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A Mathematical Model of Thyroid Tumor

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Abstract

A mathematical model of the thyroid gland function has been developed. It represents a Cauchy problem for a system of ordinary differential equations. The main biochemical reactions in the thyroid gland are accounted therein: iodine entry, its binding to thyroglobulin, thyroxine formation. The model is based on the principle of pair interactions, balanced proportions and enzyme kinetics. Arisen tumor cells are assumed in the malignant tumor model to absorb healthy ones while growing. The model of the tumor is a boundary value problem for partial differential equations. The stationary points are investigated for stability. To solve the system of nonlinear equations are used numerical methods. The estimation of the rate of tumor growth is given.

Keywords: mathematical modeling, differential equations, thyroid, enzymatic reaction, neoplasm.

Introduction

Mathematical modeling of malignant tumors in mammals is described in many papers [1 - 8]. Most of them developed models of neoplasms without considering the neighboring organs and models of specific types of tumors. One of the complex problems is not just to build mathematical models of the thyroid gland function and models of its disordered functions [9 - 11].

The normal function of the mammalian body largely depends on the thyroid gland function. Entered iodine is processed and hormones regulating various biochemical reactions are produced in it. Synthesis and release include a significant cascade of biochemical reactions. Disordered thyroid gland function at any level of hormone secretion, iodine entry into the functional space, and control over hormones transfer into the bloodstream may lead to various diseases [9, 11]. Scientific publications paid much attention to the development of models of iodine metabolism in the body or mathematical models of the endocrine system [12 - 20], accounting thyroid functions to some extent.

A mathematical model of the thyroid follicle, considering the basic biochemical reactions: iodine enter, its binding to thyroglobulin followed by the hormone $T4$ [21 - 24] formation and accumulation was developed in [25], together with Yu. Balykina. The model is represented by the Cauchy problem for a system of three ordinary differential equations.

Basic biochemical reactions. The functional unit of thyroid is a spherical follicle consisting of follicular cells (thyrocytes) [10, 11, 20, 23, 24, 26] surrounding colloid. Iodine enters into the follicular cells (*I).* Iodine becomes active under the oxidative enzymes, and then enters from the thyrocytes into colloid, wherein, after binding with thyroglobulin (Tg) molecules, thyroid hormones are produced, 95% of which are thyroxine hormones (T4). Hormones are stored in the colloid bound to a thyroglobulin. At decline in serum thyroid hormones, the hormones are cleaved from thyroglobulin and released from follicular cells into the bloodstream, for their regulatory functions [11, 21].

The proliferation of normal follicular cells of the thyroid gland is controlled by external growth factors, which, affecting membrane receptors, trigger different intracellular signaling cascades. An irreversible disorder of the regulation cascades, caused either at increased activity of stimulation mechanisms, or at lost inhibitor activity, is known to be tumor growth.

Iodine deficiency in the body causes deficiency of *T4* hormone as well, though iodine excess causes an excess of the hormones. In both cases, the body reaction to the changed amount of the produced hormones can be a signal to increase the thyroid size, in the former case, to increase *T4* hormone release, and in the latter, to recycle the excess iodine. At long-term iodine deficiency, hyperplasia and hypertrophy of thyreocytes is developed resulting in decreased thyroxine synthesis, increased thyrotropin level, and enhanced thyroid size [9, 21].

Different types of tumors may appear from the follicular epithelium cells different by structure and molecular biological characteristics [9, 27 - 30]. Tumor tissue consists of a series of small, tightly adjacent cells located among the maternal thyroid tissue. Non-epithelial tumors are possible to be developed from lymphoid cells or fibrous connective tissue of the thyroid. Thyroid tumor growth is accompanied by an increased amount of "non-functional" cells, with insignificant number of follicles or with no its formation at all, by displacement of follicles with tumor cells, by decreased total volume of thyroid follicles and, ultimately, "functional" space can be fully substituted with tumor cells, not performing function on the thyroid hormones synthesis [9, 11].

