ORIGINAL ARTICLE

Leukosis Mathematical Model

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Abstract

Aim and Scope: The present study is about developing the mathematical model of leukosis according to modern data on hematopoiesis among mammals. **Materials and Methods:** Three types of cells are considered in the model, one of which is represented by leukemic ones. The interaction of cells is considered as the competition for the functional space of dividing cells. For leukemia cells are the cells dividing at a higher speed as compared to all the others. **Results and Discussion:** The model of leukemic cells replacement with donor cells is considered as the introduction of more active cells than leukemic ones. The model is represented by the Cauchy problem for the system of ordinary differential equations. **Conclusion:** The violation of hematopoiesis functions is compared with a leading parameter change, which transfers the system from a stable steady state to an unstable one.

Key words: Cauchy problem, differential equations, leukemia, mathematical modeling, stability, stationary point

INTRODUCTION

Leukemia is one of the acute diseases. All age cohorts are subjected to it. This disease is difficult to cure; it can last for years despite any treatment. It provides a very high percentage of deaths. The disease proceeds with complications. The most common and expensive method of treatment is the transplantation of the donor bone marrow in a sick organism. However, an immune system starts to reject foreign cells and, thus, the remission is often accompanied by some disease of other organs. The treatment is carried out also by the introduction of drugs into a sick body. These drugs help to cope with the disease. With a favorable outcome of treatment, the remission does not mean that there will be no relapse. The mathematical modeling of leukemia and the variants of its treatment can help the experts treating the disease to plan the treatment both according to its terms and at its cost.

Hematogenesis

Hematogenesis is the process of platelet, erythrocyte, and leukocyte development. It includes many individual processes occurring at different levels of cell division.[1] The multiplication of cells and their mortality are determined by the system of regulatory factors, stress signals, and the interaction with the surrounding microenvironment.[2] The ancestral cells of hemopoiesis are stem cells (SCs), due to which a stable hematopoiesis is provided.[3] The result of division is that SC can develop two types of cells: Daughter cells that are identical to a parent cell, and the cells that go to the maturing fraction and begin the pathway of differentiation. Acute leukemia is a cellular clone, all elements of which are the descendants of one cell.[4] An original mutation occurs in a SC. Genetic instability leads to additional mutations, and thus the cells of a formed clone cease to differentiate, afflict the bone marrow gradually by morphologically immature hematopoietic cells with the displacement of normal cells by them.[5]

The behavior of SC is affected by their microenvironment or their niche. Niches are a heterogeneous space for SC, in which SC behavior is controlled and their abundance is regulated through the signals from cells and non-cellular factors. Depending on signals, SC can either proliferate, be at rest, or differentiate.[3,5] The differentiation and the proliferation of hematopoietic cells occur simultaneously. An equilibrium

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is maintained between different types of hematopoietic cells due to the niches.

Leukemia cells are located in the same niches as hematopoietic SC and progenitor cells, resulting in the competition for a niche. In particular, leukemic cells are able to produce excessively a colony-stimulating factor that increases the rate of their division in comparison with a normal cell division rate (myelopoiesis stimulant), which acts more specifically on leukemic than on normal hematopoietic progenitor cells.[3,4] At the same time, malignant cells have the ability to inhibit selectively the proliferation and the differentiation of normal precursors using humoral inhibitors even in small amounts.

Thus, competition takes place in a niche for the functional space between different cells.[6] The cells which proliferate faster, giving off numerous offspring, have a competitive advantage. The proliferation rate of SC is regulated by the signals coming from microenvironment cells. The violation of a niche functional state leads to cell generation rate increase or to its decrease.

Mathematical models, developed on the basis of process knowledge, leading to the emergence of serious diseases, allow us to find the rational strategies for disease prevention and treatment. Therapy is one of the treatment methods. Treatment involves several courses of therapy, each of which consists of sequential administration of drugs at predetermined periods of time.[7] SC transplantation is a difficult method of treatment.[8] Both methods are not always successful and effective ones.[9]

Experimental

Mathematical model of leukosis

The mathematical models proposed in the literature[5,10] are represented by the systems of ordinary differential equations.[11,12] In,[13,14] the model of the immune response to the appearance of leukemic cells is proposed, and in[15] they propose the options for leukemia treatment modeling. The level of blood diseases among Russian population is reflected in.[16] The concept of competition of all types of cells competition for functional space is taken as the basis for leukemia modeling.[17]

