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SOME TRENDS IN MATHEMATICAL MODELING FOR BIOTECHNOLOGY

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The purpose of this publication was to show some trends of the development of modeling methods for biotechnology according to contemporary achievements in science and technique. Common approaches were outlined, some types of classification of modeling methods were considered, the role of methods of mathematical modeling in biotechnology in conditions of intensive development of information computer technologies was highlighted. The appropriate scheme of their interrelation was proposed. Several examples and mathematical models in three dimensions (1D, 2D, 3D models) were described respectively for processes in living objects at different levels of their hierarchical organization. In course of this research, the main attention was paid to some processes modeling in neurons, as well as their aggregates of different forms, including the cellular formation of glioma (1D, 2D, 3D brain processes models). Their consideration was begun with the models that had today only theoretical importance and was completed with a description of a model that might has practical application. The work was done after the analysis of approximately 250 current publications in fields of biotechnology, including the authors' original works.

Key words: 1D, 2D, 3D modeling, mathematical methods, information technologies.

Intensive development of computer facilities, information technologies and advanced training of scientists in the field of mathematical methods made it possible to apply increasingly complex methods for modeling in biotechnology; and this practice demonstrates a lot of advantages. Using modeling, the researcher can test well the structures of complex system and processes in it without invasion into this system [1]. Simulation can also be used in situations, when the system's behavior is not clear enough (models of "black box" or "grey box") [1]. Using some models, one can simulate the dynamic behavior of the system over a period of time [1]. Also, the methods of modeling permit to study the biotechnical system in cases, if invasion in it functioning is enough expensive or can damage the system by itself (in cases of biotechnical production, processes in living organism, and etc.) [1]. In our previous publications [1, 2] we analyzed a number of mathematical analytical methods for data processing in biotechnology, and outlined that some types of mathematic analysis have already become widely used: factor, dispersion, correlation, discriminant ones; as well as methods of classification, other methods of statistical data processing [1, 2]. Special attention we paid to some powerful mathematical methods used in biotechnology, like neural networks [3], cluster analysis [4], image processing [5]. In the format of this article it was impossible to observe the great volume of publications devoted to task solutions using contemporary methods of modeling. So, at the beginning of this article some general approaches were outlined; some principles of classifications of mathematic modeling methods were suggested. Than we tried to demonstrate our understanding of the place of mathematic modeling methods among other mathematic methods from the point of view of information computer technologies (ICTs); we suggested also an appropriate scheme of their correlation. Further some case studies were represented: some suitable mathematic models are suggested for the description of different processes in living objects of different levels of organization. We would like to suggested a few models of the brain or brain elements of different level of hierarchical organization. Respectively,

these models we ordered as models of different number of dimensions (D): 1D model, 2D model and 3D model. We started from some models that have theoretical importance for today only — we outlined some examples of modeling techniques and software tools that can be used to simulate cellular networks and systems. Than we described a model of glioma with forecasting of patients life expectancy; we hope this will be important for the practice.

Mathematical models in biotechnology: basic concepts. There were a lot of contemporary publications where are stated, that mathematical models are tools that we can use to describe the past performance and predict the future performance of biotechnological processes [6–75]. Methods of mathematic modeling could be applied to processes operating at many different levels, from the action of an enzyme within a cell, to the growth of the cells within a commercial scale bioreactor; these methods were widely used for the development of bioinformatics methods, for the newest biomedical electronic information systems elaboration [1, 11, 74, 76–142]. Mathematical models could be powerful tools in both fundamental research and applied research; for their development the newest mathematic methods were used usually [1, 2–5, 41, 60–62, 66–74, 76–77, 116]. Mathematical models were important tools in the optimization of the performance of biotechnological processes. There were numerical excellent publications in this sphere with the description of analysis of mathematical models' structure, demonstrated how they contain state variables, independent variables, operating variables and parameters, and etc. [1, 7–10, 13–16, 18–28, 34, 63, 64, 75, 80]. Such publications contained usually some case studies, in which, for example, the differential equations were used to describe the operation of a simple enzyme reactor, and etc. Sure, the real experimental results and results of observations were put in base of such models [1, 12, 17, 28–40, 72–74, 134–155]. These provided the basis for discussion of the various approaches that could be used in modeling, such as empirical versus mechanistic approaches, or structured versus unstructured approaches [7].

Classification of mathematic models. Great variability of the types of mathematical methods was developed during all period of this practice existence [1, 2–5, 41, 60–62, 66–74, 76, 77, 116]. Probably, according to the most general contemporary classification all models could be subdivided to 1 — physical, 2 — mathematical, and 3 — computer ones.

1 — Physical model, for example, engineers can elaborate like any device, or smaller copy of bioreactor for biomass cultures; in such a way its functional abilities might be checked.

2 — Mathematical models were developed as a set of mathematical expressions for description of biotechnological processes; the main abstractions and regularities of modeled processes have to be revealed carefully.

3 — Computer (or program) models meaned an algorithm and/or codes for the simulation (or imitation) of biotechnological processes.

Also, there were some attempts to group mathematical modeling methods for their classification. One such classification was done by the group of Ukrainian cybernetics who worked for biology in Kyiv, on 1970-th –1980-th: Piatigorsky B.Ya., Zaitman G.A., Cherkasky V.L., Chinarov V.A.(Kyiv, Ukraine, 1985) [1, 9, 10]. Groups of modeling methods are represented below according to their works as a number of alternative pairs (Fig. 1).

In one of more recent publication there were represented another classification, also based on contradictory pairs [7]. Types of models according to these authors were following (Fig. 2).

Because of fast progress in contemporary ICTs' spheres another types of classifications were possible as well. Below in this publication there are the results of authors' original research in modeling (mathematical and program ones as well) [1–5, 15, 16, 18–37, 60–66] and mathematical processing of biological data [134–155], as well as a brief review of some other authors works in modeling [6–8, 11, 37–57, 67–133].

Contemporary information technologies: from models to information systems. Practice of mathematic modeling in biotechnology is seen as traditional one nowadays. From the other side, our époque is characterized by extremely intensive development of ICTs that obtain numerous forms and manifestations. Our task was to find the links between traditional mathematic modeling and modern ICTs; the results of such studying were described before in [1]; they are shown also at Fig. 3.

At the center of picture "Mathematical modeling" was placed as an extremely important compartment of methods and knowledge in computer disciplines, which is considered classic today. Until the early 1990s — the time of intensive development of information computer technologis — mathematical modeling occupied a priority position. This compartment produces the source data, models, methods, and etc.; all these had found an

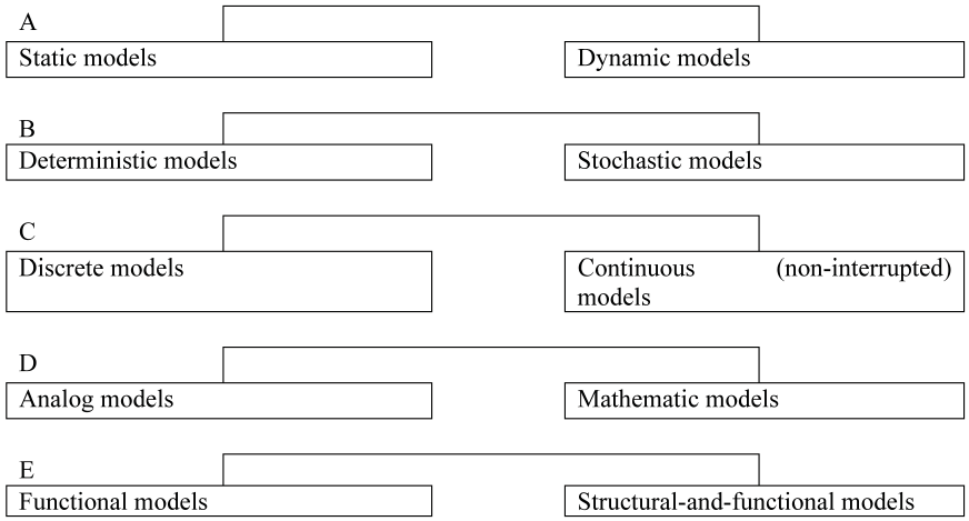

Fig. 1. **Classification of models for biological sciences:**
A, B, C, D, E are the different types — pairs of classification system groups according to [9]

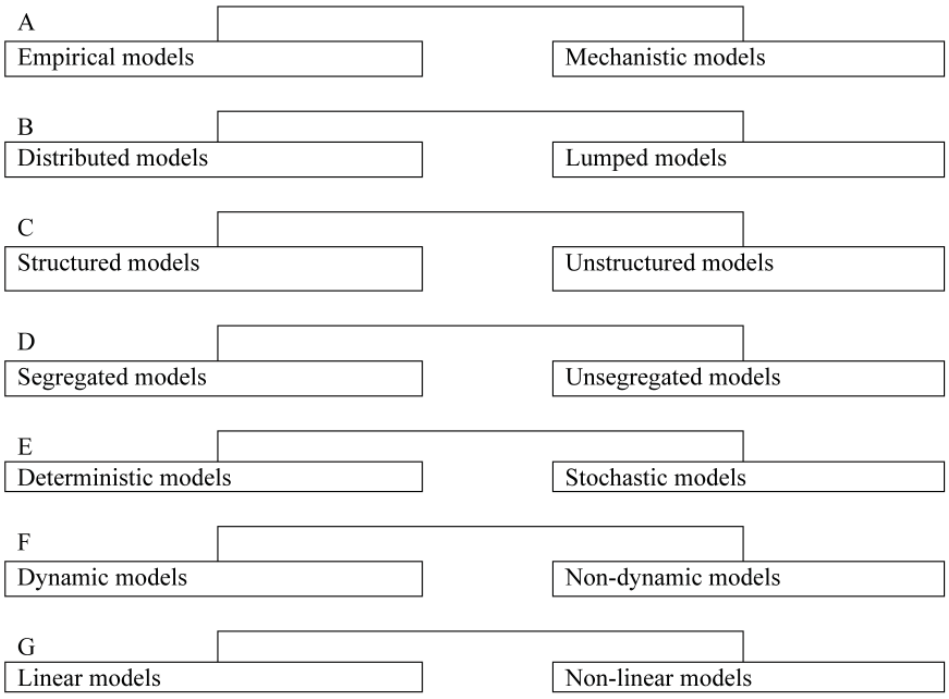

Fig. 2. **Recent classification of models for biological sciences:**
A, B, C, D, E, F, G are the different types — pairs of classification system groups according to [7]

application in practice, which is presented at figure as compartment "Technical application". Such practical application meaned elaboration of various mechanisms or devices, for example robots, expert systems, automatic devices, other computer-controlled systems.

Process of development of notion "Information computer technologies" and its correlation with notions "Databases" and "Mathematic modeling" might be demonstrated as few historical stages (Fig. 3).

1) Initially, for models that were created at the historic "Stage 1" not so much input data were needed; sometimes such data could be given even as a simple table representation on a sheet of A4 format.

2) At the "Stage 2" we showed the continuation of this historical process.

The amount of data that needed processing grew rapidly with time, and the input of "Mathematical modeling" began to present data structured in the form of simple databases (DB) (for example, using the first versions of DBase or FoxPro according to shown at (Fig. 3).

