

Mathematical Modeling of the Regulatorika of Follicular Thyroid Carcinoma

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Abstract: This article is devoted to the analysis of research work conducted using methods of mathematical modeling of the activity of the thyroid gland. The article gives a brief review of various methods of mathematical modeling of the dynamics of the thyroid gland. Most authors have indicated a mathematical modeling of the dynamics of the thyroid gland. Mathematical modeling of regulator of regulation of thyroid gland cells and computer model using Runge-Kutta method on the basis of mathematical model. Based on experimental experiments using a computer model, characteristic regimes of the dynamics of the regulatory mechanisms of the thyroid gland cells were analyzed. Qualitative and quantitative study of equations of mathematical models of cellular regulatory mechanisms community of a follicle of the thyroid gland showed the presence of a steady state modes sustainable, stable self-oscillating behavior, irregular functioning (chaos) and the effect of sudden destructive changes ("black hole") in the number of cells in the follicle of the thyroid gland. Irregular vibrations and a "black hole" can be identified by uncontrolled reproduction and a sharp destructive change in thyroid follicle cells. Parametric portrait, which clearly highlights areas of homogeneous solutions of the model equations cellular regulatory mechanisms community of a follicle of the thyroid gland, was presented.

Keywords: Regulatorika, Mathematical and Computer Models, Functional-Differential Equations, Time Delay, Functional Unit of Cellular Communities, Follicle, Chaos, Black Hole

1. Introduction

The thyroid gland is one of the main endocrine glands, synthesizing a number of hormones (thyroxin, triiodothyronine), necessary for maintaining the homeostasis of the body. The incidence of thyroid disease is 8% of the adult population of the globe and it increases annually. According to the World Health Organization (WHO), among endocrine disorders, diseases of the thyroid gland rank second after diabetes. More than 665 million people in the world have endemic goiter or suffer from other thyroid pathologies; 1.5 billion people are at risk of developing iodine deficiency diseases. However, according to statistics, the increase in the number of thyroid diseases in the world is 5% per

year [1].

Currently, one of the most important tasks in medicine is the study of the regularities of the regulatory mechanisms of the thyroid gland follicles using mathematical and computer simulation methods.

2. Materials and Methods

Many scientific papers have proposed numerous mathematical models describing the dynamics of the thyroid hormone. In this article, mathematical and computer modeling of the regulator of the number of cells of the follicle of the thyroid gland, mainly carried out at the cellular level.

P. Saratchandran, E. R. Carson, E. Reeve [2] developed a mathematical model for the regulation of human thyroid

hormones based on the most accessible experimental data. The authors suggested that the rate of stimulation of secretion of the hormone thyrotropin in the thyroid gland is proportional to the logarithm of the level of thyrotropin released into the blood. The authors conclude that in mathematical modeling of hormone secretion, it is necessary to take into account the past history of plasma hormone levels.

In D. Švitra, E. Jančys [3], the authors cite one of the first mathematical models for regulating the functioning of the thyroid gland, proposed in 1954 by Danzider and Elmegreen. The authors describe the interaction of thyrotropin (thyotropin) $P(t)$ with thyroid hormones $T(t)$ using a system of two nonlinear differential equations

$$\begin{aligned} \dot{P}(t) &= \frac{k_1 m T(t)}{1 + m T(t)} - b P(t), \\ \dot{T}(t) &= c - \frac{k_2 n P(t)}{1 + n P(t)} - g T(t) \end{aligned} \quad (1)$$

where k_1, k_2, b, c, g, m and n are positive constants.

Kolesov V. V., Roziev R. A., Matusевич E. S., Stavinsky B. C. [4] developed a mathematical model describing the kinetics of accumulation and elimination of thyroid hormone and taking into account the change in the properties of the thyroid gland during irradiation at a high dose. To describe the processes, linear and nonlinear two-chamber models were used, in which the rate of iodine excretion linearly depended on the accumulated dose and varied abruptly when the threshold dose was reached. In this case, the solution in the case of a linear model is obtained explicitly, and for non-linear models in the first case an approximate solution was used, and in the second - the exact solution. The authors obtained better results using a nonlinear model, in which the rate of elimination varied abruptly when the threshold dose was reached.

O. G. Donskaya, L. V. Nedorezov [5] analyze iodine balance in the body using a simplified mathematical model that they describe, which describes the change in iodine concentration in various organs and tissues and the iodine fixation conditions when the iodine enters the body food

Giulia Spaletta [6] developed a geometric model of the thyroid gland. In this paper, the author conducts a study of the possibility of recreating the geometry of the artery of the thyroid gland. The image analysis method is used to teach the recursive nature of the arterial tree structure of the thyroid gland. The goal is to understand independently what is real, to simulate the vascular framework of the lobe, so that it represents the correct anatomical network, why develop an organ that supports the morphological and physiological characteristics of the thyroid gland.

