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THE EFFECT OF PROCESSES LEADING TO CELL DEATH ON THE DYNAMIC REGIMES OF THE TISSUE FORMATION MODEL

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Abstract. The article generalizes a mathematical model describing the population dynamics of cell clusters, based on a system of first-order nonlinear differential equations by introducing additional parameters. It is proposed to add two types of coefficients to the model: a survival coefficient, which describes the proportion of cells that die due to some environmental influences and subsequent autophagy or as a result of intracellular processes leading to death (necrosis, apoptosis), and the aging coefficient, which describes the limitation in the rate and possibility of cell division due to reduction in the length of telomers of the cells chromosomes during mitosis. The added coefficients have a biological meaning and can be evaluated during the experiment, as required by the considered model of morphogenesis. Taking these parameters into account in the mathematical model made it possible to determine new dynamic regimes in the system of differential equations describing the behavior of multicellular clusters. For the obtained system of differential equations, an analysis of its equilibrium points and the stability of steady states corresponding to these points was carried out. The values of the parameters of the mathematical model at which the system can reach a steady state were determined. Also, limitations on the parameters were identified, at which it is impossible to estimate the stability of steady states using the Lyapunov method. It follows from the obtained conditions that one of the cases when the system of cell clusters comes to a steady state is either the extinction of all cells, or the cessation of division of cell clusters. Steady states of different type are also possible, for which the criteria of existence and possibility have yet to be determined.

Keywords: systems of nonlinear differential equations, modeling of morphogenesis, programming cell death, Hayflick limit.

AMS Subject Classification: 34A34, 34D20.

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Introduction

The simplest way to describe tissue formation processes is to quantify changes in the total number of cells in populations. Such estimates can be obtained using population models like in [1] or [2]. Their main advantage is abstraction from the nature of interaction between individual cells and the ability to evaluate scenarios for the development of the system with minimal computational costs. Possible behavioural scenarios can be estimated using dynamic regimes of a system of differential equations describing the cell populations.

An important requirement when choosing a mathematical model is the portability of results between models of different types. If a certain result is obtained using a population

model, it should qualitatively coincide with the result of using simulation models with the same system parameters (e. g., [3, 4]). A population model using a set of universal parameters in [5] satisfies these requirements.

In population models, for certain values of the system parameters, situations are possible where cell populations grow without limit. This behavior contradicts the fact that cells have a divisibility limit called the Hayflick limit [6]. If the possibility of cell population aging is not considered, an adequate assessment of the development scenarios of multicellular cluster systems is impossible.

Models of morphogenesis primarily describe interactions between cells. In addition, the impact of environment on cell populations is an important factor to consider. If environmental conditions (heat, radiation, lack of chemicals necessary for life, etc.) are too aggressive, then, regardless of the interactions between cells, some of the cells will always die out [7]. The death of some part of the cell population can also be initiated by intracellular processes (necrosis, apoptosis) [8]. A population of cells in which at least half of the cells are born dead cannot grow without limits. If these factors are not taken into account, then morphogenesis scenarios are also determined incorrectly.

The mathematical model with universal parameters does not take these factors into account. Adding parameters describing populations aging, environmental influences and intracellular processes leading to cell death allows us to more accurately determine the behavior of the system of multicellular clusters.

The added parameters must satisfy the requirement of having a clear biological meaning, as do other universal parameters from [9].

1. Description of the New Model Parameters

The main variables of the population model [5] are the sizes of the cell population $N(\tau, t)$ and the rates of their division $v_d(\tau, t)$. The change of these values over time is determined by the following expressions:

$$\frac{dN(\tau,t)}{dt} = \mathrm{Surplus}(\tau, N) - \mathrm{Loss}(\tau, N), \tag{1}$$

$$\begin{aligned}\frac{dv_d(\tau,t)}{dt} = &\left(1 - \frac{v_d(\tau,t)}{v_d^{\max}(\tau)}\right) \sum_{\acute{\tau}:K(\tau\leftarrow\acute{\tau})>0} K(\tau \leftarrow \acute{\tau})\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) \\ &+\left(\frac{v_d(\tau,t)}{v_d^{\max}(\tau)}\right) \sum_{\acute{\tau}:K(\tau\leftarrow\acute{\tau})<0} K(\tau \leftarrow \acute{\tau})\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N).\end{aligned} \tag{2}$$

The parameter $\mathrm{Loss}(\tau, N)$ determines the decrease in the number of cells of type τ per unit of time:

$$\mathrm{Loss}(\tau, N) = v_d(\tau, t)N(\tau, t). \tag{3}$$

The values $\mathrm{Surplus}(\tau, N)$ and $\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N)$ are determined by equations (4) and (5), respectively. To find them, the following parameters are taken into consideration:

$$\hat{N}(\tau) = \sigma(N(\tau) - 1 + c)N(\tau), \quad \mathrm{Disp}(\acute{\tau}, N) = \max\left(1, \sum_{\Pr(\tau^*\leftarrow\acute{\tau})>0} \hat{N}(\tau^*)\right),$$

$$\mathrm{Inf}(\tau \leftarrow \acute{\tau}, N) = \Pr(\tau \leftarrow \acute{\tau})\frac{I_s(\acute{\tau})\hat{N}(\acute{\tau})}{\mathrm{Disp}(\acute{\tau}, N)}, \quad \mathrm{SumInf}(\tau, N) = \sum_{\acute{\tau}} \mathrm{Inf}(\tau \leftarrow \acute{\tau}, N).$$

The function σ is a sigmoid or Heaviside function with parameter c: $0 < c \ll 1$.

