Commun. Optim. Theory 2022 (2022) 10 https://doi.org/10.23952/cot.2022.10

MATHRES

Communications in Optimization Theory

Available online at http://cot.mathres.org

INVESTIGATION OF SINGULAR REGIMENS IN A CONTROLLED MODEL OF PSORIASIS TREATMENT

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Dedicated to the memory of 100th birthday of Professor Jack Warga

Abstract. Psoriasis is characterized by an overgrowth of keratinocytes (skin cells) resulted from chaotic signaling in the immune system and irregular release of cytokines. Anti-inflammatory cytokines, such as $IL-21$ and $IFN-\gamma$ released by the Th_1-cells and activated killer cells (NK-cells) play a central role in pathogenesis of this disease. So, in this paper, we propose two systems of nonlinear differential equations: one system describes the growth of immune cells (T-helper cells of type I and II, as well as activated NK-cells) along with keratinocytes; another system sets the dynamics of cytokines ($IL-21$ and $IFN-\gamma$). Since these systems use different time scales, we transform them into one system of differential equations, including the immune Th_1- and Th_2-cells, activated NK-cells, and epidermal keratinocytes. Within this description of the dynamics of psoriasis, we study the effect of combined bio-therapy, including the action of the $IL-21$ inhibitor together with anti-$IFN-\gamma$ therapy. To do this, we introduce two bounded control functions into the system and formulate on a given time interval, the problem of minimizing the total cost of the applied immune therapy and its impact on the proliferation of activated NK-cells and keratinocytes at the end of the treatment time. Analysis of such a problem is carried out using the Pontryagin maximum principle. As a result of this analysis, the properties of optimal controls and their possible types are established. It is shown that each such control is either a bang-bang function over the entire time interval, or in addition to non-singular bang-bang sections, it can have a singular regimen. Possible types of singular regimens are studied; for them, the necessary optimality conditions are checked, the singular regimens's formulas are found, so as the ways the singular regimens concatenate with non-singular (bang-bang) sections. Some numerically computed optimal controls are given alone with a discussion of the numerical difficulties in detection of singular regimens.

Keywords. Lie brackets; Nonlinear control system; Pontryagin maximum principle; Switching function; Singular regimen.

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Received: May 16, 2022; Accepted: August 10, 2022.

1. INTRODUCTION

Psoriasis is an urgent medical and social problem due to the growth in recent decades of its indicators and the increase in the number of patients. This is a health problem that is resistant to various methods of treatment, reducing the quality of life of patients, social adaptation and professional activity. Psoriasis occupies one of the leading places in terms of incidence among chronic inflammatory skin diseases. Psoriasis patients experience social isolation, emotional, home and work problems, associated both with the disease itself and with the ongoing treatment. Psoriasis brings physical and moral disharmony into the lives of patients due to the need for additional organization of dietary nutrition, the rejection of cosmetics, restrictions in the choice of vacation places and interpersonal contacts. Despite a large number of studies on the research of psoriasis, the cause of the disease remains not fully understood, and the risks of an unfavorable course are unpredictable. This situation requires new research in the field of studying risk factors, developing modern approaches to optimizing medical care for patients with psoriasis. And here mathematical modeling plays an important role, since mathematical models make it possible to effectively describe the behavior of various populations of cells up to disease, during its course and treatment, without requiring the use of complex and expensive equipment and observations. Among the various models, we will especially single out models that are described by systems of differential equations. In turn, controlled mathematical models built on the basis of such systems are used to model the regimen of taking drugs and their dosage, compare the effects of various drugs on affected areas of the skin, and develop the most effective treatment methods. Within a specific model, optimal control theory is applied to find the best treatment strategies for psoriasis. Here we do not give a review of works related both to the mathematical modeling of psoriasis and the analysis of existing models of this disease, and to the search for effective strategies for its treatment based on the optimal control theory, because such a detailed review was given in [16]. The controlled mathematical models used in [16] were described on a fixed time interval (the period of psoriasis treatment) by the systems of nonlinear differential equations that are linear in control, or in controls (if there are several of them). The objective functions necessarily contain terms that reflect the total cost of the treatment used. This cost of psoriasis treatment is expressed as an integral over a fixed time interval from some given function depending on the square of the control or on the squares of the controls. After applying the Pontryagin maximum principle as a necessary optimality condition, the considered problem of optimal control is reduced to a two-point boundary value problem for the maximum principle, which is then solved numerically using the standard mathematical software. Such support is widely represented, for example, in software environments MAPLE and MATLAB. Widespread use of quadratic terms in the objective functions to estimate the total cost of psoriasis treatment is due to the fact that the right parts in the systems of differential equations in boundary value problems for the maximum principle are Lipschitz functions phase and adjoint variables. In addition, the optimal control or optimal controls also has the Lipschitz property. Note that solving the considered optimal control problems also performed well in the BOCOP and GPOPS software environments, in which, after discretization in time, the optimal control problem under study is approximated by finite-dimensional problems of nonlinear optimization of large dimension.

In optimal control problems for mathematical models not related to psoriasis ([15]), the total cost of treatment can also be expressed as an integral over a fixed period of time from some given function that depends on the control or on controls (if there are several of them), or it may be completely absent. At the same time, the models are still described by systems of non-linear differential equations that are linear in control or in controls. Then, after applying the Pontryagin maximum principle to such problems, the corresponding optimal controls can either be bang-bang functions over the entire given time interval, or, in addition to bang-bang (non-singular) sections, they can also have sections with singular regimens (singular sections) on which these controls were not determined uniquely from the maximum principle ([14]). After the existence of singular regimens has been established, the corresponding necessary conditions for their optimality have been verified, connections between singular and non-singular sections have been determined, and finding specific optimal solutions in optimal control problems is still carried out only numerically, for example, using the BOCOP and GPOPS software environments. Note, that the use of softwares based on the approximate solution of two-point boundary value problems for the maximum principle is incorrect and unstable, since there is no important Lipschitz property that guarantees the convergence of numerical procedures.

