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Spectral Analysis and Invariant Measure in Studying the Dynamics of a Metabolic Process in the Glycolysis-Gluconeogenesis System

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Abstract: The paper presents an original general mathematical model of the glycolysis-gluconeogenesis metabolic processes chain. The scenario of the appearance of auto-periodic and chaotic modes for the system is studied with the help of the Fourier series of one of the system variables. The invariant measure of the strange attractor is calculated. The histograms of the invariant measure projections of the system onto the phase space plane are constructed. Conclusions are made about the self-organization and adaptation of the system to changes in the cell and the environment.

Keywords: *self-organization; strange attractor; glycolysis; gluconeogenesis; Fourier series; invariant measure; bifurcation, protobions.*

Mathematics Subject Classification (2010): 92C05, 35B32, 42A16, 37L40.

1 Introduction

An essential task of natural sciences is a search for the general physical laws of self-organization in Nature. The gradual development of nonlinear thermodynamics led to the emergence of a new scientific direction - synergetics. The mechanism of structure formation in open nonlinear systems became clear thanks to synergetics [1]. The science of self-organization and evolution of living organisms suggests an answer about the flow of physical and chemical processes in a cell [2].

One of the general chains of metabolic reactions running in each cell is glycolysis and its inverse process, gluconeogenesis. Cells receive energy from glucose in the form of ATP

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by way of glycolysis. Cells further synthesize glucose from nonhydrocarbon substrates using gluconeogenesis.

Glycolysis and gluconeogenesis are two opposite metabolic processes in a cell, where 7 of 10 metabolic reactions are reversible. Three reactions are irreversible and are performed in gluconeogenesis via detouring thermodynamically favorable reactions.

A number of scientists have studied this chain of metabolic reactions. As a result of experimental studies of glycolysis, the auto oscillations were discovered in [3]. In order to explain the origin of auto oscillations, several mathematical models were developed. These models clarified that the oscillations in glycolysis occur as a result of the activation of phosphofructokinase by its products or due to the allosterism of this enzyme [4, 5].

The study in the present work is based on the mathematical model of glycolysis and gluconeogenesis developed in [6]. The peculiarity of this model is that for the first time, it analized the influence of the adenine nucleotide cycle and gluconeogenesis on the phosphofructokinase complex of this allosteric enzyme. It has been claimed that their effects cause fluctuations in glycolysis.

In works [7, 8], this model was improved. The system of equations of the model was refined by applying the conservation law to the intermediate reactions products. It also accounted for the description of the complete closed chain of metabolic processes of glycolysis-gluconeogenesis encircled by a positive feedback loop. The metabolic processes of glycolysis-gluconeogenesis with a positive feedback loop are the electron transfer chain $NAD \cdot H \Longleftrightarrow NAD^{+}$.

The results obtained in papers [7,8] allowed the authors to construct a general mathematical model of the chain of metabolic glycolysis-gluconeogenesis reactions as a single dissipative system of a cell.

Since gluconeogenesis uses mainly the same reversible reactions as glycolysis, the biochemical evolution of the former occurred together with glycolysis. The symbiosis of the given biochemical processes can be considered as a primary open nonlinear biochemical system in a state far from the equilibrium. As a result of self-organization of this biochemical system, a stable dissipative system emerged. It was independent of the other biochemical processes of the primary broth.

The direction of the running reactions in such a system was determined by the energy-beneficial balance. The organic molecule ATP was formed as a result of glycolysis. It became a main carrier of the energy consumed in all the other biochemical processes. But if some biochemical processes needed glucose, then the direction of biochemical reactions in the given system reversed. This chain of metabolic reactions forced all other metabolic processes in a cell to self-organize. During the subsequent biochemical evolution, the given dissipative system was preserved in all types of cells, which indicates their common prehistory. The analysis of the metabolic process allows us to state that this dissipative system probably arose in protobionts in the primary broth in the oxygen-free atmosphere of the Earth 3.5 billion years ago. This primary cell, in which life originated, was named the LUCA (the last universal common ancestor) [9, 10].

