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SECTION 2. Applied mathematics. Mathematical modeling.

Mahruy Saidalieva
PhD, Head of dept. "Regulatorika"
Centre for the development of software and hardware program complexes at Tashkent University of Informational Technologies, Tashkent, Uzbekistan
regulatorika@yahoo.com

Mohiniso Bahromovna Hidirova
PhD, Senior Scientist, dept. "Regulatorika"
Centre for the development of software and hardware program complexes at Tashkent Univesity of Informational Technologies, Tashkent, Uzbekistan
regulatorika@yahoo.com

MATHEMATICAL MODELING OF GENETIC MECHANISMS OF CANCER

Abstract: *In this paper we consider the questions on the quantitative analysis of genetic mechanisms of cancer. The equations of mathematical model quantitatively describe functioning of regulatory mechanisms of the genetic program of autonomous development in early embryogenesis and at its abnormal activation in somatic cells. The results of the quantitative analysis of model behavior show that there is carcinogenesis possibility under disturbances in the genetic program of autonomous development and it may be used for creation of systems for early diagnostics, treatment and preventive maintenance of cancer.*

Key words: *genetic mechanisms, cancer, functional-differential equations, chaos, "black hole" effect.*
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МАТЕМАТИЧЕСКОЕ МОДЕЛИРОВАНИЕ ГЕНЕТИЧЕСКИХ МЕХАНИЗМОВ РАКА

Аннотация: *В этой статье мы рассматриваем вопросы количественного анализа генетических механизмов рака. Уравнения математической модели количественно описывают функционирование механизмов регуляции генетической программы автономного развития в раннем эмбриогенезе и при аномальной активации данной программы в соматических клетках. Результаты количественного анализа поведения модели показывают возможность возникновения злокачественных новообразований вследствие нарушения работы системы автономного развития клеток, и они могут использоваться для создания систем для ранней диагностики, лечения и профилактики рака.*

Ключевые слова: *генетические механизмы, рак, функционально-дифференциальные уравнения, хаос, эффект "черной дыра".*

In the present time the important role of genetic processes in carcinogenesis is generally acknowledged. The application of quantitative methods for analyzing regulatory mechanisms of cell processes during early development and at transformation of normal cells to cancer led to the conclusion that cancer has genetic nature [1-2,3,p.85].

We quantitatively analyze cell's regulatory mechanisms at the norm and at the carcinogenesis. On the basis of firmly established biological facts and theoretical generalization of gene's regulatory system, the equations of genes activity are developed [3]. These equations are used for the analysis of possible mechanisms of carcinogenesis origin. We consider the following genetic mechanism of early development. Evolutionary formed mechanisms of organism's early development are executed on the basis of the program of autonomous development (PAD). The PAD have secured continuity of initial divisions of couple cell and set of minimum quantity of embryonic cells, necessary for further organization of embryo's development. During this process the division of totipotent cells which are independent from mother's organism is executed on the basis of messenger RNA (m-RNA) of PAD, build up reserves in nucleic-protein complexes type like ribosome and (or) informosome. The ribosome and informosome are present in mature ovum and its formation occurs

in oogenesis, probably, during "lampbrush" chromosome stage.

We consider, that quantitative researches using the methods of mathematical modeling and computing experiment may be applied for definition of regulatory mechanisms of genetic PAD formation during "lampbrush" stage of oogenesis, for discovery mechanisms of PAD activation during individual development and for analysis of possible ways for suppression of PAD functioning.

Quantitative analysis of regulatory mechanisms of genetic processes is carried out using methods of mathematical modeling on the basis of equations of living systems regulatory mechanism (regulatorika) [3-8]. At development of regulatorika equations are entered the following concepts: OR and ASTA. The OR (oscillations-regulations) is element of regulatory system, capable perception and production of a determined nature signals. The ASTA (Active System with Time Average) is the signal medium of regulatory system, where the interconnected activity of elements on the basis of feedback, by some average time is executed. The average time is the time, passing from a moment of signals formation till the moment of them effect (or them products) on the elements activity [3]. The OR together with the ASTA have make the ORASTA is a regulatory system. The geometry of similar regulatory systems is dynamic, in which the concept of stationary point loses a sense [3]. A unit of a time ORASTA is h. In nature, OR and ASTA sometimes may occur separately too. For example, OR without ASTA is a virus. ASTA without OR is a mature without nuclear erythrocytes. The equations of considered systems, constructed on the basis generalization of B. Goodwin's approaches at simulation of mechanisms regulation of intercellular processes [9], E. Eigen's and P. Schuster's approaches at simulation of mechanisms macromolecule's evaluation [10], by account of signals competition for OR, the temporary mutual relations and the availability combined feedback in ASTA [11], have the following form

$$\frac{dX_i(\mathrm{t})}{dt} = A_i^N X(\mathrm{t}-\mathrm{h})\,\mathrm{e}^{-\sum_1^N \delta_{ik} X_k(\mathrm{t}-\mathrm{h_{ik}})} - b_i X_i(\mathrm{t})$$
$$A_i^N X(\mathrm{t}-\mathrm{h}) = \gamma_{\mathrm{i}0} + \sum_1^N \Big(\sum_1^N \gamma_{ik1,\ldots,kj} \prod_1^j X_{km}(\mathrm{t}-\mathrm{h_{ikm}})\Big) \qquad (1)$$