For optimal control problem with scalar control, the analysis of singular regimens is based on successive differentiation of the corresponding switching function, which specifies the type of the optimal control according to the maximum principle. This differentiation is carried out until the corresponding derivative of even order has a nonzero term containing control. If such a term appears in the second-order derivative, then the singular regimen is of the first order. If it occurs at the derivative of the fourth order, then the singular regimen has the second order. Finally, when such a term appears in the sixth-order derivative, we are talking about a singular third-order regimen ([15, 14, 20]).

The papers [5, 6, 9, 10] considered the mathematical model psoriasis that describes, using a system of three differential equations, the relationship between populations of T-lymphocytes, keratinocytes, and dendritic cells, play an important role in occurrence, course, and treatment of psoriasis. This model contains a control function that sets the dose of a drug that suppresses the interaction between T-lymphocytes and keratinocytes. In these papers, for such a controlled model, using the Pontryagin maximum principle the problem of minimizing the concentration of keratinocytes at the end moment of a given time interval, which is the period of treatment of psoriasis, is studied. They show analytically and numerically that the corresponding optimal control can be both a bang-bang function over the entire time interval, and have singular sections with singular regimens of the second and third orders. Also in the considered model, another control function can be introduced that determines the dose of the drug, suppressing interaction between T-lymphocytes and dendritic cells. Study for such control model of a similar minimization problem due to the Pontryagin maximum principle shows the possibility of the corresponding optimal control having a singular regimen of the first order ([7]). Finally, the situation when in the model under consideration there are simultaneously both of the control functions described above, was studied in detail in [4].

As noted in [16], psoriasis is a chronic autoimmune disease, pathogenesis (origin and course) of which is caused as a violation of the balance between individual populations immune cells, and deregulation of the interaction between the immune system and skin cells. More specifically, the balance is lost between immune cells such as Th_1- and Th_2-cells, as well as activated NK-cells, on the one hand, and keratinocytes, as the most common representatives of the skin, on the other hand. Interaction between immune cells is carried out using a variety of cytokines (information molecules). In psoriasis, key roles belong to $IL-21$, mediated by Th_1-cells, and to $IFN-\gamma$, generated by activated NK-cells. Within this more modern view of the pathogenesis psoriasis, in this paper we consider a mathematical model of this disease, whose differential equations describe the relationship between the indicated populations of immune cells, keratinocytes and cytokines. This model aims to explore the inflammatory effect and ability to regulate cytokines. Therefore, we introduce control functions into the model, which reflect the inhibition (suppression) of $IL-21$ and anti-$IFN-\gamma$ therapy and are aimed at inhibition of these cytokines. For such a controlled model, in this paper, we study the minimization problem with the objective function that does not contain squares of controls and hence, the optimal controls in such problem may contain singular regimens. Much attention is paid to detailed analysis of such singular regimens in the paper. By the possible occurrence of singular regimens, our study differs from the studies for a similar model presented in [19], although is their continuation. The objective function that we use in this article is also different from the objective function used in [19].

This paper is organized as follows. Section 2 gives a description of the mathematical model of psoriasis, which after all the necessary simplifying transformations is described on a given time interval by a system of four nonlinear differential equations with corresponding initial conditions. Section 3 is devoted to the study of such properties of the components of the solution of the arisen Cauchy problem, as their positivity and boundedness, as well as the continuation of this solution for the entire given time interval. Section 4, first describes an introduction to a simplified model of psoriasis of two bounded control functions, reflecting the impact of the drugs and therapy on the course of the disease. Then, for such a controlled model, the optimal control problem is formulated, which consists in minimizing the integro-terminal objective function. This function is the weighted sum of the effect of the action from the introduced controls on the required decision components of the model; and the total cost of treatment. Finally, here we discuss the existence of an optimal solution in the considered minimization problem. Application of the Pontryagin maximum principle as a necessary condition for optimality is demonstrated in Section 5. Section 6 has auxiliary character, since it contains transformations, assumptions and statements, used in the following discussion. Section 7 is central to this paper, since it contains a detailed analysis of singular regimens that may occur in optimal controls in the considered minimization problem. In Section 8 we discuss the results of numerical calculations, which confirm the obtained analytical results, and the difficulties in detection of singular regimens. The corresponding conclusions are drawn.

2. Model of psoriasis dynamics and its modifications

We consider a mathematical model that describes the dynamics of psoriasis, which includes T-helper cells type I and II (Th_1 and Th_2), activated killer cells (NK-cells) and keratinocytes (skin cells). We assume that the densities of Th_1- and Th_2-cells, activated NK-cells and epidermal keratinocytes at any time $t \geq 0$ are given by $T_1(t)$, $T_2(t)$, $N_A(t)$, and $K(t)$, respectively. To describe the equations of changes in the densities of the considered immune cells (Th_1- and Th_2-cells, activated NK-cells), we assume that these immune cells are formed at the corresponding constant rates a_1, a_2 and b. Also, we use logistic terms to describe the proliferation of immune cells due to their self-release and other effects of cytokines. At the same time, r_1, r_2 and r_3 represent the proliferation rates of Th_1- and Th_2-cells, as well as activated NK-cells, respectively.

This proliferation continues up to certain maximum levels determined by the corresponding values of $T_1^{\max}$, $T_2^{\max}$ and $N_A^{\max}$. Further, at the rate of α_1, anti-inflammatory cytokines responsible for Th_2-cells, have a negative regulatory effect on the growth of Th_1-cells, which is described by the term $\alpha_1 T_1 T_2$ in the first equation of the system (2.1). Anti-inflammatory cytokines secreted by Th_1-cells exert a negative regulatory effect on the growth of Th_2-cells at a rate of α_2, which reflects the term $\alpha_2 T_1 T_2$ in the second equation of this system. We also believe that at the rate of β_1, activated NK-cells mediated by $IFN-\gamma$ have a negative regulatory effect on the growth of Th_2-cells. $IL-21$, released by Th_1-cells, increases the proliferation rate of NK-cells at the rate of ξ. The natural decay rates of Th_1- and Th_2-cells, as well as activated NK-cells, we denote by μ_1, μ_2 and μ_3, respectively. Then the equations for changes in the densities of the considered immune cells have the following form:

$$\begin{cases} T_1' = a_1 + r_1 T_1 \left(1 - \dfrac{T_1}{T_1^{\max}}\right) - \alpha_1 T_1 T_2 - \mu_1 T_1, \\ T_2' = a_2 + r_2 T_2 \left(1 - \dfrac{T_2}{T_2^{\max}}\right) - \alpha_2 T_1 T_2 - \beta_1 I_\gamma T_2 - \mu_2 T_2, \\ N_A' = b + r_3 N_A \left(1 - \dfrac{N_A}{N_A^{\max}}\right) + \xi I_{21} N_A - \mu_3 N_A. \end{cases} \tag{2.1}$$