2 Mathematical Model and Method of Investigation

A mathematical model of the metabolic process of glycolysis-gluconeogenesis is constructed according to the general schemes of the metabolic reactions presented in Figure 1 and the general schemes of two active and two inactive forms of the allosteric enzyme phosphofructokinase (Figure 2) [7,8]. The model describes the flow of the metabolic pro-

cess in straightforward direction, that corresponds to glycolysis, and in opposite direction during gluconeogenesis.

The mathematical model is a system of 16 nonlinear differential equations. The equations correspond to the basic sections of the metabolic process. They determine a sequence of the reactions, and they influence the stability of the process of glycolysis-gluconeogenesis. Some sections of the metabolic network that are insignificant for the self-organization are described by the equations in the extended meaning. In Figure 1, we show the sections of the metabolic network from the 1-st to 16-th. Each of them corresponds to the number of the differential equation:

$$\frac{dG}{dt} = \frac{G_0}{S}\frac{m_1}{m_1+F} - l_8V(G)V(T), \tag{1}$$

$$\frac{dF_1}{dt} = l_8V(G)V(T) - l_1V(R_1)V(F_1)V(T) + l_5\frac{1}{1+\gamma A}V(F_2) - m_3\frac{F_1}{S}, \tag{2}$$

$$\frac{dF_2}{dt} = l_1V(R_1)V(F_1)V(T) - l_5\frac{1}{1+\gamma A}V(F_2) - m_5\frac{F_2}{S}, \tag{3}$$

$$\frac{d\psi_1}{dt} = \frac{m_5(F_2/S)}{S_1+m_5(F_2/S)} - l_6V(\psi_1)V(D) + m_7V(M-N)V(P), \tag{4}$$

$$\frac{d\psi_2}{dt} = l_6V(\psi_1)V(D) - m_8\frac{\psi_2}{S}, \tag{5}$$

$$\frac{d\psi_3}{dt} = \frac{\psi_2}{S}\frac{m_2}{m_2+\psi_3} - l_2V(\psi_3)V(D) - m_4\frac{\psi_3}{S}, \tag{6}$$

$$\frac{dP}{dt} = l_2V(\psi_3)V(D) - m_6\frac{P}{S} - l_7V(N)V(P), \tag{7}$$

$$\frac{dL}{dt} = l_7V(N)V(P) - m_9\frac{L}{S}, \tag{8}$$

$$\frac{dT}{dt} = l_2V(\psi_3)V(D) - l_1V(R_1)V(F_1)V(T) + l_3\frac{A}{\delta+A}V(T) - l_4\frac{T^4}{\beta+T^4} + \\ + l_6V(\psi_1)V(D) - l_9V(G)V(T), \tag{9}$$

$$\frac{dD}{dt} = l_1V(R_1)V(F_1)V(T) - l_2V(\psi_3)V(D) + 2l_3\frac{A}{\delta+A}V(T) - l_6V(\psi_1)V(D) + \\ + l_9V(G)V(T), \tag{10}$$

$$\frac{dA}{dt} = l_4\frac{T^4}{\beta+T^4} - l_3\frac{A}{\delta+A}V(T), \tag{11}$$

$$\frac{dR_1}{dt} = k_1T_1V(F_1^2) + k_3R_2V(D^2) - k5R_1\frac{T}{1+T+\alpha A} - k_7R_1V(T^2), \tag{12}$$

$$\frac{dR_2}{dt} = k_5R_1\frac{T}{1+T+\alpha A} - k_3R_2V(D^2) + k_2T_2V(F_1^2) - k_8R_2V(T^2), \tag{13}$$

$$\frac{dT_1}{dt} = k_7 R_1 V(T^2) - k_6 T_1 \frac{T}{1+T+\alpha A} + k_4 T_2 V(D^2) - k_1 T_1 V(F_1^2), \tag{14}$$

$$\frac{dT_2}{dt} = k_6 T_1 \frac{T}{1+T+\alpha A} - k_4 T_2 V(D^2) - k_2 T_2 V(F_1^2) + k_8 R_2 V(T^2), \tag{15}$$

$$\frac{dN}{dt} = -l_7 V(N) V(P) + l_7 V(M-N) V(\psi_1), \tag{16}$$

where $V(X) = X/(1+X)$ is the function that describes the adsorption of an enzyme in the locally connected region. The variables of the system are made unitless.

