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ON FEEDBACK CONTROL BY HOPF BIFURCATION IN MATHEMATICAL MODEL OF LEUKEMIA THERAPY

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Dedicated to eminent man and mathematician Vladimir Tikhomirov

Abstract. The paper presents a mathematical model for the therapy of malignant myeloid leukemia cells. The first two equations of the model describe the changes in the number of healthy and cancer cells as a result of interaction with a drug that slows down their growth. The dynamics of the receipt of this drug is described by a separate equation. Conditions for a stable limit cycle of cancerous and healthy cells have been found in the form of feedback therapy strategy.

Keywords. Hopf bifurcation; Feedback control; Mathematical model of leukemia therapy.

2020 Mathematics Subject Classification. 90C32, 92C37, 92C50.

1. INTRODUCTION

It is known that, due to toxicity, long-term use of drugs is detrimental to the patient's health, since during therapy the population of healthy cells and cells of the immune system decreases. Therefore, the problem of finding long-term treatment strategies that do not lead to critical damage to health is urgent. One example of this approach is the diabetes treatment strategy, which has transformed the disease from a critical condition to a chronic condition controlled by regular insulin intake. The fundamental possibility of the emergence of a stable limit cycle in the system of healthy cells, cancer cells and a drug means that the number of healthy and cancer cells can fluctuate within limits that are not critical and guarantee a sufficiently long-term safe state for the patient.

2. STATEMENT OF THE PROBLEM

As a basic mathematical model, we consider the mathematical model of chemotherapy for myeloid leukemia [1, 2, 3, 4].

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This model takes into account the nonlinear laws of cell number growth, the nonlinear effects of cell-drug interactions, and competition between healthy and cancer cells for a common nutritional resource. The equations of state are

$$\begin{cases} \dot{c} = r_c c g_1(c) - h p_1(c), \\ \dot{n} = r_n n g_2(n) - h p_2(n) - \varepsilon c n, \\ \dot{h} = -h\gamma + u(t), \end{cases} \tag{2.1}$$

where $c(t)$ is the number of cancer cells at a time t; $n(t)$ is the number of healthy cells at a time t; $h(t)$ is amount of drug at a time t; r_c, r_n are growth rates of cancer and healthy cells, respectively; γ is a drug dissipation coefficient; ε is a coefficient characterizing the competitive interaction between of healthy and cancer cells; $g_2(n), p_1(c)$ and $g_2(n), p_2(n)$, are smooth functions of the variables c and n satisfying the following conditions:

$$\begin{gathered} q_i(x) > 0, 0 < x < N_i; g_i(x) = 0; x = N_i; q_i(x) < 0, x > N_i \\ p_i(0) = 0; p(x) > 0, x > 0; \\ q_i(0) = 0; q_i(x) > 0, \frac{dq(x)}{dx} > 0, x > 0, \end{gathered} \tag{2.2}$$

$u(t)$ is the control function (amount of incoming drug per unit of time). The following restrictions are imposed on the values of the control function:

$$0 \le u(t) \le \mathrm{M}, \int_0^T u(t)dt \le R. \tag{2.3}$$

The first of the inequalities (2.3) corresponds to a limitation on the intensity of drug therapy, the second is restrictions on the total volume of a drug using in the therapy process. Note that these restrictions are not independent. The problem of finding the optimal therapy strategy in a form of function in the implementation of which the number of cancer cells reaches a minimum value has been studied with various types of objective functions. Using Pontryagin's maximum principle, it was shown [5, 6, 7, 8, 9, 10, 11], that the optimal therapy strategy represents a piecewise constant function with one switching point, therefore the phase trajectories of the system do not have cycles in the (c,n,h) space. Consider the following modification of the dynamic system (2.1)

$$\begin{cases} \dot{c} = r_c c g_1(c) - h p_1(c), \\ \dot{n} = r_n n g_2(n) - h p_2(n) - \varepsilon c n, \\ \dot{h} = h\left(-\gamma + q_1(c) + q_2(n)\right). \end{cases} \tag{2.4}$$
$$c(0) = c_0 n(0) = n_0, h(0) = h_0.$$

Functions $g_1(c) = (N_1 - c)$ and $g_2(n) = (N_2 - n)$ determine the growth dynamics of species according to the logistic law. The functions $p_1(c), p_2(n)$ characterize the amount of damage from the effects of the drug with concentration h on malignant and healthy cells respectively. Functions $q_1(c) = K_1 c$ and $q_2(n) = K_2 n$ determine the intensity of drug consumption by cells c and n. We further assume that

$$p_1(c) = \frac{Ac}{c + \mathrm{B}}, \quad p_2(n) = \frac{An}{\mathrm{n} + \mathrm{D}}, \quad A, B, D, K_1, K_2 \text{ - const } > 0.$$

After introducing the appropriate dimensionless variables, system (2.4) can be reduced to the following form:

$$\begin{cases} \frac{dc}{dt} = r_c c(1-c) - \frac{ch}{c+\theta_1}, \\ \frac{dn}{dt} = r_n n(1-n) - \frac{nh}{n+\theta_2} - \varepsilon cn, \\ \frac{dh}{dt} = -\gamma h + h(k_1 c + k_2 n), \end{cases} \tag{2.5}$$

where $c(t)$ and $n(t)$ are relative cell numbers at time t; k_1, k_2 are dimensionless coefficients characterizing the intensity of drug consumption by healthy and diseased cells; θ_2, θ_1 are coefficients characterizing the degree of damage to healthy and diseased cells from the use of the drug; coefficient ε described the degree of competition between healthy and cancer cells for common resources.