In connection with the constant migration of cells from the dermal layer of the skin to the epidermal layer, we assume that the value of c determines the constant growth of keratinocytes. Under the influence of a large amount of $IFN-\gamma$, keratinocytes proliferate at a rate of β_2. In addition, the positive effect of Th_1-cells on the proliferation of keratinocytes is determined by the rate δ_1, and Th_2-cells inhibit proliferation at a rate of δ_2. The decay rate of keratinocytes is determined by the value of μ_4. Then the dynamics of keratinocytes is given by the following equation:

$$K' = c + \delta_1 T_1 K - \delta_2 T_2 K + \beta_2 I_\gamma K - \mu_4 K. \tag{2.2}$$

Based on the assumptions made above and putting together the equations from (2.1) and (2.2), we have the following model of psoriasis dynamics:

$$\begin{cases} T_1' = a_1 + r_1 T_1 \left(1 - \dfrac{T_1}{T_1^{\max}}\right) - \alpha_1 T_1 T_2 - \mu_1 T_1, \\ T_2' = a_2 + r_2 T_2 \left(1 - \dfrac{T_2}{T_2^{\max}}\right) - \alpha_2 T_1 T_2 - \beta_1 I_\gamma T_2 - \mu_2 T_2, \\ N_A' = b + r_3 N_A \left(1 - \dfrac{N_A}{N_A^{\max}}\right) + \xi I_{21} N_A - \mu_3 N_A, \\ K' = c + \delta_1 T_1 K - \delta_2 T_2 K + \beta_2 I_\gamma K - \mu_4 K. \end{cases} \tag{2.3}$$

Next, we introduce into the system (2.3) the families of the considered cytokines. Cytokine concentrations we denote $IL-21$ and $IFN-\gamma$ by $I_{21}(t)$ and $I_\gamma(t)$, respectively. For simplicity, let us assume that the corresponding immune cells produce cytokines in response to them with constant speed, and they naturally decay at a constant speed as well. We believe that the reproduction rates of $IL-21$ and $IFN-\gamma$ due to Th_1-cells and activated NK-cells are expressed by the corresponding quantities q_1 and q_2, and λ_1 and λ_2 determine the decay rates of the corresponding cytokines. Thus, we have built a system for describing the dynamics of cytokines:

$$\begin{cases} I_{21}' = q_1 T_1 - \lambda_1 I_{21}, \\ I_\gamma' = q_2 N_A - \lambda_2 I_\gamma, \end{cases} \tag{2.4}$$

which add to the system (2.3).

The dynamics of the development of psoriatic plaques, described by systems (2.3) and (2.4), uses different time scales. Proliferation of Th_1- and Th_2-cells, as well as activated NK-cells and keratinocytes occurs on a time scale from days to weeks, while the reproduction and breakdown of cytokines are carried out on a time scale from seconds to hours. Therefore, our model, consisting of systems (2.3) and (2.4), is simplified due to the use of quasi-stationary approximations for the concentrations of the considered cytokines [17]. Taking this into account, we obtain from system (2.4) the following formulas:

$$I_{21} = \frac{q_1}{\lambda_1} T_1 \ , \quad I_\gamma = \frac{q_2}{\lambda_2} N_A \ ,$$

which we substitute into system (2.3). After that we define the constants:

$$\gamma_1 = \frac{\beta_1 q_2}{\lambda_2} \ , \quad \gamma_2 = \frac{\xi q_1}{\lambda_1} \ , \quad \gamma_3 = \frac{\beta_2 q_2}{\lambda_2} \ , \tag{2.5}$$

we finally obtain the simplified model of psoriasis dynamics:

$$\begin{cases} T_1' = a_1 + r_1 T_1 \left(1 - \dfrac{T_1}{T_1^{\max}}\right) - \alpha_1 T_1 T_2 - \mu_1 T_1, \\ T_2' = a_2 + r_2 T_2 \left(1 - \dfrac{T_2}{T_2^{\max}}\right) - \alpha_2 T_1 T_2 - \gamma_1 T_2 N_A - \mu_2 T_2, \\ N_A' = b + r_3 N_A \left(1 - \dfrac{N_A}{N_A^{\max}}\right) + \gamma_2 T_1 N_A - \mu_3 N_A, \\ K' = c + \delta_1 T_1 K - \delta_2 T_2 K + \gamma_3 N_A K - \mu_4 K. \end{cases} \tag{2.6}$$

Note that the combined parameters γ_1 and γ_3 indicate the influence of the activated NK-cells on the growth of Th_2-cells and keratinocytes, respectively. On the other hand, the combined parameter γ_2 reflects the contribution of Th_1-cells to the regulation activated NK-cells.

It is easy to see that system (2.6) is a further development of the ideas previously presented in papers [19, 17, 18].

