Mathematical modelling of regulatory mechanisms of cell groups functioning at norm and at unregulated cell division

M. Saidalieva¹, M.B. Hidirova¹*, G. Yakubova², and Z.Dj. Yusupova³,⁴

¹Research Institute for the Development of Digital Technologies and Artificial Intelligence, 17A, Boz-2, 100125 Tashkent, Uzbekistan
²Tashkent State Pedagogical University, Bunyodkor avenue, 27, 100070 Tashkent, Uzbekistan
³Fiscal institute Under the State Tax Committee of the Republic of Uzbekistan, Str. Kichik Halka Yuli (Malaya koltsevaya), 3, 100173 Tashkent, Uzbekistan
⁴National Research University TIIAME, st. Kori Niyazov, house 39, 100000 Tashkent, Uzbekistan

Abstract. This paper presents a method for modeling organs and tissues based on the equations of the functional unit of organs and tissues (FUOT) and mathematical models for the main cellular functions: division, growth, differentiation, performance of specific functions, aging, apoptosis and natural death. The elements of FUOT are cells. The analysis shows that there are short circuits of regulation, which in specific realizations of cell development correspond to stable or partially stable cellular structures. This can occur as a normal phenomenon in the form of an adaptive response to stressful influences, and as an abnormal pathological condition. Such partial FUOT can be called minifuot. The study of the proliferative minifuot equations show the presence of a nonzero stable equilibrium position, and a stable limit cycle in the first quadrant. The results of these studies can be useful in studying the mechanisms of cell groups functioning at norm and at unregulated cell division.

1 Introduction

Theoretical developments regarding the structural and functional organization of living systems are very diverse and are carried out from different points of view [1-3]. In our opinion, the "principles of mathematical biology" put forward by N. Rashevsky are the most constructive [1]: the theory of organismic sets, the principle of "biological epimorphism" and relational biology, which constitute the principle of the topological representation of both biological and social "organisms" [1]. These principles can be used to model the regularities of the spatial organization of biosystems, evolutionary changes in organisms and the structural and functional organization of cellular systems in plant and animal organisms.

In the last years of the last century, much attention was devoted to the analysis of the principle of hierarchy of block organization of living systems at various levels: molecular, cellular, and supra-cellular [2-3]. It was clear that the spontaneous organization of

* Corresponding author: mhidirova@yandex.ru

© The Authors, published by EDP Sciences. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (http://creativecommons.org/licenses/by/4.0/).
molecular systems cannot lead during the Earth's existence to the observed structural and functional organizations of living systems. Only the formation of individual elementary acts, functions and structures with their further consolidation in the course of evolution and their use to build the next stages of organization of living things could provide the observed level of complex, hierarchical structural and functional organization of living systems [2].

On the other hand (taking into account the evolutionary series of increasingly complex cellular structures), the epimorphism of the totality of biological functions of organisms and the identity of their components, with the existence of a wide variety of spatial organization and functional activity of organs and tissues of animals and plant organisms, leads to the idea of the existence of universal functional unit of organs and tissues of organisms that perform the basic set of elementary functions of living systems (renewal, specialization, metabolism with the environment, fulfillment of specific functions, aging, natural death, apoptosis) - a functional unit of organs and tissues, the formations from which constitute the organs and tissues of a multicellular organism.

Worldwide development of the theory and practice of the regulatory mechanisms functioning of living systems at the main hierarchical levels of the organization is connected with its successful application to biology, medicine and agriculture, because it allows to choose the most effective ways for diseases prophylaxis and treatment, for agricultural techniques of cultivation and plant selection, to creation various biotechnology products. The works, devoted to different types of mathematical modeling of living system regulatory mechanisms, by B. Goodwin, J. Smith, M. Eigen, V.A. Ratner, E.E. Selkova, D.S. Chernavsky (subcellular level); Antomonov, Sendov, R. Tsanev (cellular level); L.I. Lischetovich, Y. Kibardin, K.K. Dzhanseitov (organ-tissue level); N. Rashevsky, A.M. Molchanov, G.I. Marchuk (organismal level) and other are discovered basics mechanisms of biosystem regulation at considered levels, permitting using mathematical modeling to solve medical and biological problems. However, to date, there is no united approach to create mathematical models and effective methods for the quantitative analyzing regulatory mechanisms of living systems, taking into account spatial and temporal organization.