The $\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N)$ parameter specifies the distribution of signals from cells of type $\acute{\tau}$ between cells capable of receiving these signals:

$$\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) = \begin{cases} \frac{\mathrm{Inf}(\tau \leftarrow \acute{\tau}, N)}{\mathrm{SumInf}(\tau, N)}, & \text{if } \mathrm{Inf}(\tau \leftarrow \acute{\tau}, N) > 0; \\ 0, & \text{otherwise.} \end{cases} \tag{4}$$

The distributional parameters $\varepsilon_d(\tau, N)$ and $\delta(\tau \leftarrow \acute{\tau}, N)$ are also considered:

$$\varepsilon_d(\tau, N) = \sum_{\acute{\tau}:\, O(\tau \leftarrow \acute{\tau})=1} \mathrm{Sig}(\tau \leftarrow \acute{\tau}, N),$$

$$\delta(\tau \leftarrow \acute{\tau}, N) = \sum_{\tau^*:\, D(\acute{\tau} \leftarrow \tau^*)=\tau} \mathrm{Sig}(\acute{\tau} \leftarrow \tau^*, N).$$

The value of $\mathrm{Surplus}(\tau, N)$ determines the increase in the number of cells of type τ per unit of time:

$$\mathrm{Surplus}(\tau, N) = v_d(\tau, t)\hat{N}(\tau, t)\varepsilon_d(\tau, N) + \sum_{\acute{\tau}} v_d(\acute{\tau})\hat{N}(\acute{\tau}, t)\delta(\tau \leftarrow \acute{\tau}, N)(2 - \varepsilon_d(\acute{\tau}, N)). \tag{5}$$

It is proposed to add the following new parameters to the considered model:

1. $S_r(\tau_1), \ldots, S_r(\tau_n)$ — survival rate, which determines the proportion of cells of type τ of each new generation that will be able to divide again in the future;

2. $\alpha(\tau_1), \ldots, \alpha(\tau_n)$ — coefficients that determine the process of cell aging. Each type of cells has a certain division limit, after which they lose the ability to divide.

The survival rate $S_r(\tau)$ should only affect the number of cells of type τ that appeared as a result of division at time t. Accordingly, the value $\mathrm{Surplus}(\tau, t)$ should be taken into account in equations with the factor $S_r(\tau)$ as a new multiplier.

The value $\alpha(\tau)$ characterizes the aging of cells due to a large number of repeated divisions or their rejuvenation caused by the appearance of new cells of type τ from cells with a large (or infinite) value of the divisibility limit (for example, from stem cells). This parameter should only affect the rate of cell division, but not their number.

Aging and rejuvenation of cells of type τ directly depend on the cell types and the division type of their parents $\acute{\tau}$. Thus, in the expression for the rate $v_d(\tau)$, one should take into account the values $\alpha(\acute{\tau})$ with the distributional indices $\varepsilon_d(\acute{\tau}, N)$, $\delta(\tau \leftarrow \acute{\tau}, N)$ and $S_r(\tau)$.

The change in the rate of division of τ-type cells is influenced by signaling influences from cells of other types, the aging of cells of type τ of the previous generation that have chosen asymmetric division, and the division of cells of other types that have changed their type to τ. The rate of division of cells that are not subjected to aging should not change over time.

The division rates $v_d(\tau, t)$ are limited below by zero, and above by the values $v_d^{\max}(\tau)$. Therefore, positive and negative values of the parameters $K(\tau \leftarrow \acute{\tau})$ and $\alpha(\tau)$ must be considered separately and included in the expression for the change of the division rate with normalization coefficients.

Taking into account the introduced parameters, equations (1) and (2) will take the following form:

$$\frac{dN(\tau, t)}{dt} = S_r(\tau)\mathrm{Surplus}(\tau, N) - \mathrm{Loss}(\tau, N), \tag{6}$$

$$\begin{aligned} \frac{dv_d(\tau, t)}{dt} = &\left(1 - \frac{v_d(\tau, t)}{v_d^{\max}(\tau)}\right)\Big(\mathrm{Sum}_{K+}(\tau) + \mathrm{Sum}_{\alpha+}(\tau)\Big) \\ &+ \left(\frac{v_d(\tau, t)}{v_d^{\max}(\tau)}\right)\Big(\mathrm{Sum}_{K-}(\tau) + \mathrm{Sum}_{\alpha-}(\tau)\Big), \end{aligned} \tag{7}$$

where the expressions for $\mathrm{Sum}_{K+}(\tau)$, $\mathrm{Sum}_{\alpha+}(\tau)$, $\mathrm{Sum}_{K-}(\tau)$, $\mathrm{Sum}_{\alpha-}(\tau)$ are defined as:

$$\begin{aligned}\mathrm{Sum}_{K+}(\tau) &= \sum_{\acute{\tau}:\, K(\tau\leftarrow\acute{\tau})>0} K(\tau \leftarrow \acute{\tau})\,\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N),\\ \mathrm{Sum}_{K-}(\tau) &= \sum_{\acute{\tau}:\, K(\tau\leftarrow\acute{\tau})<0} K(\tau \leftarrow \acute{\tau})\,\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N),\end{aligned} \tag{8}$$

$$\mathrm{Sum}_{\alpha+}(\tau) = S_r(\tau) \sum_{\acute{\tau}\neq\tau:\, \alpha(\acute{\tau})>0} (2-\varepsilon_d(\acute{\tau}, N))\delta(\tau \leftarrow \acute{\tau}, N)\alpha(\acute{\tau}, N),$$

$$\mathrm{Sum}_{\alpha-}(\tau) = \begin{cases} S_r(\tau) \sum\limits_{\acute{\tau}:\, \alpha(\acute{\tau})<0} (2-\varepsilon_d(\acute{\tau}, N))\delta(\tau \leftarrow \acute{\tau}, N)\alpha(\acute{\tau}), & \alpha(\tau) > 0;\\ S_r(\tau)\Big[\sum\limits_{\acute{\tau}:\, \alpha(\acute{\tau})<0} (2-\varepsilon_d(\acute{\tau}, N))\delta(\tau \leftarrow \acute{\tau}, N)\alpha(\acute{\tau}) + \alpha(\tau)\varepsilon_d(\tau, N)\Big], & \alpha(\tau) \leqslant 0.\end{cases} \tag{9}$$

Remark 1. The coefficient $\alpha(\tau)$ has a biological meaning.