In system (2.6), let us now perform the scaling of the phase variables T_1, T_2, N_A, K according to the formulas:

$$\widetilde{T}_1 = \frac{T_1}{T_1^{\max}} \ , \quad \widetilde{T}_2 = \frac{T_2}{T_2^{\max}} \ , \quad \widetilde{N}_A = \frac{N_A}{N_A^{\max}} \ , \quad \widetilde{K} = K.$$

As the result, we find the system:

$$\begin{cases} \widetilde{T}_1' = \widetilde{a}_1 + \widetilde{r}_1 \widetilde{T}_1 \left(1 - \widetilde{T}_1\right) - \widetilde{\alpha}_1 \widetilde{T}_1 \widetilde{T}_2 - \widetilde{\mu}_1 \widetilde{T}_1, \\ \widetilde{T}_2' = \widetilde{a}_2 + \widetilde{r}_2 \widetilde{T}_2 \left(1 - \widetilde{T}_2\right) - \widetilde{\alpha}_2 \widetilde{T}_1 \widetilde{T}_2 - \widetilde{\gamma}_1 \widetilde{T}_2 \widetilde{N}_A - \widetilde{\mu}_2 \widetilde{T}_2, \\ \widetilde{N}_A' = \widetilde{b} + \widetilde{r}_3 \widetilde{N}_A \left(1 - \widetilde{N}_A\right) + \widetilde{\gamma}_2 \widetilde{T}_1 \widetilde{N}_A - \widetilde{\mu}_3 \widetilde{N}_A, \\ \widetilde{K}' = \widetilde{c} + \widetilde{\delta}_1 \widetilde{T}_1 \widetilde{K} - \widetilde{\delta}_2 \widetilde{T}_2 \widetilde{K} + \widetilde{\gamma}_3 \widetilde{N}_A \widetilde{K} - \widetilde{\mu}_4 \widetilde{K}, \end{cases}$$

in which

$$\begin{array}{llll}
\widetilde{r}_1 = r_1, & \widetilde{r}_2 = r_2, & \widetilde{r}_3 = r_3, & \\
\widetilde{\gamma}_1 = \gamma_1 N_A^{\max}, & \widetilde{\gamma}_2 = \gamma_2 T_1^{\max}, & \widetilde{\gamma}_3 = \gamma_3 N_A^{\max}, & \\
\widetilde{a}_1 = a_1/T_1^{\max}, & \widetilde{a}_2 = a_2/T_2^{\max}, & \widetilde{b} = b/N_A^{\max}, & \widetilde{c} = c, \\
\widetilde{\alpha}_1 = \alpha_1 T_2^{\max}, & \widetilde{\alpha}_2 = \alpha_2 T_1^{\max}, & \widetilde{\delta}_1 = \delta_1 T_1^{\max}, & \widetilde{\delta}_2 = \delta_2 T_2^{\max}, \\
\widetilde{\mu}_1 = \mu_1, & \widetilde{\mu}_2 = \mu_2, & \widetilde{\mu}_3 = \mu_3, & \widetilde{\mu}_4 = \mu_4.
\end{array}$$

Omitting the tilde sign in this system, we finally obtain the following system of equations describing dynamics of psoriasis:

$$\begin{cases}
T_1' = a_1 + r_1 T_1 (1 - T_1) - \alpha_1 T_1 T_2 - \mu_1 T_1, \\
T_2' = a_2 + r_2 T_2 (1 - T_2) - \alpha_2 T_1 T_2 - \gamma_1 T_2 N_A - \mu_2 T_2, \\
N_A' = b + r_3 N_A (1 - N_A) + \gamma_2 T_1 N_A - \mu_3 N_A, \\
K' = c + \delta_1 T_1 K - \delta_2 T_2 K + \gamma_3 N_A K - \mu_4 K,
\end{cases} \tag{2.7}$$

which will be the object of our subsequent considerations. Add to system (2.7) the initial conditions:

$$T_1(0) = T_1^0, \quad T_2(0) = T_2^0, \quad N_A(0) = N_A^0, \quad K(0) = K^0, \tag{2.8}$$

where $T_1^0 > 0$, $T_2^0 > 0$, $N_A^0 > 0$, $K^0 > 0$. We will consider the Cauchy problem (2.7)-(2.8) on the fixed time interval $[0, \Theta]$, which determine the length of the treatment.

3. Properties of the Solution of the Cauchy Problem

Let us establish that the components of the solution to the Cauchy problem (2.7)-(2.8) are positive and bounded. The following lemma is true.

Lemma 3.1. *The components of the solution $(T_1(t), T_2(t), N_A(t), K(t))$ of the Cauchy problem (2.7)-(2.8) are defined on the entire interval $[0, \Theta]$ and satisfy on this interval the following inequalities:*

$$\begin{aligned}
&0 < T_1(t) < \widetilde{T}_1^{\max}, \quad 0 < T_2(t) < \widetilde{T}_2^{\max}, \\
&0 < N_A(t) < \widetilde{N}_A^{\max}, \quad 0 < K(t) < \widetilde{K}^{\max},
\end{aligned} \tag{3.1}$$

where

$$\widetilde{T}_1^{\max} = T_1^0 + \frac{4a_1 + r_1}{4\mu_1}; \quad \widetilde{T}_2^{\max} = T_2^0 + \frac{4a_2 + r_2}{4\mu_2};$$

$$\widetilde{N}_A^{\max} = \begin{cases}
N_A^0 + \dfrac{4b + r_3}{4\left(\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right)}, & \text{if } \ \mu_3 - \gamma_2 \widetilde{T}_1^{\max} > 0, \\
N_A^0 + \dfrac{4b + r_3}{4}, & \text{if } \ \mu_3 - \gamma_2 \widetilde{T}_1^{\max} = 0, \\
N_A^0 e^{\left|\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right| \Theta} + \dfrac{4b + r_3}{4\left|\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right|} \left(e^{\left|\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right| \Theta} - 1\right), & \\
\qquad \text{if } \ \mu_3 - \gamma_2 \widetilde{T}_1^{\max} < 0;
\end{cases}$$

$$\widetilde{K}^{\max}=\begin{cases}K^0+\dfrac{c}{\mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)}\,, \\ \qquad\qquad if\ \ \mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)>0, \\ K^0+c\Theta, \quad if\ \ \mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)=0, \\ K^0e^{\left|\mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)\right|\Theta} \\ \quad+\dfrac{c}{\left|\mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)\right|}\left(e^{\left|\mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)\right|\Theta}-1\right), \\ \qquad\qquad if\ \ \mu_4-\left(\delta_1\widetilde{T}_1^{\max}+\gamma_3\widetilde{N}_A^{\max}\right)<0.\end{cases}$$