The parameters of the system are: $l_1 = 0.0535$, $l_2 = 0.046$, $l_3 = 0.0017$, $l_4 = 0.01334$, $l_5 = 0.3$, $l_6 = 0.001$, $l_7 = 0.01$, $l_8 = 0.0535$, $l_9 = 0.001$, $k_1 = 0.07$, $k_2 = 0.01$, $k_3 = 0.0015$, $k_4 = 0.0005$, $k_5 = 0.05$, $k_6 = 0.005$, $k_7 = 0.03$, $k_8 = 0.005$, $m_1 = 0.3$, $m_2 = 0.15$, $m_3 = 1.6$, $m_4 = 0.0005$, $m_5 = 0.007$, $m_6 = 10$, $m_7 = 0.0001$, $m_8 = 0.0000171$, $m_9 = 0.5$, $G_0 = 18.4$, $L = 0.005$, $S = 1000$, $A = 0.6779$, $M = 0.005$, $S_1 = 150$, $\alpha = 184.5$, $\beta = 250$, $\delta = 0.3$, $\gamma = 79.7$.

At the first stage (1), glucose G_0 entering a cell is phosphorylized with the help of the enzyme hexokinase to glucose-6-phosphate. The donor of a phosphoryl group is a molecule $ATP(T)$ (1), (9). This reaction is irreversible. The molecules of glucose-6-phosphate are the allosteric inhibitor of the reaction and cannot leave the cell. If the concentration of glucose-6-phosphate in a cell increases above the normal level, then hexokinase is inhibited by glucose-6-phosphate (1). The speed of glucose-6-phosphate formation corresponds to the speed of its consumption in the subsequent reactions. Further, an inverse isomerization of glucose-6-phosphate to fructose-6-phosphate occurs. However, it does not affect the irreversibility of the process.

Equations (2) and (3) describe the processes of fructose-6-phosphate creation (F_1) and its transformation into fructose-1,6-diphosphate (F_2). The last reaction occurs under the catalytic action of the enzyme phosphofructokinase. This enzyme catalyzes the irreversible transfer of a phosphoryl group from ATP (2), (9) onto fructose-6-phosphate with its transformation into fructose-1,6-diphosphate. The substrate fructose-6-phosphate is an activator, and ATP is an inhibitor of the given process. In addition to such regulation, the enzyme is also regulated by the adenine-nucleotide cycle $ATP - ADP - AMP$ (see below). The latter helps to support the optimum stable stationary state.

The equations (2) and (3) also describe the process of gluconeogenesis. The enzyme fructose-1,6-biphosphatase catalyzes the irreversible reaction $F_2 \longrightarrow F_1$ (parameter l_5) by creating the positive feedback loop. It affects the stability of the process.

The subsequent splitting of fructose-1,6-biphosphate into glyceraldehyde-3-phosphate and dioxyacetone-phosphate occurs in a reversible way.

Equation (4) describes the formation of 1,3-diphosphoglycerate (ψ_1). The enzyme glyceraldehyde-3-phosphate is oxidized and joins phosphoric acid using glyceraldehyde-3-phosphate-dehydrigenase. In this case, the coenzyme NAD^+ is an acceptor of hydrogen. The following enzymatic restoration occurs: $NAD^+ \to NAD \cdot H$ (4), (16).

With the help of equation (5), we described a transfer process of a high-energy phosphoryl group from the carboxyl group of 1,3-diphosphoglycerate by the enzyme phosphoglycerate kinase onto ADP. As a result, ATP (9) and 3-phosphoglycerate ψ_2 (5) are formed.

Equation (6) deals with the formation of 2-phosphoglycerate with the help of the phosphoglycerate mutase enzyme. Then a molecule of water is eliminated with the creation of phosphoenolpyruvate ψ_3 (6).

