Innovative Technology for Modeling Cancer Grow Regulatory Mechanisms with Taking into Account Micro-RNA Action

Mahruy Saidalieva, Mohiniso Bahromovna Hidirova

Abstract: ***This article is devoted to modeling regulatory mechanisms of human molecular-genetic systems activity during cancer origin and development with taking into account non-coding circulating regulators. The paper draws on results made by using methods of quantitative and qualitative analysis of functional-differential equations. Computational experiments have shown that for certain values of internal and external states there are the following regimes: programmed cell death (apoptosis), stationary state, self-oscillations, irregular behavior (cancerous growths) and a sharp destructive change - the "black hole" effect (metastasis) in depending on various concentrations of micro-RNA. The paper provides a new mathematical and computer models able to describe regulatory mechanisms of cancer taking into account spatial and temporal relations.***

Keywords**: *Mathematical modeling, functional-differential equations, chaos, nonlinear systems, qualitative analysis, living systems, cancer, micro-RNA.***

I. INTRODUCTION

Cancer is the leading cause of death worldwide. It is well known that genetic factors play a major role in the cancer pathogenesis, which is a complex, multifactorial disease. Researchers use quantitative methods for the analysis of nucleotide and protein sequence alterations in cancer and for the construction of mathematical models for oncogenes regulation. The patterns of the cell protein synthesis apparatus, many molecular, subcellular and cellular processes were revealed. A large number of mathematical attempts have appeared to describe the work of genes, genetic ensembles, and biosynthetic cell activity from various points of view. These attempts have been made to formalize the concept of oncogene, functional sections of the genome and genetic ensembles. However, already there are many years after the start of these studies, it can be stated that the development of generally acceptable formalizations and the identification of regulatory mechanisms of gene activity in cancer are still actual. The situation was especially aggravated after the discovery of the phenomena of overlapping codes, gene mobility, existence of non-coding regulatory RNAs. If the first discovery removed the concept of the internal immutability of genes and the operon in a structurally-functional sense, the second phenomenon destroyed the idea of intragenomic, chromosomal structural stability of genes, and the third changed the understanding of structural-functional rearrangements at the level of genes and metabolic systems. As a result of this, many models and theoretical constructs based on the internal and external constancy of the gene have been found to be ineffective in analyzing the mechanisms of gene activity. In connection with the foregoing, it is necessary to formalize the concept of genetic units, allowing the most general functioning mechanisms, taking into account the latest achievements in the field of molecular biology and the requirements of practical implementation in the form of mathematical models and software systems. In detail, the mechanism of action of regulatory miRNAs has not yet been studied. Disclosure of the regulatory mechanisms of action of microRNAs will significantly help determine the mechanisms of formation and development of pathological conditions in cancer at the molecular genetic level and will allow us to find effective ways of targeted therapeutic and preventive effects on the human body [1]-[14]. Mathematical and computer modeling has predictive ability, allows us to simulate the main modes of the considered process.

II. METHODS AND MATHEMATICAL MODEL

B.N. Hidirov proposed a methodology for modeling the regulatory mechanisms of living systems, based on non-linear mechanisms of interaction of the regulator with repressor and effector molecules, regulation of enzyme activity based on inhibition of the final product, which makes it possible to consider a wide range of phenomena combined with the presence of a regulatory system and environment from a single approach regulation and combined feedback. He entered the concept of ORASTA, which consists of an oscillator-regulator (OR), capable of receiving, processing and transmitting signals of a certain nature, and an active medium with an ASTA (active system with time averadge), which makes it possible to carry out a feedback loop in a system finite time [15]. Thus, non-coding microRNAs can be considered as a regulatory system with an oscillator-regulator, which can freely circulate and regulate cellular functions, biosynthesis in normal and cancer conditions. According to the generally accepted form

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of mathematical models for regulatory mechanisms of living systems, we can write [16]:

$$\frac{dX(t)}{dt} = F(X(t-h)) - bX(t),$$

where $X(t)$ is the function expressing the activity of the considered OR at the time moment t; $F(\xi)$ is the function of the OR biosynthetic activity; h is the time radius; b is parameter of OR signals decay.

Let us consider two versions of the OR activity models within the framework of accepted assumptions.