2 Methods

We offer the following definition: a connected set (on the space and (or) time) of cells can be taken as a functional unit of the considered organ or tissue if it contains dividing $M$, buffer $B_1$, differentiating $D$, performing specific functions $S_1, S_2, \ldots, S_n$ and aging $B_2$ cell groups, functioning in an interconnected manner as a whole (Fig. 1).

Fig. 1. Diagram of the functional unit of organs and tissues (FUOT).

The presence of a certain resting phase after the phase of cell division, during which cell growth occurs, the formation of intracellular structures and the choice of the further path of life (division or differentiation) has led to the isolation of a separate pool of $B_1$ with buffer cells. The same zone of buffer cells $B_2$ is highlighted, after the zone of specific functions.
These cells also perform adaptive functions and, if necessary, can, through dedifferentiation, proceed to the repeated performance of specific functions.

Mathematical models of the basic cellular functions of FUOT are built on the basis of equations for the regulatorika of living systems [4-7]. Regulatorika is the science that involves the study of interconnected activity of regulatory mechanisms based on the ORASTA concept which consists of the operator-regulator OR (capable to accept, recycle and transfer signals) and ASTA (active system with time average, carrying out a feedback loop in system for finite time). Using ORASTA the functional-differential equations taking into account stimulating and inhibiting interactions, temporal relations, combined feedback and cooperativity in considered processes are developed [6]:

\[
\frac{dX_i(t)}{dt} = A_N^i(X(t-h)) \exp \left( -\sum_{k=1}^{N} \delta_{ik} x_k(t-h_{ik}) \right) - b_i X_i(t)
\]

With

\[
A_N^i(X(t-h)) = a_{i0} + \sum_{j=1}^{N} \left( \sum_{k_1,...,k_j=1}^{N} a_{i k_1,...,k_j} \prod_{m=1}^{j} x_{k_m}(t-h_{ik_m}) \right)
\]

and with initial conditions

\[
X_i(t) = \varphi_i(t) = t_0 - h \leq t \leq t_0 \quad (t_0 > h), \quad i, j, k_j = 1, 2, \ldots, N.
\]

here \(X_i(t)\) are the sizes characterizing quantity of a signals, developed by \(i\)-th OR at the time moment \(t\); \(h_{ik}\) are a time intervals necessary for \(i\)-th OR activity changing under the \(k\)-th OR activity influence; \(a_{i0}, b_i\) are parameters of formation and disintegration speeds of \(i\)-th signal, accordingly; \(\varphi_i(t)\) are continuous, positive initial functions. OR together with ASTA constitute a regulatory system - ORASTA (Fig. 2).

![Fi. 2. ORASTA Nature.](image_url)

The equations for the model of cell growth are constructed on the basis of the equations for the regulatorika of molecular-genetic systems and the equations for the biosynthetic activity of cells. The basic equations of the model for cell differentiation are based on the model of the regulation of living systems, taking into account the polynucleotide competition of alternative metabolic pathways [4-5]. Models for fulfillment of the specific functions of the considered FUOT can be built on the basis of the activity of specific organs and tissues, a quantitative description of their function. The equations for the cells aging model (cells from the B2 phase) can be constructed on the basis of regulatorika laws for the
molecular-genetic system with taking into account metabolic activity. Natural cell death in
the framework of the FUOT equations is modeled by taking into account the rate of cell
elimination from the cellular community.

It seems that in biosystems, in addition to the main chain, there are a short regulatory
chains, which correspond to stable or partially stable cellular structures in specific
realizations of cell development. This can occur both as a normal phenomenon in the form
of an adaptive response to stressful influences, and as an abnormal pathological condition.
Such partial FUOT can be called minifuot. Let us consider minifuots found in multicellular
organisms.