Thus, system (2.5) contains eight positive parameters. The fundamental difference between system (2.5) and system (2.1) is that instead of a control function that $u(t)$ depends only on time, the supply of the drug is regulated depending on the current values of the number of cancer and healthy cells. In other words, instead of strict deterministic program control, feedback control is used, which is formed depending on information about the state of the system. This control is determined by the function $R(\mathrm{c},\mathrm{n},\mathrm{h}) = h(k_1 c + k_2 n)$.

The purpose of the study is to prove the possibility of the emergence of a stable limit cycle in the phase space of the system (2.5) with a control function $R(\mathrm{c},\mathrm{n},\mathrm{h})$.

3. Necessary Conditions for the Hopf Bifurcation

Mathematical model (2.4) can be interpreted as a model of a biological community consisting of three populations. The first and second populations (autotrophic species) are prey for the third population (heterotrophic species). In addition, the first and second species compete for the same food resource. It is well known that in classical the Gause "predator-prey" model [12] under certain conditions on the parameters of the system, allows the existence of a limit cycle in the plain (c,n) [13, 14]. Therefore, an assumption arises about the existence of such system parameters, at whose values limit cycles could simultaneously exist, both in phase space (n,h) and in space (c,h). The presence of such parameters is a necessary condition for the occurrence of a limit cycle in the space of all phase variables $(\mathrm{c},\mathrm{n},\mathrm{h})$.

A necessary condition for the existence of a limit cycle in the plane (h,c) is to satisfy the following condition [14]:

$$\frac{\mathrm{d}}{\mathrm{dc}}(\mathrm{h})\Big|_{\mathrm{c}=\mathrm{c}^*} = \frac{\mathrm{d}}{\mathrm{dc}}\left(\frac{\mathrm{r_c cg(c)}}{p1(\mathrm{c})}\right)\Big|_{\mathrm{c}=\mathrm{c}^*} = \frac{\mathrm{d}}{\mathrm{dc}}\left(\mathrm{r_c}(1-\mathrm{c})(\mathrm{c}+\theta_1)\right)\Big|_{\mathrm{c}=c^*} > 0, \tag{3.1}$$

where $(k_1 c^*) = \gamma$. It follows that $0 < \Theta_1 < 1$. Here c^* is the coordinate of the internal point of rest of the first and third system of equations (2.5).

A similar necessary condition for a cycle in the plane (h,n) for sufficiently small values of the parameter ε has analogous form:

$$\frac{\mathrm{d}}{\mathrm{dn}}(\mathrm{h})\Big|_{\mathrm{n}=\mathrm{n}^*} = \frac{\mathrm{d}}{\mathrm{dn}}\left(\frac{\mathrm{r_n ng(n)}}{p2(\mathrm{n})}\right)\Big|_{\mathrm{n}=\mathrm{n}^*} = \frac{\mathrm{d}}{\mathrm{dn}}\left(\mathrm{r_n}(1-n-\varepsilon c)(\mathrm{n}+\theta_2)\right)\Big|_{\mathrm{n}=\mathrm{n}^*} > 0, \tag{3.2}$$

where $(k_2 n^*) = \gamma$. Therefore $0 < \theta_2 < 1 - \varepsilon c$. Here n^* is the coordinate of the internal rest point of the second and third system of equations (2.5).

Conditions (3.1) and (3.2) mean that the internal equilibrium positions of the systems consisting of the first and third equations (2.5) and the second and third equations of this system are unstable focus.

If there is a limit cycle in the phase space (c, n, h), then it is necessary that for the same values of the variable h the following equality holds: (here and after and $c = c^* n = n^*, h = h^*$)

$$h = \mathrm{r_c}(1-\mathrm{c})\,(\mathrm{c}+\theta_1) = (1-n-\varepsilon c)\,(\mathrm{n}+\theta_2)\,.$$

If $\varepsilon = 0$, then this equality take the form

$$p(1-c)\,(c+\theta_1) = (1-n)\,(n+\theta_2)\,,$$

where p is the ratio of the growth rate of cancer cells to the growth rate of healthy cells. We further assume that

$$p = \frac{r_c}{r_n} \geq 1.$$

The last equality can be represented in the form

$$\theta_1 = A\theta_2 + B, \tag{3.3}$$

where

$$A = \frac{1-\mathrm{n}}{\mathrm{p}(1-\mathrm{c})}, \mathrm{B} = \mathrm{n}A - \mathrm{c}.$$

