MATHEMATICAL MODELING OF BIOCHEMICAL PROCESS

UDC 577.32 doi: https://doi.org/10.15407/ubj95.06.105

INSTABILITY AND INVARIANT MEASURE IN THE MATHEMATICAL MODEL FOR OXIDATIVE PHOSPHORYLATION AND ATP SYNTHESIS IN THE CELL

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Received: 13 October 2023; **Revised:** 28 November 2023; **Accepted:** 01 December 2023

The aim of this work was to analyze the process of oxidative phosphorylation and ATP synthesis in a cell using a mathematical model. The scenario of occurrence of the autoperiodic and chaotic modes depending on the ATP dissipation values was determined. The invariant measure of the strange attractor was calculated, and histograms of its projections on the phase plane were plotted. Some recommendations were made on how to eliminate biochemically the chaotic mode and restore the stability of the self-organization of the cell biosystem.

K e y w o r d s: oxidative phosphorylation, Krebs cycle, ATP, mathematical model, self-organization, invariant measure, strange attractor, Feigenbaum scenario.

The emergence of regularity in open systems that are out of equilibrium is one of the main problems of modern natural science. These systems include, along with the causal physical systems, the biochemical systems of cells and the whole organism. The use of a synergetic approach in their mathematical description would allow explaining the phenomenon of self-organization in all living systems [1]. Many scientists try to explain the phenomenon of self-organization using different mathematical models [2, 3]. One of the most well-known examples of such systems is the Krebs cycle. It is a series of metabolic reactions that arose as early as the formation of protobionts - LUCA (last universal common ancestor). In the course of evolution, as a result of symbiosis, remaining almost unchanged, it has become part of all aerobic cells [4].

We took the mathematical model of the unstable growth of Candida utilis cells on ethanol as a base for our research reported in [5, 6]. Based on the results obtained, we then studied the mathematical model of the Krebs cycle, its self-organization and dynamic chaos [7-13].

In the present work, we further investigate the Krebs cycle, considering ATP dissipation on the cell's inner metabolic processes. The cell self-organization in a life rhythm as a whole is researched. It may enable studying the kinetics of cellular respiration and the process of electron transfer in the electron transport chain in the chaotic mode.

Mathematical Model

The general scheme of the metabolism of the *Candida utilis* cell growth on ethanol is shown in Fig. 1 [6].

According to it and given the mass balance, the mathematical model (1)-(19) was developed [7-13].