3) Due to the technical progress, increased power and speed of computers, the transition to personal computers (PCs) and the formation of networks, there were prerequisites that DB acquired their own increasing importance (Stage 3). With the time DB control systems have been so advanced and developed that many of the preparatory data operations became possible to be realized even before the data entered the part "Mathematical modeling". At the next step the level of development of input data operations became very high. This resulted in the "Information Technologies" developed with DB and included in them; and this structure could be isolated in a separate compartment as shown at figure for Stage 3. At Stage 3 of information systems (IS) development, the subset "Information technologies" included "databases".

Today we can state that at the current level of information computer technologies development the different methods and technologies coexist successfully: older in time of their invention as well as the latest ones. Their significance and role in the modern world is determined not by the time of their creation, but how much they are needed in practical human activity.

Description of some mathematic models. So, the methods of mathematic modeling could be used nowadays for the solution of different tasks in biotechnology. Such practice began even from the first steps of computer use; in Kyiv, Ukraine there were the works of 1950-60-th years of cybernetics who worked for biology: Amosov N.M., Hlushkov V.M., Kostyuk P.G., and later — representatives of their scientific schools Shkabara E.A., Ivanov-Muromsky, Piatigorsky B.Ya., Onopchuk Yu.M. and many others [1, 10, 11]. It was not possible to list all tasks solved by these representatives of Kyiv scientific schools of cybernetics during few decades until XXI century. The numerical models of different types of processes in nervous systems, in cells and cell aggregates, biological objects, biological organism functioning, models of experimental biotechnological equipment, and many others were elaborared.

Intensive works in this direction were carried out through over the world. For example, in publications [1, 6–9] there were a lot of other models' descriptions. In work of [7] there was a mathematical model developed for enzyme reactor consisted on a reservoir containing a substrate solution which circulated through the column with immobilized enzyme; the use of this model for the estimation of enzyme kinetic constants was demonstrated. Also there was a structured metabolic model developed in 1984 for the growth studying of a single Esherichia coli cell and etc. Authors in [6] outlined modeling techniques and software tools that could be used to simulate cellular networks and systems. First, they presented

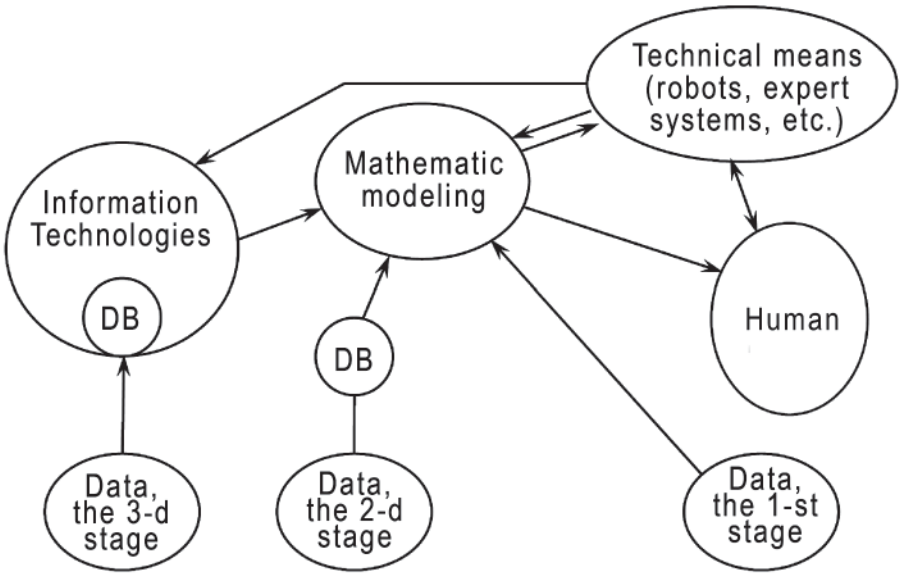

Fig. 3. **Development of notion "Information computer technologies" and their correlation with notions "Databases" and "Mathematic modeling" [1]**

a review of stoichiometric models and Flux Balance Analysis and then discuss continuous deterministic models composed of ordinary differential equations. Next, they presented the continuum descriptions, often used for the simulation of model signal transduction and gene expression programs with stochastic models. Lastly, they discussed the application of qualitative modeling tools and techniques such as fuzzy-logic and petri nets to the problem of modeling complex intracellular networks. For the illustration of abovementioned basic concepts a few case descriptions were suggested.

1D mathematic modeling of electrical currents in biocells. Electrical signal transmission through myelinized fiber. The excitation spreading in myelinized fibers is seen as classic example of 1D mathematic modeling of electrical signals transmission in nervous system. If the maximal action potential significantly exceeded the threshold and if the front of potential rise is sufficiently narrow, the potential increase was very fast. It could be assumed that the excitation transfer occurs from one Ranvier node to the nearby node and subsequent nodes influenced only slightly one on another. This task solution leaded to a problem with distributed and lumped parameters [13, 14]. In case suggested below it was supposed that the action potential is many times greater than the threshold, and the front rise of potential was equal to 1.5–2 intervals between the Ranvier nodes [13, 14]. So, the intervals between the nodes formed the distributed system and the potential change in it could be described by the equation

$$\frac{d^2\varphi(\xi)}{d\xi^2} + vRC\frac{d\varphi(\xi)}{d\xi} - Ri(\xi) = 0,$$

if $i = 0$. For simplicity there were used dimensionless variables, namely, the coordinates are measured in intervals L, and the time t — in units of R_1C_1. For such cases the equation for the potential at intervals looks like much simpler:

$$\frac{\partial\varphi}{\partial T} = \frac{\partial^2\varphi}{\partial X^2}, \qquad T = \frac{t}{R_1C_1L^2}, \qquad X = \frac{x}{L}. \quad (1)$$

Lets also suppose that at time $T = 0$ the excitation started at the node located in point $X = 0$ due to the mechanism of membrane potential changes in it, and according to (2).

$$\varphi(2, T) = \varphi_0(T) \quad (2)$$

Electrical current generated by this node initiated processes in the next node. So, charging capacity of myelinized interval and capacity of the next node located at $X = 1$. Then there were assumed that processes at the next node (charging node $X = 2$) did not occur until the time of stimulus "hopping" at excitation node $X = 1$. Therefore for boundary conditions at $X = 2$ it was possible to assume that

$$\varphi(2, T) = 0 \quad (3)$$

Presence of lumped capacitance C_2 at Ranvier node and at the point $X = 1$ was reflected by the simple expression

$$\frac{C_2}{C_1L}\frac{\partial\varphi(1,T)}{\partial T} = \frac{\partial\varphi(X,T)}{\partial X}\mathrm{I}_{x=1+0} - \frac{\partial\varphi(X,T)}{\partial T}\mathrm{I}_{x=1-0} \quad (4)$$

It was assumed that at point of process start

$$\varphi(X, 0) = 0. \quad (5)$$

This may be in case of significant difference between the threshold and action potentials, and the presence of small initial charge on the fiber had not significant influense on results.

The task was solved under the condition $0 < T < T_L$, where T_L — magnitudeless dimensionless time of excitation "hopping" from one node to another. The purpose of task was to calculate the time of excitation spreading for the pulse velocity, proportional to T_L.

Because of the lumped capacitance at the point $X = 1$ task should be divided into two parts: in the domain $0 < X < 1$, and in $1 < X < 2$.

Lets set that

$$\varphi(1, T) = \psi(T). \quad (6)$$

Then the solutions should be substituted into equation (4) and from it was possible to determine the unknown function $\psi(T)$. Solution of equation (1) in the domain $0 < X < 1$ with the boundary conditions (2) and (6) and the initial condition (5)

$$\varphi(X,T) = 2\pi\sum_{n=1}^{\infty} n\sin(n\pi X)e^{-n^2\pi^2T}\int_0^T e^{n^2\pi^2\xi}[\varphi_0(\xi) - (-1)^n\varphi(\xi)]\dot{a}\xi. \quad (7)$$

In domain $1 < X < 2$ with boundary conditions (6) and (3) and the same initial condition we get

$$\varphi(X,T) = 2\pi\sum_{n=1}^{\infty} n\sin(n\pi(X-1))e^{-n^2\pi^2T}\int_0^T e^{n^2\pi^2\xi}\varphi(\xi)\partial\xi. \quad (8)$$

For further calculations one needed to know the type of function $\varphi_0(T)$, i.e. the change of working node potential in time. We approximated this dependence by a function

$$\varphi_0(T) = \frac{\varphi_2}{T_1} T, \tag{9}$$

where φ_2 — maximum capacity; T_1 — rise time capacity. Because of abovementioned reasons, the initial value of this function can be set equal to zero.

As follows from the experimental data according to [9], such approximation is not far from the truth. Substituting (7), (8) and (9) into (4), we obtain the equation for unknown function $\psi(T)$. For its solution it is convenient to use the Laplace transform. Omitting the intermediate steps, we give the final expression for Laplace transform

$$\hat{\psi}(p) = \frac{\frac{\varphi_2}{p^2 T_1} \sum_{n=-\infty}^{\infty} \frac{(-1)^n}{p + n^2\pi^2}}{\frac{C_2}{C_1 L} + 2\sum_{n=-\infty}^{\infty} \frac{1}{p + n^2\pi^2}}. \tag{10}$$

Function $\psi(T)$ had a pole of second order at point $p = 0$, stipulated by the multiplier $1/p^2$, and a number of poles of the first order, determined by the roots of equation

$$2\sum_{n=-\infty}^{\infty} \frac{1}{p + n^2\pi^2} = -\frac{C_2}{C_1 L}. \tag{11}$$

This equation had real roots. Roots of the equation are defined as the point of intersection of some relative curves with the horizontal line drawn at the level $-C_2/C_1L$. All the roots of (11) are negative and layed to the left of $n^2\pi^2$. We denoted the found roots p_0, p_1, p_2, …, p_k, …

Knowing the poles of $\hat{\psi}(p)$ function, it is easy to do the inverse Laplace transform:

$$\psi(T) = \frac{\varphi_2}{T_1}\left[\frac{1}{2}T - \frac{C_1 L + C_2}{4C_1 L} - \frac{1}{2}\sum_{k=0}^{\infty} \frac{\frac{1}{p_k{}^2}\sum_{n=-\infty}^{\infty} \frac{(-1)^{n_e p_k T}}{p_k + n^2\pi^2}}{\sum_{n=-\infty}^{\infty} \frac{1}{(p_k + n^2\pi^2)^2}}\right] \tag{12}$$

The time of excitation "hopping" T_L from one node to another is determined by condition that at time $T = T_L$ the node potential at point $X = 1$ should reach the threshold

$$\frac{\varphi_* T_1}{\varphi_2} = \frac{1}{2}T - \frac{C_1 L + C_2}{4C_1 L} - \frac{1}{2}\sum_{k=0}^{\infty} \frac{\frac{1}{p_k{}^2}\sum_{n=-\infty}^{\infty} \frac{(-1)^n}{p_k + n^2\pi^2}}{\sum_{n=-\infty}^{\infty} \frac{1}{(p_k + n^2\pi^2)^2}} \tag{13}$$

Because the true dimensional hopping time from one node to another is $R_1 C_1 L^2 T_L$, and the distance between nodes L, then velocity of the pulse is

$$v = \frac{1}{R_1 C_1 L T_L}. \tag{14}$$

As an example, lets compare with physical processes at the frog myelinized nerve fiber described in work [14]. In cases of some known spread values, we took the average value. So, we assumed that

$L = 2\cdot 10^{-3}\ m,\ R_1 = 1{,}4\cdot 10^{10}\ Ohm/m,\ C_1 = 1{,}3\cdot 10^{-9}\ F/m,\ C_2 = 10^{-12}\ F, \varphi_2 = 0{,}116\ V, \varphi_* = 0{,}015\ V$

At the end of calculations lets study two cases: the front widths of the intervals were 1.5 and 2, i.e. when $T_1 = 1{,}5T_L$ and $T_1 = 2T_L$. For the case $T_1 = 1{,}5T_L$ the calculation gave the speed $v = 29\ m/s$. For $T_1 = 2T_L$ we obtained $v = 21\ m/s$. From other side, the experimentally measured value of velocity is 23 m/s. So, close values in all these cases demonstrated good adequacy of performed and simulations as well.