$X_i(\mathrm{t})$ is the value, describing quantity of a signal, appropriate to i-th OR. at the time moment t; h_{ik}; is the temporary distance from k-th OR till i-th OR; $\{\gamma\},\{\delta\},\{\mathrm{b}\}$ are the constants; γ_{i0} is the parameter signal formation (i-th kind) of medium: $i,j,k = 1,2,\ldots,N$. $Mc = (\mathrm{C}_1,\ldots,C_N)$ is vector, the elements signification of which are calculated using the following formulas

$$C_i = \int_0^\infty \int_0^\infty A_i^N(\mathrm{S}) \exp\Big(-\sum_1^N \delta_{ik} S_j\Big)\,\mathrm{dS}_{1\ldots}\, dS_N - b_i \qquad (2)$$
$$i = 1,2,\ldots,N$$

This vector is called the measure of system evolution. This measure defines possible variants of development (evolution), because its size allocates the possible behavior area in structural portrait of the equations (1) in case of concrete systems. On the other hand, Mc expresses mutual relation of a system by external medium, as far as its significance is defined by given concrete significance's of parameters. When $Mc = 0$, then the systems is in balance with external medium. It should be noted, that Mc differs from entered in [9] "selective restriction" for significance variable at simulation hypercycle's by the account of equations significance parameters too. The equations system (1) have concerned to a class of functional - differential equations and if we have continuous initial functions on the initial temporary section of length max $\{\mathrm{h}\}$, then its continuous decision may be received by a method of sequential integration. Using biological representations of functioning mechanisms of molecular-genetic systems the mathematical models are constructed [4]. Let us consider some possible laws going on the processes of information record from PAD at "lamp brush" stage of oogenesis and the elementary mathematical model of these records. It is possible to think, that the processes connected with autonomous development are supervised by a gene's autonomous development site, consisting from

several blocks: initiation (BI), structural (SB), packing (BP) and repression (BR). The blocks consist from several subblocks. For example, in SB there are subblocks: SBI are immortal oncogenes and SBT are tumor oncogenes. The activation of SBI during early development executes transfer of cells divisions to the initial position.

When the determine level in system development is reached then there is BI activation. The BI "starts" SB, where appropriate information of PAD is read. At the same time, BP is activated, carrying out the packing of the given information. If necessary quantity of the PAD information for realization early embryogenesis is collected then there is activated BR, reliably blocking the genetic blocks on the whole.

The realization of starling mechanism, ensured fertilization, promotes the beginning of PAD compilation, the formation of splits necessary for autonomous division of protein-enzyme and to the subsequent entry of couple cell into the phase of autonomous development. Thus the continuous division occurs using the specific protein-energetic complex of the ovum; build up reserves in her (ovum) development. The process of autonomous development, realized in early embryogenesis permits embryo to amount the necessary quantity of cells for formation organism.

In addition the PAD is not activated and then autonomous division of splitting embryogeny cells is executed on basis only build up reserves m-PNA of PAD. Natural decay of the m-RNA causes to the discontinuance of autonomous division of splitting. In further own cells genome of embryo is included and the program of individual organism's development (PID) is started. The PID realization is executed on the basis of interconnected activity of embryo cells for carrying out general functions for organism development.

The activation of PAD in organisms cells under effect of disturbance conditions of internal and external mediums during individual development causes to cells transformation. The alongside with PID are executed the functions, inherent to autonomous development, i.e. to possibility of carcinogenesis.

The analysis of PAD structurally functional organization shows necessity of the account, (at the mathematical simulation), of interconnected activity of several gene's groups. We take into account the initiation block, organization of PAD and a repression block as the main groups of genes. Let us take of them activity (at the time moment t), consisting from the value of the following functions: $X_1(t), X_2(t), X_3(t)$ accordingly. Then the equations of regulatory mechanisms of transcription from PAD, on the basis of adduced laws for its structurally- functional organization based on the system (1), can be written in the following form:

$$\frac{dX_1(t)}{dt} = \gamma_1 X_1(t-h) X_2(t-h) X_3(t-h) \exp(-\alpha X_3(t-h)) - \beta_1 X_1(t)$$
$$\frac{dX_2(t)}{dt} = \gamma_2 X_1(t-h) - \beta_2 X_2(t)$$
$$\frac{dX_3(t)}{dt} = \gamma_3 X_2(t-h) - \beta_3 X_3(t)$$

$\{\gamma\}, \{\beta\}, \alpha$ are the positive constants, expressed a level of speed formation m-RNA, its decay in appropriate gene's group and the activity suppression of gene's groups initiation accordingly.