The mathematical model assumes that leukemia has a hierarchical structure. Four types of cells are considered: Healthy, leukemic, stem, and microenvironment cells that regulate the proliferation of SCs. Leukemic, healthy, and SCs are combined into one pool of a single volume. If we assume that μ_s is the number of SCs in a niche, μ_h - healthy, μ_d - leukemic ones, then their number at the time of hematopoiesis beginning must satisfy the condition $\mu_s+\mu_h+\mu_d\leq 1$. Distribution of proliferating SCs between patients and healthy one occurs under the influence of microenvironment cells μ_α at the ratio $\alpha:1-\alpha$ $(0<\alpha\leq 1)$). Healthy, sick, and SCs can reproduce themselves at specific rates equal to μ_1, μ_2, and μ_3, respectively. The rates of healthy and sick cell transition to ϕ bloodstream are equal to μ_1 and μ_2, respectively. The rate of cell transition μ_s into healthy and diseased ones is regulated by microenvironment cells μ_α. Taking into account these assumptions, the mathematical model of leukemia is represented by the Cauchy problem for the system of four ordinary differential equations.

$$\frac{du_h}{dt}=\mu_1(1-u_h-u_d-u_s)u_h+\alpha\gamma u_a u_s-v_1u_h, \quad (1)$$

$$\frac{du_d}{dt}=\mu_2(1-u_h-u_d-u_s)u_d+(1-\alpha)\gamma u_a u_s-v_2u_d,$$

$$\frac{du_s}{dt}=\mu_3(1-u_h-u_d-u_s)u_s^2-\gamma u_s u_a,$$

$$\frac{du_a}{dt}=-\mu_4 u_a(\beta-u_s),$$

$$u_h(t=0)=u_h^0,\ u_d(t=0)=u_d^0,\ u_s(t=0)=u_s^0,\ u_a(t=0)=u_a^0$$

The multiplier $1-\mu_h-\mu_d-\mu_s$ in the first three equations is a cell-free part of the pool, and the parameter β corresponds to the number of SCs of the niche in the equilibrium state with the natural generation of all cell types.

All unknown quantities in the model are considered dimensionless. Time t is also considered dimensionless, however, as for real processes, the unit of dimensionless time can be compared with a day in a real process.

SCs μ_s leave the niche with the speed $\gamma\mu_s\mu_\alpha$ under the influence of microenvironment cells μα and pass into the profiling healthy (μ_s) and leukemic (μ_d) cells. With the increase of SC number in the niche above the threshold value β, the number of microenvironment cells that cause SC leaving rate increase from the niche with the speed $\gamma\mu_s\mu_\alpha$ also increases and with the decrease of SC number in the niche, the rate of care will be decreased.

If a niche is absent (in (1) $\gamma_1=0$, $\mu_s=0$, $\mu_\alpha=0$), the first two equations in (1) take the following form.

$$\frac{du_h}{dt}=\mu_1(1-u_h-u_d)u_h-v_1u_h, \quad (2)$$

$$\frac{du_d}{dt}=\mu_2(1-u_h-u_d)u_d-v_2u_d.$$

This system of equations has two stationary points

1. $u_h=1-\frac{v_1}{\mu_1}$, $u_d=0$;

2. $u_h=0$, $u_d=1-\frac{v_2}{\mu_2}$.

In the first stationary point, the eigenvalues of the Jacobi matrix from the right-hand side of equations (2) will be

$$\lambda_1 = -\mu_1 \text{ and } \lambda_2 = \frac{\mu_2}{\mu_1}\nu_1 - \nu_2.$$

Moreover, this stationary point will be stable if the inequality $\mu_2\nu_1 < \mu_1\nu_2$ is performed. That is, if the specific rate of tumor cell generation is small or the rate of their escape into the system is large, then cells μ_h will displace the cells μ_d in time. If this inequality is not satisfied, then the second stationary point will be a stable one.

RESULTS AND DISCUSSION

Cell transplantation model

One of the ways of treatment is the transplantation of donor cells. If their activity is higher than that of the host cells, they will displace the host cells gradually. As the practice of clinical research shows, donor cells do not always get accustomed to a new organism. Taking this into account, the model of host cell displacement by donor cells u_L will be represented by the system of differential equations.

$$\begin{aligned}\frac{du_h}{dt} &= \mu_1(1-u_h-u_L)u_h - \nu_1 u_h,\\ \frac{du_L}{dt} &= \mu_3(1-u_h-u_L)u_L - \nu_3 u_L - \gamma u_h u_L,\end{aligned} \qquad (3)$$

In which μ_3 is the specific rate of donor cell multiplication and ν_3 is the rate of donor cell transition into a bloodstream. The inhibitory effect of host cells on donor cells is taken into account by the introduction of the element $\gamma\mu_h\mu_L$ into the second equation with the parameter γ, which determines the inhibition intensity.