2D modeling of matrix of bionic element in biotechnical system. Experimental study of the structure and function of neurons in the brain and other cells is an important area of brain research [15–17] including researches with fluorescent markers as well as biotechnology during the last decades. One interesting way of further carrying of such investigations is a construction of biotechnical systems where the technical part and biological one (implants, cultured samples etc.) were combined. Such combination have good prospects for their use for organism damage corrections, for disabled peoples cure, and etc.

Despite the fact that the experiments in this area of science are extremely labor-intensive, high-tech and expensive, the number of Ukrainian researchers still keep them now in collaboration with foreign scientists [37–40]. Among Ukrainian researchers several research groups perform optical registration on the cells of various tissues and single cells [38–40]. All such studies have to be carried out under the control of luminescent, confocal microscopes using fluorescent markers, in our experiments — primulin and bis benzimid [15–17]. Tracking the processes during experiments performed the sets of digital pictures recorded in the computer memory. The sources of experimental data that were taken into account for modelings — electrophysiological experiments (patch-clamp, voltage clamp, and others [13, 14]. Results of such experiments

were combined with optical ones in attempts to construct suggested 2D model — our observed biotechnical system. Briefly, the primary relative 2D physical model for this task was following. The samples of brain neurons were inquired into the observed biotechnical system as rectangular 2D plate with cultured brain neurons constructed as 2D matrix. Taking as the base the results of electrical and optical properties of natural studied brain neurons, we developed computer models for 2D neuronal matrix (biotechnical system) with properties of memory and symbols coding.

Physical and biochemical nature of 2D matrix from bionic elements. In base of original model (version of 2-dimentional network from brain neurons) experimental results described in our previous articles are put [15–17]. The sense of registered phenomena [17] was in the fact, that input signal changes of optical properties of the neuron (luminescence of neuron) become more intensive in case of neuron excitation. Other results that were taken into account during modeling were the results of transmembrane electric currents studying in experiments with patch-clamp, voltage-clamp, and etc. [13, 14]. Basing on these facts the 2D matrix as our model was elaborated. This matrix may be imagined as an abstraction of one-layer cell culture where neurons are ordered as it was shown on Fig. 4; the signal could be transmitted from cell to cell. This abstract construction has to be incorporated into the electric circuit with measuring and information storage devices described in numerical manuals (Fig. 4). Such system was biotechnical-one, constructed using principles of bionics; some laboratories of the world reported about such constructions [1]. Developing program model, we based on abstract supposion of 2D neuron matrix existing. Schematically it is suggested below.

At the next step we would like to elaborate a program model of this neuronal matrix that was called "quasi screen" (Fig. 4) this abstract

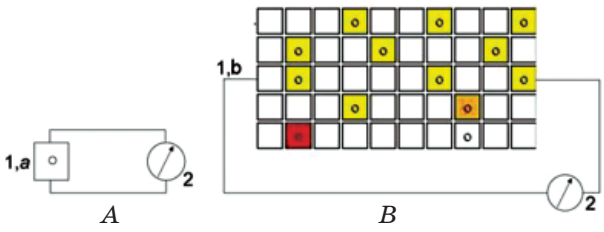

Fig. 4. **Biotechnical system as union of bionic element (*1*) and electronic element (*2*):**
1, A — for one neuron or its fragment;
1, B — for 2D neuron matrix

neurons there were ordered on 2D matrix. Simultaneously the screen pixels have been brought into compliance with these abstract neurons. All these stages of our investigations were done, and results were already published in different scientific and technical journals [15, 16]. Further stages according to our plans were following: 1- simulation of 2D "quasi-screen" functioning (model 1), and elaboration of program for the simplest symbols coding at such screen (model 2). Obtained results were suggested below.

Description of a "quasi screen" with bionic elements for biotechnical system. Probable "quasi screen" with bionic elements for biotechnical system may be imagined as 2D neuron matrix on plastic plate with cultural brain neurons in dissociated culture incorporated into electric circle with standard measuring and data stored devices. 2D neuron matrix may be imagined as a model like chessboard with alternating rows and columns that separate the cells which contain optically active elements. The structure of such a screen we described previously in details [15]. For our model we assumed that in some cells of this screen there are bionic photosensitive elements [15].

Assumptions of the model. When designing a model, we made the following assumptions.

1) Each screen pixel can be in 3 states, corresponding to 3 states of natural neuron (quiet, excited and refracter state of neuron). These 3 states were coded by "red", "yellow", "achromatic" colors respectively.

2) Also, a pixel could be described by three-phase model. Nature of these phases also corresponded to quiet, excited and refracter state of neuron.

3) The demonstrational velocity of the model has been increased 60 times: one minute of real processes in nature (as recorded in the experiment), corresponds to 1 second model.

4) Image coding it was possible to realize by establishing of different color points pattern in any set time interval.

As it was mentioned above, the light-sensitive elements of "quasi screen" were bionic elements with variable optical properties. According to our experiments these bionic elements may be following.

1) complex protein molecule and molecule optically active substance (fluorochrome);

2) "luminescent" neurons described in our article [17].

Our model was designed for the "screen" where optically active elements are the neurons with fluorochrome molecules inside. We have

developed a model based on dynamic changes in the optical characteristics of the neurons that we described previously in [17].

Dynamics of optical neuron characteristics changes in screen matrices. According to the results of the experimental neuron reaction studying, the receipt of the excitation signal can be represented as three consecutive phases that have their physical, biochemical and physiological sense (Fig. 5).

Vectors mean transition of the system from one state to another. Vertices of the triangle are three states in which the system can be (Fig. 5). These three states on the model were colored with white, red and yellow colors. Respectively,

– Top 1 corresponds to described phase 1 and 4 (achromatic).

– Top 2 corresponds to phase 2 (red).

– Points at vector 2–3 means transition (yellow, orange).

– Top 3 corresponds to phase 3 (achromatic).

This model 1 demonstrated the activity of "quasi screen" with neurons for the case when activated signal were inputted to active element at the left top of neuronal matrix and than moved to the right bottom angle. We supposed that each active element of the screen may be activated with further relaxation. Below we described these phases of activation and deactivation of each element.

1) The first phase of bionic element activation in time moment t_0, before activated signal was inputted (Fig. 5). Moment t_0 is characterized by signal amplitude A=0, fluorescence intensity was going to zero (E_0). Such pixels were achromatic at our model (Figs. 4, 6–8).

2) The second phase of bionic element excitation was at time moment (t_1). The phase was depicted at Fig. 5 as point 2. Interval t_1-t_0 =20 seconds. During system transition from the phase 1 to phase 2 the amplitude of activated signal — electrical current growed to the maximum $A = A_{max}$. Pixel luminescence was maximal (E_{max}). At model the neurons of this phase were marked by red color (Fig. 4, 7, 8).

3) Additional points were characteristic (middle points) for the excitation of bionic elements at time moment ((t_2, t_3) (depicted on Fig. 5 as point at vector between 2 and 3). Interval t_2-t_0 = 30 seconds and time points near it. At these time points the amplitudes of activated signal (electrical currents) are going to decrease (bionic element luminescence is decreased) $A = A_{min}$. Pixel luminescence decreased to minimal values (E_{min}). At model elements of this phase were marked by yellow and orange depending on current amplitudes and intensity of luminescense (Figs. 4, 7, 8).

4) The fourth phase of bionic element activation was at time moment t_4. Interval t_4–t_0 = 180 seconds. The phase was characterized by signal amplitude (electric current) A = 0, luminescence intensity was going to zero (E_0). These elements were achromatic at model too (Fig. 6).

At the "screen" at Figs. 6–8 the bionic elements were depicted by the circles at defined positions on screen matrix. This arrangement of bionic screen elements was determined by conditions in which the existence of bionic elements is possible under the experimental conditions. The initial view of the model and the initial step of the program was shown at Fig. 6.

The next figure demonstrated the model at 101th second from process start. It was possible to see that one element might be at the second phase; some other elements were at phase number three, and so on.

At the last figure there were demonstrated the program work at 120th second from process start. One can see here that all elements moved gradually, after specified period of time, from

Fig. 5. **Each pixel of the screen works by three-member cycle**

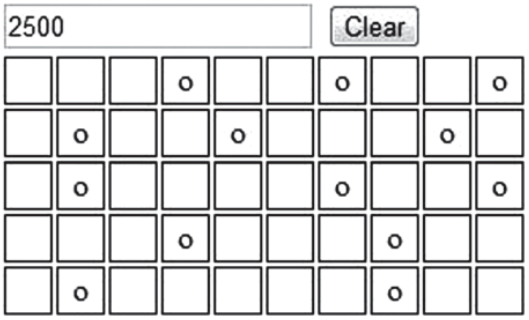

Fig. 6. **Initial phase**

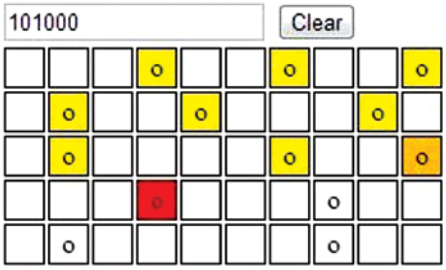

Fig. 7. **Working model at 101th second from process start**

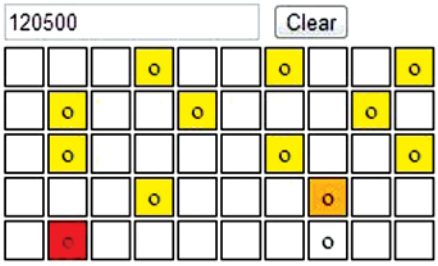

Fig. 8. **The final phase**

one phase to another. It means that activated signal moved from the upper left angle to the bott.

In developed original model of this biotechnical system two figures: triangle and circle can be coded. Systems which may be described in such ways potentially are the systems with "memory", if system can stay in some of states longer than in other states. Thus, the proposed model could be used for modeling the "screen" with elements that have properties of memory.

Model algorithm. Model described above was abstract and basic. Its algorithm was given on Fig. 9.

So, in such a way we tried to make a model of coupling between transmembrane electrical currents and their visualization using fluorescent drugs. Taking as the base the results of electrical and optical properties of natural brain neurons studying we develop computer models for 2D neuronal matrix (biotechnical system, "quasi screen") with properties of memory and possibilities of symbols coding. Program model of electrical signal propagation (and, respectively, information signal propagation) in this biotechnical system was elaborated.