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

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

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

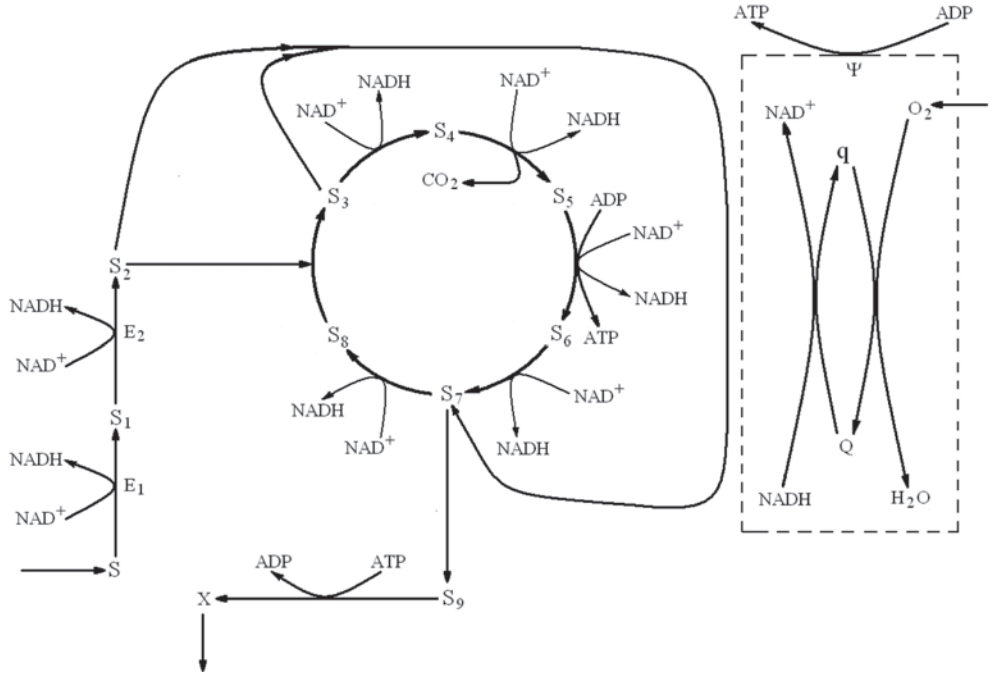

Fig. 1. General scheme of the metabolism of the Candida utilis cell growth on ethanol [6]

$$\frac{dS_3}{dt} = k_4V(S_2)V(S_8) - k_5V(N^2)V(S_3^2) - k_3V(S_2^2)V(S_3), \quad (4)$$

$$\frac{dS_4}{dt} = k_5V(N^2)V(S_3^2) - k_7V(N)V(S_4) - k_8V(N)V(S_4), \quad (5)$$

$$\frac{dS_5}{dt} = k_7V(N)V(S_4) - 2k_9V(L_1 - T)V(S_5), \quad (6)$$

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

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

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

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

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

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

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

$$\frac{dN}{dt} = -k_7V(N)V(S_4) - k_{10}V(N)\frac{S_6^2}{S_6^2 + 1 + M_1S_8} - k_{11}V(N)V(S_7) - k_5V(N^2)V(S_3^2) + k_{15}V(Q)V(L_2 - N) - k_2V(E_2)\frac{N}{K_1 + N}V(S_1) - k_1V(E_1)\frac{N}{K_1 + N}V(S), \quad (14)$$

$$\frac{dT}{dt} = k_{17}V(L_1 - T)V(\psi^2) + k_9V(L - T)V(S_3) - \alpha_4T - k_{18}k_6V(T^2)\frac{S^2}{S^2 + \beta_1}\cdot\frac{N_1}{N_1 + (S_5 + S_7)^2} - k_{19}k_{14}\frac{XTS_9}{(\mu_1 + T)[\mu_2 + S_9 + X + M_3(1 + \mu_3\psi)S]}, \quad (15)$$

$$\frac{d\psi}{dt} = 4k_{15}V(Q)V(L_2 - N) + 4k_{17}V((L_1 - T)V(\psi^2) - 2k_{12}\frac{S_7^2}{S_7^2 + 1 + M_2S_9}V(\psi^2) - \alpha\psi, \quad (16)$$

$$\frac{dE_1}{dt} = E_{1_0}\frac{S^2}{\beta_2 + S^2}\frac{N_2}{N_2 + S_1} - n_1V(E_1)\frac{N}{K_1 + N}V(S) - \alpha_5E_1, \quad (17)$$

$$\frac{dE_2}{dt} = E_{2_0}\frac{S_1^2}{\beta_3 + S_1^2}\frac{N_3}{N_3 + S_2} - n_2V(E_2)\frac{N}{K_1 + N}V(S_1) - \alpha_6E_2, \quad (18)$$

$$\frac{dC}{dt} = k_8V(N)V(S_4) - \alpha_7C, \quad (19)$$

where $V(X) = X/(1 + X)$ is the function that describes the enzyme adsorption in the localized coupling site.

The internal parameters of the system were: $k_1 = 0.3$; $k_2 = 0.3$; $k_3 = 0.2$; $k_4 = 0.6$; $k_5 = 0.16$; $k_6 = 0.7$; $k_7 = 0.08$; $k_8 = 0.022$; $k_9 = 0.1$; $k_{10} = 0.08$; $k_{11} = 0.08$; $k_{12} = 0.1$; $k_{14} = 0.7$; $k_{15} = 0.27$; $k_{16} = 0.18$; 0.022; $k_{17} = 0.141$; $k_{18} = 1$; $k_{19} = 10$; $n_1 = 0.07$; $n_2 = 0.07$; $L = 2$; $L_1 = 2$; $L_2 = 2.5$; $L_3 = 2$; $K = 2.5$; $K_1 = 0.35$; $K_2 = 2$; $M_1 = 1$; $M_2 = 0.35$; $M_3 = 1$; $N_1 = 0.6$; $N_2 = 0.03$; $N_3 = 0.01$; $\mu_1 = 1.37$; $\mu_2 = 0.3$; $\mu 3 = 0.01$; $\gamma = 0.7$; $\gamma_1 = 0.7$; $\beta_1 = 0.5$; $\beta_2 = 0.4$; $\beta_3 = 0.4$; $E_{1_0} = 2$; $E_{2_0} = 2$.

