end it returns with profit.

In general, the transformation of one glucose molecule yields two ATF molecules.

Three-carbon compounds (C_3) being at the bottom of the scheme and six-carbon compounds (C_6) being at the top of the scheme, there are twice as many ATF molecules than it was spent.

We can select some narrw links in the scheme which will determine the process kinetics. The 1st narrow link is denoted in the scheme (item 1). This reaction is catalyzed by the hexons enzyme (HX) and is insensitive to the following substances. Therefore, its speed can be considered constant (we denote it by v_0). There is a fast and reversible reaction between six-carbon sugars C_6' and C_6''. We can replace the fast kinetic equations with algebraic relationships which are reduced to the fact that concentrations C_6' and C_6'' are proportional to each other. As the independent variable, we can choose the concentration of any of them and denote it by x.

Thus, the profit x by the 1st reaction has the form:

$$\left(\frac{dx}{dt}\right)_+ = v_0. \tag{1}$$

The next narrow link is a reaction in item 2 which is catalyzed by phosphofructokinase enzyme (FFK). This enzyme has a remarkable property: it is activated with its products, i.e. substances placed between item2 nad item 3.

Further, there are fast and reverse reactions between item 2 and item 3. We associate concentrations of these substances to each other. As a dynamic variable, we choose any variable and denote it by y. The profit y by the reaction of item 2 will depend on both concentrations of the substrate x and on the concentrations of the product y, since y is associated with the concentration of the activator:

$$\left(\frac{dy}{dt}\right)_+ = c\frac{x}{K_x + x} \times \frac{y}{K_y + y}.$$

Then we can write (the speed of profit y being equal to the speed of loss x):

$$\left(\frac{dy}{dt}\right)_+ = -\left(\frac{dx}{dt}\right)_- = c\frac{x}{K_x + x} \times \frac{y}{K_y + y}. \tag{2}$$

C_6 glucose

item$_1$ UEC

HX

ADF

C_6' Glucose phosphate

C_6'' Fructose phosphate

item$_2$ UEC

FFK

ADF

C_6 Fructose diphosphate

C_3

C_3 Phosphohlyceryne aldehyde (triose)