A mathematical model of the thyroid. The thyroid gland represents a combination of various different sized follicles [11, 31], functioning same way. I.e., colloid and its surrounding thyrocytes of all follicles can be assumed to be uniformly distributed over the whole space occupied by the thyroid gland. Therefore, the thyroid is represented in the mathematical model by combination of colloid and thyrocytes. The main processes in thyroid are considered: entered active iodine, iodine binding to thyroglobulin, *T4* hormone production, its binding to thyroglobulin and *T4* hormone release through the outer membrane of the thyroid [11]. Thyroglobulin is retained in the thyroid, does not release to the external environment. The main part of the secreted hormone accounts for *T4,* so its synthesis is considered in the model. The environment with the reaction is assumed to be homogeneous. Approaches were applied in the mathematical model which analogous to those used in [12, 15, 18, 32].

Let u_I is active iodine concentration in the thyroid, u_{Tg} is thyroglobulin concentration, u_{T4} is hormone *T4* concentration. The rates of binding reactions of iodine and thyroglobulin, and of thyroglobulin and hormone are assumed to be proportional to their concentrations: thyroglobulin formation rate is proportional to iodine concentration, and hormone formation rate $T4$ is proportional to thyroglobulin concentration. Under these assumptions, the first reaction is described by the function $a_1 u_I u_{Tg}$, and the second one $a_2 u_{Tg} u_{T4}$. Considering these input designations and hypotheses about the reactions, the system of differential equations describing the processes in the thyroid, is shown as follows:

$$\frac{du_I}{dt} = v(u_I^0 - u_I) - a_1 u_I u_{Tg},$$
$$\frac{du_{Tg}}{dt} = \alpha a_1 u_I u_{Tg} - a_2 u_{Tg} u_{T4},$$
$$\frac{du_{T4}}{dt} = \beta a_2 u_{Tg} u_{T4} - P_{T4} u_{T4}. \qquad (1)$$

In these equations P_{T4} is permeability of the outer membrane of the thyroid, v is the rate of iodine penetration into the thyroid, u_I^0 is equilibrium concentration of iodine at absence of reactions, a_1, a_2, α and β are positive constants characterizing the reaction rate.

The first equation in (1) describes the rate of change of the iodine concentration: iodine enter into the colloid and its residues release (summand $v(u_I^0 - u_I)$) and the rate of iodine binding to thyroglobulin (summand $a_1 u_I u_{Tg}$). Thus iodine is considered to be active. The second equation in (1) describes the rate of change of the thyroglobulin concentration: summand $\alpha a_1 u_I u_{Tg}$ is the rate of thyroglobulin formation, summand $a_2 u_{Tg} u_{T4}$ is the rate of thyroglobulin binding to *T4* hormone. The third equation in (1) describes the formation of thyroid *T4* hormone: summand $\beta a_2 u_{Tg} u_{T4}$ is the rate of hormone *T4* formation, summand $P_{T4} u_{T4}$ is the rate of hormone *T4* release through the outer thyroid membrane into the bloodstream.

Analysis of the stationary states of the system. The system of equations (1) has a stationary point $u_I = u_I^0$, $u_{Tg} = u_{T4} = 0$. One of three eigenvalues $\lambda_1 = -v$, $\lambda_2 = u_I^0 \alpha a_1$, $\lambda_3 = -P_{T4}$ of the Jacobian matrix of the right-hand side of the equation system (1) at this stationary point is positive, and accordingly, this point will be unstable [33]. Instability of the equilibrium position is considered as the beginning of the natural function of the thyroid gland.

The system of equations (1) contains another stationary point, which is a solution of the recurrent equations

$$u_{Tg}^s = \frac{P_{T4}}{\beta a_2}, \quad u_I^s = \frac{v u_I^0}{v + a_1 u_{Tg}^s}, \quad u_{T4}^s = \frac{\alpha a_1 u_I^s}{a_2}. \qquad (2)$$

Characteristic polynomial

$$\lambda^3 + \left(v + a_1 u_{Tg}\right)\lambda^2 + \left(\beta a_2^2 u_{T4} + a_1^2 \alpha u_I\right) u_{Tg} \lambda + \beta a_2^2 u_{Tg} u_{T4} \left(v + a_1 u_{Tg}\right) = 0$$

of the Jacobi matrix of the right-hand side of the equation in this stationary point, according to Hurwitz criterion and Budan-Fourier theorem, has one negative eigenvalue and two either negative or complex conjugate with negative real parts. Therefore, this fixed point is stable.