The external parameters of the experiment were: $S_0 = 0.05055$; $O_{2_0} = 0.06$; $\alpha = 0.002$; $\alpha_1 = 0.02$; $\mu_0 = 0.004$; $\alpha_3 = 0.01$; $\alpha_4 = 0.01$; $\alpha_5 = 0.01$; $\alpha_6 = 0.01$; $\alpha_7 = 0.0001$.

The model covers the substrate-enzyme oxidation of ethanol to acetate, the tricarboxylic and dicarboxylic acid cycle, the glyoxylate cycle and the respiratory chain. Model (1)–(19) is improved as compared with the model used in [4], since it involves the formation of CO_2 in the Krebs cycle, which affects the running of the metabolic process, is also accounted for. Some parameters of our model are taken from [6].

Ethanol S entering the cell is oxidized by alcohol dehydrogenase E_1 to acetaldehyde S_1 (1) and then by acetaldehydrogenase E_2 to acetate S_2 (2), (3).

The acetate formed can either be involved in cell metabolism or exchanged with the external environment. In the model, this is accounted for by the level of acetyl-CoA. In the first stage of the Krebs cycle, acetyl-CoA and oxaloacetate S_8, generated in the Krebs cycle, through the citrate synthase reaction, produce citrate S_3 (4). Further, S_4-S_8 are formed successively in the stages (5)-(9).

The Krebs cycle in the model is represented only by those substrates that are involved in NADH reduction and phosphorylation: ADP→ATP. Acetyl-CoA converted through the chain to malate, represented in the model as intramitochondrial S_7 (8) and cytosolic S_9 (10). Malate can also be synthesized via another pathway involving the activity of two enzymes: isocitrate lyase and malate synthetase. The first catalyzes the cleavage of isocitrate to succinate, while the second catalyzes the condensation of acetyl-CoA to glyoxylate, yielding malate. The glyoxylate pathway is represented as an enzymatic reaction with the consumption of S_2 and S_3 and the formation of S_7. The parameter k_3 regulates the activity of the glyoxylate pathway (3), (4), (8). The release of S_7 into the cytosol is regulated by its level, which can be elevated due to S_9, causing inhibition of its transport involving protons of mitochondrial membrane ψ.

The generated malate S_9 is used by the cell for its growth: namely, for the biosynthesis of protein X (11). The energy for this process is provided by the ATP-ADP cycle.

The presence of ethanol in the external solution causes “aging” of the outer cell membranes, which leads to inhibition of the process. The inhibition also occurs due to the increased kinetic membrane potential ψ. The parameter μ characterizes cell lysis and washout.

The respiratory chain of a cell is represented in two forms: oxidized Q (12) and reduced q. For them, the integral of motion is realized $Q(t) + q(t) = const = L_3$.

The change in oxygen concentration in the respiratory chain is described by equation (13).

The intensity of the respiratory chain is dependen on the level of NAD^+ (14). Its high level leads to increased endogenous respiration in the reduced stage of the respiratory chain (parameter k_{15}). NADH accumulation occurs as a result of NAD^+ reduction at ethanol conversion and in the Krebs cycle. In the model, these variables obey the integral of motion $NAD^+(t) + NADH(t) = L_2$.

Thus, the level of ATP, generated in the redox reactions of the respiratory chain ADP→ATP, determines the intensity of the Krebs cycle and protein biosynthesis.

A kinetic membrane potential ψ (16) is formed during reduction reactions $Q \rightarrow q$ in the respiratory chain, It is consumed at substrate phosphorylation ADP→ATP in the respiratory chain and in the Krebs

cycle. Its increased level inhibits protein biosynthesis and the reduction reactions of the respiratory chain.