$\lhd$ If the coefficient $\alpha(\tau) < 0$, then we consider a system consisting of one population in the absence of all factors except the aging of population itself. The equation for the division rate in this case is:

$$\frac{dv_d(\tau,t)}{dt} = S_r(\tau)\left(\frac{v_d(\tau,t)}{v_d^{\max}(\tau)}\right)\big[(2-\varepsilon_d(\tau,N))\delta(\tau\leftarrow\tau,N)\alpha(\tau) + \alpha(\tau)\varepsilon_d(\tau,N)\big].$$

In the case of a system consisting of only one type of cells, $\varepsilon_d(\tau, N) = O(\tau \leftarrow \tau) = 0$, $\delta(\tau \leftarrow \tau, N) = 1$. Then the parameter $\alpha(\tau)$ can be found as:

$$\alpha(\tau) = \frac{v_d^{\max}(\tau)}{2S_r(\tau)t}\ln\frac{v_d(\tau,t)}{v_0}$$

taking into account the initial condition $v_d(\tau, 0) = v_0$.

Accordingly, the parameter $\alpha(\tau)$ can be estimated directly from the moment in time when the rate of cell division becomes negligibly small, that is, from the divisibility limit of cells of type τ.

Let us consider a system of two populations of types τ_0 and τ_1, where $\alpha(\tau_0) > 0$, $\alpha(\tau_1) = 0$. During division, cells differentiate as follows: $\tau_0 \to \tau_1$, $\tau_1 \to \tau_1$. Cells exchange signals only within their populations. All interaction effects, except rejuvenation, are absent. The equation for the rate of cell division of type τ_1 is:

$$\frac{dv_d(\tau_1,t)}{dt} = \left(1-\frac{v_d(\tau_1,t)}{v_d^{\max}(\tau_1)}\right)(2-\varepsilon_d(\tau_0,N))\delta(\tau_1\leftarrow\tau_0,N)\alpha(\tau_0).$$

Under given conditions $\varepsilon_d(\tau_0, N) = O(\tau_0 \leftarrow \tau_0) = 0$, $\delta(\tau_1 \leftarrow \tau_0, N) = 1$. Then the parameter $\alpha(\tau_0)$ can be found:

$$\alpha(\tau_0) = \frac{v_d^{\max}(\tau_1)}{2t}\ln\left(\frac{v_d^{\max}(\tau_1)-v_0}{v_d^{\max}(\tau_1)-v_d(\tau_1,t)}\right).$$

That is, the coefficient $\alpha(\tau_0)$ can be estimated at the moment of time t, when the division rate becomes close to its maximum value.

If cells with $\alpha(\tau_0) > 0$ are differentiated into several other types, then among all the values found, the largest value of $\alpha(\tau_0)$ can be selected.

The $\alpha(\tau_0)$ parameter is not included in the $\mathrm{Sum}_{\alpha+}(\tau_0)$ of the expression (9) due to the $\acute{\tau} \neq \tau_0$ summation condition. For this reason, the parameter $\alpha(\tau_0)$ does not affect the change in the cell division rate $v_d(\tau_0, t)$. $\triangleright$

The coefficient $S_r(\tau)$ can be estimated by definition as the proportion of surviving cells among those that appeared as a result of division.

The model that takes into account population aging must have steady states. This hypotesis is based on the fact that over time, the number of cells of certain types should stop changing due to a decrease in the rate of division. As it turns out, the system of differential equations under consideration actually has equilibrium points corresponding to such steady states. Important issues are the studying of the stability of steady states of the system and the identifying of the dependence of the stability of these states on the values of the model parameters.

2. Steady States of the System and Their Stability

Let us write the system under consideration in the following form:

$$\begin{cases} \frac{dN(\tau_i,t)}{dt} = f_i(\tau_i, t); \\ \frac{dv(\tau_i,t)}{dt} = g_i(\tau_i, t), \end{cases} \qquad i = 1, \ldots, n. \tag{10}$$

To assess the stability of steady states, we use the Lyapunov stability criterion.

It turns out that for some equilibrium points of systems it is possible to derive stationarity conditions and draw a conclusion about the stability of such states.

Proposition 1. *If there is a moment of time t_0 such that for any cell type τ at $t \geqslant t_0$ at least one of the conditions is satisfied:*

1. $N(\tau, t) = 0$;

2. $v_d(\tau, t) = 0$ *and* $\forall\, \acute{\tau}\ K(\tau \leftarrow \acute{\tau}) > 0$, $\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) = 0$ *and* $\forall\, \acute{\tau} \neq \tau$, $\alpha(\acute{\tau}) > 0 : \forall\, \tau^*\ D(\acute{\tau} \leftarrow \tau^*) = \tau : \ \mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) = 0$.

Then the set of values $(N(\tau_1), N(\tau_2), \ldots, N(\tau_n), v_d(\tau_1), v_d(\tau_2), \ldots, v_d(\tau_n))$ is an equilibrium point of the system (10).