The system of equations (3) has three non-trivial stationary points

1. $u_L = 0, u_h = 1 - \frac{\nu_1}{\mu_1}$;

2. $u_h = 0, u_L = 1 - \frac{\nu_3}{\mu_3}$;

3. $u_h = \frac{\nu_3}{\gamma}\left(\frac{\mu_3}{\mu_1}\frac{\nu_1}{\nu_3} - 1\right), u_L = 1 - \frac{\nu_1}{\mu_1} - \frac{\nu_3}{\gamma}\left(\frac{\mu_3}{\mu_1}\frac{\nu_1}{\nu_3} - 1\right)$.

The third stationary point exists if the following inequalities are performed:

$$1 < \frac{\mu_3}{\mu_1}\frac{\nu_1}{\nu_3} < 1 + \frac{\gamma}{\nu_3}\left(1 - \frac{\nu_1}{\mu_1}\right).$$

In the first stationary point, one of the eigenvalues of the Jacobi matrix from the right-hand side of equations (3) will be positive one if the following inequality is performed.

$$\frac{\mu_3}{\mu_1}\frac{\nu_1}{\nu_3} > 1 + \frac{\gamma}{\nu_3}\left(1 - \frac{\nu_1}{\mu_1}\right).$$

This inequality for the model (3) is the condition for the replacement of host cells by donor cells.

The second stationary point will be a stable one[18,19] if the inequality $\mu_3\nu_1 < \mu_1\nu_3$ is performed.

The third stationary point has the characteristic polynomial of the Jacobi matrix from the right-hand side of equations (3)

$$P(\lambda) = \lambda^2 + (\mu_1\mu_h + \mu_3\mu_L)\lambda - \gamma\mu_1\mu_h\mu_L$$

has the roots of opposite signs. Therefore, this stationary point will be unstable one.

Thus, the donor cells of the model (3) either displace host cells, or the host cells displace them.

The model (3) for the case of healthy and leukemic cell presence takes the following form

$$\begin{aligned}\frac{du_h}{dt} &= \mu_1(1-u_h-u_d-u_L)u_h - \nu_1 u_h,\\ \frac{du_d}{dt} &= \mu_2(1-u_h-u_d-u_L)u_d - \nu_2 u_d,\\ \frac{du_L}{dt} &= \mu_3(1-u_h-u_d-u_L)u_L - \gamma(u_h+u_d)u_L - \nu_3 u_L\end{aligned}$$

The solution of these equations for the case $\nu_1=\nu_2=\nu_3=0.1$, $\mu_1=1.0$, $\mu_2=1.5$, and $\mu_1=2.0$, $\gamma=0.007$ is shown in Figure 1. The dotted line marks the time (t=60) of donor cell transplantation. In this example, donor cells displace both healthy and leukemic cells.

Stationary points

The stationary values of equation system (1) and their stability are studied by numerical methods. For the case of constants $\mu_3=20$, $\alpha=0.98$, $\nu_1=0.5$, $\nu_2=0.5$, Figure 2 shows the dependence of the stationary values μ_h on the parameter values β. Curve 1 corresponds to the values $\mu_1=1.0$, $\mu_2=1.0$, and curve 2 - $\mu_1=1.0$, $\mu_2=1.5$. The dashed line represents the boundary between the region of stable ($Re\lambda<0$) and the region of unstable ($Re\lambda<0$) stationary points. The curve 1 and 2 almost coincide in the region of stable stationary points.

The stationary points of equation (1) system depending on the values of the parameter β can be either stable or unstable ones. Oscillations appear in the system at small values of the parameter β. The latter is interpreted as the emergence of disease with a shortage of SCs. Figure 3 with the values of the parameters $\beta=0.2$, $\mu_1=1.0$, $\mu_2=1.5$, $\mu_3=20$, $\alpha=0.98$, $\nu_1=0.5$, $\nu_2=0.5$ shoes the change of $\mu_h(t)$, $\mu_d(t)$, and $\mu_s(t)$ in time. The stationary point in the case under consideration is not stable, periodic oscillations appear in its neighborhood.

