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Mathematical Modeling of the Thyroid Regulatory Mechanisms

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Abstract Mathematical and computational modeling is a promising field in practical study on functioning of regulatory mechanisms (RMs) in live systems at the level of cell communities and tissues. In this article we attempted to describe a computer model to control number of thyroid follicles in both normal conditions and malignancy. The software above was conceived as a computer model to simulate functioning of regulatory mechanisms of a thyroid structural unit, follicular cell community. Prognostic data about cell proliferative behavior, particularly upon alterations taking place as a result of therapeutic effects of external signals, such as, changes in concentrations of thyroxine and triiodothyronine or cytotoxic effects of drugs is of high significance in study on the thyroid pathologies, especially, on malignantly transformed cells of the organ. Both experimental evidence and theoretical data about the thyroid structural – functional organization at the cellular level allow creating mathematical models to quantitavely assess number of a follicular cell community in both normal and abnormal conditions of the basis of the method of live system RM's modeling and cell community RMs equations.

Keywords: *mathematical modeling, thyroid follicles, malignancy*

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1. Introduction

Mathematical and computational modeling is a promising field in practical study on functioning of regulatory mechanisms (RMs) in live systems at the level of cell communities and tissues [1]. Computational modeling significantly broadens opportunities for other methods of investigation. As it was mentioned in the previous study [2], the model provides auxiliary facility in experiments presenting to a researcher a live cell or organ analogue more accessible to manipulation than its prototype. Relatively self-sustaining behavior of the model as well as its abstraction from its prototype prompts novel hypotheses as well as exploratory and pilot experiments. Since its inaccuracy either prevents a functional computer model from functioning or promptly results in findings apparently discriminating it from its prototype this type of models can serve as a definite criterion of accuracy of regulations and theories realized in them. In addition, as it is, any model is a unity of theory and practice since it contributes to formal characterization and qualification of data about subject being examined, facilitating hypothesis generation and verification. Finally, an efficiently functioning computer model, reflecting processes of intrinsic interaction and representing end effects of the interaction can be used not only for research but also in clinical situations to predict cell or organ "behavior" in response to the drug-induced or any other effect.

In this article we attempted to describe a computer model to control number of thyroid follicles in both normal conditions and malignancy.

Thyroid is a principal endocrine gland synthesizing a number of hormones (thyroxine, triiodothyronine) essential for a human organism's homeostasis sustaining. Thyroid follicle (*folliculus glandulae thyrodeae*) is its basic structural and functional unit [3]. It consists of epithelial cells actively participating in formation of thyroid hormones. Life activity of the follicular cells includes phases of growth, differentiation, performance of specific functions associated with hormone formation and death. Mathematical and computational modeling of the organ's regulatory mechanisms allows studying quantitative principles of functioning of the follicular system cell communities in the process of synthesis of thyroid basic hormones as well as their disturbance triggering various types of malignancies. Thus, the model in question allows predicting alterations in follicular cell proliferative activity as well as proliferative tissue behavior by the quantitative parameters introduced.

Here are the issues of RMs mathematical modeling for the thyroid follicular cell community. Let us consider a variant of study on regulatory mechanisms of the thyroid follicular cell number at the various phases of their life

activity, including mitosis (M), growth and development (B_1), differentiation (D), performance of specific function, such as, hormone formation (S) and ageing (B_2) (Figure 1) by means of differential equations representing regulation of a functional unit, cell community [4,5]. Let $X_1(t)$, $X_2(t)$, …, $X_5(t)$ are the values, respectively, characterizing number of follicular cells dividing, growing, differentiating, performing specific function and ageing at t moment of time. Let set up equations to quantitatively describe alterations in number of the thyroid follicular cells at each phase of their life activity. The follicular cell replication taking place, functionally the phase of mitosis is the most significant one. Cell replication rate generally depends on a number of potentially replicable cells as well as on nature of the agent facilitating the mitosis [6].