$\triangleleft$ Further we will assume that $t \geqslant t_0$. The equation for $f(\tau)$ can be written as follows:

$$f(\tau) = v_d(\tau)\hat{N}(\tau)\big[S_r(\tau)\varepsilon_d(\tau, N) + S_r(\tau)\delta(\tau \leftarrow \tau, N)(2 - \varepsilon_d(\tau, N)) - 1\big] + S_r(\tau)\sum_{\acute{\tau} \neq \tau} v_d(\acute{\tau})\hat{N}(\acute{\tau})\delta(\tau \leftarrow \acute{\tau}, N)(2 - \varepsilon_d(\acute{\tau}, N)).$$

Since each term contains the value $v_d(\tau^*)N(\tau^*)$, then when the conditions of the proposition are met, all terms will be equal to zero. Thus, $f(\tau) = 0$.

Let us show that the same is true for $g(\tau)$.

When $v_d(\tau) = 0$ the equation takes the form:

$$g(\tau) = \mathrm{Sum}_{K+}(\tau) + \mathrm{Sum}_{\alpha+}(\tau).$$

The fulfillment of the condition $\forall\, \acute{\tau}\ K(\tau \leftarrow \acute{\tau}) > 0$, $\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) = 0$ implies $\mathrm{Sum}_{K+}(\tau) = 0$. The fulfillment of the condition $\forall\, \acute{\tau} \neq \tau$, $\alpha(\acute{\tau}) > 0 : \forall\, \tau^*\ D(\acute{\tau} \leftarrow \tau^*) = \tau : \mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) = 0$ implies $\mathrm{Sum}_{\alpha+}(\tau) = 0$. Accordingly, $v_d(\tau) = 0$ is a solution to the equation $g(\tau) = 0$.

Let us consider the case when the condition $v_d(\tau) \neq 0$ is not satisfied for the type τ. Since the equation $g(\tau) = 0$ is linear with respect to $v_d(\tau)$, we can write the equation for $v_d(\tau)$:

$$v_d(\tau) = v_d^{\max}(\tau)\frac{\mathrm{Sum}_{K+}(\tau) + \mathrm{Sum}_{\alpha+}(\tau)}{(\mathrm{Sum}_{K+}(\tau) + \mathrm{Sum}_{\alpha+}(\tau)) - (\mathrm{Sum}_{K-}(\tau) + \mathrm{Sum}_{\alpha-}(\tau))}.$$

If the denominator of this fraction is not equal to zero, then the equation $g(\tau) = 0$ has the solution $v_d(\tau) \neq 0$. Let us assume the opposite. The denominator of the fraction can be written as follows:

$$\mathrm{Sum}_{K+}(\tau) + \mathrm{Sum}_{\alpha+}(\tau) + (-\mathrm{Sum}_{K-}(\tau)) + (-\mathrm{Sum}_{\alpha-}(\tau)).$$

All terms in the sums $\mathrm{Sum}_{K-}(\tau)$ and $\mathrm{Sum}_{\alpha-}(\tau)$ are non-positive, so we can assume that all terms in the denominator are non-negative. Accordingly, the denominator is equal to zero when each term is equal to zero. But in this case $g(\tau) = 0$ for any value of $v_d(\tau)$. Thus, there is a contradiction with the assumption that there are no solutions.

It can be assumed that if the conditions of the proposition are met, the equation $g(\tau) = 0$ is solvable. ▷

Proposition 2. *If a equilibrium point satisfies the conditions of Proposition* 1 *and for at least one type of cells* $\tilde{\theta}$ $N(\tilde{\theta}) = 0$ *is true, then it is impossible to determine the stability of the steady state corresponding to this point from the eigenvalues of the matrix of the linearized system.*

◁ Let us show that when the conditions of the proposition are satisfied, the column of the matrix of the linearized system corresponding to the derivative with respect to $N(\tilde{\theta})$ is equal to zero. In this case, one of the eigenvalues of the matrix is equal to zero and it is impossible to draw a conclusion about the stability of the steady state.

Let us consider the derivatives of $\frac{\partial f(\tau,t)}{\partial N(\theta)}$:

$$\frac{\partial f(\tau,t)}{\partial N(\theta)} = S_r(\tau)\Bigg[v_d(\tau)\delta_{\tau\theta}h_\theta\varepsilon_d(\tau,N) + v_d(\tau)\hat{N}(\tau)\frac{\partial\varepsilon_d(\tau,N)}{\partial N(\theta)}$$

$$+v_d(\theta)h_\theta\delta(\tau\leftarrow\theta,N)(2-\varepsilon_d(\theta,N))\Bigg] + S_r(\tau)\sum_{\acute{\tau}}\Bigg[v_d(\acute{v})\hat{N}(\acute{\tau})\frac{\partial\delta(\tau\leftarrow\acute{\tau})}{\partial N(\theta)}(2-\varepsilon_d(\acute{\tau},N))$$

$$-v_d(\acute{\tau})\hat{N}(\acute{\tau})\delta(\tau\leftarrow\acute{\tau},N)\frac{\partial\varepsilon_d(\acute{\tau},N)}{\partial N(\theta)}\Bigg] - v_d(\tau)\delta_{\tau\theta}h_\theta,$$

where $\delta_{\tau\theta}$ is the Kronecker delta, $h_\theta = h(N(\theta) - 1 + c)$ is the Heaviside function.

Since each term contains the value $v_d(\tau^*)N(\tau^*)$ or $v_d(\theta)h_\theta$, and for each type of cell the conditions of proposition 1 are true, then $\frac{\partial f(\tau,t)}{\partial N(\theta)} = 0$.