3D model: mathematical model of estimation of hypoxia development in brain gliomas. As it was noted in our previous publication [1], the state of hypoxia in tissues (the brain in particular) can occur dye to the low oxygen concentration at altitudes, due to diseases or metabolic disorders, and etc. The development of tumors of the brain — glioma — also leads to the development of hypoxic phenomena. The study of these phenomena were done by Prof. Onopchuk Yu.M. (Glushkov Instituite of Cybernetics, NAS of Ukraine, Kyiv) and researcher Guzhavskaya N.V. (Institute of Neurosurgery, NAS of Ukraine, Kyiv) [31].

Estimating the degree of tumor influence on organism, researches were faced a number

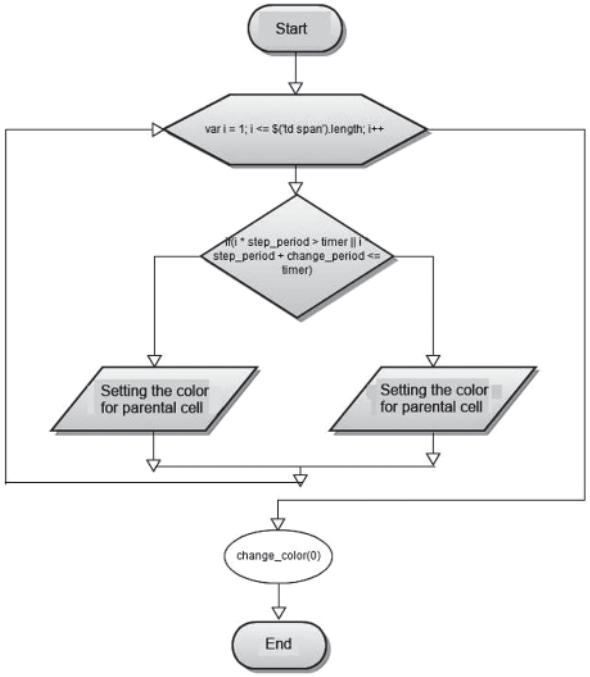

Fig. 9. **Algorithm of basic model for electrical signal linear propagation in 2D neuron matrix**

of problems that they tried to solve by analyzing the clinical and laboratory data obtained during the patient examination. Based on these data, they would determine how much the initial loading caused by the tumor affects the patient life expectancy in the catamnesis, how to predict the possible time intervals of the tumor recurrence, the possibility of complications during the operation and in the early postoperative period. The process of tumor development in organism was considered as an stochastic one, although it is often preceded by functional changes in the organism, caused by the influence of adverse and extreme external environmental conditions, in which the vital activity of the organism was carried out. Therefore, the methods of the theory of reliability of complex systems were used to estimate the tumor pressure on the organism and the degree of risk

to patient's health. Consequently, the refuse of the system from functioning is associated with the achievement of the load function S (t), which reflects the degree of tumor influence on organism, a certain boundary level S (t). Naturally, the effectiveness of conservative or surgical treatment can be estimated using the scale [0, S(t)].

First of all, let's observe the model of clinical data of patients with brain glioma. When a patient arrived to hospital for treatment, a number of clinical indices of his condition were determined. Among the most important were: the degree of malignancy of the tumor (indicator f_1**), tumor localization (f_2**), the presence of mediastinal structures of the brain displacement (f_3**), the presence of perifocal edema (f_4**), tumor density (f_5**), the presence of cysts formation (f_6**), the type of disease course (f_7**), the severity of general brain symptomatic (f_8**), the severity of the focal symptomatic (f_9**), the severity of stagnation in fundus (f_{10}**), the tumor's consistency (f_{11}**), the connection of the tumor with main vessels (f_{12}**). Most of these indices were determined by tomographic, laboratory and exclusive research.

The values of each of these functions (f_i**, i=1,12), which significantly affected the condition of patient with brain gliomas of different degrees of malignancy. They determined the functional capabilities of organism in life processes realisation, and they can be called a discrete set. We can assume that this value ws equal to:

M (f_1^{**}) = 1, if gliomas of the first degree were detected,
2, with gliomas of the second degree,
3, with ependymomes, gliomas of the third degree,
4, with gliomas of the fourth degree.

Location of the tumor was enough important. Therefore, we estimated M (f_2^{**}) as follows:

M (f_2^{**}) = 1 — convectional localization, forehead, crown, temporal,
3 — damage of medial structures,
4 — subcortical localization.

Tomographic studies made it possible to estimate the region of values M (f_3^{**}):

M (f_3^{**}) = 0 — shifts were absent,
1 — presence of brain median structures shifts, up to 4 mm,
2 — brain median structures shifts from 4 mm to 7 mm,
3 — brain median structures shifts from 7 mm to 10 mm,
4 — shifts were more than 10 mm

In the same way the area of values of function M (f_4^{**}) and M (f_5^{**}) was estimated:

M (f_4^{**}) = 0 — if perifocal cerebral edema is 1–1.5 cm or it was absent,
1 — diameter of perifocal edema was 1.5–2 cm;
2 — perifocal edema was 2–3 cm,
3 — edema was 3–4 cm.

M (f_5^{**}) = 1 — tumor density was 15–20 conventional units (c.u.)
2 — tumor density was 20–25 c.u.
3 — tumor density was more than 25 c.u.

Indicators of functions f_6-f_{11}** were important for the evaluation of brain tumor loading on organism. Clinicians defined the set of their values as follows:

M f_6^{**} = 0 — cysts were absent,
1 — overwhelming was present,
2 — necrosis, cysts were present,

M f_7^{**} = 1 — the consistency of the tumor was soft,
2 — consistency of the tumor was dense,
3 — tumor was chalked.

A number of indicators used for the estimation of the quantitative value of tumor loading were determined by doctor indirectly, exclusively, in the process of patient examination. It was stated that functions f_8^{**}, f_9^{**} and f_{10}^{**} may have two values "0" or "1".

M (f_8^{**}) = 0 — there was no general brain symptomatology,
1— symptomatology was followed.

M (f_9^{**}) = 0 — focal symptomatology was not observed,
1 — symptomatics was present?

M (f_{10}^{**}) = 0 — stagnation on the fundus was absent or there was a moderate stagnation,
1 — stagnation on the fundus was clearly expressed.

The indices f_7^{**} and f_{12}^{**} were linked with possible influence on functional changes of the whole organism:

M (f_{11}^{**}) = 1 — epileptic type of disease,
2 — hypertensive type of disease,
3 — vascular type of disease.

M (f_{12}^{**}) = 0 — vessels were immured in a tumor,
1 — main vessels did not belong to the tumor,
3 — main vessels were loosely soldered.

The influence of tumor on human organism studied only through clinical parameters, could be estimated by a linearly weighted function:

$$F^{cl} = \sum \delta_i * f_i, \quad (1)$$

where δ_i were coefficients of importance of some indices in the system of organism estimation, which could be determined as a result of factor analysis of the data. In general, δ_i was taken into account during the construction of the sets M (f_i, i=1,12), and therefore in the simplest case we could assume that

$$F^{cl} = \sum f_i^{cl} \quad (2)$$

Models of laboratory data of patients with brain glioma. The development of a malignant tumor of different nosology required the strengthening of the circulatory system functions in places of tumor localization, which supplied oxygen to the cells of the brain, enzymes and other essential substances for vital activity. Therefore, for the estimation of the degree of tumor influence on the systemic states of the organism, it was necessary to take into account the parameters of laboratory examinations of patients. In the practice of neurosurgical clinics among the most important laboratory indices were:

f_1^* — severity of hemoglobin content in blood,
f_2^* — severity of leukocyte contents in blood,
f_3^* — severity of sugar abnormalities in blood,
f_4^* — violation of the level of the prothrombin index,
f_5^* — violation of fibrinogen content.

The weight of these violations was estimated by the ball system, which forms the values of functions fi, i = 1,5.

M (f_1^*) = 1, if Hb <= 130 g/l,
2, if Hb > 130 g/l;
M (f_2^*) = 1, if 0 <= leukocytes <= 4 (*10^9 /l),
2, if leukocytes >4 (*10^9 /l);
M (f_3^*) = 1, if 0 < sugar <= 4 mmol/l
2, if sugar >= 6.6 mmol/l.

The authors denoted the prothrombin index as PI

M (f_4^*) = 1, if PI <= 80 (%),
2, if 80 <= PI <= 100,
3, if PI >100.

The authors denoted the fibrinogen through F.

M (f_5^{**}) = 1, if F<= 3 g/l,
2, if 3 <= F <= 4 g/l,
3, if F > 4 g/l.

The data of laboratory tests of patient were used for the estimation of tumor influence on organism state according to laboratory indices:

$$F^l = \sum f_i^l \quad (3)$$

and complex influence of clinical and laboratory indices:

$$F = F^{cl} + F^l = \sum f_i^{cl} + \sum f_i^l \quad (4)$$

Thus, when determining the limiting value of the tumor load on human organism using the linear regression equation (4), we used the clinical and laboratory data of the patients of the neurosurgical clinic. The analysis of estimations of loading demonstrated that after the reaching of the limit value S, equal to 18 points, 421 patients (58%) had a life expectancy of about 3 years in catamnesis. 300 people have lived less than 3 years — the loading of their tumor was less than 18 points. Statistical data analysis demonstrates that obtained data were reliable ($P < 0.01$). For people who lived in catamnesis up to 15 months, the average tumor loading was 18.03 ± 0.05 points, from 15 months to 3 years — 18.15 ± 0.12 points, from 3 years to 5 years — 17.07 ± 0.03 points, and more than 5 years — 16.04 ± 0.02 points. Thus, an essential correlation of value of tumor loading with the duration of life in the catamnesis was found (Fig. 10).

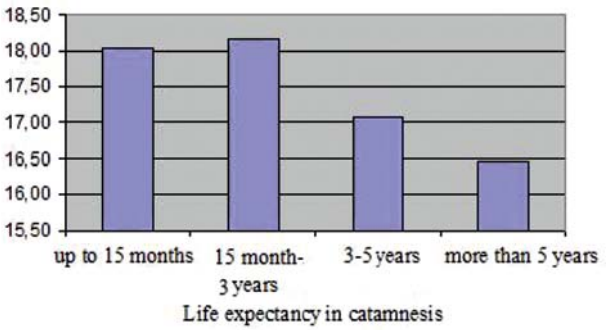

Fig. 10. **Life expectancy depends on the size of the tumor load**

For patients with relapses of disease in catamnesis up to 15 months, the average tumor load was set at 18,18 ± 0,1 point (IV), from 15 months to 3 years — 18,17 ± 0.06 points (III), from 3 years up to 5 years — 16.17 ± 0.3 points, more than 5 years — 17.6 ± 0.42 points. For patients with relapses of the disease in catamnesis, 179 people (56%) had a load of more than 18 points, 139 people (44%) — below 18 points. The differences were statistically significant ($P < 0.05$). Thus, it can be argued that value of tumor load on organism, found basing on clinical and laboratory data of patient in hospital, substantially influences on the possibility of tumor relapses. The calculation of tumor load on organism according to formulas above demonstrates that patients with a load of 19.48 ± 0.2 points had complications during the surgical operation; the load of patients

without operational complications was 16.86 ± 0.43 points.