Proof. By virtue of the existence and uniqueness theorem [8] the Cauchy problem (2.7)-(2.8) has a solution $(T_1(t),T_2(t),N_A(t),K(t))$ that is defined on the interval $[0,t_0)$, which is the maximum interval for the existence of such a solution. Next, we rewrite the equations of system (2.7) as follows

$$\begin{cases}T_1'(t)=a_1+\left\{r_1\left(1-T_1(t)\right)-\alpha_1T_2(t)-\mu_1\right\}T_1(t) \\ \qquad\quad =a_1+f_1(t)T_1(t), \\ T_2'(t)=a_2+\left\{r_2\left(1-T_2(t)\right)-\alpha_2T_1(t)-\gamma_1N_A(t)-\mu_2\right\}T_2(t) \\ \qquad\quad =a_2+f_2(t)T_2(t), \\ N_A'(t)=b+\left\{r_3\left(1-N_A(t)\right)+\gamma_2T_1(t)-\mu_3\right\}N_A(t) \\ \qquad\quad =b+f_3(t)N_A(t), \\ K'(t)=c+\left\{\delta_1T_1(t)-\delta_2T_2(t)+\gamma_3N_A(t)-\mu_4\right\}K(t) \\ \qquad\quad =c+f_4(t)K(t),\end{cases} \tag{3.2}$$

where functions $f_i(t)$, $i=1,2,3,4$ define corresponding expressions in the braces. These equations are linear nonautonomous differential equations of the first order with positive inhomogeneities and positive initial conditions (2.8). Integrating each equation of the system (3.2) in the interval $[0,t_0)$, for example by the Lagrange constant variation method [8], we can see that their solutions $T_1(t)$, $T_2(t)$, $N_A(t)$, $K(t)$ are positive on the entire interval $[0,t_0)$. Therefore the left inequalities in each relationship from (3.1) are justified.

Let us show the validity of the right inequalities in these relationships. Consider the first two equations of system (2.7). Using the already established positiveness of function $T_1(t)$, $T_2(t)$ and $N_A(t)$, as well as the fact that the maximum values of the quadratic polynomials $r_iT_i(1-T_i)$ equal $r_i/4$, $i=1,2$, respectively, we obtain differential inequalities:

$$T_i'<\left(a_i+\frac{r_i}{4}\right)-\mu_iT_i=\mu_i\left(\widetilde{T}_i^{\max}-T_i^0\right)-\mu_iT_i,\quad i=1,2.$$

By integrating these inequalities with the corresponding initial conditions $T_i(0)=T_i^0$, $i=1,2$ on the interval $[0,t_0)$ and using the comparison principle [1], we find the inequalities:

$$0<T_i(t)<T_i^0e^{-\mu_it}+\left(\widetilde{T}_i^{\max}-T_i^0\right)\left(1-e^{-\mu_it}\right)\leq\widetilde{T}_i^{\max},\quad i=1,2,$$

from which the validity of the first two relationships of (3.1) follows.

Let us carry out similar reasoning for the third equation of the system (2.7). Using the already obtained inequality for the function $T_1(t)$, we have the differential inequality:

$$N_A' < \left(b + \frac{r_3}{4}\right) - \left(\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right) N_A.$$

By integrating this inequality with the corresponding initial condition $N_A(0) = N_A^0$ on the interval $[0, t_0)$ and applying the comparison principle, we arrive the inequality:

$$0 < N_A(t) < N_A^0 e^{-\left(\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right)t} + \frac{4b + r_3}{4\left(\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right)} \left(1 - e^{-\left(\mu_3 - \gamma_2 \widetilde{T}_1^{\max}\right)t}\right),$$

from which we obtain from the definition of $\widetilde{N}_A^{\max}$ the third relationship in (3.1).

Finally, consider the fourth equation of system (2.7). Applying the previously obtained inequalities for $T_1(t)$ and $N_A(t)$, we find the differential inequality:

$$K' < c - \left(\mu_4 - \left(\delta_1 \widetilde{T}_1^{\max} + \gamma_3 \widetilde{N}_A^{\max}\right)\right) K.$$

Integrating this inequality with the corresponding initial condition $K(0) = K^0$ on the interval $[0, t_0)$ and using the comparison principle again, we have the inequality:

$$\begin{aligned} 0 < K(t) < K^0 e^{-\left(\mu_4 - \left(\delta_1 \widetilde{T}_1^{\max} + \gamma_3 \widetilde{N}_A^{\max}\right)\right)t} \\ + \frac{c}{\mu_4 - \left(\delta_1 \widetilde{T}_1^{\max} + \gamma_3 \widetilde{N}_A^{\max}\right)} \left(1 - e^{-\left(\mu_4 - \left(\delta_1 \widetilde{T}_1^{\max} + \gamma_3 \widetilde{N}_A^{\max}\right)\right)t}\right), \end{aligned}$$

which, due to the definition of $\widetilde{K}^{\max}$, leads to the fulfillment fourth relationship in (3.1).

Thus we have established the validity of the inequalities (3.1) on the maximum interval $[0, t_0)$ of the existence of the considered solution $(T_1(t), T_2(t), N_A(t), K(t))$. When $t_0 \le \Theta$, this fact guarantees the extension of such a solution to the entire interval $[0, \Theta]$ ([8]) and satisfying the relations (3.1) on it. The required assertion is justified. □

Let us establish the validity of the following lemma which refines the left constraint on function $K(t)$.