A mathematical model of the ORASTA functioning without taking into account external regulators. In this case, only the OR signals are allowed to exist in the medium and it is assumed that the regulatory medium does not have a generative ability. Then, in the absence of signals in the environment, the OR cannot function: to start the operation mode, the system must have "onset" signals. In other words, we have:

$$\frac{dX(t)}{dt} = aX(t-h)e^{-cX(t-h)} - bX(t)$$

in the observer coordinate system and

$$X(t) = \frac{a}{b}X(t-h)e^{-cX(t-h)}$$

in own coordinate system. Here a, b, c are positive constants and $b \geq b_0 > 0$.

A mathematical model of the ORASTA functioning with taking into account external regulators. In many cases, external regulatory systems that support the OR activity at its very low activities take part in the regulation of hereditary units. In these cases, the activity of the signal medium should be taken into account and equations have the following form:

$$\frac{dX(t)}{dt} = a_0 e^{-c_0 X(t-h)} + a_1 X(t-h)e^{-c_1 X(t-h)} - bX(t) \qquad (1)$$

in the observer coordinate system and

$$X(t) = \frac{a_0}{b}e^{-c_0 X(t-h)} + \frac{a_1}{b}X(t-h)e^{-c_1 X(t-h)}$$

in own coordinate system. Here a_0, a_1, b, c_0, c_1 are positive constants.

Qualitative and quantitative researches

Eq. (1) (in case $a \geq a_0 > 0$ and $b \geq b_0 > 0$) has the ability of self-excitation and used to study the regulatory mechanisms of the functioning of genetic systems associated with the metabolic system, taking into account the receipt of external hereditary cancer factors and activity of non-coding regulatory microRNAs.

Let us consider main results of a qualitative analysis of the mathematical model of independent ORs. We consider Eq. (1) as the equation of the most general type of similar models. We write the equation in a dimensionless form. First, we will replace $t = h\tau$, $X(h\xi) = \alpha Y(\xi)$.

Here

$$\alpha\frac{dY(\tau)}{hd\tau} = [\alpha_0 + a_1\alpha Y(\tau-1)]e^{-cdY(\tau-1)} - b\alpha Y(\tau)$$

with grouping, we have

$$\frac{1}{bh}\frac{dY(\tau)}{d\tau} = \left[\frac{\alpha_0}{\alpha b} + \frac{a_1}{b}Y(\tau-1)\right]e^{-cdY(\tau-1)} - Y(\tau). \qquad (2)$$

If we take α is equal to $\frac{\alpha_0}{b}$ and

$$\gamma = \frac{1}{bh}, \qquad \alpha = \frac{\alpha_1}{b}, \qquad d = c\frac{\alpha_0}{b},$$

then we have

$$\gamma\frac{dY(\tau)}{d\tau} = (1+\alpha Y(\tau-1))e^{-dY(\tau-1)} - Y(t);$$

$\gamma,\ \alpha,\ d > 0.$

Here, the time radius and the effect of the external controller are centered. To determine the equilibrium position, we have the following transcendental equation

$$(1+a\beta) = \beta e^{\alpha\beta}.$$

We have one positive equilibrium position (β_0). We present the results of a qualitative study (2) near the equilibrium position. Let us take the function

$$\eta(z) = (1+\alpha z)e^{-dz} - z$$

and we linearize it near β_0. Let Z be an infinitesimal. Then

$$\eta(\beta_0 + z) = (1+\alpha(\beta_0+z))e^{-d\beta_0 - dz} - z - \beta_0 \cong$$
$$\cong (1+\alpha\beta_0 + \alpha z)(1-dz)e^{-d\beta_0} - z - \beta_0 \cong$$
$$\cong (1+\alpha\beta_0 - dz - \alpha\beta_0 dz + \alpha z)e^{-d\beta_0} - z - \beta_0 =$$
$$= (\alpha - \alpha\beta_0 d - d)\frac{\beta_0}{1+\alpha\beta_0}z - z = \left(\frac{\alpha}{1+\alpha\beta_0} - d\right)z - z.$$