Using inequalities $(1-c)c \leq 0.25$ and $(1-n)n \leq 0.25$, we obtain the following estimates for the values of A and B:

$$0 < A < 4(1-n)c, \quad \frac{1-\mathrm{p}}{4p(1-c)} \leq \mathrm{B} \leq \frac{1}{4p(1-c)}.$$

Consequently, for any internal equilibrium positions there $c = c^*, n = n^*$ be such values $0 < \Theta_1 < 1$ and $0 < \theta_2 < 1$ for which equality (3.3) will be satisfied. Due to continuity, this equality will be satisfied for sufficiently small values of the parameter ε, which characterizes the degree of competition of cells for common resources. Without loss of generality, we further assume that this value is much less than r_n and r_c :

$$\varepsilon \ll \max(\mathrm{r_c}, r_n)\,. \tag{3.4}$$

The equilibrium positions of system (2.5) on the boundary of the first octant are given by the following equalities:

$$A_0 = (0;0;0), A_c = (1;0;0), A_{ch} = \left(\frac{\gamma}{k_1}; 0; r_c\left(1-\frac{\gamma}{k_1}\right)\left(\frac{\gamma}{k_1}+\theta_1\right)\right),$$
$$A_n = (0;1;0), A_{nh} = \left(0; \frac{\gamma}{k_2}; r_n\left(1-\frac{\gamma}{k_2}\right)\left(\frac{\gamma}{k_2}+\theta_2\right)\right), A_{cn} = \left(1; 1-\frac{\varepsilon}{r_n}; 0\right).$$

The Jacobi matrix of (2.5) has the form

$$J(c,n,h) =$$
$$= \begin{pmatrix} r_c g_1(c) + r_c c g_1'(c) - h p_1'(c) & 0 & -p_1(c) \\ -\varepsilon n & r_n g_2(n) + r_n n g_2'(n) - h p_2'(n) - \varepsilon c & -p_2(n) \\ h\varphi'(c) & h q'(n) & -\gamma + q_1(c) + q_2(n) \end{pmatrix}. \tag{3.5}$$

Direct analysis shows that the equilibrium positions A_0, A_c and A_n are saddles. At a point, A_{ch} matrix (2.5) is given by the equality:

$$J(A_{ch}) = \\ = \begin{pmatrix} -\frac{r_c\left(1-\frac{\gamma}{k_1}\right)\theta_1}{\left(\frac{\gamma}{k_1}+\theta_1\right)} + r_c\left(1-2\frac{\gamma}{k_1}\right) & 0 & -\frac{\frac{\gamma}{k_1}}{\frac{\gamma}{k_1}+\theta_1} \\ 0 & r_n - \frac{r_c\left(1-\frac{\gamma}{k_1}\right)\left(\frac{\gamma}{k_1}+\theta_1\right)}{\theta_2} - \varepsilon\frac{\gamma}{k_1} & 0 \\ r_c\left(1-\frac{\gamma}{k_1}\right)\left(\frac{\gamma}{k_1}+\theta_1\right)k_1 & r_c\left(1-\frac{\gamma}{k_1}\right)\left(\frac{\gamma}{k_1}+\theta_1\right)k_2 & 0 \end{pmatrix}.$$

Analysis of the eigenvalues of this matrix shows that the equilibrium position A_{ch} is a saddle if $\frac{\gamma}{k_1} < \frac{1-\theta_1}{2}$. A similar analysis of the eigenvalues of matrix (2.5) shows that the equilibrium position A_{ch} is also a saddle if $\frac{\gamma}{k_2} < \frac{1-\theta_2}{2}$. The last two inequalities will be satisfied if the parameter value γ is small enough. At the point, A_{cn} the Jacobi matrix (3.5) has the form:

$$J(A_{cn}) = \begin{pmatrix} -r_c & 0 & -\frac{1}{1+\theta_1} \\ -\varepsilon\left(1-\frac{\varepsilon}{r_n}\right) & -r_n+\varepsilon & -\frac{1-\frac{\varepsilon}{r_n}}{1-\frac{\varepsilon}{r_n}+\theta_2} \\ 0 & 0 & -\gamma+k_1+k_2\left(1-\frac{\varepsilon}{r_n}\right) \end{pmatrix}.$$