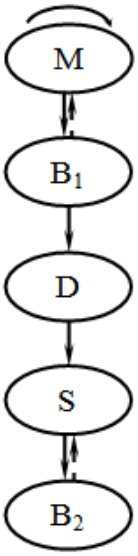

Figure 1. Elementary chart of transitions in the model of the thyroid follicular cell community regulation

Since in the course of evolution follicles with valuable functions to produce hormones have been formed, it is more easily to assume that number of effectors and nutrients entering the mitotic zone depends on ability of a cell community to perform these specific functions. In other words it depends on a number of cells in the **S** phase. Taking into account this effect (end product inhibition) and possibility for the cells from **M** phase to pass to the **B1** phase the following equation representing dynamics of the replicating follicular cell number can be written:

$$\frac{dX_1(t)}{dt} = a_1 X_1(t-1) X_4(t-1) e^{-\delta X_4(t-1)} + b_1 X_2(t-1) - a_2 X_1(t), \quad (1)$$

where a_1 is a mitosis rate constant, b_1, a_2 are constants of rate of transition from phase **M** to phase $\mathbf{B_1}$ and backward and δ is a coefficient characterizing degree of end product inhibition in the system simulated.

The transitions from one phase of life activity to another taken into account, the following system of functional-differential equations representing alterations in cell number in the $\mathbf{B_1}$, **D, S** and $\mathbf{B_2}$ phases can be offered:

$$\begin{aligned}
\frac{dX_2(t)}{dt} &= a_2 X_1(t-1) - (b_1 + a_3) X_2(t); \\
\frac{dX_3(t)}{dt} &= a_3 X_2(t-1) - (b_2 + a_4 + \alpha) X_3(t); \\
\frac{dX_4(t)}{dt} &= a_4 X_3(t-1) + b_3 X_5(t-1) - (a_5 + \beta) X_4(t); \\
\frac{dX_5(t)}{dt} &= a_5 X_4(t-1) - (b_3 + \gamma) X_5(t),
\end{aligned} \quad (2)$$

where α, β, γ are constants of rate of apoptosis for differentiating, performing specific function and ageing cell communities, respectively (Figure 2). The program was create in the programming environment Delphi 7.

