Chaotic Modeling and Simulation (CMSIM) **1: 35-50, 2021**

Spectral analysis and invariant measure in studies of the dynamics of the Krebs cycle

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This work continues the study of a mathematical model of the Krebs cycle. With the help of spectral analysis of the kinetics of the process obtained at the variation in a small parameter, the scenario of changes in the cyclicity and the appearance of a strange attractor in the metabolic process of the Krebs cycle is found. The projections of a phase portrait and the histograms of projections of the invariant measure of a strange attractor are constructed. Some conclusions on the connection between the functional state of a cell and the self-organization in the Krebs cycle are presented.

Keywords: *Krebs cycle, self-organization, strange attractor, Fourier series, invariant measure, bifurcation.*

One of the most important problems of the natural science is the search for the common physical laws of self-organization in the Nature. A particular place is occupied by the studies of the life origin and the way in which the catalyzed enzymatic reactions create the internal space-time ordering in the life of cells.

Among the various metabolic processes, the Krebs cycle is general for all cells [1]. The principal place is occupied by the cycle of tricarboxylic acids. Practically all metabolic paths converge to it. Its study will allow one to find the general regularities of the functioning of a cell [2-10].

Received: 8 December 2020 / Accepted: 27 January 2021

ISSN 2241-0503

But, it is impossible to construct a reliable mathematical model of only the Krebs cycle, because the internal parameters of a cell are unknown. Without the comparison of solutions of the model with experimental characteristics, the model will be abstract and will not correspond to the real dynamics of the metabolic process. Therefore, as the base of the process, we will take the well-known biotechnological process of growth of cells *Candida utilis* on ethanol [11]. For it, the experimental characteristics are available, and the mathematical model was constructed in [12,13]. The calculated parameters of the model describe properly this process.

Taking the mentioned model of the biotechnological process as a base, a new improved mathematical model of the dynamics of the metabolic process of the Krebs cycle in a cell was developed in [14-16].

In the study of that model, we obtained the following results.

The autocatalytic processes resulting in the appearance of the self-organization in the Krebs cycle and the cyclicity in its dynamics are determined. The structural-functional connections creating the synchronism between the auto-periodic transfer of electrons along the respiratory chain and oxidative phosphorylation are considered. The conditions for the violation of the synchronism of processes, increase in the multiplicity of their cyclicity, and appearance of chaotic modes are established. The phase parametric diagram of the cascade of bifurcations, which indicates that the transition chaotic modes occurs by the Feigenbaum scenario, was obtained. The fractal nature of the calculated cascade of bifurcations was demonstrated. The strange attractors that are formed due to the folding are found.

In addition, we studied a change in the cyclicity of the Krebs cycle as a function of the amount of accumulated carbon dioxide, being the final product of the oxidation. The scenarios of various oscillatory modes of the system were constructed and studied. The bifurcations with the doubling of periods and the appearance of chaotic modes were determined. The cycle multiplicity is doubled by the Feigenbaum scenario, until the aperiodic modes of strange attractors have arisen eventually. From them, new stable periodic

modes arise due to the self-organization. This means that the system is adapted to the variable conditions of a medium. The complete spectra of Lyapunov's indices and the divergences for various modes were calculated. For strange attractors, we calculated the KS-entropies, "predictability horizons," and Lyapunov's dimensions of attractors.

The consistency and stability of the cycle of tricarboxylic acids that depend on the dissipation of a transmembrane potential formed by the respiratory chain in the plasmatic membrane of a cell were studied. The phase parametric characteristic of the dependence of the dynamics of a changing level of ATP in the dissipation of a transmembrane potential were constructed. The scenario of the formation of multiple autoperiodic and chaotic modes was found. The Poincaré cross-sections and mappings were constructed. The stability of modes and the fractality of the calculated bifurcations were studied. Some conclusions about the structural-functional connections of the cycle of tricarboxylic acids and their influence on the stability of the metabolic process were made.

In the present work, we will account for the formation of carbon dioxide in the Krebs cycle and its influence on the metabolic process in a cell. Moreover, with the help of spectral analysis, projections of phase portraits, and the invariant measure, we will study the formation of strange attractors.