Considering published relative values of the constants [15, 34] in the model can be taken as follows $\alpha \approx 0.2$, $a_1/a_2 \approx 50$. The remaining constants are selected from conditions to ensure the set output characteristics basing on the ratio (3): iodine conversion is 90%, and at output the ratio of the hormone and thyroglobulin concentration is 4:1 [30, 35 - 38]. The constant is taken as a unit a_2. Considering this, it is accepted in the model: $u_I^0 = 1$, $v = 1$, $a_1 = 50$, $\alpha = 0.2$, $a_2 = 1$, $\beta = 5.5$, $P_{T4} = 1$. At accepted constants, a unit of time in the model corresponds to twenty-four hours, and the concentration of substances is considered to be dimensionless. Thus at the stable state $u_{Tg}^s = 0.25$, $u_{T4}^s = 1.00$, $u_I^s = 0.1$. This stationary point is considered as "natural" equilibrium position (euterioid state), and any deviation is considered a disordered thyroid function.

The thyroid tumor model. One possible cause of the thyroid malfunction may be an appeared tumor. The tumor growth is assumed in the model to be accompanied with elimination of acting follicles, decrease in the thyroid volume, and ultimately full substitution of "functional" space with tumor cells, thus constantly growing tumor cells are expected not performing function on the thyroid hormones synthesis [5, 7, 27, 11, 39].

Experimental data on the kinetics of growth of different tissues demonstrate their exponential growth [27, 28, 40, 41]. If u_{Tu} is concentration of tumor cells, thus kinetics of its own unlimited growth is described by the equation [27, 34]

$$\frac{du_{Tu}}{dt} = \mu_{Tu} u_{Tu},$$

where μ_{Tu} is constant. According to the study [26], constant μ_{Tu} for the tumor growth in mice was changed depending on an experience in the range from 0.01 to 0.1 1/day [11]. According to clinical studies in human, it was approximately 0.001 1/day [26].

The arisen tumor cells are assumed in the tumor model u_{Tu} to be multiplied absorbing u_{Tg} and u_{T4} and replacing them this way. The rate of decrease u_{Tg} and u_{T4} due to tumor cells is proportional to their number and the amount of tumor cells. Thus it is assumed that at full replacement u_{Tg} and u_{T4} from the function space, the tumor stops growing.

The rate of tumor cells growth is considered to be proportional to the amount $u_{Tg}+u_{T4}$ at the current time. Since in the stable state $u_{Tg}=u_{Tg}^{s}$ and $u_{T4}=u_{T4}^{s}$, it is assumed in the model that the inequality is supposed to be $u_{Tu}\le u_{Tg}^{s}+u_{T4}^{s}$. Increase in the tumor cells is accompanied by a decreased iodine enter, and at $u_{Tu}=u_{Tg}^{s}+u_{T4}^{s}$ iodine ceases to enter. The thyroid is represented with a sphere of radius R.

Then the mathematical model of the thyroid with a growing tumor is represented as a system of differential equations

$$\begin{aligned}
&\frac{\partial u_I}{\partial t}=v\left(u_I^0\left(1-\frac{u_{Tu}}{u_{Tg}^{s}+u_{T4}^{s}}\right)-u_I\right)-a_1u_Iu_{Tg},\\
&\frac{\partial u_{Tg}}{\partial t}=\alpha a_1u_Iu_{Tg}-a_2u_{Tg}u_{T4}-\mu_{Tg}u_{Tg}u_{Tu},\\
&\frac{\partial u_{T4}}{\partial t}=\beta a_2u_{Tg}u_{T4}-\mu_{T4}u_{T4}u_{Tu}-P_{T4}u_{T4},\\
&\frac{\partial u_{Tu}}{\partial t}=\mu_{Tu}u_{Tu}\left(u_{Tg}+u_{T4}\right)\left(1-\frac{u_{Tu}}{u_{Tg}^{s}+u_{T4}^{s}}\right)+D\frac{1}{r}\frac{\partial^2(ru_{Tu})}{\partial r^2},
\end{aligned}\qquad(2)$$

where μ_{Tg}, μ_{T4} and μ_{Tu} are constants, D is the coefficient of the tumor cells diffusion.