For $\varepsilon < r_n$ and sufficiently small values γ such that $k_1 + k_2\left(1-\frac{\varepsilon}{r_n}\right) > \gamma$ the point A_{cn} is saddle. As a result, if the above conditions are met, then there is a unique equilibrium position $A_{cnh} = (c^*, n^*, h^*) \in \operatorname{int}\mathbb{R}^3_+$. Let us show that a limit cycle A_{cnh} can arise in the vicinity of the equilibrium position. The Jacobi matrix at a point A_{cnh} has the form:

$$J(A_{\text{cnh}}) = \\ \begin{pmatrix} r_c(1-2c^*) - \frac{h^*\theta_1}{(c^*+\theta_1)^2} & 0 & -\frac{c^*}{c^*+\theta_1} \\ -\varepsilon n^* & r_n(1-2n) - \frac{h^*\theta_2}{(n+\theta_2)^2} - \varepsilon c^* & -\frac{n^*}{n^*+\theta_2} \\ h^*\mu k_2 & h^* k_2 & 0 \end{pmatrix}. \tag{3.6}$$

Here and after, μ is the bifurcation parameter of the system, determined by the relation:

$$\mu = \frac{k_1}{k_2}. \tag{3.7}$$

The value of this parameter determines the ratio of the intensities of drug consumption by cancer and healthy cells, respectively. If a supercritical Hopf bifurcation, with the birth of a stable limit cycle took place, it is necessary and sufficient for the following conditions to be fulfilled [15]:

a). The Jacobi matrix (3.6) has two different complex conjugate eigenvalues and the third eigenvalue has a negative real part $\lambda_{1,2} = \alpha(\mu) \pm i\omega(\mu)$, $\operatorname{Re}\lambda_3 < 0$.

b). At some critical value of the bifurcation parameter μ_0 the real part of the eigenvalues becomes zero, $\alpha(\mu_0) = 0$. Moreover, $\alpha(\mu) < 0$ if $\mu < \mu_0$ and $\alpha(\mu) > 0$ if $\mu > \mu_0$.

c). The equilibrium position A_{cnh} is asymptotically stable if $\mu = \mu_0$.

Let us move to analyzing the eigenvalues of matrix (3.6). Using equalities (3.1) and (3.2), we can represent the first two diagonal terms of this matrix in the following form:

$$A_{11} = (p_1(s))^{-1} \frac{d}{dc}\left(\frac{r_c cg(c)}{p1(c)}\right)\Big|_{c=c^*}, \quad A_{22} = (p_2(n))^{-1} \frac{d}{dn}\left(\frac{r_n ng(n)}{p2(n)}\right)\Big|_{n=n^*}.$$

Therefore, these terms are positive. Let $\varepsilon = 0$. The characteristic equation for the eigenvalues of matrix (3.6) is a cubic equation of the form

$$X^3 - AX^2 + BX - C = 0, \tag{3.8}$$

where $A > 0,\ B > 0, C > 0$.

Consider the expression:

$$\alpha = 1/3\left(A^2/3 - B\right). \tag{3.9}$$

From the results of [16] it follows that if $\alpha > 0$, then equation (3.8) can have one negative and two purely imaginary eigenvalues. Analysis of expression (3.9) shows that the choice of a positive parameter value μ for which $\alpha > 0$ is always possible. Due to continuity, this property is preserved even at sufficiently small values of the parameter ε. Despite the obtained estimates for the values of the parameters $\theta_1, \theta_2, \varepsilon, r_c$ and r_n, finding the exact conditions for the existence of two purely imaginary and one negative eigenvalue depending on the values of all eight parameters of the system is a rather difficult task if purely analytical methods are used. But this task is not the goal of our research. Our goal is to demonstrate the possibility of the existence of a non-empty set of actually observed parameters of the system for which the Hopf bifurcation occurs with the formation of a stable limit cycle describing the interaction of the drug with cells. Therefore, we will consider a number of examples, with specific parameter values and a single bifurcation parameter (3.7).

Example 3.1. We consider the following parameter values: $r_c = 0.014, r_n = 0.01, \theta_1 = 0.32, \theta_2 = 0.9, k_2 = 0.00025, \gamma = 0.00054, \varepsilon = 0.0006$. Initial conditions of system (2.5):

$$c_0 = 0.8, n_0 = 0.6, h_0 = 0.001.$$

In this case, the critical value of the bifurcation parameter $\mu_0 = 4.831$. With this value of the parameter, the Jacobian matrix (2.5) has two purely imaginary and one real negative eigenvalue: $\lambda_{1,2} = \pm 0.0019i, \lambda_3 < -0.0039$. If $\mu < \mu_0$, then $\mathrm{Re}\,\lambda_{1,2} < 0$, and when $\mu > \mu_0, \mathrm{Re}\,\lambda_{1,2} > 0$.

The simulation demonstrates a typical process of the origin of a limit cycle. If $\mu < 4.831$, then the phase trajectory starting from the point c_0, n_0, h_0 tends to an equilibrium position, and the projection of the trajectory onto the plane (c, h) represents a stable focus, and the projection onto the oh axis stable node (Fig. 1). At $\mu = 4.831$ the equilibrium position remains stable (Fig. 2), and $\mu > 4.831$ a stable limit cycle arises (Fig. 3).