Let us show that if there is a cell type $\tilde{\theta}$ for which $N(\tilde{\theta}) = 0$, then $\frac{\partial g(\tau,t)}{\partial N(\tilde{\theta})} = 0$.

$$\frac{\partial\,\mathrm{Inf}(\tau\leftarrow\acute{\tau},N)}{\partial N(\tilde{\theta})} = \begin{cases}\Pr(\tau\leftarrow\acute{\tau})I_s(\acute{\tau})\frac{\delta_{\acute{\tau}\tilde{\theta}}h_{\tilde{\theta}}\mathrm{Disp}(\acute{\tau},N)-\hat{N}(\acute{\tau})h_{\tilde{\theta}}}{\mathrm{Disp}(\acute{\tau},N)^2}, & \text{if } \Pr(\tau\leftarrow\acute{\tau})\hat{N}(\acute{\tau}) > 0;\\ 0, & \text{if } \Pr(\tau\leftarrow\acute{\tau})\hat{N}(\acute{\tau}) = 0.\end{cases}$$

Both expressions in the numerator are either equal to zero or depend on $h_{\tilde{\theta}}$, which is also equal to zero at $N(\tilde{\theta}) = 0$.

The equality to zero of the derivatives $\mathrm{Inf}(\tau\leftarrow\acute{\tau},N)$ implies the equality to zero of the derivatives $\mathrm{Sig}(\tau\leftarrow\acute{\tau},N)$, $\varepsilon_d(\tau,N)$, $\delta(\tau\leftarrow\acute{\tau},N)$, $\mathrm{Sum}_{K+}(\tau,N)$, $\mathrm{Sum}_{\alpha+}(\tau,N)$, $\mathrm{Sum}_{K-}(\tau,N)$, $\mathrm{Sum}_{\alpha-}(\tau,N)$. This implies that the derivatives of $\frac{\partial g(\tau,t)}{\partial N(\tilde{\theta})}$ are equal to zero for all values of τ. ▷

An exception to the situation under consideration is the equilibrium point, at which the conditions $N(\tau) \neq 0$, $v_d(\tau) = 0$ are satisfied for all cell types. We will show that in this case it is also impossible to estimate the stability of the steady state using the sign of the eigenvalues of the matrix of the linearized system.

Proposition 3. *If there is a moment of time t_0 such that for any cell type τ at $t \geqslant t_0$ at least one of the conditions is true:*

1. $N(\tau, t) \neq 0$;

2. $v_d(\tau, t) = 0$ *and* $\forall\, \acute{\tau}\ K(\tau \leftarrow \acute{\tau}) > 0 : Pr(\tau \leftarrow \acute{\tau}) = 0$ *and* $\forall\, \acute{\tau} \neq \tau\ \alpha(\acute{\tau}) > 0$, $O(\tau \leftarrow \acute{\tau}) = 1 : Pr(\tau \leftarrow \acute{\tau}) = 0$ *and* $\forall\, \acute{\tau} \neq \tau\ \alpha(\acute{\tau}) > 0$, $\forall\, \tau^*\ D(\acute{\tau} \leftarrow \tau^*) = \tau : Pr(\tau \leftarrow \acute{\tau}) = 0$.

Then the set of values $(N(\tau_1), N(\tau_2), \ldots, N(\tau_n), v_d(\tau_1), v_d(\tau_2), \ldots, v_d(\tau_n))$ *is an equilibrium point of the system* (10).

◁ This proposition is a special case of Proposition 1. For such equilibrium points, the second condition of this proposition is satisfied for all types. The conditions $\mathrm{Sig}(\tau \leftarrow \acute{\tau}, N) = 0$ are satisfied when $\Pr(\tau \leftarrow \acute{\tau}) = 0$. ▷

Proposition 4. *If the equilibrium point satisfies the conditions of Proposition* 3*, then it is impossible to determine the stability of the corresponding steady state from the eigenvalues of the matrix of the linearized system.*

◁ This proposition is proved similarly to Proposition 2.

Since each term in the expression for $\frac{\partial f(\tau,t)}{\partial N(\theta)}$ contains $v_d(\tau)$, $v_d(\acute{\tau})$ or $v_d(\theta)$, the entire sum is equal to zero. Accordingly, all derivatives $\frac{\partial f(\tau,t)}{\partial N(\theta)} = 0$.

Let us consider the derivative $\frac{\partial g(\tau,t)}{\partial N(\theta)}$. When $v_d(\tau) = 0$, the expression for it takes the form:

$$\frac{\partial g(\tau, t)}{\partial N(\theta)} = \frac{\partial \mathrm{Sum}_{K+}(\tau)}{\partial N(\theta)} + \frac{\partial \mathrm{Sum}_{\alpha+}(\tau)}{\partial N(\theta)}.$$

The fulfillment of the condition $\forall\, \acute{\tau}\ K(\tau \leftarrow \acute{\tau}) > 0 : \Pr(\tau \leftarrow \acute{\tau}) = 0$ implies $\frac{\partial \mathrm{Sum}_{K+}(\tau)}{\partial N(\theta)} = 0$.

The fulfillment of the conditions $\forall\, \acute{\tau} \neq \tau\ \alpha(\acute{\tau}) > 0$, $O(\tau \leftarrow \acute{\tau}) = 1 : \Pr(\tau \leftarrow \acute{\tau}) = 0$ and $\forall\, \acute{\tau} \neq \tau\ \alpha(\acute{\tau})) > 0$, $\forall\, \tau^*\ D(\acute{\tau} \leftarrow \tau^*) = \tau : \Pr(\tau \leftarrow \acute{\tau}) = 0$ implies that the derivatives $\frac{\partial \varepsilon_d(\tau,N)}{\partial N(\theta)}$ and $\frac{\partial \delta(\tau \leftarrow \acute{\tau})}{\partial N(\theta)}$. It follows that $\frac{\partial \mathrm{Sum}_{\alpha+}(\tau)}{\partial N(\theta)} = 0$. ▷

Thus, for the specified types of equilibrium points it is necessary to use other methods of stability research. In addition to the considered types of equilibrium points, another case is possible: equality to zero of the function $f(\tau)$ can be achieved not only if all terms defining this expression are equal to zero, but also if the condition is met:

$$S_r(\tau)\varepsilon_d(\tau, N) + S_r(\tau)\delta(\tau \leftarrow \tau, N)(2 - \varepsilon_d(\tau, N)) - 1 < 0.$$

In this case, the first term will be negative and other solutions of the equation are possible. The existence of equilibrium points of this type needs to be checked. It is also necessary to assess the possibility of using the eigenvalues of the matrix of the linearized system to determine the stability of such steady states.