MATHEMATICAL MODEL

The general scheme of the metabolic process in cells *Candida utilis* in the biotechnological process of growth of cells on ethanol is presented in Fig. 1. With regard for the mass balance, we will develop a mathematical model of the given process (1) - (19). Though the equations describe the whole metabolic process in a cell, we will focus only on the metabolic process of the Krebs cycle. The introduced additional equations do not complicate the solution of the problem, but make it more substantiated and practical.

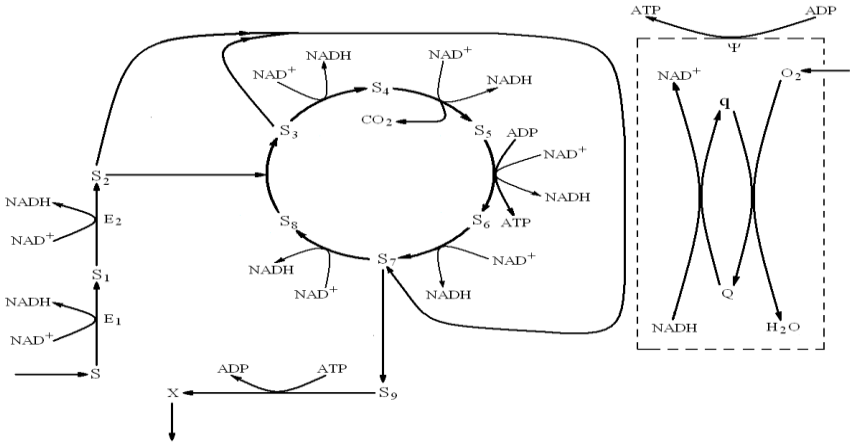

Fig. 1. General scheme of the metabolic process in a cell *Candida utilis* in the biotechnological process of growth of cells on ethanol.

$$\frac{dS}{dt} = S_0 \frac{K}{K + S + \gamma\psi} - k_1 V(E_1) \frac{N}{K_1 + N} V(S) - \alpha_1 S, \quad (1)$$

$$\frac{dS_1}{dt} = k_1 V(E_1) \frac{N}{K_1 + N} V(S) - k_2 V(E_2) \frac{N}{K_1 + N} V(S_1), \quad (2)$$

$$\frac{dS_2}{dt} = k_2 V(E_2) \frac{N}{K_1 + N} V(S_1) - k_3 V(S_2^2) V(S_3) - k_4 V(S_2) V(S_8), \quad (3)$$

$$\frac{dS_3}{dt} = k_4 V(S_2) V(S_8) - k_5 V(N^2) V(S_3^2) - k_3 V(S_2^2) V(S_3), \quad (4)$$

$$\frac{dS_4}{dt} = k_5 V(N^2) V(S_3^2) - k_7 V(N) V(S_4) - k_8 V(N) V(S_4), \quad (5)$$

$$\frac{dS_5}{dt} = k_7 V(N) V(S_4) - 2k_9 V(L_1 - T) V(S_5), \quad (6)$$

$$\frac{dS_6}{dt} = 2k_9V(L_1 - T)V(S_5) - k_{10}V(N)\frac{S_6^2}{S_6^2 + 1 + M_1S_8}, \quad (7)$$

$$\frac{dS_7}{dt} = k_{10}V(N)\frac{S_6^2}{S_6^2 + 1 + M_1S_8} - k_{11}V(N)V(S_7) - k_{12}\frac{S_7^2}{S_7^2 + 1 + M_2S_9}V(\psi^2) + k_3V(S_2^2)V(S_3), \quad (8)$$

$$\frac{dS_8}{dt} = k_{11}V(N)V(S_7) - k_4V(S_2)V(S_8) + k_6V(T^2)\frac{S^2}{S^2 + \beta_1}\cdot\frac{N_1}{N_1 + (S_5 + S_7)^2}, \quad (9)$$

$$\frac{dS_9}{dt} = k_{12}\frac{S_7^2}{S_7^2 + 1 + M_2S_9}V(\psi^2) - k_{14}\frac{XTS_9}{(\mu_1 + T)[(\mu_2 + S_9 + X + M_3(1 + \mu_3\psi)]S}, \quad (10)$$