Disease treatment model

The appearance of the disease in the model (1) is considered as the change in the time moment t_0 of the parameter β, which transfers a stable stationary state to an unstable one. Then, treatment is considered as such an effect on this parameter, under which it returns to the "normal" state. In this case, the administration of the drug occurs from the moment of time t_1 to the moment of time t_2. Let, Δβ is the parameter β deviation from the initial value, and Drug(t) is the law of drug administration which changes the disturbance value. Then, the model of cell generation disruption and the treatment of malfunctions have the following form taking into account the fourth equation in (1)

$$\frac{du_a}{dt} = -\mu_4 u_a \left(\beta + \Delta\beta - u_s\right).$$

$$\frac{d\Delta\beta}{dt} = -\Delta\beta \mathrm{Drug}(t).$$

Drugs can be given continuously in time (Drug(t)=const) or periodically. The model of periodic impact can be represented by the following function:

(Drug(t)=Dsin(ωt), if sin(ωt)>0,

(Drug(t)=0, if sin(ωt)≤0.

The simulation results for this function are shown in Figure 4 in the form of the following dependencies: $\mu_h(t)$, $\mu_d(t)$, and $\mu_s(t)$.

For the case of the constants β=0.35, μ_1=1.0, μ_2=1.5, μ_3=20, α=0.98, ν_1=0.5, ν_2=0.5, the stationary point μ_h=0.526, μ_d=0.031, μ_α=0.646, and μ_s=0.359 is a stable one in the time interval $[0,t_0]$ (zone A on Figure 4). At the time moment $t=t_0$, the parameter β takes the value . The stationary point of the equation system (1) will be unstable one at this value of the parameter β [Figure 2]. There are oscillations in the system (zone B of Figure 4). That is, the system goes into an unstable state. The drug is introduced D=0.12 and ω=2π/20 (Drug zone on Figure 4) from the time moment $t=t_1$ till the time moment $t=t_2$. A gradual

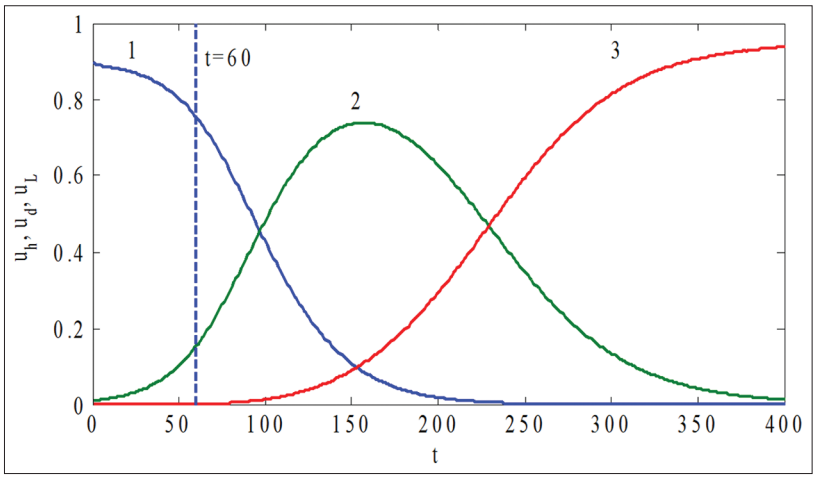

Figure 1: Function dependence $\mu_h(t)$ (curve 1), $\mu_d(t)$ (curve 2), $\mu_L(t)$ (curve 3) on t provided that $\mu_L(t)$=0 at t <60 for the case μ_1=1.0, μ_2=1.5

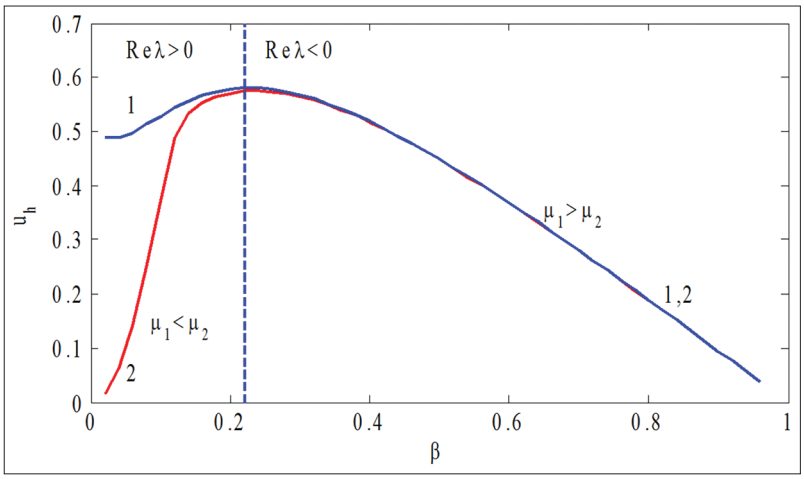

Figure 2: The graphs of stationary value dependence μ_h on the parameter β. Curve 1 - μ_1=1.0, μ_1=1.5, curve 2 - μ_1=1.0, μ_2=1.0. The dashed line represents the interface between the regions of stable (Reλ<0) and unstable (Reλ<0) stationary points