Equations (17) and (18) describe the activity of enzymes E_1 and E_2, respectively. Their biosynthesis (E_{1_0} and E_{2_0}) and inactivation in the course of the enzymatic reaction (n_1 and n_2) as well as any irreversible inactivation (α_5 and α_6) are considered.

Equation (19) describes the generation of carbon dioxide. Its release from the solution into the external environment (α_C) is taken into account. Its formation occurs in the Krebs cycle (5). Moreover, it replaces oxygen in the solution (13), thereby decreasing the activity of the respiratory chain.

The system (1)-(19) was studied using the Runge-Kuta-Merson method. The modes were analyzed when the system reached the asymptotic trajectory of the attractor. For this reason, the calculation time was taken to be 10^6. The solution accuracy was defined to be 10^{-12}.

Classical tools of nonlinear dynamics were used to study the model [14].

Results and Discussion

Using the developed mathematical model (1)-(19), we analyzed the dependence of the oxidative phosphorylation and ATP synthesis cycles on changes in the ATP dissipation value in cell metabolic processes. The phase-parametric diagram of the obtained attractors of the system was plotted for $\alpha_4 \in (0.01,0.026)$ (Fig. 3).

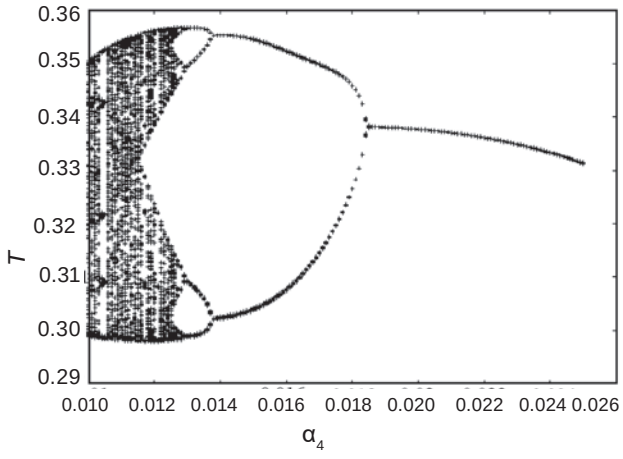

Fig. 2. Phase-parametric diagram of the system. The study of the dependence of the cycle of oxidative phosphorylation and ATP synthesis on the value of ATP dissipation affecting the cell metabolic processes: $\alpha_4 \in (0.01,0.026)$

When dissipation decreases, the cycle multiplicity changes – from stationary to a single autooscillatory – 1×2^0, then – successive doublings of the 2-fold period and the emergence of the chaotic mode of the strange attractor occur:$1\times2^0\rightarrow1\times2^1\rightarrow1\times2^2\rightarrow1\times2^x$ (Fig. 4).

The sequence of the complexity of the process cycle corresponds to the Feigenbaum scenario. The