3. Modeling

To assess the adequacy of the influence of the introduced parameters $\alpha(\tau)$ and $S_r(\tau)$, modeling of the populataion dynamics of multicellular clusters was carried out for different values of the parameters under consideration. The modeling results are presented in the graphs below.

1) Division of cells of arbitrary type $\alpha(\tau) < 0$.

As the population ages, its rate of division decreases to zero. Fig. 1 shows that at a certain point in time, cells stop dividing and the system reaches a steady state.

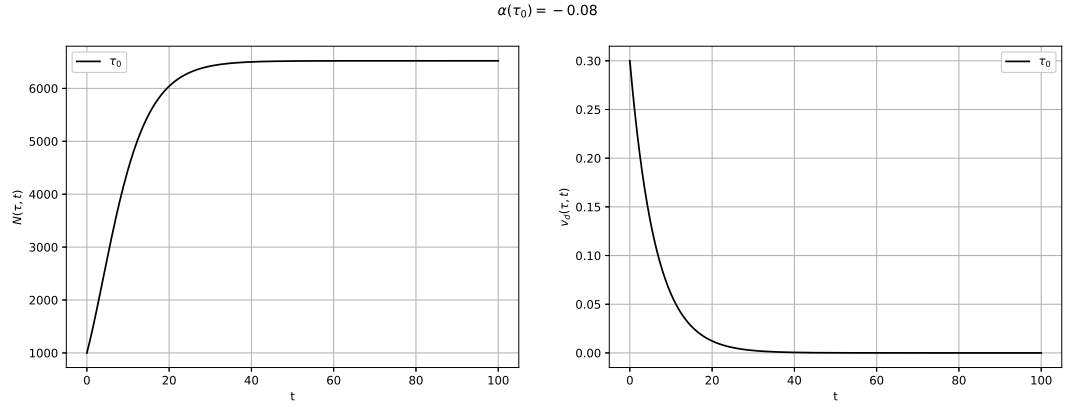

Fig. 1.

2) Two cell types (stem cells τ_0 and arbitrary type τ_1). $\alpha(\tau_0) > 0$, $\alpha(\tau_1) < 0$. All stem cells differentiate into τ_1. All cells of type τ_1 divide into cells of the same type.

Fig. 2 shows that after all stem cells have differentiated into τ_1, the number of τ_1 cells continues to increase in a different way for some time and then stops changing.

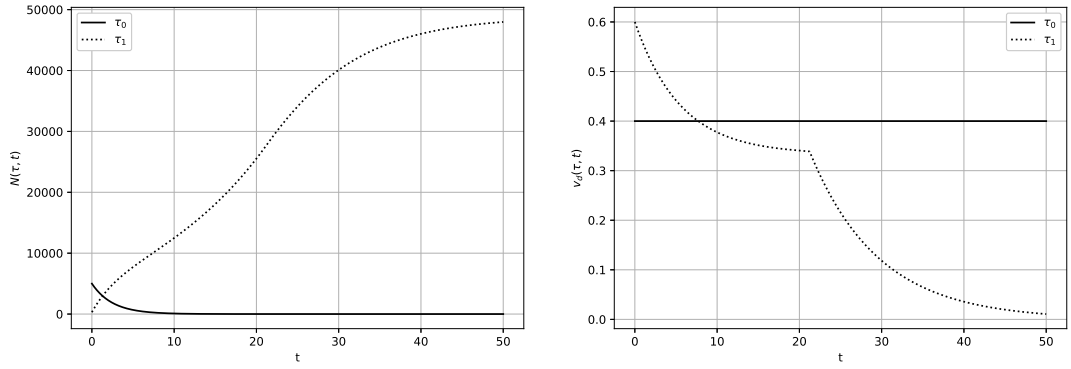

Fig. 2.

3) Division of stem cells. No effect of population aging.

The simulation was performed with different values of the population survival rate. The simulation results are presented in Figure 3.

The graphs show three possible scenarios for the development of a cell population:

1. $S_r(\tau_0) > 0.5$: the population is growing.

2. $S_r(\tau_0) = 0.5$: the number of new cells is exactly twice as large as the number of dead cells — the population size does not change.

3. $S_r(\tau_0) < 0.5$: the population goes extinct.

To confirm the adequacy of the above propositions describing the type and stability of the steady states of the system, a modeling of change in the number of cells and the rate of their division was carried out. The values of the system parameters were generated randomly. For each system, the eigenvalues of the matrices of the linearized systems were found. The results of the modeling are presented in the graphs.

4) The steady state of the system, satisfying the conditions of Proposition 1.

Several eigenvalues of the matrix of the linearized system are equal to zero. Fig. 4 shows an example of an equilibrium point. It is clear that if the population size is not equal to zero, then the division rate is equal to zero (types τ_0 and τ_3) and, conversely, if the population size is equal to zero, then the division rate is not equal to zero (types τ_1, τ_2).

5) The steady state of the system, satisfying the conditions of Proposition 3.

Several eigenvalues of the matrix of the linearized system are also equal to zero when all division rates are equal to zero.