Rapid proliferating cells under normal conditions are found mainly in the early phase of
the development of the organism, in the epithelial tissues of animals and in the cambial
tissues of plant organisms. In this case, the $B_1 \rightarrow M$ transition has turned from weak
(indicated on the FUOT diagram (Figure 1) by a dotted line) into a solid one, indicated by a
solid arrow (Fig. 3).

Fig. 3. Community of reproducing cells.

This case also includes an unequal division of the egg cells at initial stages of
embryonic development. In the case of extreme influences (mainly during resection,
trauma, etc.), the minifuot arises in rapidly renewing tissues as an adaptive reaction, which
leads to rapid tissue regeneration.

The connection between the buffer cells and the specialized cells is lost. Let's analyze
this case. In some cases, this minifuot can occurs in normal tissues and organs. This leads to
the formation of outgrowths, and in the case of stabilization of minifuots, may give rise to
the formation of autonomous, proliferating groups of cells, very similar in characteristics to
the cellular communities in cancer development.

Minifuot with an inferior specialization. These minifuots are rarely found in normal
conditions. For example, the community of lymphocytes, without completing
specialization, passes into the circulating blood and finally specializes in contact with alien
cells or viruses. Basically, this minifuot occurs in the case of a cellular disease of the body.
An analysis based on the schemes of cell relationships (see Fig. 4) shows that in this case,
immature cells are formed in these tissues and this area atrophies, unable to perform its
normal functions. This is especially often observed, apparently, under skin diseases.

Fig. 4. Three cases of incomplete differentiation in cell communities.
3 Results

Let us consider the results of the analysis of cellular communities functioning based on a proliferative minifuot. The proliferative minifuot consists mainly of dividing M and B1 buffer cells. Cells in B1 area grow, can go back to M, or end their life in buffer zone by natural death or apoptosis. Based on the general equations for the regulatory mechanisms of living systems for a proliferative minifuot, we have the following equations:

\[
\begin{align*}
\frac{dX_1(t)}{dt} &= f_1(X_1(t-\tau), X_2(t-\tau)) - \alpha X_1(t); \\
\frac{dX_2(t)}{dt} &= f_2(X_1(t-\tau), X_2(t-\tau)) - \beta X_2(t),
\end{align*}
\]

(1)

with initial conditions

\[
\begin{align*}
X_1(t) &= \theta_1(t); t \in [0; \tau]; \\
X_2(t) &= \theta_2(t); t \in [0; \tau],
\end{align*}
\]

where \(X_1(t), X_2(t)\) are the number of cells in zones M and B1, respectively; \(\tau\) - transition time between zones M and B1. The right side of (1) consists of terms expressing the rates of "multiplication" and "death".

Let us consider the case when cells from B1 to M do not arrive directly. Since the multiplication of cells requires the presence of at least one cell in M, the rate of reproduction is a homogeneous function of \(X_1(t)\). Assuming that the specific rate of cell reproduction \(f\) depends only on \(X_2(t)\), we can write

\[
\begin{align*}
f_1 &= X_1(t-\tau)f(X_2(t-\tau)); \\
f_2 &= \alpha X_1(t-\tau).
\end{align*}
\]

(2)

Here, the rate of cell migration in B1 is taken proportional to \(X1\). For preliminary studies, we will consider the value \(\tau\) so small that its influence on the process under consideration can be neglected. Then we have

\[
\begin{align*}
\frac{dX_1(t)}{dt} &= X_1(t)f(X_2(t)) - \alpha X_1(t); \\
\frac{dX_2(t)}{dt} &= \alpha X_1(t) - \beta X_2(t).
\end{align*}
\]

(3)