In the first equation, the rate of iodine enter into the thyroid is described by the function $vu_I^0\left(1-u_{Tu}/(u_{Tg}^{s}+u_{T4}^{s})\right)$ and becomes equal to zero if the tumor occupies all the functional space. In the second equation, the summand $\mu_{Tg}u_{Tg}u_{Tu}$ is the rate of thyroglobulin absorption by tumor cells is considered to be proportional to their concentrations, and the summand $\mu_{T4}u_{T4}u_{Tu}$ in the fourth equation is the rate of the hormone absorption by tumor cells $T4$. The tumor in the proposed model is growing due to absorption of the thyroglobulin and hormone $T4$. The rate of its growth is accepted in accordance with the experimental data [34, 38] proportional to the product $u_{Tu}\left(u_{Tg}+u_{T4}\right)$.

Because the initial total concentration of thyroglobulin and hormone is $u_{Tg}^{s}+u_{T4}^{s}$, thus at achievement u_{Tu} of this value the tumor is supposed to stop growing. This is ensured by a multiplier $1-u_{Tu}/(u_{Tg}^{s}+u_{T4}^{s})$ in the fourth equation.

Boundary and initial conditions should be added to the system of equations (3). If the tumor arises at the initial time, and the system of equations (3) is in a stable position of equilibrium, then as the initial conditions (at $t=0$) are taken as follows

$$u_I = u_I^s,\ u_{Tg} = u_{Tg}^s,\ u_{T4} = u_{T4}^s,$$

$$u_{Tu} = \begin{cases} u_{Tu}^0, & if\ r < \varepsilon, \\ 0, & if\ \varepsilon < r \le R. \end{cases}$$

where $\varepsilon \ll R$, and u_{Tu}^0 are a small positive number. It means that tumor cells are assumed to appear in the center of the sphere in an insignificant amount.

The limited function $u_{Tu}(t,r)$ is taken as boundary conditions at the center of the sphere as well as the equal-zero of the tumor cells flow through the sphere surface:

$$\lim_{r\to 0} r u_{Tu} = 0 \text{ and } \frac{\partial u_{Tu}}{\partial r} = 0 \text{ at } r = R. \qquad (4)$$

Homogeneous solution. A stationary system of equations (3) has two homogeneous solutions.
The first solution

$$u_I = u_I^s,\ u_{Tg} = u_{Tg}^s,\ u_{T4} = u_{T4}^s,\ u_{Tu} = 0$$

corresponds to the absence of tumor cells. In the neighborhood of this solution for small values u_{Tu} the fourth equation in (3) takes the following form

$$\frac{\partial u_{Tu}}{\partial t} = \mu_{Tu} u_{Tu}\left(u_{Tg}^s + u_{T4}^s\right) + D\frac{1}{r}\frac{\partial^2 (r u_{Tu})}{\partial r^2}.$$

The solution of this equation is represented as a trigonometric series

$$u(t,r) = \frac{1}{r} \mathrm{e}^{\mu_{Tu}(u_{Tg}^s + u_{T4}^s)t} \sum_{k=1}^{\infty} A_k e^{-D\lambda_k^2 t} \sin \lambda_k r.$$

This solution will satisfy the conditions (4), if values λ_k ($k = 1,2,...$) are roots of the equation $\sin(\lambda_k R) - R\lambda_k \cos(\lambda_k R) = 0$. Constant coefficients A_k are found to meet the initial conditions.
At solving of the inequality $\mu_{Tu}(u_{Tg}^s + u_{T4}^s) > D\lambda_1^2$ function $u(t,r)$ will be a decreasing function of time, regardless of its value at the initial time and, accordingly, the considered homogeneous solution would be unstable.
The second solution: $u_I = 0$, $u_{Tg} = 0$, $u_{T4} = 0$, $u_{Tu} = u_{Tu}^s = u_{Tg}^s + u_{T4}^s$
corresponds to the cessation of the thyroid gland function. Let along with this solution, another solution, close to it, exist