$$\frac{dX}{dt} = k_{14}\frac{XTS_9}{(\mu_1 + T)[(\mu_2 + S_9 + X + M_3(1 + \mu_3\psi)]S} - \mu_0X, \quad (11)$$

$$\frac{dQ}{dt} = -k_{15}V(Q)V(L_2 - N) + 4k_{16}V(L_3 - Q)V(O_2)\frac{1}{1 + \gamma_1\psi^2}, \quad (12)$$

$$\frac{dO_2}{dt} = O_{2_0}\frac{K_2}{K_2 + O_2} - k_{16}(L_3 - Q)V(O_2)\frac{1}{1 + \gamma_1\psi} - k_8V(N)V(S_4) - \alpha_3O_2, \quad (13)$$

$$\frac{dN}{dt} = -k_7V(N)V(S_4) - k_{10}V(N)\frac{S_6^2}{S_6^2 + 1 + M_1S_8} - k_{11}V(N)V(S_7) - k_5V(N^2)V(S_3^2) +$$

$$+ k_{15}V(Q)V(L_2 - N) - k_2V(E_2)\frac{N}{K_1 + N}V(S_1) - k_1V(E_1)\frac{N}{K_1 + N}V(S), \quad (14)$$

$$\frac{dT}{dt} = k_{17}V(L_1 - T)V(\psi^2) + k_9V(L - T)V(S_3) - \alpha_4T -$$

$$- k_{18}k_6V(T^2)\frac{S^2}{S^2 + \beta_1}\cdot\frac{N_1}{N_1 + (S_5 + S_7)^2} - k_{19}k_{14}\frac{XTS_9}{(\mu_1 + T)[\mu_2 + S_9 + X + M_3(1 + \mu_3\psi)S]}, \quad (15)$$

$$\frac{d\psi}{dt} = 4k_{15}V(Q)V(L_2 - N) + 4k_{17}V((L_1 - T)V(\psi^2) - 2k_{12}\frac{S_7^2}{S_7^2 + 1 + M_2 S_9}V(\psi^2) - \alpha\psi, \quad (16)$$

$$\frac{dE_1}{dt} = E_{1_0}\frac{S^2}{\beta_2 + S^2}\frac{N_2}{N_2 + S_1} - n_1 V(E_1)\frac{N}{K_1 + N}V(S) - \alpha_5 E_1, \quad (17)$$

$$\frac{dE_2}{dt} = E_{2_0}\frac{S_1^2}{\beta_3 + S_1^2}\frac{N_3}{N_3 + S_2} - n_2 V(E_2)\frac{N}{K_1 + N}V(S_1) - \alpha_6 E_2, \quad (18)$$

$$\frac{dC}{dt} = k_8 V(N)V(S_4) - \alpha_7 C, \quad (19)$$

where: $V(X) = X/(1+X)$ is a function related to the adsorption of the enzyme in a region of local coupling. The variables of the system of equations are dimensionless.

Internal parameters of the system:

$k_1 = 0.3;\ k_2 = 0.3;\ k_3 = 0.2;\ k_4 = 0.6;\ k_5 = 0.16;\ k_6 = 0.7;$ $k_7 = 0.08;\ k_8 = 0.022;$

$k_9 = 0.1;\ k_{10} = 0.08;\ k_{11} = 0.08;\ k_{12} = 0.1;\ k_{14} = 0.7;$ $k_{15} = 0.27;\ k_{16} = 0.18;$

$k_{17} = 0.14;\ k_{18} = 1;\ k_{19} = 10;\ n_1 = 0.07;\ n_2 = 0.07;\ L = 2;$ $L_1 = 2;\ L_2 = 2.5;\ L_3 = 2;$

$K = 2.5;\ K_1 = 0.35;\ K_2 = 2;\ M_1 = 1;\ M_2 = 0.35;\ M_3 = 1;$ $N_1 = 0.6;\ N_2 = 0.03;$

$N_3 = 0.01;\ \mu_1 = 1.37;\ \mu_2 = 0.3;\ \mu_3 = 0.01;\ \gamma = 0.7;\ \gamma_1 = 0.7;$ $\beta_1 = 0.5;\ \beta_2 = 0.4;$