Let \(f(\xi)(\xi \geq 0)\) be an analytic function. Since an increase in the number of cells in B1 leads to inhibition of division due to competition for resources, it can be assumed that the function \(f(\xi)\) monotonically decreases with an increase \(\xi\). The equilibrium position \(\xi(\xi_1, \xi_2)\) for the system (3) is determined from the relations

\[
\begin{align*}
\xi_1 f(\xi_2) - \alpha \xi_1 &= 0; \\
\alpha \xi_1 - \beta \xi_2 &= 0.
\end{align*}
\]

Obviously, a trivial equilibrium exists. For non-trivial equilibria, we have

\[
\begin{align*}
f(\xi_2) - \alpha &= 0; \\
\alpha \xi_1 - \beta \xi_2 &= 0.
\end{align*}
\]

Then there exist \(\xi_1, \xi_2\) in the first quadrant, which are the phase coordinates of the equilibrium position for (3), if the initial value of the specific reproduction rate is greater than the value \(\alpha\), i.e. \(f_0 > \alpha\). Indeed, in this case we can determine \(\xi_2\) from the first equation and, substituting this value into the second equation, we find \(\xi_1\). If \(f_0 < \alpha\), then
we have only a trivial equilibrium position. Therefore, \( P = f_0 / \alpha \) is a characteristic parameter of the equations. At \( P = 1 \), we have a bifurcation of equilibrium positions. If \( P > 1 \), then system (3) has, in addition to zero, and a positive equilibrium position. Let us consider the nature of the behavior of solutions near the critical points \( O(0,0) \) and \( \xi(\xi_1, \xi_2) \).

Near a trivial equilibrium position, we can write

\[
\begin{align*}
\frac{dX_1(t)}{dt} &= (f_0 - \alpha)X_1(t); \\
\frac{dX_2(t)}{dt} &= \alpha X_1(t) - \beta X_2(t).
\end{align*}
\] (4)

It is clearly, that if \( P < 1 \), then the point \( O(0,0) \) is stable, at \( P > 1 \) - unstable, and at \( P = 1 \) - neutral. Let \( P > 1 \). Let us investigate the behavior of solutions (3) near \( \xi(\xi_1, \xi_2) \).

\[
\begin{align*}
X_i(t) &= \xi_i + \gamma_i(t), i = 1,2, \\
\frac{d\gamma_1(t)}{dt} &= a \xi_1 \gamma_2(t); \\
\frac{d\gamma_2(t)}{dt} &= \alpha \gamma_1(t) - \beta \gamma_2(t), \\
\frac{df}{dX_2(\xi_2)} &= a
\end{align*}
\]

We have

\[
\begin{align*}
\frac{d\gamma_1(t)}{dt} &= a \xi_1 \gamma_2(t); \\
\frac{d\gamma_2(t)}{dt} &= \alpha \gamma_1(t) - \beta \gamma_2(t).
\end{align*}
\]

From the following solutions of characteristic equation

\[
\lambda (\lambda + \beta) - a a \xi_1 = 0
\]

\( \lambda_1, \lambda_2 < 0 \) and a non-trivial equilibrium position (3) is a stable node (Fig. 4).

**Fig. 4.** Phase portrait.

Let us consider the important case of continuous division without a buffer zone B1. Then we have

\[
\frac{dX_1(t)}{dt} = X_1(t - \tau) g(X_1(t - \tau)) - \alpha X_1(t).
\] (5)
where \( g(\xi) \) is the analytical function expressing the specific rate of reproduction; \( \alpha \) is the cell death parameter in zone M. Let \( g(\xi) \) be a monotonically decreasing function with \( g_0 = g(0) \) and

\[
\lim_{\xi \to \infty} \xi g(\xi) = 0.
\]

Then \( g_0 \) is the maximum specific rate of cell reproduction. The equilibrium position of the considered equation is determined from the relation:

\[
\xi_0 g(\xi_0) - \alpha \xi_0 = 0.
\]

Here, for \( P = \frac{g_0}{\alpha} > 1 \) we have two equilibrium positions: trivial and nontrivial \( \xi_0 \), determined from

\[
g(\xi_0) = \alpha.
\]

The qualitative analysis shows the stability of the trivial equilibrium at \( P < 1 \) and loss of stability at \( P > 1 \).