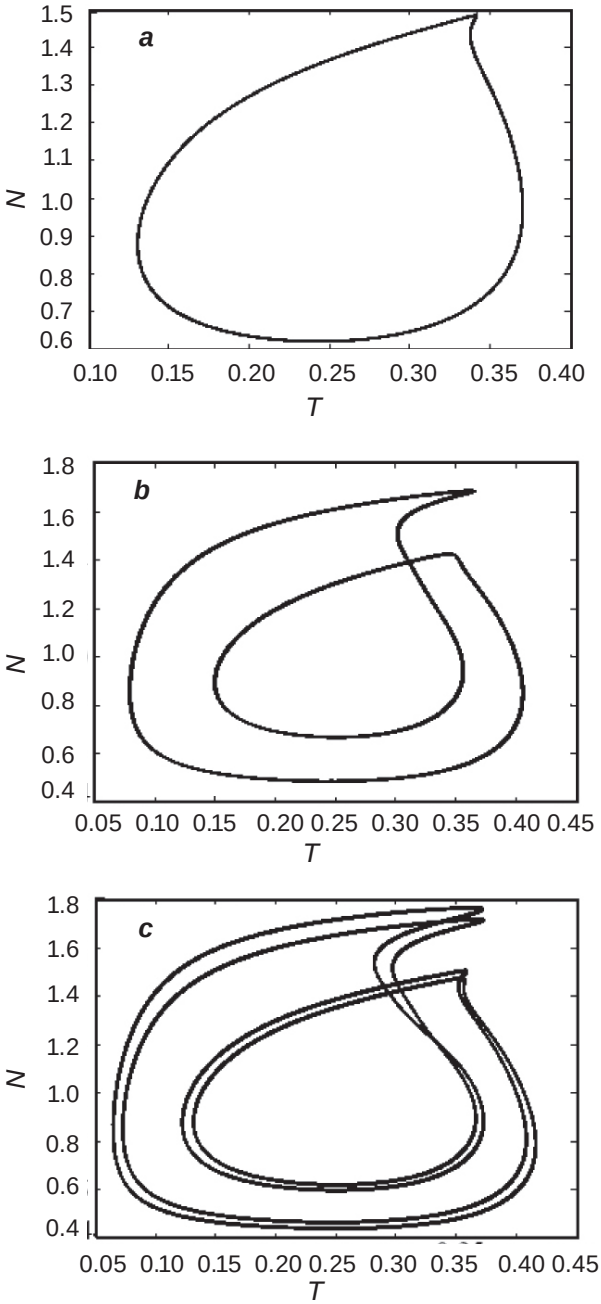

*Fig. 3. Phase portraits of the period doubling of the attractor of the system: **a** – 1-fold periodic cycle 1×2^0 ($\alpha_4 = 0.02$); **b** – 2-fold periodic cycle 1×2^1 ($\alpha_4 = 0.016$); **c** – 4-fold periodic cycle 1×2^2 ($\alpha_4 = .0135$)*