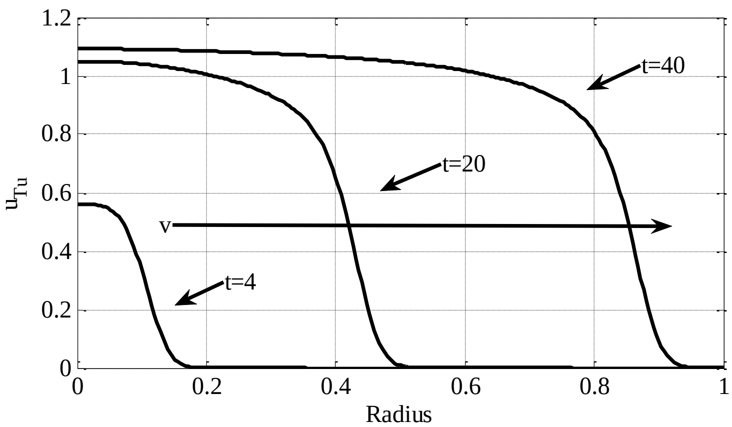
$u_I = \delta u_I$, $u_{Tg} = \delta u_{Tg}$, $u_{T4} = \delta u_{T4}$, $u_{T4} = u_{Tu}^s + \delta u_{Tu}$ so that δu_I, δu_{Tg}, δu_{T4} are small positive values, and δu_{Tu} small compared with u_{Tu}^s value. Then the linear approximation of the system of equations (3) in the neighborhood of the stationary point has the form

$$\begin{aligned} &\frac{\partial \delta u_I}{\partial t} = -v\delta u_I - \frac{v u_I^0}{u_{Tg}^s + u_{T4}^s}\delta u_{Tu}, \\ &\frac{\partial \delta u_{Tg}}{\partial t} = -\mu_{Tg} u_{Tu}^s \delta u_{Tg}, \\ &\frac{\partial \delta u_{T4}}{\partial t} = -\left(\mu_{T4} u_{Tu}^s + P_{T4}\right)\delta u_{T4}, \\ &\frac{\partial \delta u_{Tu}}{\partial t} = -\mu_{Tu}\left(\delta u_{Tg} + \delta u_{T4}\right)\delta u_{Tu} + D\frac{1}{r}\frac{\partial^2 (r\delta u_{Tu})}{\partial r^2}. \end{aligned} \quad (5)$$

As it follows from the second and third equations in (5) δu_{Tg} and δu_{T4} would be positive decreasing function of time. Therefore, δu_{Tu} at the boundary conditions (4) will also be a decreasing function of time. Therefore, the second homogeneous solution will be stable.

The system of equations (3) is non-linear. To build its analytical solution is not considered as possible. The numerical solution of the equations (3) was based on a discretization of differential operators - spatial derivatives are approximated by difference quotients. The obtained system of the nonlinear ordinary differential equations was solved with methods proposed in [42, 43].

The figure for the constants $u_I^0 = 1$, $v = 1$, $a_1 = 50$, $a_2 = 1$, $\alpha = 0.2$, $\beta = 5.5$, $P_{T4} = 1$, $\mu_{Tg} = 0.4$, $\mu_{T4} = 0.4$, $\mu_{Tu} = 1$ a solution at the time points is presented $t = 4, 20, 40$. According to the analysis of numerical experiments, in the first approximation, the solution is represented a wave propagating at the speed $c = 2\sqrt{\mu_{Tu} D\left(u_{Tg}^s + u_{T4}^s\right)}$.



Conclusion

Growth of the thyroid gland tumor, as shown by analysis of clinical trials, is accompanied by its disordered functions. Therefore, the developed mathematical model of a growing tumor is distinguished from most models proposed for description of neoplasms as individual objects in living organisms - the growth of tumor cells occurs in a functioning organ. However, the common feature is admitted that tumor growth is interpreted as autowave motion.

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