The Eq. (2) near the equilibrium position have the following form:

$$\gamma\frac{dY(\tau)}{d\tau} = \eta Y(\tau-1) - Y(\tau),$$

where

$$\eta = \beta_0\left(\frac{\alpha}{1+\alpha\beta_0} - d\right).$$

The characteristic equation has the following form:

$$(\lambda+\theta)e^{\lambda} + \xi = 0,$$

where

$$\theta = \frac{1}{\gamma}, \qquad \xi = -\frac{\eta}{\gamma} = -\eta\theta.$$

According to the Hayes stability condition [17], it is necessary

1. $\theta > -1$ or $\frac{1}{\gamma} > -1$;
2. $\xi + \theta > 0$ or

$$\frac{\beta_0}{d}\left(d - \frac{\alpha}{1+\alpha\beta_0}\right) + \frac{1}{\gamma} > 0;$$

3.

$\xi < \varphi\sin\varphi - \theta\cos\varphi$,

where φ is the root of the equation $\varphi = \theta tg\varphi$.

Note that the first condition is always satisfied. Since, then

$$d > -\frac{1}{\beta_0^2}e^{-d\beta_0} \Rightarrow d > \left(1-\frac{e^{-d\beta_0}}{\beta_0}-1\right)\frac{1}{\beta_0} \Rightarrow$$

$$\Rightarrow d > \left(\frac{\beta_0}{\beta_0}-\frac{e^{-d\beta_0}}{\beta_0}-1\right)\frac{1}{\beta_0}.$$

$$d > \left(\frac{\beta_0 - e^{-d\beta_0}}{\beta_0}-1\right)\frac{1}{\beta_0}, \quad \frac{\beta - e^{-d\beta_0}}{\beta_0^2} = \frac{\alpha}{1+\alpha\beta_0}.$$

$$d > \frac{\alpha}{1+\alpha\beta_0} - \frac{1}{\beta_0} \Rightarrow \left(d - \frac{\alpha}{1+\alpha\beta_0}\right) > -\frac{1}{\beta_0}$$

Consequently, as a result we have

or

$$\beta_0\left(d - \frac{\alpha}{1+\alpha\beta_0}\right) > -1,$$

We find that the second condition is fulfilled.

Let us consider the third condition of Hayes. We have

$$\frac{\beta_0}{\gamma}\left(d - \frac{\alpha}{1+\alpha\beta_0}\right) < \varphi\sin\varphi - \frac{1}{\gamma}\cos\varphi$$

or

$$\beta_0\left(d - \frac{\alpha}{1+\alpha\beta_0}\right) < \gamma\varphi\sin\varphi - \cos\varphi.$$

Suppose, that

$y(\gamma) = \gamma\varphi\sin\varphi - \cos\varphi$, where $-\pi/2 < \varphi < \pi$,

then

$$y(0) = -\cos\pi = 1;$$

$$y(\infty) = \gamma\varphi\sin\varphi - \cos\varphi\big|_{\gamma=\infty} = \frac{\pi}{2}\gamma\big|_{\gamma=\infty} = \infty;$$

$$y(\gamma) > 0 \quad \text{for all} \quad \gamma \in (0,\infty).$$

Therefore, there exists a constant $\delta > 0$, such that

$$y(\gamma) > \delta\gamma.$$

Then, if

$$\beta_0\left(d - \frac{\alpha}{1+\alpha\beta_0}\right) < \delta\gamma, \tag{3}$$

the third condition is always satisfied. For (3) we have

$$d\beta_0 - \frac{\beta_0 - e^{-d\beta_0}}{\beta_0} < \delta\gamma.$$

Since $\gamma = (bh)^{-1}$, we have

$$bh < \frac{\delta\beta_0}{d\beta_0^2 - \beta_0 + e^{-d\beta_0}}.$$

Thus, if

$$bh < \frac{\delta\beta_0}{d\beta_0^2 - \beta_0 + e^{-d\beta_0}} \tag{4}$$

then the equilibrium position β_0 is stable. This shows that the proposed equation for modeling regulatory mechanisms of genetic systems activity with taking into account non-coding circulating regulator has one positive equilibrium position, which is stable under (4). If (4) is not satisfied, then (2) has an oscillatory behavior (Fig. 1). For certain values of internal and external influences there is chaotic behavior of genes and its regulatory network linkages, which leads to an abnormal state and death (Fig. 2). This equation can be used to simulate the activity of genetic systems, taking into account external regulators [18].