Fig. 4 shows the dynamics of changes in the relative number of cancerous and healthy cells. At the beginning of the process, the number of cancer cells increases, after which there is a sharp drop in their number, which is replaced by fluctuations ranging from 0.095 to 0.61. At the same time, the number of healthy cells, after a short-term drop, ranges from 0.55 to 0.72. The average integral values of the number of cancerous and healthy cells in one period of oscillations in the cycle are calculated using the formulas:

$$c_{cp} = \frac{1}{T}\int_0^T c(t)dt, \quad n_{cp} = \frac{1}{T}\int_0^T n(t)dt$$

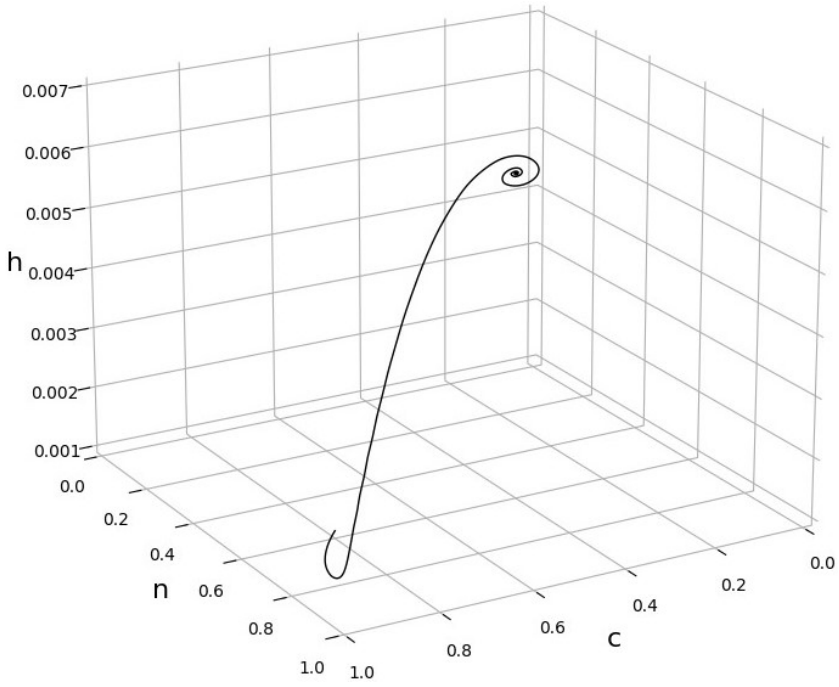

FIGURE 1. Phase trajectory at $\mu < 4.831$.

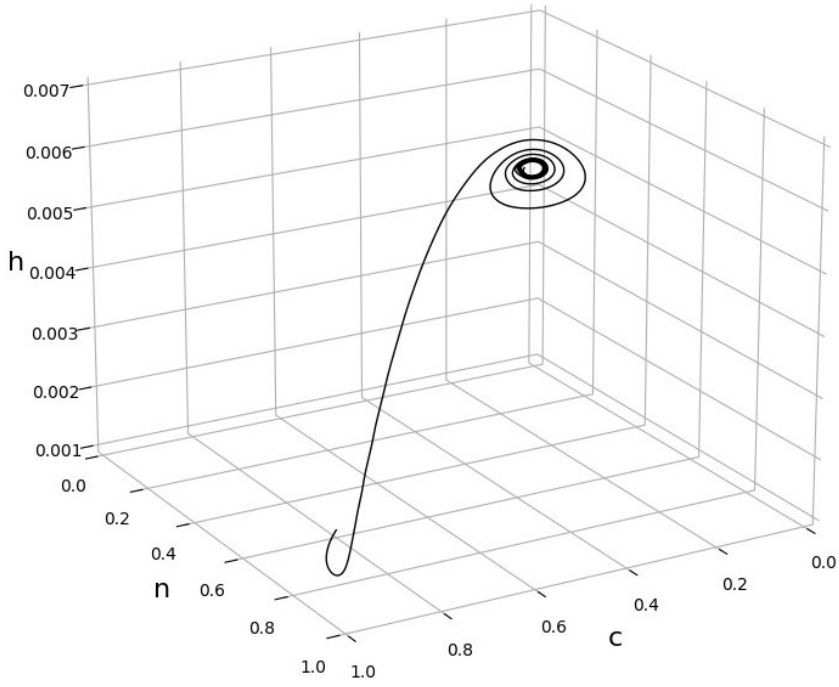

FIGURE 2. Phase trajectory at $\mu = 4.831$.

and are equal to $c_{cp} = 0.296, n_{cp} = 0.628$, and oscillation period T = 4.0 (hereinafter T is dimensionless time). These figures show that the average number of healthy cells is greater, while the average number of cancer cells is less than the same values at the beginning of the therapy process, which reflects the positive dynamics of cyclic therapy. The value of the bifurcation