$\beta_3 = 0.4;\ E_{1_0} = 2;\ E_{2_0} = 2.$

External parameters of the system that determine the running conditions of a bioreactor:

$S_0 = 0.05055;\quad O_{2_0} = 0.06;\quad \alpha = 0.002;\quad \alpha_1 = 0.02;$

$\mu_0 = 0.004;\ \alpha_3 = 0.01;$

$\alpha_4 = 0.01;\ \alpha_5 = 0.01;\ \alpha_6 = 0.01;\ \alpha_7 = 0.0001.$

The model includes the processes of substrate-enzymatic oxidation of ethanol to acetate, cycle of tricarboxylic and dicarboxylic acids, glyoxylate cycle, and the respiratory chain.

The study of the solutions of the given mathematical model (1)-(19) was carried out with the help of the theory of nonlinear differential equations [17,18] and the developed methods of mathematical modeling of biochemical systems [19-47].

RESULTS OF STUDIES

We now consider how the final product of catabolism of hydrocarbons, CO_2, influences the cyclicity of the process with tricarboxylic acids. In Fig. 2, we show the phase parametric diagram of the dependence of the dynamics of the process on the rate of formation of CO_2 in a cell. It is regulated by the parameter k_8 and affects the level of the oxygen breathing of a cell. The value of this parameter depends on the intensity of gas exchange of a cell with the environment. The high level of CO_2 in a cell decreases the concentration of oxygen which is necessary for the full-value breathing of a cell, so, the respiratory chain is not oxidized opportunely. On the contrary, if the level of oxygen is high, the intense oxidation of the respiratory chain and the rapid turnover of the Krebs cycle occur, and the cyclicity multiplicity of the process grows.

The diagram is constructed for the variable $E_1(t)$ with $k_8 \in (0-0.4)$. It is seen that the transitions between the auto-periodic modes and to the chaos are realized by the Feigenbaum scenario. From the diagram, we find the most characteristic modes for the Krebs cycle such as the auto-periodic cycles of the regular

attractors: $2\times 2^0(k_8=0.2482)$; $4\times 2^0(k_8=0.251)$; $8\times 2^0(k_8=0.2517)$ and strange attractor: $2\times 2^x(k_8=0.267)$.

For them, we constructed the spectral patterns of the expansion of the kinetic curve $T(x)$ in a trigonometric Fourier series. They are shown in the upper right corner for each spectrum. In the expansion, we took 1000 harmonics, and the expansion interval $2l=8000$ which is equal to the interval for the kinetics of a strange attractor Fig. 3,d. This allows us to correctly calculate all harmonics for possible oscillatory modes of the system, including those for a strange attractor. The multiplicity doubling for a periodic mode (see the transition from Fig.3,a to Fig.3,b and to Fig.3,c) causes the doubling of the number of basic harmonics that characterize the multiplicity of the laminavrity of a phase trajectory of the attractor. At the transition from Fig. 3,c to Fig.3,d, the cycle is not doubled. Therefore, the multiplicity of basic harmonics was not increased. In Fig.3,d, we see a significant increase in the harmonics both turbulence (compare Fig.3,d and plots in Fig.3,a,b,c). The phase trajectory of the system becomes unstable and is characterized as a strange attractor. In such mode, the strict synchronism between the Krebs cycle and the oxidative phospholylation is violated. The desynchronized Krebs cycle continues to execute its function, but without a strict periodicity, which means the adaptation of the metabolism of a cell to the external conditions.

Thus, the spectral patterns of the expansion of a kinetics of the metabolic process in a Fourier series describe the scenario of formation of attractors in the system, as a small parameter varies. This enables us to study the other unknown modes.