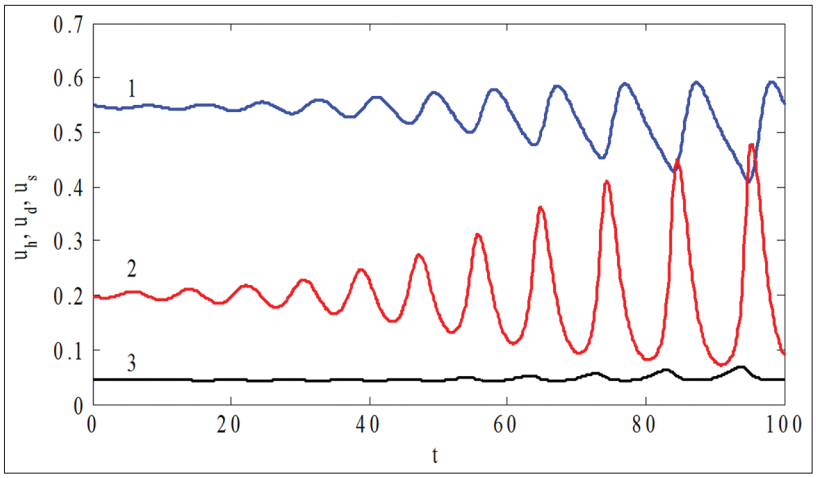

Figure 3: The graphs of function dependence $\mu_h(t)$ (curve 1), $\mu_s(t)$ (curve 2), $\mu_d(t)$ from t at small initial deviations from an unstable stationary point

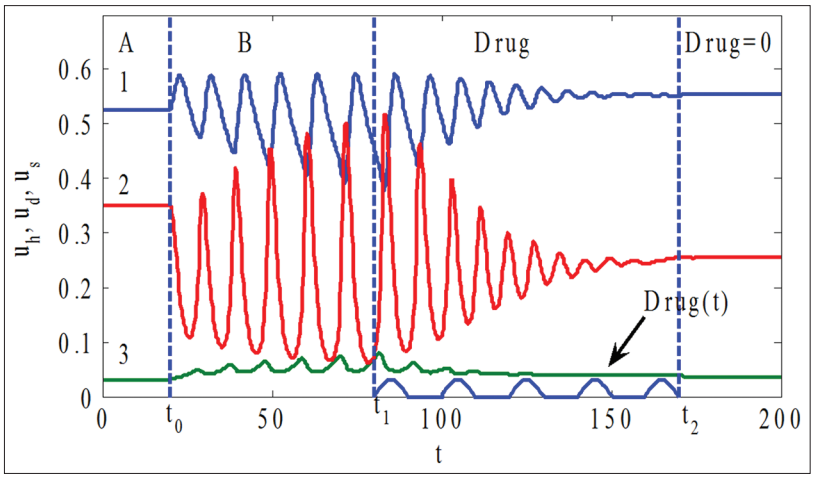

Figure 4: Function dependence graphs $\mu_h(t)$ (curve 1), $\mu_s(t)$ (curve 2), $\mu_d(t)$ (curve 3), and Drug(t) on t. At the interval $[0,t_0]$, the system is in an unstable state (zone A), at the interval $[t_0,t_1]$, the system is in an unstable state (zone B), at the interval $[t_1t_2]$ (zone Drug), the system returns to a stable state

decrease of the parameter β excitation transforms the system into the region of stable stationary points.

CONCLUSION

The solution of the Cauchy problem for the systems of differential equations was carried out using the Runge–Kutta method in Dormand-Prince modification within the programming environment of the mathematical package MatLab. The built-in function ode45 was used. The parameters of the equation systems μ_1, μ_2, and μ_3, determining the reaction rates, can differ by 2–3 times as follows from the results of clinical studies. In this range, the differences of equation system parameters are not rigid ones. Nevertheless, since the solutions were developed in the vicinity of unstable points, the solution results were compared with the solutions developed by the use of ode23tb function, designed to solve "hard" systems. The results, which were developed by both functions with the accuracy of 10^{-6}, coincided in the studied range of parameter variation.

Thus, the developed model explains the mechanism of several types of cells interaction as the competition for the functional space with the displacement of all cells from it by more active cells, and the disturbance of hematopoiesis functions explains the transition of the system from a stable region to an unstable one.

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