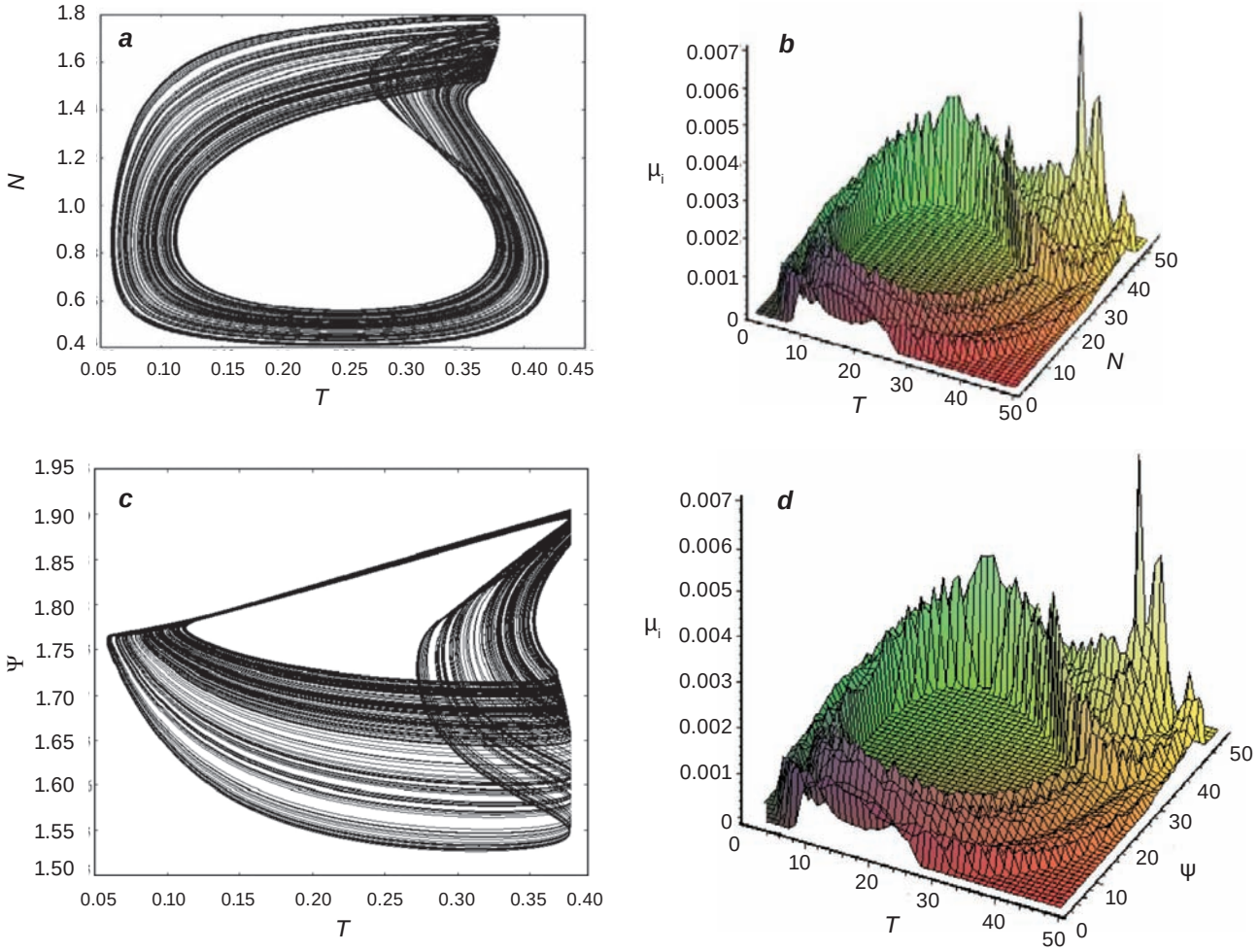

*Fig.4. Strange attractor of the system 1×2^x (α_4 = 0.011) t ϵ (10^6–10^6+10^5): **a** – projection of its phase portrait in (T, N) coordinates; **b** – histogram of the projection of the invariant measure μ_i of the attractor 1×2^x on the plane (T, N) t ϵ (10^6–10^6+10^5); **c** – projection of the phase portrait of the attractor 1×2^x in (T, Ψ) coordinates; **d** – histogram of the projection of the invariant measure μ_i of the attractor 1×2^x on the plane (T, N) t ϵ (10^6–10^6+10^5)*

projection of the phase portrait of the strange attractor in coordinates (*T, N*) is shown in Fig. 4, *a*, and in coordinates (*T*, Ψ) – in Fig. 4, *c*.

The invariant measure μ (i.e., μ(*P*) = 1) for the dynamical system $\varphi^t(x)$ was calculated, according to the Krylov-Bogolyubov theorem [15], for the found mode of the strange attractor 1×2^x and histograms of projections of this invariant measure on the phase plane were plotted - for variables (*T, N*) Fig. 4, *b* and variables (*T*, Ψ) Fig. 4, *d*. These histograms were chosen because it is the NaDH and Ψ variables that affect the functioning of the cell electron transport chain and thus ATP production via oxidative phosphorylation. NaDH realizes electron transport and the proton gradient Ψ is used to drive ATP synthesis. These components mainly determine the instability of the cycle of the oxidative phosphorylation process.

It is possible to restore an effective stable cell cycle by changing the cell's NaDH or Ψ level, upon the corresponding biochemical effect on these parameters.

By creating histograms of the invariant measure for other variables, we can also determine their influence on the stability of the biosystem attractor. In this case, the biochemical effect on the cell will be different. For our results we took number of points $N = 50^{10}$ and the time of solving is t ϵ (10^6–10^6+10^5).

Conclusions. In this work, the mathematical model of oxidative phosphorylation and ATP synthesis in the cell was developed. The invariant measure was calculated and histograms of projections of the invariant measure of the system variables most unstable in the chaotic mode of the model: NADH and Ψ were plotted. The components of the metabolic

process causing instability in cell self-organization: NADH and Ψ, which correspond to the mathematical model calculations, were identified. Recommendations on how to eliminate biochemically the chaotic mode and restore the stability of the cell life cycle were provided.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/ coi_disclosure.pdf and declare no conflict of interest.

Funding. 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 №0120U101347 "Noise-induced dynamics and correlations in non-equilibrium RC systems".