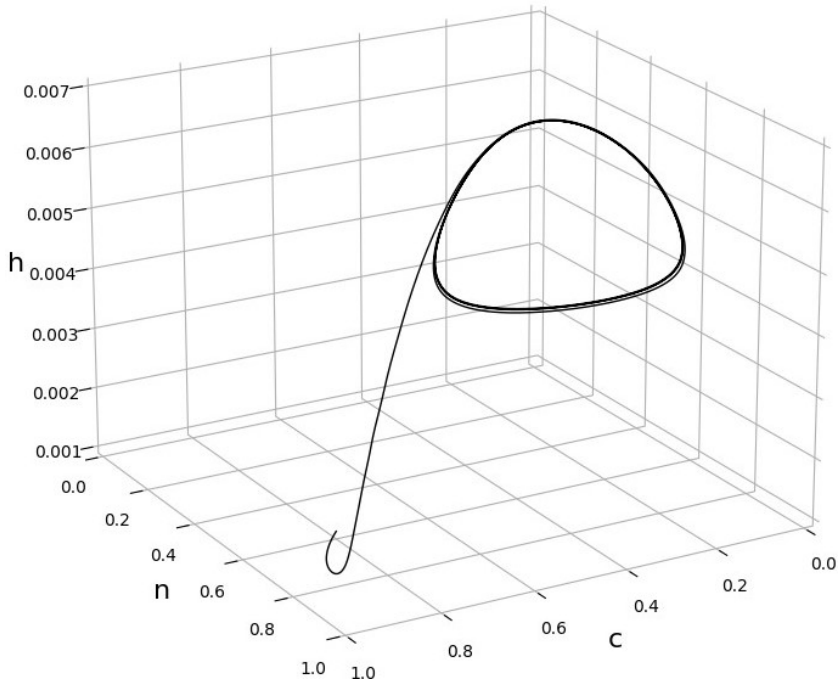

FIGURE 3. Phase trajectory at $\mu > 4.831$.

parameter $\mu_0 = 4.831$, shows that in this case the intensity of drug consumption by cancer cells is almost five times greater than by normal cells. The latter circumstance means that the drug used is quite effective and has low toxicity to healthy cells of the body.

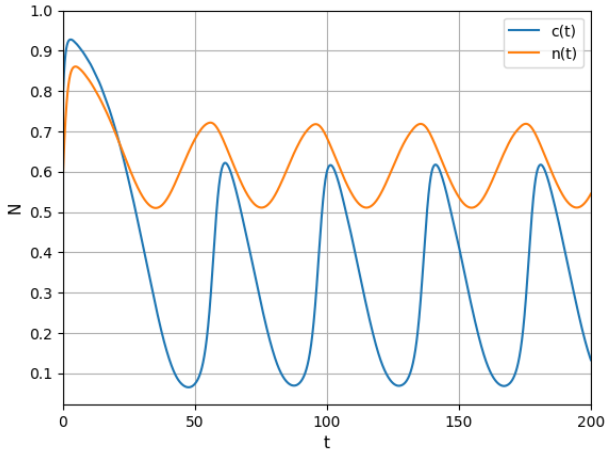

FIGURE 4. Changes in the relative number of cancer and healthy cells.

The dynamics of changes in drug consumption are presented in Fig. 5. After a short-term increase in the consumption of the amount of drug at the beginning of the process, periodic oscillations arise with a fairly small oscillation amplitude and $h_{cp} = 0.00556$. This value characterizes the relatively low consumption of this drug during the therapy process.

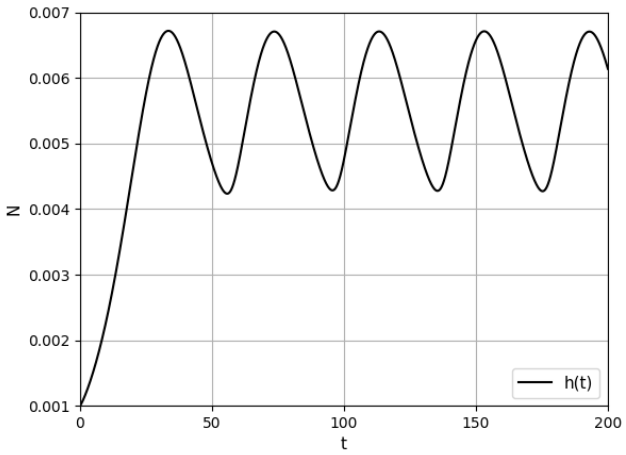

FIGURE 5. Changes in drug consumption.

The ratio of the time the system trajectory reaches the limit cycle to the time of the oscillation period at the limit cycle is 0.8. Most of the drug is consumed when the system reaches the limit cycle. Total expense of drug H=1.21.

Example 3.2. In this case, the following system parameter values are considered: $r_c = 0.01, r_n = 0.0075, \theta_1 = 0.4, \theta_2 = 0.8, k_2 = 0.0003, \gamma = 0.00034, \varepsilon = 0.0005$. Initial conditions:

$$c_0 = 0.7, n_0 = 0.5, h_0 = 0.0001.$$

Bifurcation occurs at a critical value of the parameter $\mu_0 = 2.463$. In this case, the intensity of drug consumption by cancer cells is only almost 2.5 times greater than by normal cells, which corresponds to the rather high toxicity of this drug.