Lemma 3.2. *The component $K(t)$ of the solution $(T_1(t), T_2(t), N_A(t), K(t))$ of the Cauchy problem (2.7)-(2.8) on the entire segment $[0, \Theta]$ satisfies the inequality:*

$$K(t) > K^{\min} > 0, \tag{3.3}$$

where

$$K^{\min} = K^0 e^{-\left(\delta_2 \widetilde{T}_2^{\max} + \mu_4\right)\Theta}.$$

Proof. Lemma 3.1 allows to write for the fourth equation of system (2.7) the following differential inequality:

$$K' > c - \left(\delta_2 \widetilde{T}_2^{\max} + \mu_4\right) K,$$

that is true for all $t \in [0, \Theta]$. Integrating this inequality with the corresponding initial condition $K(0) = K^0$ on the interval $[0, \Theta]$ and using the comparison principle from [1] lead us to the chain of the relationships:

$$K(t) > K^0 e^{-\left(\delta_2 \widetilde{T}_2^{\max} + \mu_4\right)t} + \frac{c}{\delta_2 \widetilde{T}_2^{\max} + \mu_4}\left(1 - e^{-\left(\delta_2 \widetilde{T}_2^{\max} + \mu_4\right)t}\right)$$
$$\geq K^0 e^{-\left(\delta_2 \widetilde{T}_2^{\max} + \mu_4\right)\Theta} = K^{\min},$$

from which the validity of the inequality (3.3) follows. □

Note that in our study we found both the invariant set of system (2.7) and its equilibria. The existence of a unique equilibrium state with positive coordinates located in the invariant set is established, and its stability is also scrutinized. However, in this paper, we do not demonstrate the results of this study, since here we will specifically focus only on a detailed study of the optimal control problem for system (2.7)-(2.8).

4. Optimal Control Problem

The Cauchy problem (2.7)-(2.8) considered on a given time interval $[0,\Theta]$, is a mathematical model of the dynamics of psoriasis, which includes Th_1- and Th_2-cells, activated NK-cells, and epidermal keratinocytes. Based on this model, we see that psoriasis is an inflammatory skin disease mediated by Th_1-cells and activated NK-cells, where $IL-21$ and $IFN-\gamma$ play a dominant role. Therefore, in the fight against this disease, it is important to suppress the effects that exert $IL-21$ and $IFN-\gamma$ on various immune cells. Proceeding from this, we introduce into the system (2.7) two control functions $\widetilde{u}_1(t)$ and $\widetilde{u}_2(t)$ subject to the following restrictions:

$$0 \leq \widetilde{u}_1(t) \leq \widetilde{u}_1^{\max} < 1, \quad 0 \leq \widetilde{u}_2(t) \leq \widetilde{u}_2^{\max} < 1. \tag{4.1}$$

The $\widetilde{u}_1(t)$ control reflects the action of the $IL-21$ inhibitor, and the control $\widetilde{u}_2(t)$ describes the effect of treatment against $IFN-\gamma$. As a result, on the interval $[0,\Theta]$ we have a controlled system:

$$\begin{cases} T_1'(t) = a_1 + r_1 T_1(t)\left(1 - T_1(t)\right) - \alpha_1 T_1(t) T_2(t) - \mu_1 T_1(t), \\ T_2'(t) = a_2 + r_2 T_2(t)\left(1 - T_2(t)\right) - \alpha_2 T_1(t) T_2(t) \\ \qquad\qquad - \gamma_1\left(1 - \widetilde{u}_2(t)\right) T_2(t) N_A(t) - \mu_2 T_2(t), \\ N_A'(t) = b + r_3 N_A(t)\left(1 - N_A(t)\right) \\ \qquad\qquad + \gamma_2\left(1 - \widetilde{u}_1(t)\right) T_1(t) N_A(t) - \mu_3 N_A(t), \\ K'(t) = c + \delta_1 T_1(t) K(t) - \delta_2 T_2(t) K(t) \\ \qquad\qquad + \gamma_3\left(1 - \widetilde{u}_2(t)\right) N_A(t) K(t) - \mu_4 K(t), \\ T_1(0) = T_1^0,\ T_2(0) = T_2^0,\ N_A(0) = N_A^0,\ K(0) = K^0; \\ T_1^0 > 0,\ T_2^0 > 0,\ N_A^0 > 0,\ K^0 > 0. \end{cases} \tag{4.2}$$

For this system, the set of admissible controls $\widetilde{\Omega}$ consists of all possible pairs of Lebesgue measurable functions $(\widetilde{u}_1(t), \widetilde{u}_2(t))$, which for almost all values of $t \in [0,\Theta]$ satisfy the inequalities (4.1).

Note that for $\widetilde{u}_1(t) = 0$ and $\widetilde{u}_2(t) = 0$ the system (4.2) becomes a Cauchy problem (2.7)-(2.8). Various manifestations of controls $\widetilde{u}_1(t)$ and $\widetilde{u}_2(t)$ in system (4.2) show why the dependence of the corresponding terms in the equations of this system on controls is so important in studying the consequences of the combined action of the $IL-21$ inhibitor and anti-$IFN-\gamma$ therapy. Also, we do not take into account the side effects of this combined biological treatment.

For the system (4.2) on the set of admissible controls $\widetilde{\Omega}$, we consider optimal control problem, which consists in minimizing the integro-terminal objective function:

$$\widetilde{J}(\widetilde{u}_1,\widetilde{u}_2)=\Big(K(\Theta)+\sigma N_A(\Theta)\Big)+\int\limits_0^{\Theta}\Big(\chi\widetilde{u}_1(t)T_1(t)+\nu\widetilde{u}_2(t)N_A(t)\Big)dt, \tag{4.3}$$

where σ, χ, and ν are positive weight coefficients. In this objective function, the terminal part describes the effect of the $IL-21$ inhibitor and anti-$IFN-\gamma$ therapy on populations of epidermal keratinocytes and activated NK-cells in final moment Θ of treatment period $[0,\Theta]$. The integral part specifies the total cost considered combined biological treatment. This cost depends not only on the price χ of the used inhibitor $\widetilde{u}_1(t)$ and the price ν of the applied therapy $\widetilde{u}_2(t)$, but also from the corresponding populations of Th_1-cells and activated NK-cells exposed to them. In more detail, such terms in the objective functions are discussed in [3, 13]. Note also that in the papers [18, 19] the general cost of such biological treatment is determined in a different way, namely the integral part of the type:

$$\int\limits_0^{\Theta}\Big(\chi\widetilde{u}_1^2(t)+\nu\widetilde{u}_2^2(t)\Big)dt.$$