III. RESULT AND DISCUSSION

Results of qualitative and quantitative researches have allowed to define some regularities of cancer development and to consider questions of possible ways of treatment.

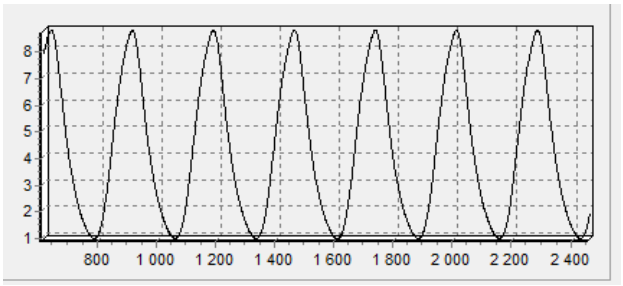

Fig. 1. Periodic oscillations in gene activity.

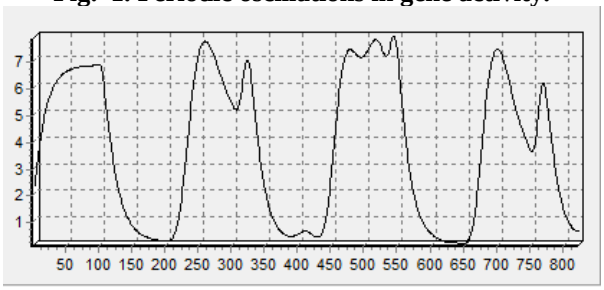

Fig. 2. Chaotic behavior of genes and its regulatory network linkages.

During computer experiment using the developed program based on functional-differential equation, conditions were obtained for modeling the normal cells functioning and the occurrence of malignant neoplasms. Based on the results of qualitative research and quantitative calculations, a parametric portrait for model systems (2) was developed with the following behavior: the trivial attractor, the stationary regime, Poincare-type limit cycles, dynamic chaos, destructive changes – the "black hole" effect. The domains of normal behavior are generally considered as the region B with stable equilibrium (characterized by a constant concentration of substances (homeostasis, stationary states)) and the region C with regular oscillations (provide periodic undamped fluctuations in the concentrations of certain groups of substances (oscillations, cycles)). It can be assumed that region B is a region of cells functional activity, and region C is a region of cells mitotic activity. The area of dynamic anomalies is usually considered to be the region of dynamic chaos – D and the region of the "black hole" effect – E. The region of dynamic chaos is characterized by irregular fluctuations in cell division (cancer start and grow) and can be identified as a regulation loss in the considered system and beginning the tumorigenesis process. It borders on one side with the region of limit cycles of the Poincaré type (where the behavior of the system is characterized by two-sidedly stable periodic oscillations), and on the other hand with the region of sharp destructive changes-the "black hole" effect. The extinction area can be identified with the area of programmed cell death – apoptosis, and the "black hole" region – with necrosis.

IV. CONCLUSION

A general analysis of the equations for regulatory mechanisms of living systems at the considered levels of organization shows the possibility of accepting the functional differential equations type (2) as the main equation for mathematical modeling of tumorigenesis process with taking into account non-coding circulating regulators. The requirement of the presence of a positive attractor with a finite pool allows us to analyze the nature of the stability of nontrivial equilibrium by the Lyapunov method using the Hayes criterion to analyze solutions of the characteristic equation. The methods of qualitative analysis and chaos degree assessment allow us to determine the characteristic features of the behavior of dynamic systems in the areas of anomalies. Thus, an extremely important role in the functioning of the human body at normal and diseases belongs to molecular genetic regulatory mechanisms that ensure the performance of vital organs functions: maintain stable states in the body characterized by a constant concentration of substances; provide periodic undamped fluctuations in the concentrations of certain groups of substances; control irreversible processes: development, growth, differentiation, apoptosis. The results of a series of computational experiments showed that functional differential equations allow us to consider the main modes of functioning of the regulatory mechanisms of cells: programmed cell death (apoptosis), stationary state, self-oscillations, irregular behavior (cancerous growths) and a sharp destructive change - the "black hole" effect (metastasis) in depending on various concentrations of micro-RNA.

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