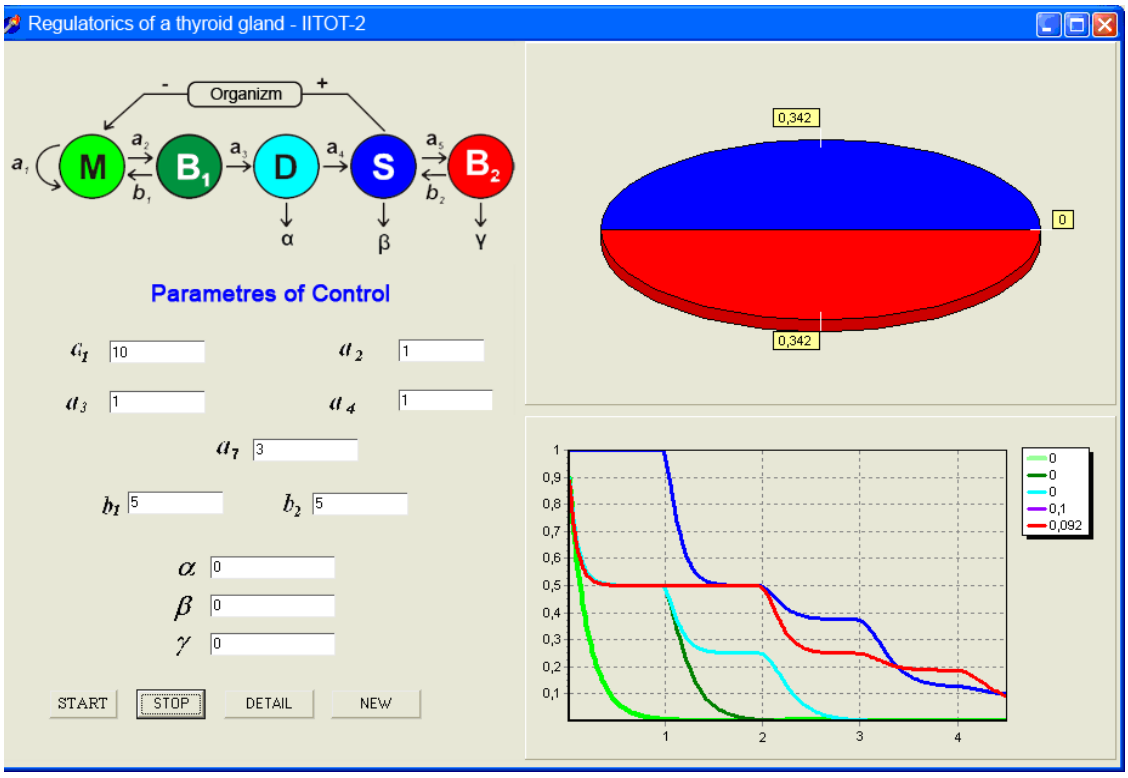

Figure 2. View of display with the computer model to control the thyroid follicular cell community's regulatory mechanisms

Equations (1) and (2) represent a closed system of functional-differential equations of the follicular cell number dynamics. The equations can be solved on a computer with Bellman-Cook's method of successive integration [7] by representation of initial function at the unit length intercept. A dialogue box of the program designed on the basis of the mathematical model to control thyroid follicular cell community's regulatory mechanisms can be seen in Figure 2. As it can be seen from Figure 2, in the **M** → **B**$_1$ → **D** → **S** → **B**$_2$ chain of characteristics any adjustment of numeric parameters regulating rate of signals responsible for both cell transitions forward to the next or back to the previous stages of differentiation as well as for exit of cells beyond the cell community's limits (cell death) is possible. Let us consider separate parameters to control the thyroid follicular cell regulatory mechanisms in detail. Values of the $X_1(t)$ variables at the initial moment of time $X_1(0)$ (i=1,2,…,5) allow specifying the starting value of cell number in the community, that is, to use initial number of the follicular cells for further modeling. By means of a_1 parameter rate of follicular cell replication can be controlled. These values are significant for conduction of a specific cell population behavior analysis in any particular case. Thus, a real base background for any separate virtual experiment which allows (in the course of modeling) obtaining numeric data correlating with quantitative characteristics of the follicular cell distribution in a live organism has been created.

Values of a_2, a_3, a_4, a_5 parameters allow adjusting rate of transitions in the **M** → **B**$_1$ → **D** → **S** → **B**$_2$ chain of characteristics, that is, from cell mitosis to its ageing. Possibility to adjust the parameters is significant for real picture of the thyroid follicular processes in any specific clinical situation. Since each endocrine cell has a potential for transformation, each endocrine gland is known to have some foci of hyperplasia or malignancy. Hyperplasia goes first, followed by benign and malignant tumor. That is the reason why the disease progressed gradually and may not manifest till 35-40 years of age. Clinical picture and laboratory parameters depend on the stage the thyroid tumor was diagnosed on [8]. Thus, obtaining initial morphological picture of the thyroid tissue with quantitative parameters of the follicular cell proliferation, we can determine a_2, a_3, a_4, a_5 transition rates, first, to significantly increase confidence of mathematical analysis and process progression prognosis using the computer program discussed, and, second, to calculate quantitative characteristics of production of hormones (thyroxine and triiodothyronine) at the S stage.

Values of b_1 parameter allow setting the rate of possible thyroid follicular cell transitions from initial growth phase (**B**$_1$) back to mitotic activity phase (**M**). b_1 parameter values represent possibility for cell transition from **B**$_2$ phase (ageing) back to active hormone production phase (**S**). The parameters are introduced into the program aiming at simulating stress situations possible for the follicular cell community. Alterations in b_1 and b_2 parameters allow considering theoretical variants of cell behavior upon acute reductions (or excesses) in the concentrations of hormones produced by them into the medium (into the organism or into blood). Thus, by introducing backward transitions into the modeled system we are able:

1. to increase accuracy of results obtained in the system simulated and
2. to get an opportunity to study cell community behavior upon alterations in exogenous factors (external signals, that is, hormone concentrations in the medium).