Clinical and laboratory data of patients examination in the early postoperative period gave a possibility to found that complications in this period had patients whose load in the preoperative period was 18.74 ± 0.06 points, while for patients without complications — 17.35 ± 0.04 points . It should be noted that among patients with a load above 18 points, 39% had no complications in the postoperative period. The average load of the tumor on organism depending on the group of glioma demonstrated that at stage I of malignancy the average load was set at the level of 14.9 points, at the stage II — 16.14 points, at stage III — 18.75 points, and at stage IV — 19.08 points (Fig. 11).

The analysis of the data obtained using linear regression about the value of tumor load on organism demonstrated a high correlation with the Karnovsky index, which is used for the estimation of disease severity (Table).

Thus, the use of linear regression method for the processing of clinical and laboratory data of patients with brain gliomas allowed us to determine the limit value (18 points) of the tumor load on organism; and in each case of the disease permitted to plan an individual strategy for patient treatment.

Thus, in present publication the analysis of some ways of modeling methods development for biotechnology according to contemporary achievements in science and technique was done. At the beginning of this article the general approaches were demonstrated, some types of classifications of modeling methods were observed. Previously we outlined some types of mathematic analysis widely used for modeling purposes: factor, dispersion, correlation, discriminant ones; as well as methods of classification, other methods of statistical data processing. Special attention it was necessary to pay to such powerful mathematical methods used in biotechnology as neural networks, cluster analysis, and image processing. The role of mathematic methods modeling for biotechnology in present époque of information computer technologies intensive development was studied and appropriate scheme of interrelation of all these spheres was suggested. Further in our article some case studies are given; as well as some mathematic models developed for processes in living objects of different levels of hierarchic organization. Actually, the models for objects of 1D, 2D, 3D cases were suggested. In course of this the main attention was paid to some processes modeling in neurons as well as in their aggregates of different forms, including glioma of the brain. Starting from the models that have only theoretical importance for today, we suggested 1D and 2D models for some processes at neurons. In 2D model of neuronal matrix we tried to make a model of coupling between chemosensitive transmembrane electrical currents and their visualization using fluorescent drugs taking as the base the results of electrical and optical properties of natural brain neurons studying. Program model of signal propagation and symbols coding in this biotechnical system was done as well.

In present article we outlined modeling techniques to simulate neuronal processes not for single neurons or their 2D networks and systems only. As an example of 3D modeling we suggested the model of glioma with its analysis; this work we see as extremely important for the practice. Such analysis of the data obtained using linear regression about the value of tumor load on organism demonstrated a high correlation with the Karnovsky index, which is used for the estimation of disease severity. So, the use of linear regression method for the processing of clinical and laboratory data of patients with brain gliomas allowed the authors of this model to determine the limit value (18 points) of the tumor load on organism and in each case of the disease permitted to plan individual strategy for patient treatment.

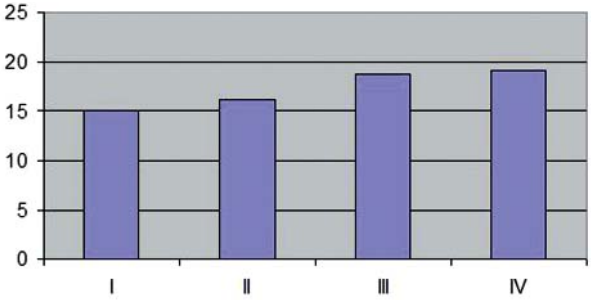

Fig. 11. **Average load of the tumor on organism depending on the group of astrocytoma (in scores)**

Comparative analysis of the Karnovsky index and estimation of load weight by the linear regression method

Tumor loading before surgery	Tumor loading after surgery
17.9	18.15
18.15	18.09
7.23	17.87
15.28	17.15
15.3	16.7

REFERENCES

1. *Klyuchko O. M.* Information and computer technologies in biology and medicine. *Kyiv: NAU-druk.* 2008, 252 p. (In Ukrainian).
2. *Klyuchko O. M.* On the mathematical methods in biology and medicine. *Biotechnol. acta.* 2017, 10(3), 31–40. https://doi.org/10.15407/biotech10.03.031
3. *Klyuchko O. M.* Application of artificial neural networks method in biotechnology. *Biotechnol. acta.* 2017, 10(4), 5–13. https://doi.org/10.15407/biotech10.04.005
4. *Klyuchko O. M.* Cluster analysis in biotechnology. *Biotechnol. acta.* 2017, 10(5), 5–18. https://doi.org/10.15407/biotech10.05.005.
5. *Klyuchko O. M.* Technologies of brain images processing. *Biotechnol. acta.* 2017, 10 (6), 5–17. https://doi.org/10.15407/biotech10.05.005
6. *Tasseff R. A.* Mathematical Models in Biotechnology. *PLoS One*, 5:e8864, 2010.
7. *Mata-Alvarez J.* Mathematical Modeling in Biotechnology. *Biotechnology.* V. II. 2004. https://www.eolss.net/sample-chapters/C17/E6-58-02-04.pdf
8. *Gordeev L. S.* Mathematical Modeling in Chemical Engineering and Biotechnology. *Theoretical Foundations of Chemical Engineering.* 2014, 48 (3), 225–229. https://link.springer.com/article/10.1134/S0040579514030099
9. *Piatigorsky B. Ya.* Automatic electrophysiological experiment. *Kyiv: Nauk. Dumka*. 1985. 216 p. (In Russian).
10. *Malinovsky B. N.* The History of Computing Technique in Persons. *Kyiv: KIT*. 1995. 384 p. (In Russian).
11. *Rana B. K., Insel P. A.* G-protein-coupled receptor websites. *Trend. Pharmacol. Sci.* 2002, 23 (11), 535–536. doi: http://dx.doi.org/10.1016/S0165-6147(02)02113-2
12. *Patent* 1370136 USSR, МКИ C12N 5/00. The method for dissociation of hippocampal cells. Klyuchko E. M., Tzyndrenko A. Ya. Priority: 31.01.1986; Issued: 30.01.1988, Bull. No 4, 3 p.
13. *Sigworth F.* Single channel registration. *Moskva: Mir,* 1987. 448 p. (In Russian).
14. *Kostyuk P. G.* Mechanisms of electrical excitability of nerve cells. *Moskva: Nauka*, 1981, 208 p. (In Russian).
15. *Klyuchko O. M., Pashkivsky A. O., Sheremet D. Y.* Computer modeling of some nanoelements for radio and television systems. *Electronics and control system*. 2012. 3 (33), 102–107. (In Ukrainian).
16. *Klyuchko O. M., Hayrutdinov R. R.* Modeling of electrical signals propagation in neurons and its nanostructures. *Electronics and control system*. 2011, 2 (28), 120–124. (In Ukrainian).
17. *Trinus K. F., Klyuchko O. M.* Mediators influence on motoneurons retrogradly marked by primulin. *Physiological Journal*. 1984. 30 (6), 730–733 (In Russian).
18. *Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V.* Algorithmic and program support for optimization of interval hypoxic training modes selection of pilots. *Electronics and Control Systems*. 2017, 2 (52), 85–93.
19. *Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V.* Mathematic and program models for investigation of reliability of operator professional activity in "Human-Machine" systems. *Electronics and Control Systems*. 2017, 1 (51), 105–113.
20. *Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V.* Mathematical model for research of organism restoring for operators of continuously interacted systems. *Electronics and Control Systems*. 2016, 3 (49), 100–105.
21. *Aralova N. I., Klyuchko O. M., Mashkin V. I., Mashkina I. V.* Investigation of reliability of operators work at fluctuating temperature conditions. *Electronics and Control Systems*. 2016, 2 (48), 132–139.
22. *Plakhotnij S. A., Klyuchko O. M., Krotinova M. V.* Information support for automatic industrial environment monitoring systems. *Electronics and Control Systems*. 2016, 1 (47), 19–34.
23. *Onopchuk Yu. M., Aralova N. I., Klyuchko O. M., Beloshitsky P. V.* Mathematic models and integral estimation of organism systems reliability in extreme conditions. *Electronics and Control Systems*. 2015, 4 (46), 109–115.
24. *Onopchuk Yu. M., Aralova N. I., Klyuchko O. M., Beloshitsky P. V.* Integral estimations of human reliability and working capacity in sports wrestling. *Journal of the Engineering Academy*. 2015, 3, P. 145–148 (In Russian).
25. *Klyuchko O. M., Shutko V. N., Navrotskyi D. O., Mikolushko A. M.* The set of program models for ecological monitoring technical system based on principles of biophysics. *Electronics and Control Systems*. 2014, 4 (42), 135–142.
26. *Klyuchko O. M., Sheremet D. Yu.* Computer simulation of biological nanogenerator functions. *Electronics and Control Systems*. 2014, 2 (40), 103–111.
27. *Klyuchko O. M., Shutko V. N.* Computer modeling of auto-oscillating phenomena in neuron complexes. *Electronics and Control Systems*. 2014, 1 (39), 127–132.
28. *Klyuchko O. M., Sheremet D. Yu.* Computer modeling of biologic voltage-activated nanostructures. *Electronics and Control Systems*. 2014, 1 (39), 133–139.
29. *Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu. M.* Radiation damage of organism and its correction in conditions of adaptation to high-mountain meteorological factors. *Bulletin of NAU*. 2010, V.1, P. 224–231 (In Ukrainian).
30. *Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu., Makarenko M. V.* Estimation of psycho-physiological functions of a person and operator work in extreme conditions. *Bulletin of NAU*. 2009, No 3, P. 96–104 (In Ukrainian).