In Fig. 6 shows the phase trajectory of the system at $\mu_0 > 2.463$. The dynamics of changes in the relative number of cancer and healthy cells and the dynamics of changes in drug consumption are presented in Figs. 7 and 8.

In this case, the oscillation period is $T = 6.5$, with $c_{cp} = 0.17781$ and $n_{cp} = 0.54349, h_{cp} = 0.00437$. In the process of oscillations during the cycle, the number of cancer cells does not exceed the value of 0.6 , and the number of healthy cells does not fall below the value of 0.38 . Decrease in value n_{cp} compared to the first example reflects the rather high toxicity of this drug towards healthy cells. The ratio of the time the system trajectory reaches the limit cycle to the time of the oscillation period at the limit cycle is 0.88. Total expense of drug $H = 0.962$.

4. ACCOUNTING FOR THE DYNAMICS OF NUTRIENT SUPPLY

It is known that with an increase in the number of cancer cells, the supply of nutrient medium (oxygen, glucose) increases. To take into account the influence of changes in the concentration of the nutrient medium on the behavior of the system, we add a fourth equation to system (2.5).

$$\frac{ds}{dt} = -\delta s + \beta$$

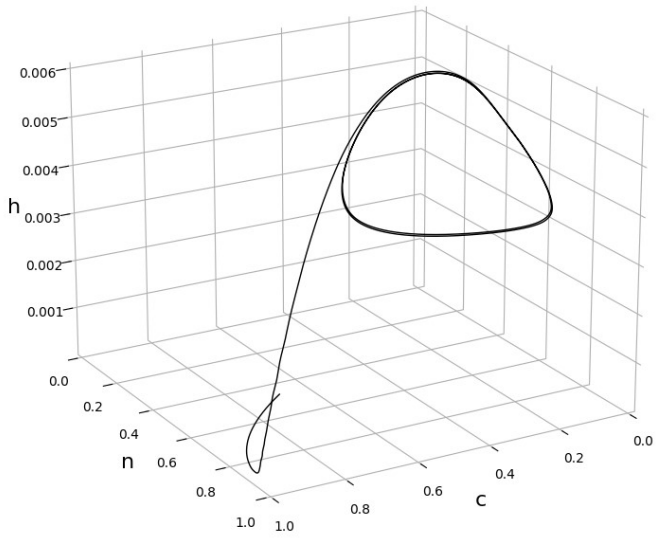

FIGURE 6. Phase trajectory of the system at $\mu_0 > 2.463$.

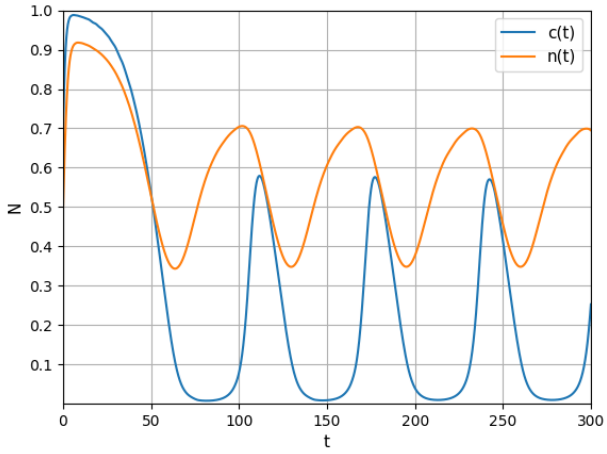

FIGURE 7. Changes in the relative number of cancer and healthy cells.

Here δ is the dissipation coefficient β is the intensity of nutrient supply. As a result, we obtain the system:

$$\begin{cases} \frac{dc}{dt} = r_c c(s-c) - \frac{ch}{c+\theta_1}, \\ \frac{dn}{dt} = r_n n(s-n) - \frac{nh}{n+\theta_2} - \varepsilon cn, \\ \frac{dh}{dt} = -\gamma h + h(k_1 c + k_2 n), \\ \frac{ds}{dt} = -\delta s + \beta. \end{cases} \tag{4.1}$$

Let us consider the same values of parameters and initial data values as in the case of example 3.1 , assuming $\delta = 0.001, \beta = 0.0012$. In this case, bifurcation occurs at a critical value of the bifurcation parameter $\mu_0 = 5.442$, which corresponds to the high effectiveness of the drug and its low toxicity. The eigenvalues of the corresponding Jacobi matrix in the spatial position of equilibrium are determined by the following equalities: $\lambda_{1,2} = \pm 0.0023i, \lambda_3 = -0.001, \lambda_4 = -0.0042$.