α, β, γ values allow adjusting rate of natural cell loss (cell death or apoptosis) from the system simulated. Introduction of the parameters allows assessing rates and extent of cell death upon various characteristics of variable transitions **M** → **B**$_1$ → **D** → **S** → **B**$_2$ (from cell mitosis to its ageing) as well as predicting cell community progression upon pathologies and alterations in external regulatory signals.

Based on the up-to-date information technology tools, the program was checked out with general principles of functioning of the thyroid follicular cell communities taken into account. In the course of its checkout conditions to simulate not only normal thyroid follicular cell community functioning, but also onset and progression of malignancy [9,10] were obtained. The computer calculations showed acceptability of the relevant variables, parameters and regulatory pattern used for quantitative study on regulatory mechanism functioning of the thyroid follicular cell communities.

A comparative analysis of the characteristic behaviors of computer models suggest the presence of a variety of modes regulatory number of cells of the follicle: tranquility (α), a stable stationary state (β), periodic (γ) and irregular fluctuations (δ), and the existence of a sharp collapse of the vibrational solutions - the effect of "black hole "(μ). Irregular fluctuations and the "black hole" can be identify by the uncontrolled multiplication and a sharp destructive change in the number of thyroid follicular cells.

Regularities occurrence and development irregular fluctuations and "black holes" were investigated by analyzing the dynamics of the values of the Lyapunov exponent (Figure 3) on the PC using a special software "SW-FDE-3", implemented in environment Delphi 7. Numerical experiments are carry out for any possible biological reasonable numerical data.

Computational experiments with computer models showed that successive increase of the parameter of reproduction observed in the growth of the load on the simulated system, leading to the sequence of transitions $\beta \to \gamma \to \delta \to \mu$, for completion sharp destructive cellular homeostasis of thyroid gland.

In the case of finding the cell community thyroid follicle in anomalies conditions (δ and μ) arises the question of taking her to regular oscillations (γ) and (or) to stationary mode (β). The results of Computer Science showed the existence in the field δ of small regions of regular behavior (r-windows) considered system (Figure 3).

Presence in the field δ r-windows allows you to temporarily solve the problem of normalization of the number of cells in the follicle

by entering the system to the nearest r-window, and then to bring the system out of the field δ. Therefore, an effective route is to organize the disposal of the area of irregular δ to γ the chain consisting of r-windows. The transience of destructive changes in the case of the effect of "black hole" complicates matters cell behavior management community thyroid follicles. Here

assessment is required of the time spent in the "black hole" and the development of efficient (in time) measures the transfer system in the area of deterministic chaos, and then a zone of regular oscillations.