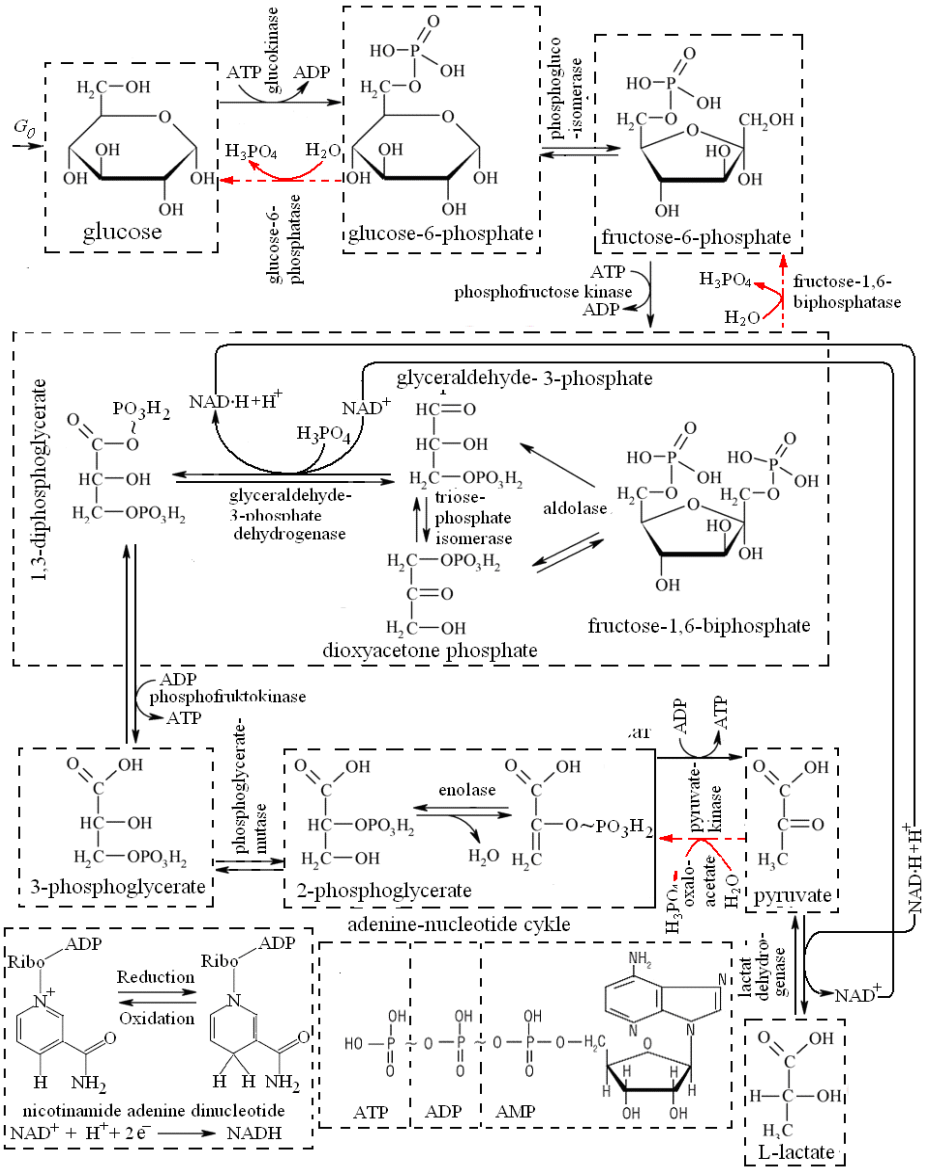

Figure 1: The general scheme of the metabolic process of glycolysis-gluconeogenesis.

The formation of the pyruvate P was considered in (7) under the action of the pyruvate kinase enzyme. So, the phosphorylation of the substrate occurs.

Equation (8) describes the formation of lactate L, which is the second product. With

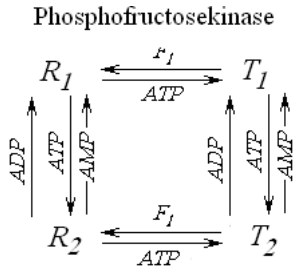

Figure 2: The general scheme of mutual transformations of two active and two nonactive forms of the allosteric enzyme phosphofructokinase.

the help of the lactate dehydrogenase enzyme, the enzymatic oxidation happens: $NAD \cdot H \to NAD^+$. The balance between NAD^+ and $NAD^+ \cdot H$ is preserved, see equation (16).