31. *BeloshitskyP.V.,KlyuchkoO.M.,OnopchukYu., Kolchinska A. Z.* Results of research of higher nervous activity problems by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2009, No 2, P. 105–112 (In Ukrainian).
32. *BeloshitskyP.V.,KlyuchkoO.M.,OnopchukYu.* Results of research of structural and functional interdependencies by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2009, No 1, P. 61–67 (In Ukrainian).
33. *BeloshitskyP.V.,KlyuchkoO.M.,OnopchukYu.* Results of research of highlands factors influence on health and longevity by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2008, No 4, P. 108–117 (In Ukrainian).
34. *Onopchuk Yu. M., Klyuchko O. M., Beloshitsky P. V.* Development of mathematical models basing on researches of Ukrainian scientists at Elbrus. *Bulletin of NAU*. 2008, No 3, P. 146–155 (In Ukrainian).
35. *BeloshitskyP.V.,KlyuchkoO.M.,OnopchukYu.* Results of research of adaptation problems by Ukrainian scientists in Prielbrussie. *Bulletin of NAU*. 2008, No 1, P. 102–108 (In Ukrainian).
36. *Beloshitsky P. V., Klyuchko O. M., Onopchuk Yu.* Results of research of hypoxia problems by Ukrainian scientists in Elbrus region. *Bulletin of NAU*. 2007, No 3–4, P. 44–50 *(*In Ukrainian).
37. *BeloshitskyP.V.,KlyuchkoO.M.,OnopchukYu.* Results of medical and biological research of Ukrainian scientists at Elbrus. *Bulletin of NAU*. 2007, No 2, P. 10–16 (In Ukrainian).
38. *Belan P. V., Gerasimenko O. V., Tepikin A. V., Petersen O. H.* Localization of Ca^{++} extrusion sites in pancreatic acinar cells. *Journal of Biological Chemistry*. 1996, V. 271, P. 7615–7619.
39. *Belan P.* Extracellular Ca^{++} spikes due to secretory events in salivary gland cells. *Journal of Biological Chemistry*. 1998, V. 273, P. 4106–4111.
40. *Jabs R., Pivneva T., Huttmann K.* Synaptic transmission onto hyppocampal glial cells with hGFAP promoter activity. *Journal of Cell Science*. 2005, V. 118, P. 3791–3803.
41. *Gavrilovich M.* Spectra image processing and application in biotechnology and pathology. Dissertation for Ph.D. *Acta Universitatis Upsaliensis. Upsala*. 2011, 63 p.
42. *Perner P., Salvetti O.* Advances in Mass Data Analysis of Images and Signals in Medicine, Biotechnology, Chemistry and Food Industry. *Third International Conference, Leipzig, (Germany)*: *Springer, 2008, Proceedings*. 2008, 173 p.
43. *Baert P., Meesen G., De Schynkel S., Poffijn A., Oostveldt P. V.* Simultaneous in situ profiling of DNA lesion endpoints based on image *cytometry* and a single cell database approach. *Micron*. 2005, 36 (4), 321330. https://doi.org/10.1016/j.micron.2005.01.005.
44. *Berks G., Ghassemi A., von Keyserlingk D. G.* Spatial registration of digital brain atlases based on fuzzy set theory. *Comp. Med. Imag. Graph*. 2001, 25 (1), 1–10. https://doi.org/10.1016/S0895-6111(00)00038-0.
45. *Nowinski W. L., Belov D.* The Cerefy Neuroradiology Atlas: a Talairach–Tournoux atlas-based tool for analysis of neuroimages available over the internet. *NeuroImage*. 2003, 20(1), 50–57. https://doi.org/10.1016/S1053-8119(03)00252-0.
46. *Chaplot S., Patnaik L. M., Jagannathan N. R.* Classification of magnetic resonance brain images using wavelets as input to support vector machine and neural network. *Biomed. Signal Process. Control*. 2006, 1 (1), 86–92. https://doi.org/10.1016/j.bspc.2006.05.002.
47. *Kovalev V. A., Petrou M., Suckling J.* Detection of structural differences between the brains of schizophrenic patients and controls. *Psychiatry Research: Neuroimaging*. 2003, 124 (3), 177–189. https://doi.org/10.1016/S0925-4927(03) 00070-2.
48. *Araújo T.* Classification of breast cancer histology images using Convolutional Neural Networks. *PloS One*. 2017, 12 (6), e0177544.
49. *Vecht-Lifshitz S. E., Ison A. P.* Biotechnological applications of image analysis: present and future prospects. *J. Biotechnol*. 1992, 23 (1), 1–18.
50. *Toga A. W., Thompson P. M.* The role of image registration in brain mapping. *Image and Vision Computing*. 2001, 19 (1–2), 3–24.
51. *Carro S. A., Scharcanski J.* A framework for medical visual information exchange on the WEB. *Computers in Biology and Medicine*. 2006, V. 4, P.327–338.
52. *Chakravarty M. M., Bertrand G., Hodge C. P., Sadikot A. F., Collins D. L.* The creation of a brain atlas for image guided neurosurgery using serial histological data. *NeuroImage*. 2006, 30 (2), 359–376. doi: 10.1016/ j.neuroimage.2005.09.041.
53. *Dikshit A., Wu D., Wu C., Zhao W.* An online interactive simulation system for medical imaging education. *Comp. Med. Imag. Graph*. 2005, 29 (6), 395–404. https://doi.org/10.1016/j.compmedimag.2005.02.001.
54. *Singh R., Schwarz N., Taesombut N., Lee D., Jeong B., Renambot L., Lin A. W., West R., Otsuka H., Naito S., Peltier S. T., Martone M. E., Nozaki K., Leigh J., EllismanM.H.* Real-time multi-scale brain data acquisition, assembly, and analysis using an end-to-end. *OptIPuter Future Generation Computer Systems*. 2006, 22, 1032–1039.
55. *Stefanescu R., Pennec X., Ayache N.* Grid powered nonlinear image registration with locally adaptive regularization. *Medical Image Analysis*. 2004. 8 (3), 325–342.
56. *Ma Y., Hof P. R., Grant S. C., Blackband S. J., Bennett R., Slatest L., McGuigan M. D., Benveniste H.* A three-dimensional digital atlas database of the adult C57BL/6J mouse brain by magnetic resonance microscopy. *Neuroscience*. 2005, 135 (4), 12031215. doi: 10.1016/j.neuroscience.2005.07.014.

57. *Yu-Len Huang*. Computer-aided Diagnosis Using Neural Networks and Support Vector Machines for Breast Ultrasonography. *J. Med. Ultrasound*. 2009,17 (1), 17–24.
58. *Prachi Damodhar Shahare, Ram Nivas Giri*. Comparative Analysis of Artificial Neural Network and Support Vector Machine Classification for Breast Cancer Detection. *International Research Journal of Engineering and Technology (IRJET)*. 2015, 2 (9).
59. *Natrajan R., Sailem H., Mardakheh F. K., Garcia M. F., Tape C. G., Dowsett M., Bakal C., Yuan Y*. Microenvironmental heterogeneity parallels breast cancer progression: a histology–genomic integration analysis. *PLoS medicine*. 2016. 13(2), e1001961. https://doi.org/10.1371/journal.pmed.1001961.
60. *Klyuchko O. M*. Brain images in information systems for neurosurgery and neurophysiology. *Electronics and control systems*. 2009, 3(21), 152–156. (In Ukrainian)
61. *Klyuchko O. M*. Using of images' databases for diagnostics of pathological changes in organism tissues. *Electronics and control systems*. 2009, 2 (20), 62–68. (In Ukrainian).
62. *Klyuchko O. M*. Elements of different level organization of the brain as material for electronic databases with images. *Electronics and control systems*. 2009, 1 (19), 69–75. (In Ukrainian).
63. *Steimann F*. On the representation of roles in object-oriented and conceptual modelling. *Data& Knowedge Engineering*. 2000, 35 (1), 83–106.
64. *Klyuchko O. M., Managadze Yu. L., Pashkivsky A. O*. Program models of 2D neuronal matrix for ecological monitoring and images' coding. *Bulletin of the Engineering Academy*. 2013, No 3–4, P. 77–82. (In Ukrainian).
65. *KlyuchkoO.M., PiatchaninaT.V., MazurM.G*. Combined use of relation databases of images for diagnostics, therapy and prognosis of oncology diseases. «Integrated robototechnic complexes». X IIRTC-2017 Conference Proceedings. P. 275–276 (In Ukrainian).
66. *Shutko V. M, Shutko O. M., Kolganova O. O*. Methods and means of compression of information. *Kyiv: Nauk. dumka*. 2012. 168 p. (In Ukrainian).
67. *Jecheva V., Nikolova E*. Some clustering-based methodology applications to anomaly intrusion detection systems. *Int. J. Secur. Appl*. 2016, 10 (1), 215–228. http://dx.doi.org/10.14257/ijsia.2016.10.1.20.
68. *Iakovidis D. K., Maroulis D. E., Karkanis S. A*. Texture multichannel measurements for cancer precursors' identification using support vector machines. *Measurement*. 2004, V. 36, P. 297–313. 2004.09.010 https://doi.org/10.1016/j.measurement.
69. *NguyenH.Q.,Carrieri-KohlmanV.,RankinS.H., Slaughter R., Stulbarg M. S*. Internet-based patient education and support interventions: a review of evaluation studies and directions for future research. *Comp. Biol. Med*. 2004, 34 (2), 95–112. doi: 10.1016/S0010-4825(03)00046-5.
70. *Jézéquel P., Loussouarn L., Guérin-Charbonnel C., Campion L., Vanier A., Gouraud W., Lasla H., Guette C., Valo I., Verrièle V., Campone M*. Gene-expression molecular subtyping of triple-negative breast cancer tumours: importance of immune response. *Breast Cancer Res*. 2015, 17 (1), 43. https://doi.org/10.1186/s13058-015-0550-y.
71. *Bozhenko V. K*. Multivariable analysis of laboratory blood parameters for obtaining diagnostic information in experimental and clinical oncology. The dissertation author's abstract on scientific degree editions. *Dc. Med. Study. Moscow*. 2004 (In Russian).
72. *Ko J. H., Ko E. A., Gu W., Lim I., Bang H., Zhou T*. Expression profiling of ion channel genes predicts clinical outcome in breast cancer. *Mol. Cancer*. 2013, 12 (1), 106. doi: 10.1186/1476-4598-12-106.
73. *Kawai M., Nakashima A., Kamada S., Kikkawa U*. Midostaurin preferentially attenuates proliferation of triple-negative breast cancer cell lines through inhibition of Aurora kinase family. *J. Bbiomed. Sci*. 2015, 22 (1), 48. doi: 10.1186/s12929-015-0150-2.
74. *Uhr K., Wendy J. C., Prager-van der Smissen, Anouk A. J. Heine, Bahar Ozturk, Marcel Smid, Hinrich W. H. Göhlmann, Agnes Jager, John A. Foekens, John W. M. Martens*. Understanding drugs in breast cancer through drug sensitivity screening. *SpringerPlus*. 2015, 4(1), 611. doi: 10.1186/s40064-015-1406-8.
75. *OnopchukYu.M.,BiloshitskyP.V.,KlyuchkoO.M*. Development of mathematical models based on the results of researches of Ukrainian scientists at Elbrus. *Visnyk NAU*. 2008, No 3, P. 146155. (In Ukrainian).
76. *Ankur Poudel, Dhruba Bahadur Thapa, Manoj Sapkota*. Cluster Analysis of Wheat (*Triticum aestivum* L.) Genotypes Based Upon Response to Terminal Heat Stress. *Int. J. Appl. Sci. Biotechnol*. 2017, 5 (2), 188–193. doi: http://dx.doi.org/10.3126/ijasbt.v5i2.17614.
77. *Zaslavsky L., Ciufo S., Fedorov B., Tatusova T*. Clustering analysis of proteins from microbial genomes at multiple levels of resolution. *BMC Bioinform*. 2016, 17 (8), 276. Published online 2016 Aug 31. doi: 10.1186/s12859-016-1112-8.
78. *Zhou J., Richardson A. J., Rudd K. E*. EcoGene-RefSeq: EcoGene tools applied to the RefSeq prokaryotic genomes. *Bioinformatics*. 2013, 29 (15), 1917–1918. Published: 04 June 2013. doi: 10.1093/bioinformatics/btt302.
79. *Zhang J., Wu G., Hu X., Li S., Hao S*. A Parallel Clustering Algorithm with MPI – MKmeans. *J. Comput*. 2013, 8 (1), 1017. doi: 10.1109/PAAP. 2011.17.