The thyroid gland in the endocrine system of mammals carries the main functional load associated with the development of the organism. The hormones secreted by it promote growth and normal functioning of the body. To date, the main signaling pathways within the thyroid gland and biochemical processes have been identified that help to

understand some of the disruptions in its work, leading to various diseases of the body as a whole. [7]

In the proposed mathematical model, the following main processes are taken into account: iodine intake into the thyroid gland from the outside, the formation of thyroglobulin inside the thyroid gland, iodination of thyroglobulin, the formation of triiodothyronine (T_3) and thyroxine (T_4) with their subsequent release from the thyroid gland. Mathematically, the model is a Cauchy problem for a system of ordinary differential equations.

$$\begin{aligned} \frac{du_J}{dt} &= \nu(u_J^0 - u_J) - a_{13} u_{Tg} \frac{u_J}{1 + u_J}, \\ \frac{du_{Tg}}{dt} &= \mu_{Tg} u_{Tg} \frac{u_J}{1 + u_J} (1 - u_{Tg}) - a_{31} u_{Tg} \frac{u_J}{1 + u_J}, \\ \frac{du_{T3}}{dt} &= \mu_{T3} u_{Tg} \frac{u_J}{1 + u_J} - \lambda_{T3} u_{T3}, \\ \frac{du_{T4}}{dt} &= \mu_{T4} u_{Tg} \frac{u_J}{1 + u_J} - \lambda_{T4} u_{T4}. \end{aligned} \quad (2)$$

In these equations, u_J is the amount of iodine in the thyroid gland, u_{Tg} is thyroglobulin, u_{T3} is the hormone T_3 , u_{T4} is the hormone T_4 ; the maximum amount of thyroglobulin that the thyroid gland can produce is taken as a unit, $\nu, a_{13}, a_{31}, \mu_{Tg}, \mu_{T3}, \mu_{T4}, \lambda_{Tg}, \lambda_{T3}, \lambda_{T4}$ are the constants characterizing the reaction rates, u_J^0 is the concentration of iodine entering the thyroid gland. The values of the constants were selected on the basis of experimental data published in the literature. The stationary point in this case is a steady focus. The study of the influence of various parameters included in the equations on the synthesis of hormones.

The thyroid gland produces the necessary hormone thyroxine. The main structural and functional unit of the thyroid gland is the follicle. It consists of epithelial cells that are actively involved in the formation of the major thyroid hormones [8].

Currently, large-scale studies of living systems at the molecular-genetic level, at the level of cell communities, at the level of tissues and organs are conducted in the world. We model at the level of cell communities based on the allocation of a functional unit of cell communities. This approach was developed by Doctor of Technical Sciences, Head of the Regulatory Studies Laboratory of the Scientific Innovation Center for Information and Communication Technologies at TUIT M. Saidalieva [9].

During the life of the cells of the follicle pass the phase of division, growth, differentiation, perform specific functions associated with the formation of hormones and aging. Let X_1 be the number of dividing cells; X_2 - the number of growing cells; X_3 - the number of differentiating cells; X_4 - the number of cells that perform specific functions; X_5 - the number of senescent cells. The general patterns of functioning of the thyroid follicles can be investigated on the

basis of a system of functional differential equations with delay [10]:

$$\begin{aligned} \frac{dX_1(t)}{dt} &= \frac{a_1 X_1(t-1) X_4(t-1)}{1 + d \prod_{j=1}^5 X_j(t-1)} + b_1 X_2(t-1) - a_2 X_1(t); \\ \frac{dX_2(t)}{dt} &= a_2 X_1(t-1) - (b_1 + a_3) X_2(t); \\ \frac{dX_3(t)}{dt} &= a_3 X_2(t-1) + b_2 X_5(t) - (a_4 + a) X_3(t); \\ \frac{dX_4(t)}{dt} &= a_4 X_3(t-1) - (a_5 + b) X_4(t); \\ \frac{dX_5(t)}{dt} &= a_5 X_4(t-1) - (b_2 + c) X_5(t). \end{aligned} \tag{3}$$

Where X_1, X_2, \dots, X_5 - the values characterizing the number of dividing, growing, differentiating, performing a specific function and aging cells of the follicle at time t ; a_i ($i = 1, 2, 3, 4, 5$), b_j ($j = 1, 2$) - constant cell transition rates between the corresponding phases; a, b, c - constant cell death rates.