Equations (9)-(11) are related to the kinetics of the changes in the levels of ATP (9), ADP (10), and AMP (11) according to the metabolic scheme of glycolysis-gluconeogenesis (see above). In general, the adenine-nucleotide cycle arises between given reagents with mutual transitions: $ATP - ADP - AMP$. The adenine-nucleotide cycle helps to conserve the optimum stationary state of the metabolic process.

Equations (12)-(15) demonstrate the kinetics of levels of the allosteric phosphofructokinase enzyme (Figure 2).

We assume that the enzyme has two active forms: R_1 (12) and R_2 (13), and two nonactive: T_1 (14) and T_2 (15). In this case, we can observe the mutual transformation of the forms T_1 and R_1, as well as T_2 and R_2. The equations show the general scheme of regulatory connections. The form R_1 (12) was created from the form T_1 as a result of the saturation of the two allosteric centers by molecules F_1 and the form R_2 with the participation of two molecules D. Inactivation of the form R_1 takes place at the expense of T and with the formation of R_2 (13) and two molecules T (12) with the formation of the form T_1 (14). The invertible inactivation is inhibited by an increase of A according to a high level of T (parameter α) (12). Equations (13)-(15) were constructed in a similar way.

Equation (16) represents the kinetics of changes in the nicotinamide adenine dinucleotide recovered form $NAD \cdot H$ according to its consumption and recovery of the oxidized form NAD^+ (4). The balance between the recovered and oxidized forms is preserved in the glycolytic cycle in invariable form. In this case, the integral of motion is $NAD \cdot H(t) + NAD^+(t) = M$.

The stability dynamics is investigated using the second Liapunov method [12]. The chaotic dynamics of mathematical models can be studied using harmonic analysis [13].

In this paper, we used the Fourier series and invariant measure [14] for system investigation. Let us write down the system (1)-(16) in generalized form

$$\dot{x} = F(x), x \in R^n, \tag{17}$$

where $F(x) = (f_1(x), f_2(x), ..., f_n(x))^T$, the continuous dynamical system $\varphi^t(x)$ is defined by the system of differential equations. Such dynamical system for each τ generates a cascade of

$$x_{k+1} = f(x_k) \equiv \varphi^\tau(x_k). \tag{18}$$

Definition 2.1 The measure μ is an invariant measure of dynamical system (18) if for any measurable set A, the following relation fulfills:

$$\mu(A) = \mu(f^{-1}(A)).$$

Theorem 2.1 *(the Krylov–Bogolyubov theorem on the existence of invariant measures) If a compact set $A \subset P$ is invariant for the dynamic system $\varphi^t(x)$, then there exists at least one probability measure μ (where $\mu(P) = 1$) which is invariant for φ [14].*

Let us divide some phase space region into small enough subsets A_i. The result of solution for the system of differential equations (17) will be trajectories x_k, where $k = \overline{1, N}$, N is a big enough number of points. The measure of each set is estimated as

$$\mu(A_i) = N_i/N, \tag{19}$$

where N_i is the number of points in the subset A_i.

Theorem 2.2 *(The Fourier coefficients) The Fourier series representation of $f(x)$ defined on $[0, 2\pi]$, when it exists, is given by*

$$f(x) = \frac{a_0}{2} + \sum_{n=1}^{\infty} \left(a_n cosnx + b_n sinnx\right), \tag{20}$$

with the Fourier coefficients

$$a_n = \frac{1}{\pi}\int_0^{2\pi} f(x)cosnxdx, \quad b_n = \frac{1}{\pi}\int_0^{2\pi} f(x)sinnxdx, \quad n = 0, 1, 2...$$

3 Result of Studies

The mathematical model is the system of nonlinear differential equations (1)-(16). It describes the open nonlinear biochemical system of glycolysis-gluconeogenesis. Input and output flows for the model are glucose and lactate, respectively. The concentrations of these substances determine the straightforward or inverse directions of the metabolic process dynamics. Both processes are irreversible and are running in the open nonlinear system, far from the equilibrium point. The presence of glycolysis and gluconeogenesis in the system is a cause for autocatalysis in the system. Besides, the whole metabolic process of glycolysis contains the feedback formed by $NAD{\cdot}H$ and the adenine-nucleotide cycle. These factors influence the appearance of instability in the given metabolic system.