F_{in}

C_3 Diphosphoglucerine aldehyde

ADF

UEC

C_3 phosphophenylpyruvate

item$_3$ ADF
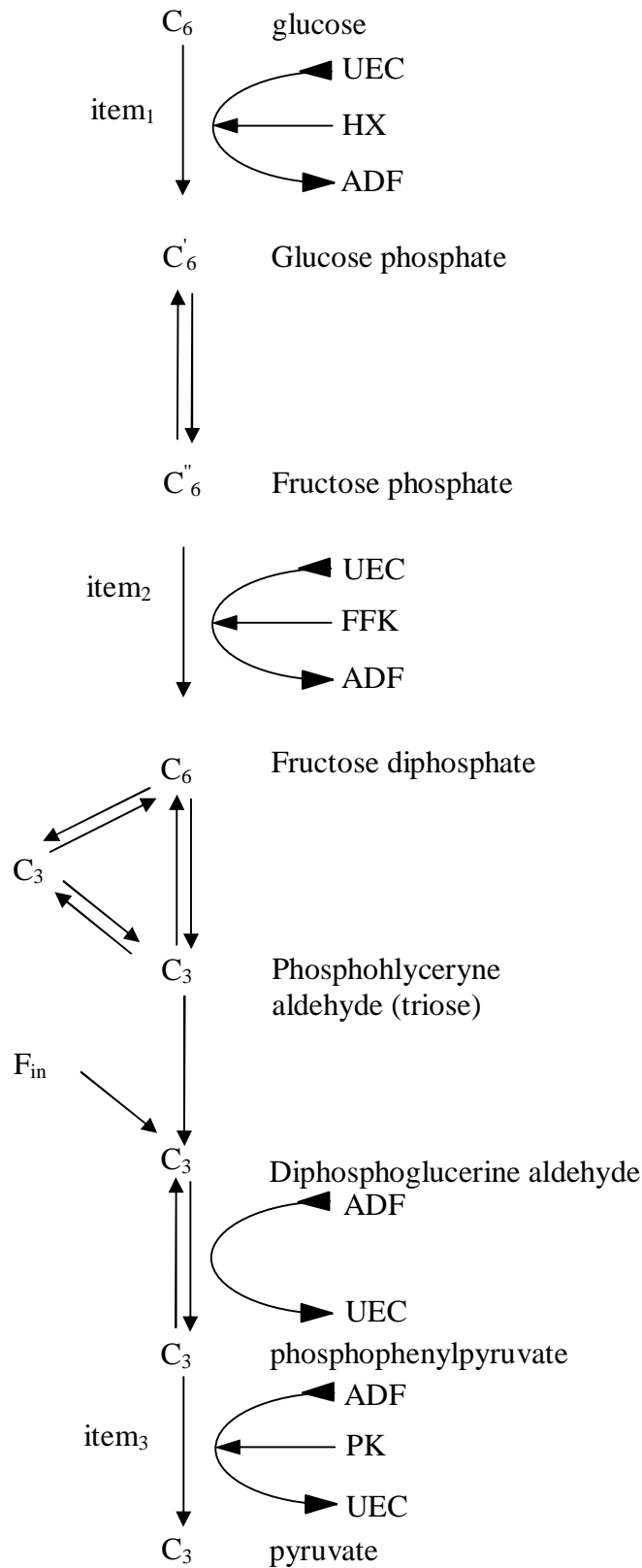
PK

UEC

C_3 pyruvate

Fig. 1

In item 3 of the scheme, there is the last slow and irreversible reaction which provides flow of products from its scope. It is catalyzed by pyruvate kinase (PK). The speed of the loss *y* by the reaction has the form:

$$\left(\frac{dy}{dt}\right)_{-} = -\frac{qy}{\overline{K} + y}. \tag{3}$$

Taking into account formulas (1)–(3) and the system of differential equations

$$\begin{cases} \dfrac{dx}{dt} = \left(\dfrac{dx}{dt}\right)_{+} + \left(\dfrac{dx}{dt}\right)_{-}, \\[2mm] \dfrac{dy}{dt} = \left(\dfrac{dy}{dt}\right)_{+} + \left(\dfrac{dy}{dt}\right)_{-}, \end{cases} \tag{4}$$

we obtain the closed system of differential equations:

$$\begin{cases} \dfrac{dx}{dt} = v_0 - c\,\dfrac{x}{K_x + x} \times \dfrac{y}{K_y + y}, \\[3mm] \dfrac{dy}{dt} = c\,\dfrac{x}{K_x + x} \times \dfrac{y}{K_y + y} - q \times \dfrac{y}{\overline{K} + y}. \end{cases} \tag{5}$$

We assume that under real conditions $K_x \gg x$ and $K_y \gg y$. Then system of differential equations (5) takes on the form

$$\begin{cases} \dfrac{dx}{dt} = v_0 - c_1 xy, \\[3mm] \dfrac{dy}{dt} = c_1 xy - q_1\,\dfrac{y}{1 + \dfrac{y}{\overline{K}}}, \end{cases} \tag{6}$$

where $c_1 = \dfrac{c}{K_x K_y}$, $q_1 = \dfrac{q}{\overline{K}}$.

Note that constants of equations are proportional to concentrations of corresponding enzymes: v_0 is proportional to the content of HK, c_1 is proportional to the content of FFK and q_1 is proportional to the content of PK.

To investigate the model, we introduce dimensionless variables putting

$$x_1 = \frac{x}{\overline{x}}, \quad y_1 = \frac{y}{\overline{y}},$$

where $\overline{x}$ і $\overline{y}$ are steady-state concentrations which we obtain from system of differential equations (6), substituting $\overline{x}, \overline{y}$ for x, y:

$$\begin{cases} \dfrac{d\overline{x}}{dt} = v_0 - c_1 \overline{x}\,\overline{y}, \\[3mm] \dfrac{d\overline{y}}{dt} = c_1 \overline{x}\,\overline{y} - q_1\,\dfrac{\overline{y}}{1 + \dfrac{\overline{y}}{\overline{K}}} \end{cases} \Rightarrow \begin{cases} 0 = v_0 - c_1 \overline{x}\,\overline{y}, \\[3mm] 0 = c_1 \overline{x}\,\overline{y} - q_1\,\dfrac{\overline{y}}{1 + \dfrac{\overline{y}}{\overline{K}}}, \end{cases}$$

whence

$$\overline{y} = \frac{v_0}{q_1 - \dfrac{v_0}{\overline{K}}}, \quad \overline{x} = \frac{v_0}{c_1 \overline{y}} = \frac{q_1 - \dfrac{v_0}{\overline{K}}}{c_1}. \tag{7}$$