Under certain conditions, the given system of equations has trivial and non-trivial states of equilibrium. The qualitative analysis of these equations has shown existence the continuous positive solutions of the given equation system at fulfillment the following inequality:

$$4\gamma_1\gamma_2\gamma_3 > \alpha^2 e^2 \beta_1\beta_2\beta_3 \qquad (3)$$

and at giving initial conditions as the continuous functions (on the time interval by length nor less then h) on the first quadrant of the phase space. Disturbance of (2) causes to trying of decisions to reach the trivial states of equilibrium and hence, to the termination of PAD activity.

The stability of stationary decisions is determined on the basis of Hayes's criterion [12-13]. Quantitative researches of model system for considered equations

$$X(\tau) = \gamma X^3(\tau - 1)\exp(\alpha X(\tau - 1))$$
$$\gamma = \gamma_1 / \beta_1; \qquad (4)$$
$$X(\tau) = X_1(t-h)$$

(which can be received, under certain conditions, from biophysical reasons and using results from theorem by Tihonov about reduction of a differential equations system [14]) and its discreet analogue

$$X_{k+1} = \gamma X_k^3 \exp(-\alpha X_k) \qquad (5)$$

by calculation of Lypunov's value, Hausdorff and others dimensions using computer has revealed the existence of dynamic chaos (fig. 1) and effect of decisions break-down to trivial states of equilibrium (one of variants of the so-called "black hole" effect).

The "black hole" effect may be a mechanism of PAD functional blocking after the completion of transcription in ovogenesis conditions and may be obstacle development transformation in cells of organism.

The results of model researches show that, at favorable conditions (the earning out (3) in ovum's during "lampbrush" stage) occurs consecutive activation of initialization gene's groups PAD organization and repression. It promotes to realization record of the program of autonomous development (used on early phase of organism's development), storage and its blocking.

Obviously, in the cells of healthy organism, the condition (2) is not observed and hence, the activation of PAD does not occur (by exception oocytes). Carrying out (3) (owing to celled conditions in cells of organisms on account of genetic disturbances) causes to occurrence nontrivial decisions of (2), that means PAD activation.

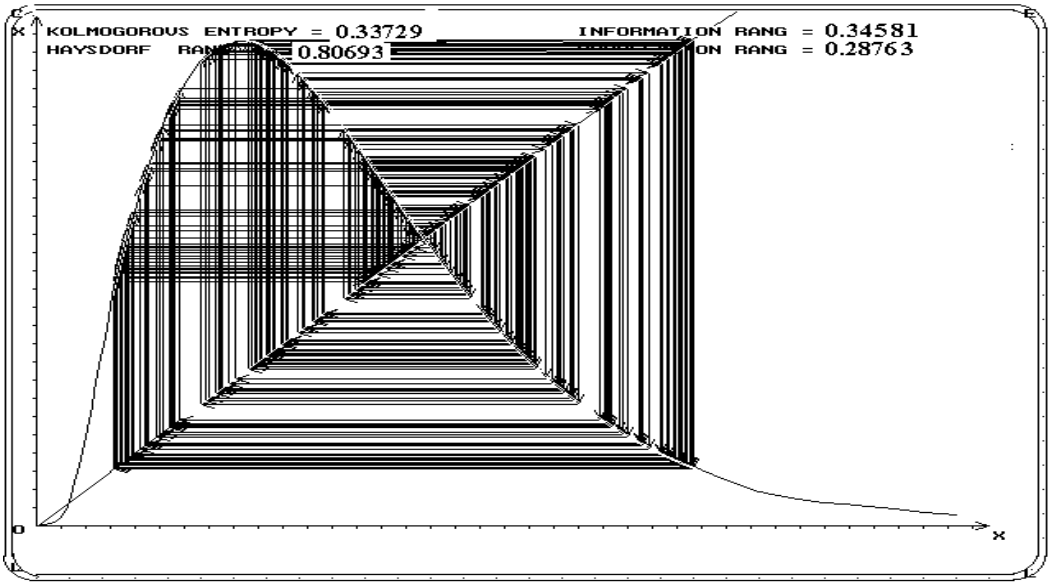

Figure 1 - Chaotic regime of (5).
$(\gamma = 0.003;\ \alpha = 0.022)$

Since the activity of PAD in somatic cells occurs together with carrying out of other functions, then character of a feedback in PAD is infringed and the functional blocking (the effect of "black hole") is not realized. Then we have uncontrollable reproduction carcinogenesis.

In this article we propose the technique for analyzing living systems regulatory mechanisms on genetic, cellular and subcellular levels. The quantitative analysis of genetic mechanisms of carcinogenesis is carried out. According to results there is existence opportunity of system of functional blocking of the autonomous development program, disturbance of which may be the beginning of carcinogenesis. Further quantitative researches will able to allow of the functioning law for cellular systems of organisms at carcinogenesis at the accepted assumptions.

Thus researches will help to develop recommendations for early diagnostics and preventive maintenance of cancer. In frameworks of accepted designations of considered genetic blocks the definition in organisms of products BI permits to execute early diagnostics of cancer. SB is the illness degree and natural analogues of BR are products for cancer treatment and preventive maintenance.

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