Let us investigate the dependence of the dynamics of the metabolic glycolysis-glucogenesis process on the activity of gluconeogenesis, which is regulated by a small parameter l_5. The authors want to show that the fluctuations of fructose-6-phosphate [1,2] can be explained by gluconeogenesis, which occurs under the action of enzyme fructose-1,6-bisphosphatase in the area: fructose-1,6-bisphosphate - fructose-6-phosphate. This is different from the commonly used explanation by phosphofructokinase enzyme allosteric-ity.

In [9], the phasoparametric diagrams of the process dynamics dependence on the parameter l_5 were constructed. Bifurcation points for doubling of the period and the transition to chaos according to Feigenbaum's scenario were found. When the parameter l_5 decreases, the following stable modes are formed:

$$2 \times 2^1(l_5 = 0.268), 2 \times 2^2(l_5 = 0.264), 2 \times 2^4(l_5 = 0.262), 2^x(l_5 = 0.25).$$

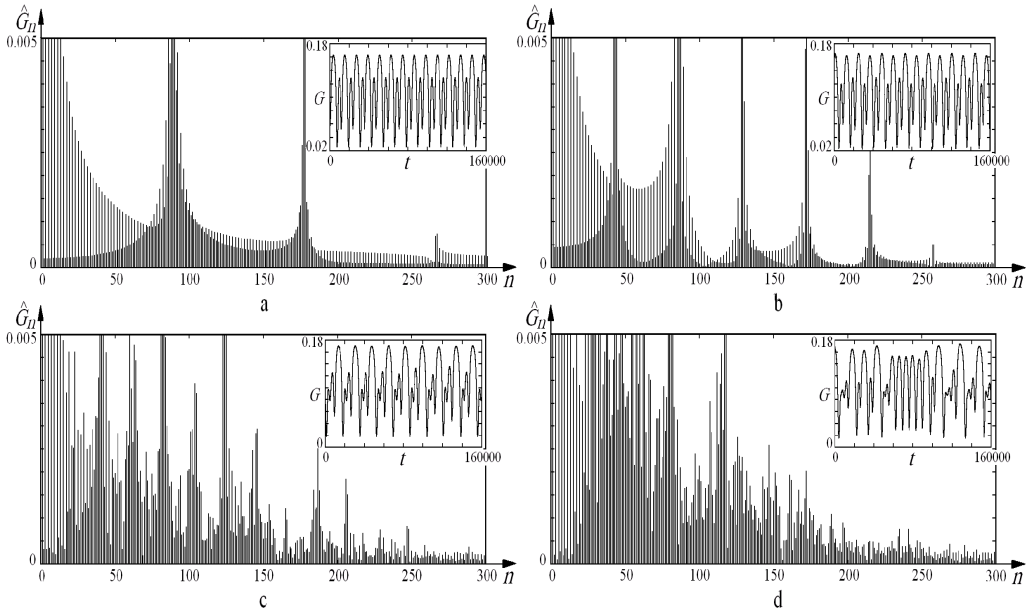

Figure 3: The distribution of the harmonics of the Fourier spectrum for a metabolic process in the system of glycolysis-gluconeogenesis in the modes: a - the autoperiodic process $2 \times 2^1(l_5 = 0.268)$; b – the autoperiodic process $2 \times 2^2(l_5 = 0.264)$; c – the autoperiodic process $2 \times 2^4(l_5 = 0.262)$; d - the chaos mode $2^x(l_5 = 0.25)$.