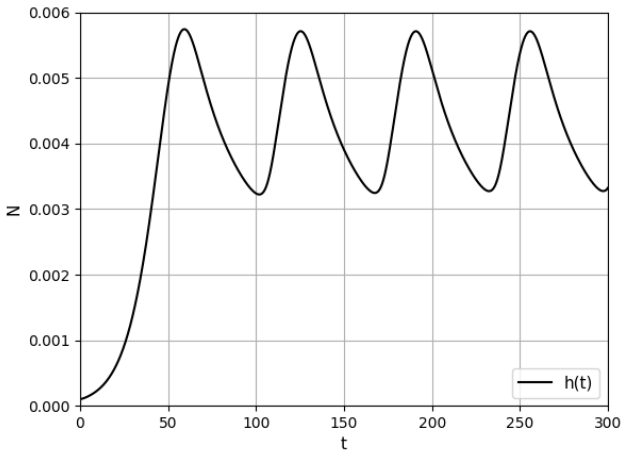

FIGURE 8. Changes in drug consumption.

The phase trajectory in space (c,n,h) for $\mu > 5.442$ shown in the Fig.9.

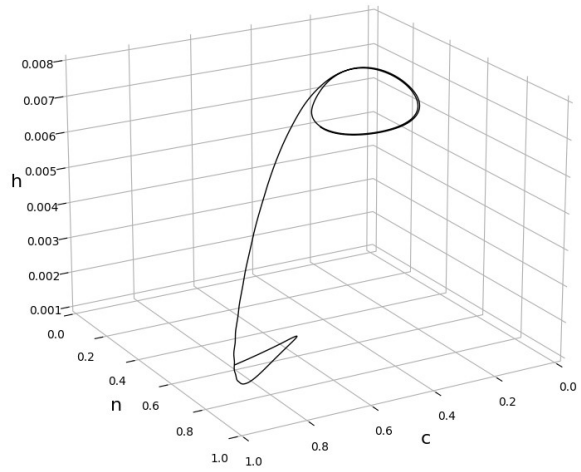

FIGURE 9. Phase trajectory of system (4.1) at $\mu > 4.831$.

The dynamics of changes in the relative number of cancer and healthy cells and the supply of nutrient medium are presented in Fig. 10. Comparison with the case of the absence of a nutrient medium (example 3.1, Fig. 4) shows that in this case the average integral value for the period T = 3.02 of the number of cancer cells and cells increases significantly: $c_{cp} = 0.6802$ while the average number of healthy cells decreases: $n_{cp} = 0.4404$. This effect is explained by the fact that the growth rate of cancer cells $(r_c = 0.014)$ is 1.4 times greater than the same rate for normal cells $(r_n = 0.010)$. Therefore, the additional supply of the nutrient medium (the phenomenon of angiogenesis) causes a greater increase in the number of cancer cells, which have a negative impact on the population of healthy cells due to competitive interaction. The ratio of the time the system trajectory reaches the limit cycle to the time of the oscillation period at the limit cycle also increases and is equal to 1.66. Total expense of drug $H = 1.47$.

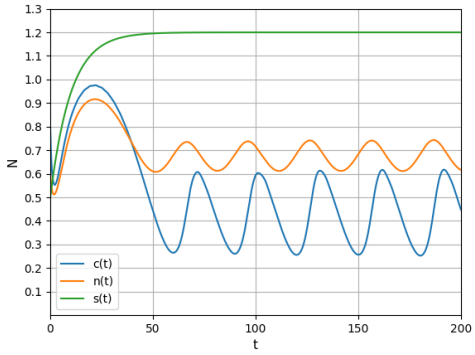

FIGURE 10. Dynamics of changes in the relative number of cancer and healthy cells and the dynamics of the supply of nutrient medium.

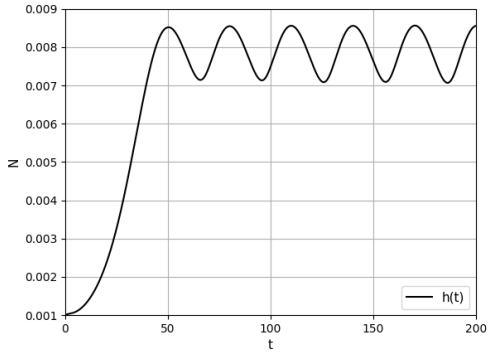

FIGURE 11. Dynamics of drug supply.

5. CONCLUSION

The results obtained show that in the mathematical model of myeloid leukemia (2.5) it is possible to implement control of the therapy process by constructing a feedback control $R(c,n,h) = h(k_1c + k_2n)$, which doses the supply of the drug depending on the current values of cell numbers. It is shown that this control leads to appearance of a stable limit cycle in the phase space with at relatively low drug costs.

The presented results confirm that in the presence of current information on the number of cancer and healthy cells, it is fundamentally possible to implement a therapy strategy in which their number fluctuates within specified limits over a sufficiently large period of time. Note that taking into account many additional factors, such as the nature of the disease, the specific type of cancer cells and the degree of toxicity of the drugs, requires additional research.

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