Let us consider the solutions characteristics of (5). Linearization of the equation near a nontrivial equilibrium position leads to the equation

\[
\frac{dY(t)}{dt} = (\beta \xi_0 + \alpha)Y(t - \tau) - \alpha Y(t).
\]

Here, for \( P = \frac{g_0}{\alpha} > 1 \) we have two equilibrium positions: trivial and nontrivial \( \xi_0 \), determined from

\[
g(\xi_0) = \alpha.
\]

The qualitative analysis shows the stability of the trivial equilibrium at \( P < 1 \) and loss of stability at \( P > 1 \).

Let us consider the solutions characteristics of (5). Linearization of the equation near a nontrivial equilibrium position leads to the equation

\[
\frac{dY(t)}{dt} = (\beta \xi_0 + \alpha)Y(t - \tau) - \alpha Y(t).
\]

Here, for \( P = \frac{g_0}{\alpha} > 1 \) we have two equilibrium positions: trivial and nontrivial \( \xi_0 \), determined from

\[
g(\xi_0) = \alpha.
\]

The characteristic equation for (6) has the form

\[
(\lambda + \tau \alpha) e^\lambda - \tau (\beta \xi_0 + \alpha) = 0.
\]

According to the Hayes criterion [8], the roots of (7) are negative if and only if

1. \( \tau \alpha > -1 \);
2. \( -\tau \beta \xi_0 > 0 \);
3. \( -\tau (\beta \xi_0 + \alpha) < \xi \sin \xi - \alpha \tau \cos \xi \),

where \( \xi \) is the root of the equation \( \xi = \alpha \tau g(\xi) \). The first condition is fulfilled, since \( \tau \alpha > 0 \), and the second condition is also fulfilled due to the accepted condition \( \beta < 0 \) (\( g(\xi) \) is a positively decreasing function). Analysis of the third inequality shows that, for certain values of the coefficients, it may not be fulfilled, and then the equilibrium position \( \xi_0 \) loses stability. Let's consider this case in more detail. Let \( -\alpha \tau = 1 \) for simplicity. Then the third condition takes the form

\[
-\tau \beta \xi_0 - 1 < 2,2
\]

and the stability condition is

\[
-\tau \xi_0 \frac{dg(\xi)}{d\xi} \bigg|_{\xi_0} < 3,2
\]

If this condition is violated, then there is a limit cycle, since the trivial equilibrium position is unstable and solutions of (5) are bounded.
Thus, with the monotonically decreasing functions of the specific reproduction rate considered, the proliferative minifuot has a stable trivial equilibrium position, which, with an increase in the parameter P, allows bifurcation to unstable trivial and nontrivial critical points. The nontrivial equilibrium point, under certain conditions, can lose stability and lead to the appearance of a limit cycle. The results of the qualitative analysis show that the role of the delay is significant in this case.

4 Discussion

The method for modelling organs and tissues based on the allocation of a functional unit of organs and tissues (FUOT) makes it possible to simulate the main modes of the considered process and to identify regulatory mechanisms and laws of cellular communities functioning, has a prognostic ability. Since functional-differential equations with delay have an innate tendency to the presence of an oscillatory mode of solutions, their use as equations of FUOT models is reasonable and justified.

Qualitative studies of the proliferative minifuot show the presence of a nonzero stable equilibrium position, and sometimes a stable limit cycle in the first quadrant. Biologically, this means that if a cellular system of enhanced proliferation has been formed, then it can function for an arbitrarily long time. The results of these studies can be useful in studying the mechanisms of functioning of cell groups in normal conditions and during tumors development.

References

2. L.N. Seravin, Protistology 2(1), 6–14 (2001)
6. B.N. Hidirov, Selected works on mathematical modeling of the regulatorika of living systems (Publ. House, Moscow, Izhevsk, 2014)