НЕСТІЙКІСТЬ ТА ІНВАРІАНТНА МІРА В МАТЕМАТИЧНІЙ МОДЕЛІ ОКИСНОГО ФОСФОРИЛЮВАННЯ І СИНТЕЗУ АТР КЛІТИНИ

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Досліджено процес окисного фосфорилювання і синтезу АТР клітини в рамках запропонованої математичної моделі. Знайдено сценарій виникнення автоперіодичних та хаотичних режимів у такій біосистемі в залежності від величени дисипації АТР. Розраховано інваріантну міру дивного атрактора та побудовані гістограми її проекцій на площині фазового простору системи. Запропоновано рекомендації як позбутися хаотичного режиму і відновити стійкість самоорганізації біосистеми клітини.

Ключові слова: самоорганізація, гістограма інваріантної міри, дивний атрактор, сценарій Фейгенбаума, метаболічні процеси, цикл Кребса, окисне фосфорилювання.

References

1. Nicolis G, Prigogine I. Self-Organization in Nonequilibrium Systems. From Dissipative Structures to Order through Fluctuations. Wiley, New York, 1977. 512 p.
2. Buzaneva E, Karlash A, Yakovkin K, Shtogun Ya, Putselyk S, Zherebetskiy D, Gorchinskiy A, Popova G Prilutska S, Matyshevska O, Prilutskyy Yu, Lytvyn P, Scharff P, Eklund P. DNA nanotechnology of carbon nanotube cells: physico-chemical models of self-organization and properties. *Mater Sci Engineer C*. 2002; 19(1-2): 41-45.
3. Prylutskyy YuI, Yashchuk VM, Kushnir KM, Golub AA, Kudrenko VA, Prylutska SV, Grynyuk II, Buzaneva EV, Scharff P, Braun T, Matyshevska OP. Biophysical studies of fullerene-based composite for bio-nanotechnology. *Mater Sci Engineer C*. 200; 23(1-2): 109-111.
4. Miller SL. A production of amino acids under possible primitive earth conditions. *Science*. 1953; 117(3046): 528-529.
5. Armiger WB, Moreira AR, Phillips JA, Humphrey AE. Modeling cellulose digestion for single cell protein. Utilization of cellulose materials in inconventional food production. New York: Plenum Press, 1979. P. 111-117.
6. Gachok VP. Strange Attractors in Biosystems. Kiev: Naukova Dumka, 1989. 236 p. (In Russian).
7. Grytsay VI, Musatenko IV. Self-organization and fractality in a metabolic processes of the Krebs cycle. *Ukr Biokhim Zhurn*. 2013; 85(5): 191-200.
8. Grytsay VI, Musatenko IV. The Structure of a Chaos of Strange Attractors within a Mathematical Model of the Metabolism of a Cell. *Ukr J Phys*. 2013; 58(7): 677.
9. Grytsay VI, Musatenko IV. A mathematical model of the metabolism of a cell. Self-organisation and chaos. *Chaotic Modeling and Simulation (CMSIM)*. 2013; 4: 539-552.
10. Grytsay VI, Musatenko IV. Self-organization and chaos in the metabolism of a cell. *Biopolym Cell*. 2014; 30(5): 403-409.

11. Grytsay V, Musatenko I. Nonlinear self-organization dynamics of a metabolic process of the Krebs cycle. *Chaotic Modeling and Simmulation (CMSIM).* 2014; 3: 207-220.
12. Grytsay VI. Lyapunov indices and the Poincare mapping in a study of the stability of the Krebs cycle. *Ukr J Phys.* 2015; 60(6): 561.
13. Grytsay V. Spectral analysis and invariant measure in studies of the dynamics of the Krebs cycle. *Chaotic Modeling and Simulation (CMSIM).* 2021; 1: 35-50.
14. Kuznetsov SP. Dynamical Chaos. Fizmatlit, 2001. 296 p.
15. Kryloff N, Bogoliouboff N. La Theorie Generale De La Mesure Dans Son Application A L'Etude Des Systemes Dynamiques De la Mecanique Non Lineaire. *Ann Math Second Ser.* 1937; 38(1): 65-113. (In French).