80. *Tatusova T., Zaslavsky L., Fedorov B., Haddad D., Vatsan A., Ako-adjei D., Blinkova O., Ghazal H.* Protein Clusters. *The NCBI Handbook [Internet]. 2nd edition.* Available at https://www.ncbi.nlm.nih.gov/books/NBK242632.
81. *Anderson J. G.* Evaluation in health informatics: computer simulation. *Computers in Biology and Medicine*. 2002, 32 (3), 151–164. https://doi.org/10.1016/S0010-4825(02)00012-4.
82. *Aruna P., Puviarasan N., Palaniappan B.* An investigation of neuro-fuzzy systems in psychosomatic disorders. *Exp. Syst. Appl.* 2005, 28 (4), 673–679. https://doi.org/10.1016/j.eswa.2004.12.024.
83. *Bange M. P., Deutscher S. A., Larsen D., Linsley D., Whiteside S.* A handheld decision support system to facilitate improved insect pest management in Australian cotton systems. *Comp. Electron. Agricult.* 2004, 43 (2), 131–147. https://doi.org/10.1016/j.compag.2003.12.003.
84. *Beaulieu A.* From brainbank to database: the informational turn in the study of the brain. *Stud. Hist. Phil. Biol. Biomed. Sci.* 2004, V. 35, P. 367–390. https://doi.org/10.1016/j.shpsc.2004.03.011.
85. *Bedathur S. J., Haritsa J. R., Sen U. S.* The building of BODHI, a bio-diversity database system. *Inform. Syst.* 2003, 28 (4), 347–367. https://doi.org/ 10.1016/S0306-4379(02)00073-X.
86. *Brake I.* Unifying revisionary taxonomy: insect exemplar groups. *Abstr. XV SEL Congr. Berlin (Germany).* 2007.
87. *Braxton S. M., Onstad D. W., Dockter D. E., Giordano R., Larsson R., Humber R. A.* Description and analysis of two internet-based databases of insect pathogens: EDWIP and VIDIL. *J. Invertebr. Pathol.* 2003, 83 (3), 185–195. doi: 10.1016/S0022-2011(03)00089-2.
88. *Breaux A., Cochrane S., Evens J., Martindaled M., Pavlike B., Suera L., Benner D.* Wetland ecological and compliance assessments in the San Francisco Bay Region, California, USA. *J. Environm. Manag.* 2005, 74 (3), 217237.
89. *Buduru A., Fhilippe Cudré-Mauroux P., Aberer K.* From bioinformatic web portals to semantically integrated Data Grid networks. *Future Generation Computer Systems*. 2007, 23 (3), 281–522. doi: 10.1016/j.jenvman.2004.08.017.
90. *Burns G., Stephan K. E., Ludäscher B., Gupta A., Kötter R.* Towards a federated neuroscientific knowledge management system using brain atlases. *Neurocomputing*. 2001, V. 3840, P. 1633–1641. https://doi.org/10.1016/S0925-2312(01)00520-3.
91. *Butenko S., Wilhelm W. E.* Clique-detection models in computational biochemistry and genomics. *Eur. J. Oper. Res.* 2006, 173 (1), 117. https://doi.org/ 10.1016/j.ejor.2005.05.026.
92. *Carro S. A., Scharcanski J.* Framework for medical visual information exchange on the WEB. *Comp. Biol. Med.* 2006, 36 (4), 327–338. doi: 10.1016/ j.compbiomed.2004.10.004.
93. *Chau M., Huang Z., Qin J., Zhou Y., Chen H.* Building a scientific knowledge web portal: The NanoPort experience. *Decision Support Systems.* 2006. https://doi.org/10.1016/j.dss.2006.01.004.
94. *Chen M., Hofestädt R.* A medical bioinformatics approach for metabolic disorders: Biomedical data prediction, modeling, and systematic analysis. *J. Biomed. Inform.* 2006, 39 (2), 147–159. https://doi.org/10.1016/j.jbi.2005.05.005.
95. *Chli M., De Wilde P.* Internet search: Subdivision-based interactive query expansion and the soft semantic web Applied Soft Computing. 2006. https://doi.org/10.1016/j.asoc.2005.11.003.
96. *Despont-Gros C., Mueller H., Lovis C.* Evaluating user interactions with clinical information systems: A model based on human–computer interaction models. *J. Biomed. Inform.* 2005, 38 (3), 244–255. https://doi.org/10.1016/ j.jbi.2004.12.004.
97. *Sun W., Starly B., Nam J., Darling A.* Bio-CAD modelling and its applications in computer-aided tissue engineering. *Computer-Aided Design*. 2005, 37 (11), 1097–1114.
98. *Marios D., Dikaiakos M. D.* Intermediary infrastructures for the World Wide Web. *Comp. Networks.* 2004, V. 45, P. 421–447. https://doi.org/ 10.1016/j.comnet.2004.02.008.
99. *Dimitrov S. D., Mekenyan O. G, Sinks G. D., Schultz T. W.* Global modeling of narcotic chemicals: ciliate and fish toxicity. *J. Mol. Struc.: Theochem*. 2003, 622 (12), 63–70. https://doi.org/10.1016/S0166-1280(02)00618-8.
100. *Dong Y., Zhuang Y., Chen K., Tai X.* A hierarchical clustering algorithm based on fuzzy graph connectedness. *Fuzzy Sets. Syst.* 2006, V. 157, P. 1760–1774. https://doi.org/10.1016/j.fss.2006.01.001.
101. *Duan Y., Edwards J. S., Xu M. X.* Web-based expert systems: benefits and challenges. *Inf. Manag.* 2005, 42 (6), 799–811. https://doi.org/10.1016/j.im.2004. 08.005.
102. *Essen van D. C.* Windows on the brain: the emerging role of atlases and databases in neuroscience. *Curr. Opin. Neurobiol.* 2002, 12 (5), 574–579. https://doi.org/10.1016/S0959-4388(02)00361-6.
103. *Fellbaum C., Hahn U., Smith B.* Towards new information resources for public health From Word Net to Medical Word Net. *J. Biomed. Inform.* 2006, 39 (3), 321–332. doi: 10.1016/j.jbi.2005.09.004.
104. *Ferraris M., Frixione P., Squarcia S.* Network oriented radiological and medical archive. *Comp. Physics Commun.* 2001, V. 140, P. 226–232. https://doi.org/10.1016/S0010-4655(01)00273-9.
105. *Flower D. R., Attwood T. K.* Integrative bioinformatics for functional genome annotation: trawling for G protein-coupled receptors.

Semin. Cell. Dev. Biol. 2004, 15 (6), 693–701. doi: 10.1016/j.semcdb.2004.09.008.
106. *Fink E., Kokku P. K., Nikiforou S., Hall L. O., Goldgof D. B, Krischer J. P.* Selection of patients for clinical trials: an interactive web-based system. A*rt. Intell. Med.* 2004, 31 (3), 241–254. doi: 10.1016/j.artmed.2004.01.017.
107. *Fitzpatrick M. J., Ben-Shahar Y., Smid H. M., Vet L. E., Robinson G. E., Sokolowski M. B.* Candidate genes for behavioural ecology. *Trend Ecol. Evol.* 2005, 20 (2), P. 96–104. doi: 10.1016/j.tree.2004.11.017.
108. *Fox J., Alabassi A., Patkar V., Rose T., Black E.* An ontological approach to modelling tasks and goals. *Comp. Biol. Med.* 2006, V. 36, P. 837–856. https://doi.org/10.1016/j.compbiomed.2005.04.011.
109. *Fu Zetian, Xu Feng, Zhou Yun, Shuan X. Z.* Pig-vet: a web-based expert system for pig disease diagnosis. 2006. https://doi.org/10.1016/j.eswa.2005.01.011.
110. *Gaulton A., Attwood T. K.* Bioinformatics approaches for the classification of G-protein-coupled receptors. *Curr. Opin. Pharmacol.* 2003, 3 (2), 114–120. doi: 10.1016/S1471-4892(03)00005-5.
111. *Gevrey M., Worner S., Kasabov N., Pitt J., Giraudel J. L.* Estimating risk of events using SOM models: A case study on invasive species establishment. *Ecol. Modell.* 2006, 197 (34), 361–372. https://doi.org/10.1016/j.ecolmodel. 2006.03.032.
112. *Glenisson P., Glänzel W., Janssens F., Moor B. D.* Combining full text and bibliometric information in mapping scientific disciplines. *Inf. Proc. Manag.* 2005, 41 (6), 1548–1572. https://doi.org/10.1016/j.ipm.2005.03.021.
113. *Goldys E. M.* Fluorescence Applications in Biotechnology and the Life Sciences. *USA: John Wiley & Sons*. 2009, 367 p.
114. *Graham C. H., Ferrier S., Huettman F., Moritz C., Peterson A. T.* New developments in museum-based informatics and applications in biodiversity analysis. *Trend. Ecol. Evol.* 2004, 19 (9), 497–503. https://doi.org/10.1016/ j.tree.2004.07.006.
115. *Gruber T. R.* A translation approach to portable ontologies. *Knowledge Acquisition*. 1993, 5 (2), 199–220. doi: 10.1006/knac.1993.1008.
116. *Hirano S., Sun X., Tsumoto S.* Comparison of clustering methods for clinical databases. *Inform. Sci.* 2004, 159 (34), P. 155–165. https://doi.org/ 10.1016/j.ins.2003.03.011.
117. *Hong Yu., Hatzivassiloglou V., Rzhetsky A., Wilbur W. J.* Automatically identifying gene/protein terms in MEDLINE abstracts. *J. Biomed. Inform.* 2002, 35 (56), 322–330. https://doi.org/10.1016/S1532-0464(03)00032-7.
118. *Horn W.* AI in medicine on its way from knowledge-intensive to data-intensive systems. *Artificial Intelligence in Medicine. Elsevier.* 2001, 23 (1), 512. https://doi.org/10.1016/S0933-3657(01)00072-0.
119. *Hsi-Chieh Lee, Szu-Wei Huang, Li E. Y.* Mining protein–protein interaction information on the internet. *Exp. Syst. Appl. Elsevier.* 2006, 30 (1), 142–148. https://doi.org/10.1016/j.eswa.2005.09.083.
120. *Young R.* Genetic toxicology: web–resources. *Toxicology*. 2002, 173 (1–2), P. 103–121.
121. *Johnson S. B., Friedman R.* Bridging the gap between biological and clinical informatics in a graduate training program. *J. Biomed. Inform.* 2007, 40 (1), 59–66. Epub. 2006 Mar 15. doi: 10.1016/j.jbi.2006.02.011.
122. *Kaiser M., Hilgetag C. C.* Modelling the development of cortical systems networks. *Neurocomputing.* 2004, V. 5860, P. 297–302. https://doi.org/ 10.1016/j.neucom.2004.01.059.
123. *Kane M. D., Brewer J. L.* An information technology emphasis in biomedical informatics education. *J. Biomed. Inform.* 2007, 40 (1), 67–72. https://doi.org/10.1016/j.jbi.2006.02.006.
124. *Kannathal N., Acharya U. R., Lim C. M., Sadasivan P. K.* Characterization of EEG. A comparative stud*y. Comp. Meth. Progr. Biomed.* 2005, 80 (1), 17–23. https://doi.org/10.1016/j.cmpb.2005.06.005.
125. *Koh W., McCormick B. H.* Brain microstructure database system: an exoskeleton to 3D reconstruction and modelling. *Neurocomputing.* 2002, V. 4446, P. 1099–1105. https://doi.org/10.1016/S0925-2312(02)00426-5.
126. *Koh W., McCormick B. H.* Registration of a 3D mouse brain atlas with brain microstructure data. *Neurocomputing*. 2003, V. 5254, P. 307–312. https://doi.org/10.1016/S0925-2312(02)00793-2.
127. *Kulish V., Sourin A., Sourina O.* Human electro encephalograms seen as fractal time series: Mathematical analysis and visualization. *Comp. Biol. Med.* 2006, 36 (3), 291–302. doi: 10.1016/j.compbiomed.2004.12.003.
128. *Lubitz von D., Wickramasinghe N.* Network-centric healthcare and bioinformatics: Unified operations within three domains of knowledge. *Exp. Syst. Appl.* 2006, 30 (1), 11–23. https://doi.org/10.1016/j.eswa.2005.09.069.
129. *Martin-Sanchez F., Iakovidis I., Norager S., Maojo V., de Groen P., Van der Lei J., Jones T., Abraham-Fuchs K., Apweiler R., Babic A., Baud R., Breton V., Cinquin P., Doupi P., Dugas M., Eils R., Engelbrecht R., Ghazal P., Jehenson P., Kulikowski C., Lampe K., DeMoor G., Orphanoudakis S., Rossing N., Sarachan B., Sousa A., Spekowius G., Thireos G., Zahlmann G., Zvárová J., Hermosilla I., Vicente F. J.* Synergy between medical informatics and bioinformatics: facilitating genomic medicine for future health care. *J. Biomed. Inform.* 2004, 37 (1), 30–42. doi:10.1016/j.jbi.2003.09.003.
130. *Masseroli M., Visconti A., Bano S. G.* Pinciroli F. He@lthCo-op: a web-based system to