Equations (3) constitute a closed system of functional-differential equations for the regulyatorika of the number of cell communities. Existence and uniqueness theorems for continuous solutions, as well as approximate solutions of these equations on the PC, can be obtained using the Bellman-Cook sequential integration method when specifying the initial function on a unit length segment [10].

The use of previously obtained results [10] for equations (3) leads to the possibility of a quantitative study of the regulatory sequence of the number of cells of the thyroid gland follicle on the basis of the following functional differential equation

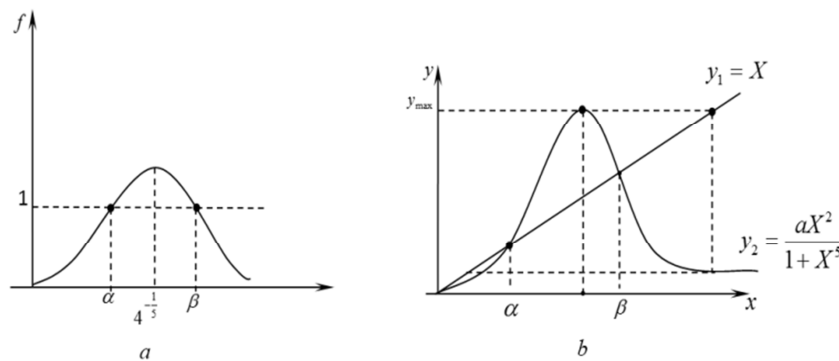


Figure 1. The existence of non-trivial equilibrium positions (5).

Apply the Hayes criterion to (5). The characteristic equation (5) is

$$(\lambda + 1)e^\lambda + 3\beta^4 - \frac{2}{\beta\epsilon} = 0.$$

The first condition of Hayes: $\frac{1}{\epsilon} > -1$, is fulfilled.

$$\epsilon \frac{dX(t)}{dt} = \frac{aX^2(t-1)}{1 + X^5(t-1)} - X(t), \tag{4}$$

where $X(t)$ is a function expressing the number of dividing cells of the follicle of the thyroid gland; $\epsilon = \frac{\theta}{h}$, where θ is the average lifetime of these cells; h is the time interval required for feedback in the hormonal system of the body; a is a parameter expressing the rate of division of cells of the follicle of the thyroid gland.

3. Results and Discussions

In some cases, model systems (2) may be used in the form of a functional equation

$$X(t) = \frac{aX^2(t-1)}{1 + X^5(t-1)} \tag{5}$$

and its discrete analog

$$X_{k+1} = \frac{aX_k^2}{1 + X_k^5}, \quad k = 0, 1, \dots, \tag{6}$$

where X_k is the value expressing the number of dividing cells of the follicle of the thyroid gland at the k -th step of their vital activity.

The trivial equilibrium state of equation (5) always exists. For the existence of non-trivial equilibrium positions (α, β) , the condition must be met (Figure 1):

$$0 < \alpha < 4^{\frac{1}{5}} < \beta < \infty$$

The second condition of Hayes: $\beta > \frac{5}{1 + 3a}$.

The third condition is $3\beta^4 - \frac{2}{\beta} < 2.24$.

At $a \rightarrow \infty$, $\beta \rightarrow \infty$, because $\frac{1}{\beta} + \beta^4 = a$ ($\beta < 4^{\frac{1}{5}}$).