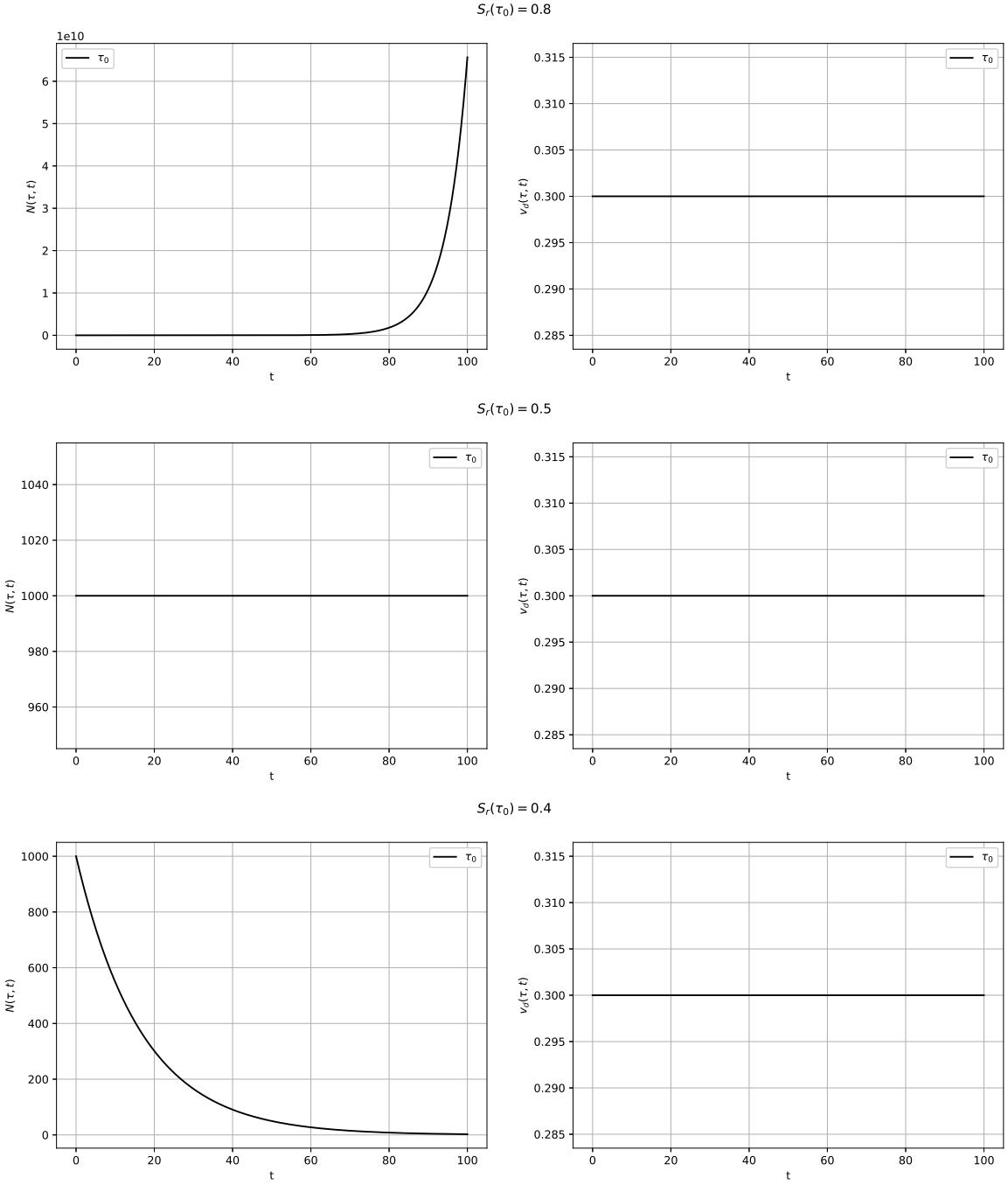

Fig. 3.

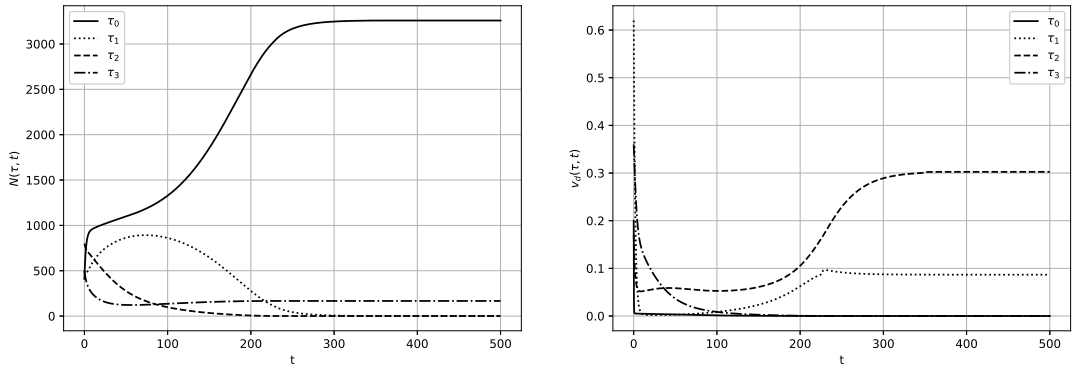

Fig. 4.

Fig. 5 shows an example of an equilibrium point at which all cell types have non-zero population sizes and all division rates is equal to zero.

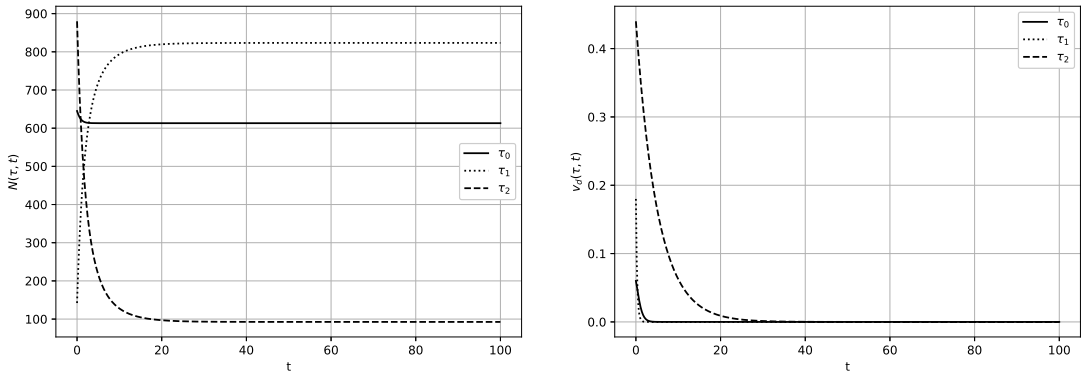

Fig. 5.