support distributed healthcare co-operative work. *Comp. Biol. Med.* 2006, 36 (2), 109–127. doi:10.1016/j.compbiomed.2004.09.005.

131. *Moon S., Byun Y., Han K.* FSDB: A frameshift signal database. *Comp. Biol. Chem.* 2007, 31 (4), 298–302. doi: 10.1016/j.compbiolchem.2007.05.004.
132. *Orgun B., Vu J.* HL7 ontology and mobile agents for interoperability in heterogeneous medical information systems. *Comp. Biol. Med.* 2006, 36 (78), 817–836. https://doi.org/10.1016/j.compbiomed.2005.04.010.
133. *Pérez-Rey D., Maojo V., García-Remesal M., Alonso-Calvo R., Billhardt H., Martin-Sánchez F., Sousa A.* Ontofusion: Ontology-based integration of genomic and clinical databases. *Comp. Biol. Med*. 2006, 36 (78), 712–730. doi: 10.1016/j.compbiomed.2005.02.004.
134. *Krishtal O.A., Kiskin N.I., Tsyndrenko A.Ya., Klyuchko E. M.* Pharmacological properties of amino acid receptors in isolated hippocampal neurons. *In: Receptors and ion channels. Ed. By Ovchinnikov Y.A.*, Hucho F. *Berlin-New York: Walter de Gruyter*, 1987, P. 127–137.
135. *Klyuchko E.M, Klyuchko Z.F., Beloshitsky P.V.* Some adaptation characteristics of insects in mountains of Prielbrussie. *Nalchik (Russia), "Hypoxia: automatic analysis of hypoxic states of healthy people and sick ones"*. 2005, V.1, P.137–140 (In Russian).
136. *Klyuchko Z. F., Klyuchko E. M.* Analysis of taxonomic structure of moth fauna (Lepidoptera: Noctuidae s.l.) of Ukraine according to monitoring data. *Eversmannia,* 2012, 3 (33), 41–45. (In Russian).
137. *Klyuchko Z. F., Klyuchko E. M.* Moth (Lepidoptera: Noctuidae s. l.) of Chercasska region of Ukraine according to results of many-year monitoring. *Eversmannia.* 2014, No 37, 32–49 (In Russian).
138. *Gonchar O., Klyuchko E., Mankovskaya I.* Role of complex nucleosides in the reversal of oxidative stress and metabolic disorders induced by acute nitrite poisoning Indian Journal of Pharmacology. 2006, 38 (6), 414–418.
139. *Gonchar O., Klyuchko E., Seredenko M., Oliynik S.* Corrections of prooxidant – antioxidant homeostasis of organism under hypoxia of different genesis by yackton, new pharmacological preparation. *Acta Physiol. Pharmacol. Bulg.* 2003, V. 27, P. 53–58.
140. *Klyuchko O., Klyuchko Z., Lizunova A.* Electronic Noctuidae database: some problems and solutions. *Proceed. 16th European Congress of Lepidopterology. Cluj (Romania),* 2009, P. 31–32.
141. *Klyuchko O., Klyuchko Z., Lizunova A.* Noctuidae fauna of Ukrainian Karpathy: results of monitoring (1956–2008), *Proceed. 16th European Congress of Lepidopterology. Cluj (Romania),* 2009. P. 31.
142. *Klyuchko O.M., Klyuchko Z.F., Lizunova A.G.* Development Of Database For Noctuidae Species In Ukraine. *5-th International Conference On the Biology Of Butterflies, Roma*, 2007.
143. *Klyuchko Z. F., Klyuchko O. M.* Diversity and biogeography Of Noctuidae Species In Ukraine. *5-th International Conference On the Biology Of Butterflies, Roma,* 2007.
144. *Klyuchko O. M., Beloshitsky P. V.* Investigation of insect adaptation characteristics in Prielbrussie in 2004–2005. *Mater. VIII World Congress of International Society for Adaptive Medicine (ISAM).* Moskva (Russia). 2006, P. 165–166.
145. *Beloshitsky P. V., Klyuchko O. M.* Contribution of Sirotinin's school into adaptation medicine. *Mater. VIII World Congress of International Society for Adaptive Medicine (ISAM). Moskva (Russia),* 2006. P. 158.
146. *Klyuchko O. M., Klyuchko Z. F.* Ukrainian Noctuidae Database. *Mater. Of XIV SEL Congress. Roma (Italy),* 2005, P. 49.
147. *Klyuchko Z. F., Klyuchko O. M.* Noctuidae (Lepidoptera) of Donbass, Ukraine. *Mater. Of XIV SEL Congress. Roma (Italy),* 2005, P. 41–42.
148. *Beloshitsky P., Klyuchko O., Onopchuck Yu., Onopchuck G.* Mathematic model for hypoxic states development for healthy people and ones with ischemic heart disease. *High altitude medicine and biology: Mater. ISMM Congress. Beijing (China),* 2004, V. 5, P. 251.
149. *Beloshitsky P., Klyuchko O., Kostyuk O., Beloshitsky S.* Peculiarities of high mountain factors influence on organism. *High altitude medicine and biology: Mater. ISMM Congress. Beijing (China),* 2004, V. 5, P. 250.
150. *Gonchar O., Klyuchko O., Beloshitsky P.* Ways of myocardial metabolic disorders correction at hypoxia by new pharmacological preparations. *High altitude medicine and biology: Mater. ISMM Congress. Beijing (China).* 2004, V. 5, P. 249.
151. *Gonchar O., Klyuchko O., Seredenko M., Oliynyk B.* Correction of metabolic disorders at hypoxia by new pharmacological preparations. *Mater. 3 FEPS Congress. Nice (France),* 2003, P. 228.
152. *Troyan V., Klyuchko O., Taran N.* About some ways to change gender standards. *Standard: abweichung: Mater. Intl. Kongress in Natur wissenschaft und Technik. Berlin (Germany),* 2003. P. 208.
153. *Seredenko M., Gonchar O., Klyuchko O., Oliynyk S.* Peculiarities of prooxidant – antioxidant balance of organism under hypoxia of different genesis and its corrections by new pharmacological preparations. *Acta Physiologica Hungarica. Budapest (Hungary).* 2002, 89 (1–3), 292.

154. *Klyuchko O. M., Kiskin N. I., Krishtal O. A., Tsyndrenko A. Ya* Araneidae toxins as antagonists of excitatory amino acid responses in isolated hippocampal neurons. *X School on biophysics of membrane transport. Szczyrk (Poland),* 1990, V. 2, P. 271.

155. *AkaikeN.,KawaiN.,KiskinN.I.,KrishtalO.A., Tsyndrenko A. Ya., Klyuchko O. M.* Spider toxin blocks excitatory amino acid responses in isolated hippocampal pyramidal neurons. *Neurosci. Lett*. 1987, V. 79, P. 326–330.

ДЕЯКІ ТЕНДЕНЦІЇ В МАТЕМАТИЧНОМУ МОДЕЛЮВАННІ ДЛЯ БІОТЕХНОЛОГІЇ

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Мета роботи — показати деякі тенденції в розробленні методів моделювання для біотехнології відповідно до сучасних досягнень науки і техніки. Окреслено загальні підходи, розглянуто деякі типи класифікації методів моделювання, висвітлено роль математичних методів моделювання у біотехнології за сучасного інтенсивного розвитку інформаційних комп'ютерних технологій. Запропоновано відповідну схему їх взаємозв'язку. Наведено кілька прикладів і відповідно кілька математичних моделей у трьох вимірах (1D, 2D, 3D моделі) для процесів у живих об'єктах на різних рівнях їх ієрархічної організації. Під час цього дослідження основну увагу було приділено моделюванню деяких процесів у нейронах, їхніх агрегатах декількох різних форм, включаючи клітинне утворення гліоми (1D, 2D, 3D моделі процесів у мозку). Їх розгляд розпочато з моделей, що мають на сьогодні лише теоретичне значення, а завершено описом моделі, яка може набути практичного застосування. Роботу виконано після аналізу близько 250 публікацій з біотехнології, включаючи оригінальні авторські розробки.

Ключові слова: 1D, 2D, 3D моделювання, математичні методи, інформаційні технології.

НЕКОТОРЫЕ ТЕНДЕНЦИИ В МАТЕМАТИЧЕСКОМ МОДЕЛИРОВАНИИ ДЛЯ БИОТЕХНОЛОГИИ

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Цель работы — показать некоторые тенденции в разработке методов моделирования для биотехнологии в соответствии с современными достижениями в области науки и техники. Изложены общие подходы, рассмотрены некоторые типы классификации методов моделирования, освещена роль методов математического моделирования в биотехнологии в условиях интенсивного развития информационных компьютерных технологий. Предложена соответствующая схема их взаимосвязи. Приведено несколько примеров и соответственно несколько математических моделей в трех измерениях (1D, 2D, 3D модели) для процессов в живых объектах на разных уровнях их иерархической организации. Во время этого исследования основное внимание уделялось моделированию некоторых процессов в нейронах, а также их агрегатах нескольких различных форм, в том числе и клеточном образовании глиомы (1D, 2D, 3D модели процессов в мозге). Их рассмотрение начато с моделей, имеющих сегодня только теоретическое значение, а завершено описанием модели, которая может иметь практическое применение. Работа выполнена после анализа около 250 публикаций в области биотехнологии,включая оригинальные авторские разработки.

Ключевые слова: 1D, 2D, 3D моделирование, математические методы, информационные технологии.