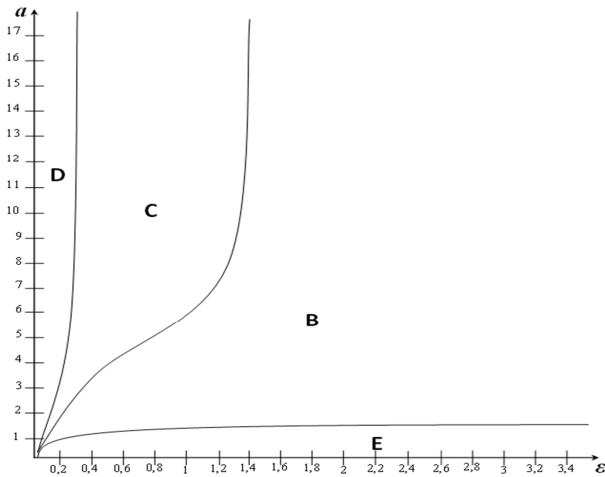


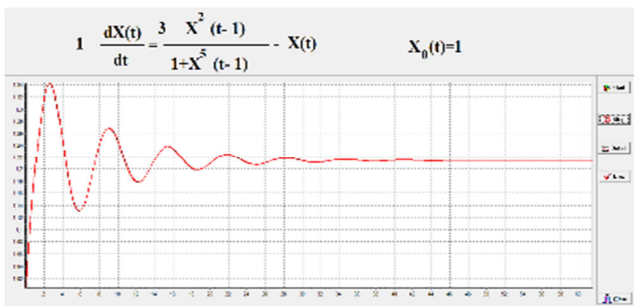
Figure 2. Parametric portrait of the equations of the regulatory community of the cellular community of the thyroid gland follicle.

This means that the third Hayes condition can be violated. Thus, the equation under study has a functional attractor β .

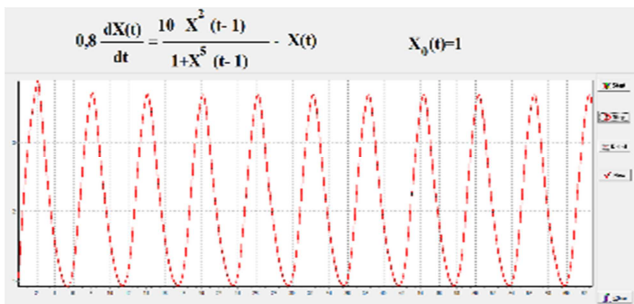
A computer analysis of the characteristic behaviors of solutions (4) - (6) shows the presence in the model of the regulator of the cellular communities of the follicular system of the thyroid gland areas of uniform behavior that correspond to the steady state steady state (B), stable self-oscillatory behavior (C), irregular functioning (D) and the effect of sharp destructive changes (E) - the effect of the "black hole" (Figure 2).

Irregular behavior and the "black hole" can be identified by uncontrolled reproduction (malignant neoplasm) and drastic destructive changes in the regulatory regimen of the thyroid follicle cell communities (metastasis).

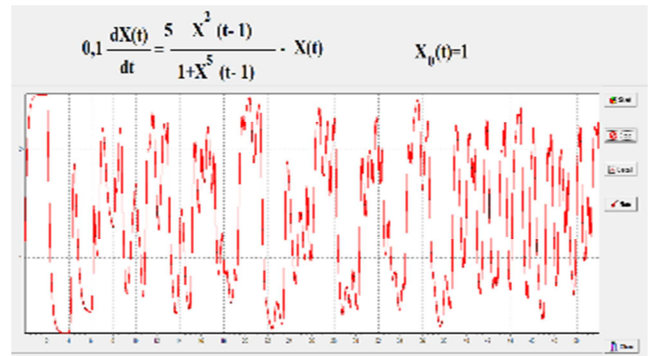
In Figure 3 shows the characteristic phase trajectories of solutions (4).



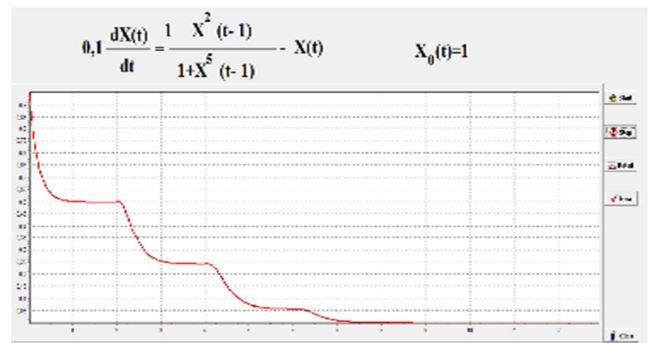
a) Stationary regime



b) Limit cycle



c) Chaos regime



d) "Black hole" regime

Figure 3. Typical phase trajectories of solutions (4), obtained using PC. 3a - stationary regime; 3b - limit cycle; 3c - irregular oscillation (chaos), 3d - "black hole".

4. Conclusions

Thus, the existing biological experimental data and theoretical propositions about the structural and functional organization of the thyroid gland at the cellular level make it possible to build mathematical models for a quantitative analysis of the size of the cellular community of the follicle of the thyroid gland in normal conditions and follicular thyroid carcinoma based on the method of modeling the regulatory mechanisms of living systems and cell communities regulator equations. Quantitative studies show that the regulator cell communities of the thyroid gland follicle have modes of extinction, stable steady state, stable self-oscillatory behavior, irregular functioning and the effect of abrupt destructive changes - the "black hole" effect.

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