The dimensionless time t_1 is introduced by the formula:

$$t_1 = \frac{t}{\overline{t}}, \tag{8}$$

where $\bar{t}$ is time which we obtain from the 1st equation of system (6) using the 1st equation of system (4) and formula (1) taking into account that $\left(\dfrac{dx}{dt}\right)_{-} = -\dfrac{\bar{x}}{\bar{t}}$ (for $x(t) = kt$) and substituting $\bar{x}$, $\bar{y}$ for x, y

respectively: $\bar{t} = \dfrac{1}{c_1 \bar{y}} = \dfrac{q_1 - \dfrac{v_0}{K}}{c_1 v_0}$. Then system of differential equations (6) can be written in the form

$$\begin{cases} \dfrac{dx_1}{dt_1} = 1 - x_1 y_1, \\[2mm] \dfrac{dy_1}{dt_1} = a y_1 \left(x_1 - \dfrac{1 + r}{1 + r y_1} \right), \end{cases} \qquad (9)$$

where $a = \dfrac{\left(q_1 - \dfrac{v_0}{K} \right)^2}{v_0 c_1}$, $r = \dfrac{\bar{y}}{K} = \dfrac{\dfrac{v_0}{K}}{q_1 - \dfrac{v_0}{K}}$.

Let us show how to obtain the 1st equation of system (9) from the 1st equation of system (6):

$$\frac{dx}{dt} = v_0 - c_1 xy \ \triangleright\ \frac{d(\bar{x}x_1)}{d(\bar{t}t_1)} = v_0 - c_1 \bar{x}x_1 \bar{y}y_1 \ \triangleright$$

$$\frac{\bar{x}dx_1}{\bar{t}dt_1} = v_0 - c_1 \bar{x}x_1 \bar{y}y_1 \ \triangleright\ \frac{\bar{x}dx_1}{\dfrac{1}{c_1 \bar{y}} dt_1} = v_0 - c_1 \bar{x}x_1 \bar{y}y_1 \ \triangleright$$

$$c_1 \bar{x}\,\bar{y}\frac{dx_1}{dt_1} = v_0 - c_1 \bar{x}\,\bar{y}x_1 y_1 \ \triangleright\ \frac{dx_1}{dt_1} = \frac{v_0}{c_1 \bar{x}\,\bar{y}} - x_1 y_1 \ \triangleright$$

$$\frac{dx_1}{dt_1} = \frac{v_0}{c_1 \dfrac{v_0}{c_1}} - x_1 y_1 \ \triangleright\ \frac{dx_1}{dt_1} = 1 - x_1 y_1.$$

We can obtain the 2nd equation of system (9) from the 2nd equation of system (6).

Performing the linearization of system differential equations (9), we investigate the nature of the stability of a singular point. The roots of a characteristic equation are

$$l_{1,2} = -\frac{1}{2}\left(1 - \frac{ar}{1 + r} \right) \pm \frac{1}{2}\sqrt{\left(1 - \frac{ar}{1 + r} \right)^2 - \frac{4a}{1 + r}}. \quad (10)$$

Hence, one can see that for $\dfrac{4a}{1 + r} > \left(1 - \dfrac{ar}{1 + r} \right)^2$, the singular point is of type focus. If

$\dfrac{ar}{1 + r} < 1$, then the focus is steady; if $\dfrac{ar}{1 + r} > 1$, then the focus is unsteady. Then there may be a limit cycle near the focus.

Thus, the value of the parameter $\dfrac{ar}{1 + r} = 1$ is bifurcation, i.e. it separates the range of values in which there may be only damped oscillations in the system of differential equations from the most important range in which self-oscillations are with constant amplitude.

Near the point of bifurcation when $\left| \dfrac{ar}{1 + r} - 1 \right| \ll 1$, the frequency of oscillations is equal to the imaginary part of the characteristic root, respectively, is equal to

$$w_1 \gg \sqrt{\frac{a}{1 + r}}. \qquad (11)$$

Dimensionless period of oscillations is

$$T_1 = \frac{2p}{w_1} = 2p\sqrt{\frac{1+r}{a}}.$$

Having conducted the study, we obtain the following conclusions.

Conclusions. The 1st and the most important conclusion is that system of differential equations (5) describes appearance of the self-oscillation mode unde some conditions. Increasing parameter a continutes appearance of self oscillations, decreasing parameter a continutes damping. Using the expression for a and formulas (10), we can see that decreasing of c_1 and of influx speed v_0 must cause the self-excitation of oscillations. Increasing q_1 must lead to the same effect (supplement PK). Replacement of glucose with other sugar in experiments and decreasing feed rate of glucose led to the appearance of self-oscillations.

The 2nd conclusion is that the values x_1 and y_1 oscillate almost in antiphase: small values y_1 correspond to greater values x_1, and vice versa.

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