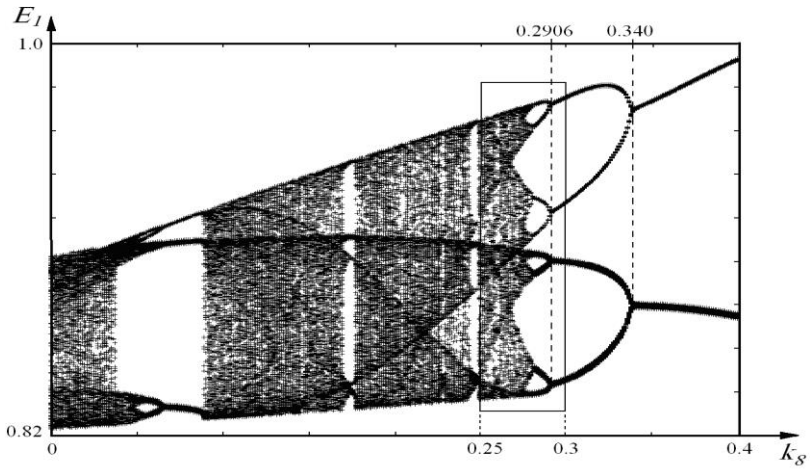

Fig.2. Phase parametric diagram of the system for the variable $E_1(t)$.

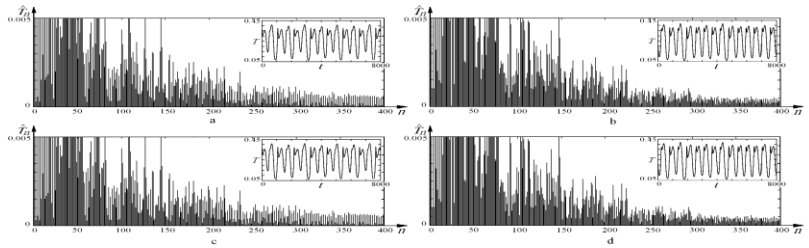

Fig.3. Distribution of harmonics of the Fourier spectrum in modes of the metabolic process of the Krebs cycle:

a – regular attractor $2\times 2^0(k_8 = 0.2482)$;

b – regular attractor $4\times 2^0(k_8 = 0.251)$;

c – regular attractor $8\times 2^0(k_8 = 0.2517)$;

d - strange attractor $2\times 2^x(k_8 = 0.267)$.

In Fig.4,a-f, we present the projections of a phase portrait of the strange attractor $2\times 2^x(k_8 = 0.267)$. It is seen from these projections that the given chaotic attractor is formed due to the

presence of a funnel. Any turbulence in this region of the phase space causes the violation of the stable laminar motion along a trajectory of the system. The process becomes unstable and holds only in a vicinity of the trajectory. Thus, the metabolic process of the Krebs cycle continues to operate, by adapting to changes in the environment.

For a clearer representation of the motion of a trajectory of the system in the phase space, we calculated the invariant measure of the given strange attractor and constructed the histograms of projections of the invariant measure on various planes (Fig.5,a-d). These histograms are more informative than the projection of a phase portrait and give the idea of solutions of the system in the phase space in the strange attractor mode.