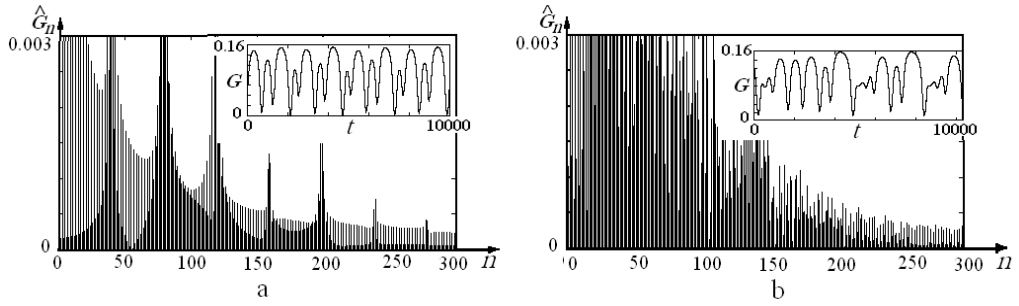

Figure 4: The distribution of the harmonics of the Fourier spectrum for the metabolic process in the system of glycolysis-gluconeogenesis for the parameter $l_5 = 0.3$ in the following modes: a – the quasistable autoperiodic process $2 \times 2^2(G_0 = 17.25)$; b – the chaos mode $2^x(G_0 = 16.8)$.

The spectral plots of the decomposition into a trigonometric Fourier series (20) of the kinetic curve $G(t)$ from equation (1) were constructed for the found self-oscillating modes. $\widehat{G_i}$, $i = \overline{1,n}$, are the harmonics of the Fourier series and they were obtained using equation (20). The kinetic curves for each spectrum are presented in the upper right corner of the corresponding figure. The basis of the decomposition is 1000 harmonics. The decomposition interval is $2l = 8000$, which is equal to the decomposition interval of the kinetics of the strange attractor (Figure 3d). This allowed us to accurately calculate

all the harmonics of the possible oscillating modes of the system, including for the strange attractor.

Doubling of the multiplicity of the periodic regime (see the transition from Figure 3a to Figure 3b and to Figure 3c) leads to the doubling of the number of fundamental harmonics that characterize the multiplicity of periodicity in the laminar phase trajectory of the attractor.

In the transition from Figure 3c to Figure 3d, there was no doubling of the cycle. So there was no increase in the multiplicity of fundamental harmonics. The graph (Figure 3d) shows a significant increase in the turbulence harmonics (compare Figure 3d with the graphs Figure 3a, b, c). The phase trajectory of the system becomes unstable and is characterized as a strange attractor. In this mode, the strict synchronicity of the metabolic processes of the system is violated. The desynchronized chain of glycolysis-gluconeogenesis reactions continues to execute its function, but not strictly periodically, which means the adaptation of cell metabolism to the changes in the cell and to the environment.

Figure 4a and Figure 4b show the distributions of the Fourier spectra of the variable $G(t)$ kinetics, with the increase of the parameter of gluconeogenesis to $l_5 = 0.3$ and with the change of the parameter G_0, for the following two modes: the quasi-stable autoperiodic process - $2 \times 2^2 (G_0 = 17.25)$ (a) and the chaos mode $2^x (G_0 = 16.8)$ (b).