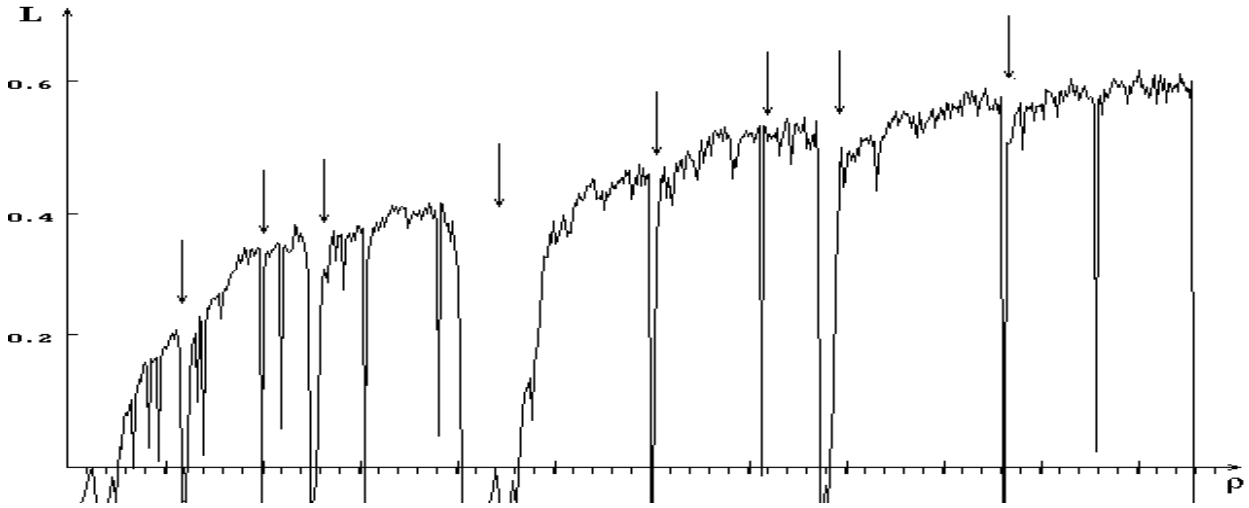

Figure 3. Dynamics of the Lyapunov exponent of discrete analog of the model system (1) - (2) in the field irregular fluctuations δ (arrows indicate the r-windows)

2. Discussion

The software above was conceived as a computer model to simulate functioning of regulatory mechanisms of a thyroid structural unit, follicular cell community. Prognostic data about cell proliferative behavior, particularly upon alterations taking place as a result of therapeutic effects of external signals, such as, changes in concentrations of thyroxine and triiodothyronine or cytotoxic effects of drugs is of high significance in study on the thyroid pathologies, especially, on malignantly transformed cells of the organ.

Computer modeling in biology is becoming more widely spread method of research. Biology has to do with complex system with strong intrinsic many-sided and even multistage various organizational levels, such as, molecular, cellular as well as those of an organ, an organism and a population [13]. However, so complex a tool by no means always is necessary to be used in modeling a biological object. Developing the computer model we aimed at preserving strict sequence of signal RMs, assuming possibility of insignificant distortions in the general simulated picture. To our mind introduction of so many relevant factors into mathematic analysis could have result in complication of the logical construction in general and consequently in reduction of accuracy of the end numerical data obtained. That was the reason why we thought it reasonable to come to nothing more than to use simple logical connections to get quantitative results.

Today the computer program to mathematically simulate regulatory mechanism functioning of the thyroid follicular cell communities can not be considered as a fully-featured commercial product. For the product to be commercialized much work is to be done. Direct dependences of the adjusted values on really existing norms, for instance, thyroid hormone concentrations in peripheral blood or mean values of endocrine tissue mitotic activity are the first to be dealt with. Still the existing computer program is used in our group research to study thyroid oncopathologies.

On the basis of modeling technique of regulatory mechanisms of living systems and equations regulyatoriki cellular communities have developed mathematical and computer models for the quantitative analysis of the population dynamics of the cellular community thyroid follicles in normal and pathological conditions. We have developed a qualitative analysis of functional differential equations for all possible biologically reasonable initial conditions and data. Due to the discreteness of the experimental data is conducted the initial approximation of functions on the basis of discrete values of variables and equations to obtain approximate solutions for a finite number of them. Modeling research shows that chronic increase in the value of the parameter reproduction leads to anomalous behavior of the number of cell community follicular thyroid: disturbed stationary state oscillations occur with the transition to the irregular fluctuations unpredictable reproduction follicle cells of the thyroid gland and then - to the effect of "black hole". The existence of anomalies in the field regular behavior of small regions (r-windows) to temporarily solve the problem of normalization of the number of cells by entering the follicle of to the nearest r-window, and then to bring the system out of the field of chaos.

Thus, the developed software tool for analyzing the regulatory mechanisms of origin, development and diseases consequences of the thyroid gland important for: ensuring of objective, rapid, ecologically clean and resource-saving technologies for analysis of regulatory mechanisms of the thyroid gland, to identify effective points of impact on the system and its regulatory to optimize the functional activity of the thyroid cancer in order to achieve normal modes of its effective life

3. Conclusion

Both experimental evidence and theoretical data about the thyroid structural – functional organization at the cellular level allow creating mathematical models to quantitavely assess number of a follicular cell community in both normal and abnormal conditions of the basis of the

method of live system RM's modeling and cell community RMs equations.

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