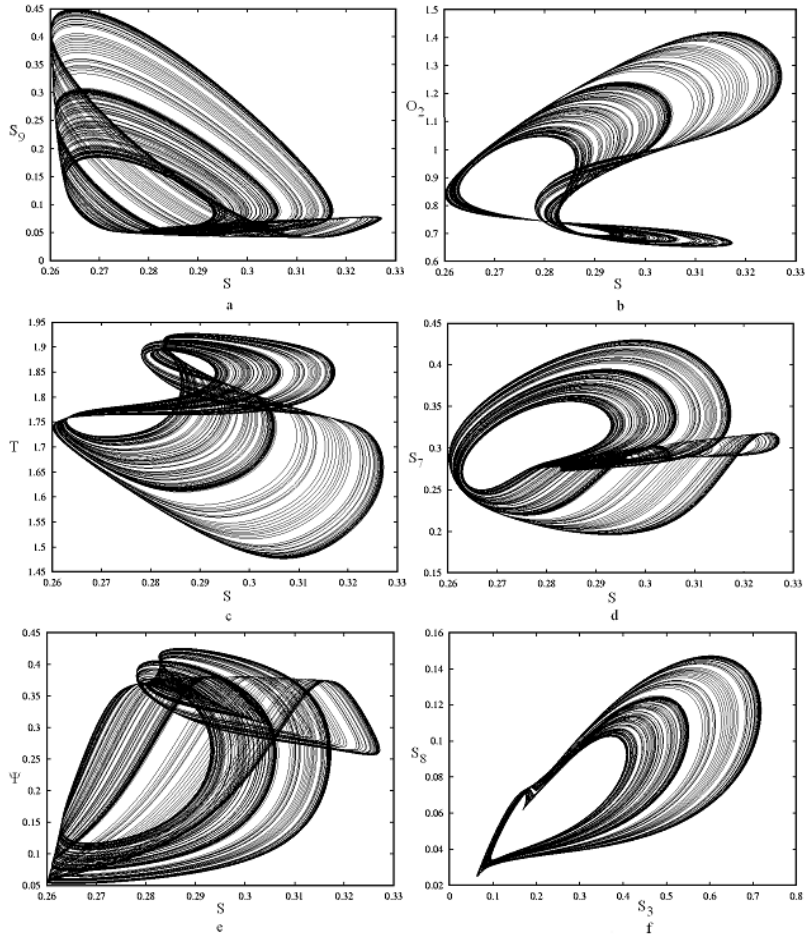

Fig.4. Projections of a phase portrait of the strange attractor $2\times 2^{x}(k_8 = 0.267)$.

a – on the plane S, S_9; b - on the plane S, O_2; c - on the plane S, T;

d - on the plane S, S_7; e - on the plane S, Ψ; f - on the plane S_3, S_8.

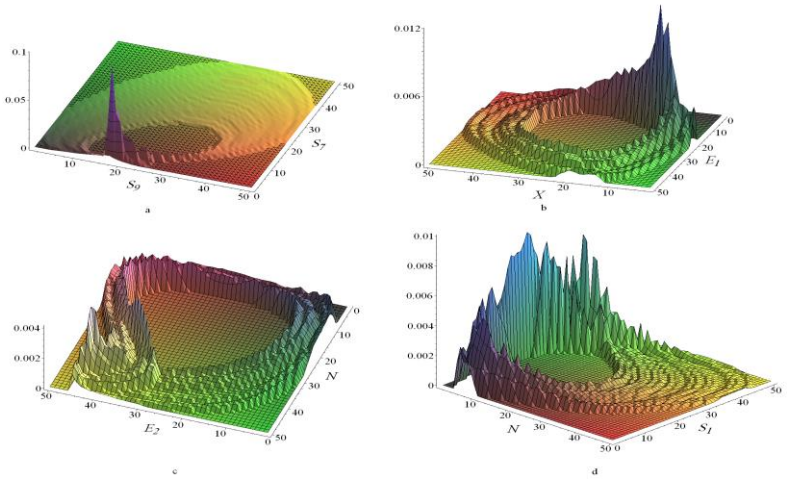

Fig.5. Histograms of projections of the invariant measure of a strange attractor $2\times 2^{x}(k_8 = 0.267)$, $t\in[10^6;(10^6+10^5)]$:

a – on the plane S_9, S_7; b – on the plane X, E_1;

c – on the plane N, E_2; d – on the plane N, S_1.

CONCLUSIONS

With the help of the expansion of the kinetic curve for a variable of the system in a trigonometric Fourier series, we determined the scenario of changes in the cyclicity of the process and the appearance of a strange attractor within the mathematical model of the Krebs cycle. We constructed the projections of a phase portrait and the histograms of projections of the invariant measure of a strange attractor. Some conclusions about the functional dependence of the self-organization of the metabolic process of the Krebs cycle on the amount of the final product of oxidation, carbon dioxide, are made. If the synchronism between the process of the Krebs cycle and oxidative phospholylation is violated, a strange attractor appears in the dynamics of the metabolic process, which

means the adaptation of metabolism of a cell to changes in the environment.

The present work was partially supported by the Program of Fundamental Research of the Department of Physics and Astronomy of the National Academy of Sciences of Ukraine "Mathematics models of non-equilibrium process in open system" N 0120U100857.

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