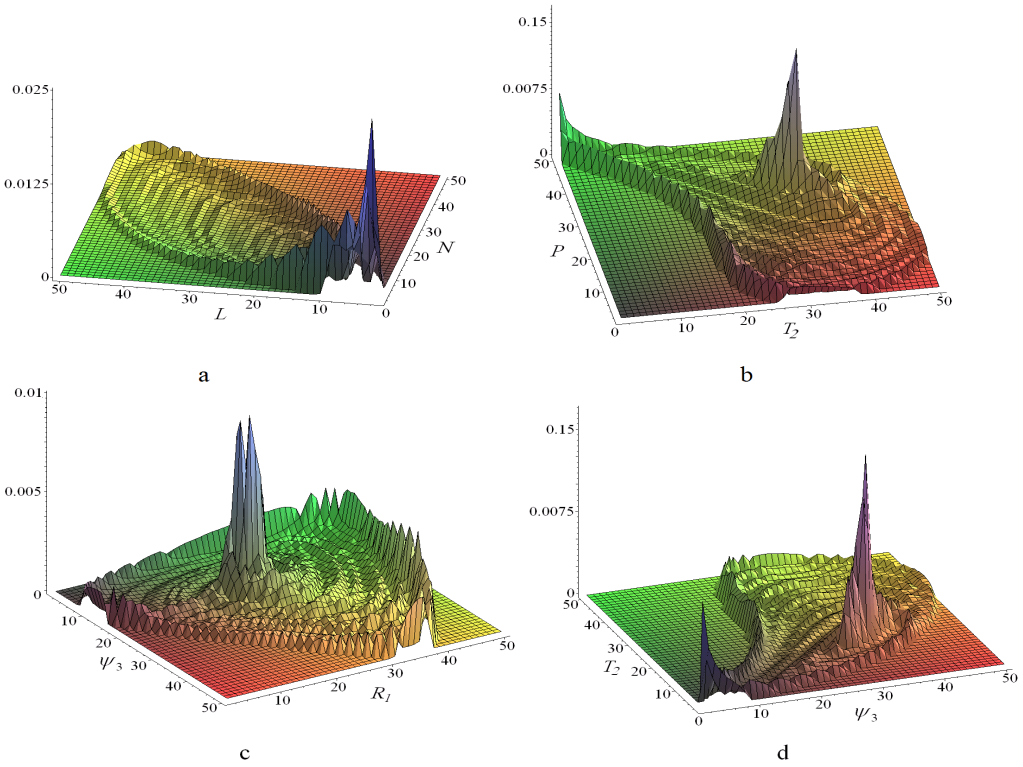

Figure 5: The histograms of the projections of the invariant measure of the strange attractor 2^x, at $l_5 = 0.25$: $t \in [10^6, 10^6 + 8 \cdot 10^5]$: a - onto the plane (L, N); b - onto the plane (T_2, P); c - onto the plane (R_1, ψ_3); d - onto the plane (T_2, ψ_3)

In order to more clearly represent the dynamics of the metabolic process of the glycolysis-gluconeogenesis system, the invariant measure (19) of the strange attractor 2^x was calculated for $l_5 = 0.25$: $t \in [10^6, 10^6 + 8 \cdot 10^5]$.

The histograms of the projections of the invariant measure onto some planes of the phase space of the system (Figure 5) were constructed, using the obtained values. For our results, we took the number of points $N = 50^{10}$ and the time of solving $t \in (10^6, 10^6 + 8 \times 10^5)$.

The histograms of projections of the invariant measure make it possible to generally evaluate the projections of the invariant measure of the corresponding variables of the system and to find its largest value. And this means that the found cell with the maximum of the projection of the invariant measure is also a place of instability in the variables of the system, where bifurcations and the chaotic regime of the strange attractor occur. This makes it possible to determine the sources of instability in the modeled cell biosystem dynamics.

From the presented diagrams, the largest projection of the invariant measure $\mu = 0.01875$ is obtained in Figure 5a, onto the coordinate plane (L, N). These variable models describe the change in lactate levels (8) and $NAD \cdot H$ (16). This means that the instability of these values in the metabolic process of glycolysis-gluconeogenesis most likely leads to the violation of the stability of the biosystem's attractor and the emergence of a strange attractor regime.

So, on the basis of the obtained results, in order to get rid of the chaotic regime and establish the stability of the attractor of the cell biosystem, we recommend to change the level $NAD \cdot H$ (electron carrier) or ψ (kinetic potential of the cell) via the corresponding biochemical action influencing these values.

We calculated the histograms of the invariant measure for other variables. It is also possible to determine their influence on the stability of the biosystem's attractor. In this case, the biochemical effect on the cell will be different.

4 Conclusion

The constructed mathematical model of glycolysis-gluconeogenesis is one of the main constructed models of synergy in biology. Using this model, the authors managed to simulate the structure of protobionts: the LUCA (the last universal common ancestor), from which the life of the primary cell could get its origin and get sustained. Thanks to biological evolution, this process has been reproduced in all living cells.

It was found that the cause of the auto-oscillating process in glycolysis is cell gluconeogenesis.

The results of the paper are as follows.

- The spectrum of the Fourier harmonic decomposition of the kinetics of system attractor formation was calculated. It can be used to determine system modes.

- For the first time, the invariant measures and the histograms of the invariant measures for the chaotic attractors of a dynamic system were calculated using a computer program for the mathematical model of glycolysis-gluconeogenesis.

- The histograms of the invariant measure of the strange attractor of the cell biosystem were constructed.

- Recommendations are made on how to biochemically get rid of the chaotic regime and restore the stability of the cell's life cycle.

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