6) A steady state of the system that does not satisfy the conditions of Proposition 1.

One of the eigenvalues is also equal to zero. Presumably, this is due to the fact that one of the values of the division rate at the equilibrium point is equal to zero. Fig. 6 shows an example of an equilibrium point at which the population sizes and cell division rates of types τ_0 and τ_1 are not equal to zero simultaneously.

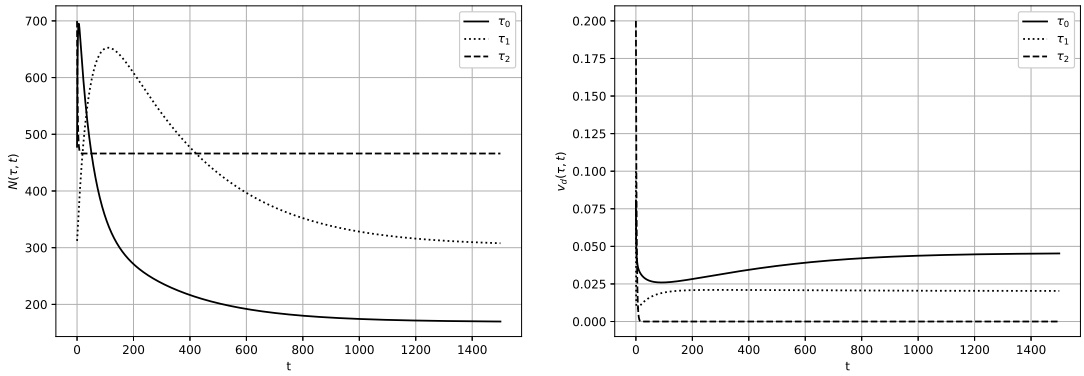

Fig. 6.

4. Results

Adding the cell division limit and the survival rate to the consideration allows us to take into account a larger number of scenarios for the development of multicellular cluster systems. Aging of cell populations and limitation of their growth due to the influence of the environmental and intracellular processes for necrosis and apoptosis leads to the emergence of steady states in systems. In mathematical models that do not take these factors into account, the behavior of systems will show unlimited population growth instead of establishing a steady state, which does not allow for an adequate assessment of dynamic regimes.

The main limitation in the obtained model is the impossibility of assessing the stability of steady states using the eigenvalues of the matrix of the linearized system. Many of the equilibrium points of the system of differential equations have either zero values of the population size $N(\tau)$ or the cell division rate $v_d(\tau)$. Such situations arise in two cases:

1. The population goes extinct due to aggressive external conditions ($S_r(\tau) < 0.5$) or when differentiating into cells of a different type.

2. The population loses the ability to divide due to signaling interactions between cells ($K(\tau \leftarrow \acute{\tau}) < 0$) or natural aging of the population ($\alpha(\tau) < 0$).

In systems with a large number of cell types, the possibility of such development scenarios cannot be excluded. Determining the stability of these steady states is problematic. To adequately assess possible scenarios for the morphogenesis of systems with a large number of cell types, it is necessary to answer the following questions:

1. are steady states of other types possible;

2. is it possible to estimate the stability of steady states of other types using the Lyapunov method;

3. what are the conditions for the emergence of steady states of other types.

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О ВЛИЯНИИ ПРОЦЕССОВ, ВЕДУЩИХ К СМЕРТИ КЛЕТОК, НА ДИНАМИЧЕСКИЕ РЕЖИМЫ МОДЕЛИ ТКАНЕОБРАЗОВАНИЯ

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Аннотация. В статье за счет введения дополнительных параметров обобщается математическая модель, которая описывает популяционную динамику клеточных скоплений на основе системы нелинейных дифференциальных уравнений первого порядка. Предлагается добавить в модель два типа коэффициентов: коэффициент выживаемости, описывающий долю клеток, погибающих в результате воздействия на клетки внешней среды и последующего процесса аутофагии или из-за внутриклеточных процессов, ведущих к смерти (некроз, апоптоз), и коэффициент старения, описывающий ограничение в скорости и возможности деления клеток из-за сокращения длины теломер хромосом клеток при митозе. Добавляемые коэффициенты обладают биологическим смыслом и могут быть оценены в ходе эксперимента, как того требует исходная рассмотренная модель. Учет в математической модели этих параметров позволил определить у системы дифференциальных уравнений, описывающей поведение многоклеточных скоплений, новые динамические режимы. Для полученной системы дифференциальных уравнений был проведен анализ ее особых точек и устойчивости стационарных состояний, которые соответствуют этим точкам. Были определены значения параметров математической модели, при которых система переходит в стационарное состояние. Также были выявлены ограничения на значения параметров, при которых оценка устойчивости стационарных состояний по методу Ляпунова невозможна. Из полученных условий следует, что одним из случаев, когда система клеточных скоплений приходит к стационарному состоянию, является вымирание или прекращение деления клеток каждой популяции. Возможны также и стационарные состояния другого вида, для которых критерии существования и устойчивости еще предстоит оценить.

Ключевые слова: системы нелинейных дифференциальных уравнений, моделирование морфогенеза, программируемая клеточная смерть, предел Хейфлика.

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