To simplify the subsequent calculations, in the optimal control problem (4.1)–(4.3), we will change the controls according to the formulas:

$$u_1=1-\widetilde{u}_1,\quad u_2=1-\widetilde{u}_2.$$

Thus system (4.2) is transformed into the system:

$$\begin{cases} T_1'(t)=a_1+r_1T_1(t)\,(1-T_1(t))-\alpha_1T_1(t)T_2(t)-\mu_1T_1(t),\\ T_2'(t)=a_2+r_2T_2(t)\,(1-T_2(t))-\alpha_2T_1(t)T_2(t)\\ \qquad\qquad -\gamma_1u_2(t)T_2(t)N_A(t)-\mu_2T_2(t),\\ N_A'(t)=b+r_3N_A(t)\,(1-N_A(t))\\ \qquad\qquad +\gamma_2u_1(t)T_1(t)N_A(t)-\mu_3N_A(t),\\ K'(t)=c+\delta_1T_1(t)K(t)-\delta_2T_2(t)K(t)\\ \qquad\qquad +\gamma_3u_2(t)N_A(t)K(t)-\mu_4K(t),\\ T_1(0)=T_1^0,\ T_2(0)=T_2^0,\ N_A(0)=N_A^0,\ K(0)=K^0;\\ T_1^0>0,\ T_2^0>0,\ N_A^0>0,\ K^0>0. \end{cases} \tag{4.4}$$

Moreover, the restrictions (4.1) on the controls $\widetilde{u}_1(t)$ and $\widetilde{u}_2(t)$ go into the restrictions:

$$0<u_1^{\min}\le u_1(t)\le 1,\quad 0<u_2^{\min}\le u_2(t)\le 1, \tag{4.5}$$

where

$$u_1^{\min}=1-\widetilde{u}_1^{\max},\quad u_2^{\min}=1-\widetilde{u}_2^{\max}.$$

The set of admissible controls $\widetilde{\Omega}$ is transformed into the corresponding set Ω consisting of all possible pairs of Lebesgue measurable functions $(u_1(t),u_2(t))$, which for almost all $t\in[0,\Theta]$

satisfy inequalities (4.5). The objective function $\widetilde{J}(\widetilde{u}_1,\widetilde{u}_2)$ goes into the objective function:

$$J(u_1,u_2) = \Big(K(\Theta)+\sigma N_A(\Theta)\Big) + \int_0^\Theta \Big(\chi\,(1-u_1(t))\,T_1(t) + \nu\,(1-u_2(t))\,N_A(t)\Big)dt. \quad (4.6)$$

Thus minimization problem (4.1)–(4.3) is transformed into the minimization problem (4.4)–(4.6), which we will consider further.

Due to the restrictions (4.5) on the controls $u_1(t)$ and $u_2(t)$, the differential inequalities appearing in the justification of Lemmas 3.1 and 3.2, do not change. Therefore, these lemmas remain valid for the controlled system (4.4) with only minor changes.

Lemma 4.1. *For arbitrary admissible controls $(u_1(t),u_2(t))$ the absolutely continuous solution $(T_1(t),T_2(t),N_A(t),K(t))$ of the system (4.4) is defined on the entire segment $[0,\Theta]$, and its components satisfy the following inequalities on this segment:*

$$\begin{aligned} &0 < T_1(t) < \widetilde{T}_1^{\max}, \quad 0 < T_2(t) < \widetilde{T}_2^{\max}, \\ &0 < N_A(t) < \widetilde{N}_A^{\max}, \quad 0 < K^{\min} < K(t) < \widetilde{K}^{\max}. \end{aligned} \quad (4.7)$$

It is easy to see that for the minimization problem (4.4)–(4.6) the assumptions of Corollary 2 to Theorem 4 from Chapter 4 ([11]) are satisfied. Namely, the inequalities (4.7) in the Lemma 4.1 give a uniform estimate on the interval $[0,\Theta]$ of the solution $(T_1(t),T_2(t),N_A(t),K(t))$ of the system (4.4) corresponding to an arbitrary pair of controls $(u_1(t),u_2(t))$ from Ω. Moreover, system (4.4) is linear in the controls $u_1(t)$ and $u_2(t)$, and the integrand

$$\big(\chi\,(1-u_1)\,T_1 + \nu\,(1-u_2)\,N_A\big)$$

in the objective function (4.6) is also linear with respect to $u_i \in \big[u_i^{\min},1\big]$, $i=1,2$. Therefore, all these facts guarantee the existence of an optimal solution in the minimization problem under consideration which consists of a pair of the optimal controls $(u_1^*(t),u_2^*(t))$ and the corresponding optimal solution $(T_1^*(t),T_2^*(t),N_A^*(t),K^*(t))$ of system (4.4).

5. Pontryagin Maximum Principle

To analyze the optimal solution in minimization problem (4.4)–(4.6), we apply the Pontryagin's maximum principle [12] which is a necessary condition of the optimality for this problem. To do this, we first write out the corresponding Hamiltonian:

$$\begin{aligned} &H(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4) \\ &\quad = -\Big\{\chi\,(1-u_1)\,T_1 + \nu\,(1-u_2)\,N_A\Big\} \\ &\quad\quad + \Big\{a_1 + r_1T_1\,(1-T_1) - \alpha_1T_1T_2 - \mu_1T_1\Big\}\psi_1 \\ &\quad\quad + \Big\{a_2 + r_2T_2\,(1-T_2) - \alpha_2T_1T_2 - \gamma_1u_2T_2N_A - \mu_2T_2\Big\}\psi_2 \\ &\quad\quad + \Big\{b + r_3N_A\,(1-N_A) + \gamma_2u_1T_1N_A - \mu_3N_A\Big\}\psi_3 \\ &\quad\quad + \Big\{c + \delta_1T_1K - \delta_2T_2K + \gamma_3u_2N_AK - \mu_4K\Big\}\psi_4, \end{aligned}$$

where ψ_i, $i=1,2,3,4$ are the adjoint variables. Next we evaluate the partial derivatives of this Hamiltonian with respect to the phase variables:

$$\begin{aligned}
&H'_{T_1}(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4)\\
&\qquad=(r_1(1-2T_1)-\alpha_1T_2-\mu_1)\psi_1-\alpha_2T_2\psi_2+\gamma_2u_1N_A\psi_3+\delta_1K\psi_4-\chi(1-u_1),\\
&H'_{T_2}(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4)\\
&\qquad=-\alpha_1T_1\psi_1+(r_2(1-2T_2)-\alpha_2T_1-\gamma_1u_2N_A-\mu_2)\psi_2-\delta_2K\psi_4,\\
&H'_{N_A}(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4)\\
&\qquad=-\gamma_1u_2T_2\psi_2+(r_3(1-2N_A)+\gamma_2u_1T_1-\mu_3)\psi_3+\gamma_3u_2K\psi_4-\nu(1-u_2),\\
&H'_K(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4)\\
&\qquad=(\delta_1T_1-\delta_2T_2+\gamma_3u_2N_A-\mu_4)\psi_4
\end{aligned}$$

and with respect to controls:

$$\begin{aligned}
&H'_{u_1}(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4)=\gamma_2T_1N_A\psi_3+\chi T_1,\\
&H'_{u_2}(T_1,T_2,N_A,K,u_1,u_2,\psi_1,\psi_2,\psi_3,\psi_4)=-\gamma_1T_2N_A\psi_2+\gamma_3N_AK\psi_4+\nu N_A.
\end{aligned}$$

Then with respect to the Pontryagin maximum principle for a pair of the optimal controls $(u_1^*(t),u_2^*(t))$ and corresponding to it optimal solution $(T_1^*(t),T_2^*(t),N_A^*(t),K^*(t))$ of system (4.4), there exists such an adjoint variable $\psi^*(t)=\big(\psi_1^*(t),\psi_2^*(t),\psi_3^*(t),\psi_4^*(t)\big)$, that the following statements are valid.

• Function $\psi^*(t)$ is a nontrivial solution of the adjoint system:

$$\begin{cases}
\psi_1^{*\prime}=-H'_{T_1}(T_1^*,T_2^*,N_A^*,K^*,u_1^*,u_2^*,\psi_1^*,\psi_2^*,\psi_3^*,\psi_4^*)\\
\quad=-(r_1(1-2T_1^*)-\alpha_1T_2^*-\mu_1)\psi_1^*+\alpha_2T_2^*\psi_2^*-\gamma_2u_1^*N_A^*\psi_3^*\\
\qquad-\delta_1K^*\psi_4^*+\chi(1-u_1^*),\\
\psi_2^{*\prime}=-H'_{T_2}(T_1^*,T_2^*,N_A^*,K^*,u_1^*,u_2^*,\psi_1^*,\psi_2^*,\psi_3^*,\psi_4^*)\\
\quad=\alpha_1T_1^*\psi_1^*-(r_2(1-2T_2^*)-\alpha_2T_1^*-\gamma_1u_2^*N_A^*-\mu_2)\psi_2^*+\delta_2K^*\psi_4^*,\\
\psi_3^{*\prime}=-H'_{N_A}(T_1^*,T_2^*,N_A^*,K^*,u_1^*,u_2^*,\psi_1^*,\psi_2^*,\psi_3^*,\psi_4^*)\\
\quad=\gamma_1u_2^*T_2^*\psi_2^*-(r_3(1-2N_A^*)+\gamma_2u_1^*T_1^*-\mu_3)\psi_3^*-\gamma_3u_2^*K^*\psi_4^*+\nu(1-u_2^*),\\
\psi_4^{*\prime}=-H'_K(T_1^*,T_2^*,N_A^*,K^*,u_1^*,u_2^*,\psi_1^*,\psi_2^*,\psi_3^*,\psi_4^*)\\
\quad=-(\delta_1T_1^*-\delta_2T_2^*+\gamma_3u_2^*N_A^*-\mu_4)\psi_4^*,\\
\psi_1^*(\Theta)=0,\ \psi_2^*(\Theta)=0,\ \psi_3^*(\Theta)=-\sigma,\ \psi_4^*(\Theta)=-1.
\end{cases}\tag{5.1}$$

• Optimal controls $u_1^*(t)$ and $u_2^*(t)$ supply maximum of the Hamiltonian

$$H(T_1^*(t),T_2^*(t),N_A^*(t),K^*(t),u_1,u_2,\psi_1^*(t),\psi_2^*(t),\psi_3^*(t),\psi_4^*(t))$$

for almost all $t\in[0,\Theta]$ by the variables $u_i\in\big[u_i^{\min},1\big]$, $i=1,2$, and so, these controls satisfy the relationships:

$$u_1^*(t)=\begin{cases}
u_1^{\min} & ,\ \text{if}\quad \Phi_{u_1}(t)<0,\\
\text{any } u_1\in\big[u_1^{\min},1\big] & ,\ \text{if}\quad \Phi_{u_1}(t)=0,\\
1 & ,\ \text{if}\quad \Phi_{u_1}(t)>0,
\end{cases}\tag{5.2}$$

$$u_2^*(t) = \begin{cases} u_2^{\min} & , \text{ if } \quad \Phi_{u_2}(t) < 0, \\ \text{any } u_2 \in \left[u_2^{\min}, 1\right] & , \text{ if } \quad \Phi_{u_2}(t) = 0, \\ 1 & , \text{ if } \quad \Phi_{u_2}(t) > 0. \end{cases} \tag{5.3}$$

Here functions $\Phi_{u_1}(t)$ and $\Phi_{u_2}(t)$, expressed by formulas:

$$\begin{aligned} \Phi_{u_1}(t) &= H'_{u_1}(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), u_1^*(t), u_2^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t), \psi_4^*(t)) \\ &= \gamma_2 T_1^*(t) N_A^*(t) \psi_3^*(t) + \chi T_1^*(t), \\ \Phi_{u_2}(t) &= H'_{u_2}(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), u_1^*(t), u_2^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t), \psi_4^*(t)) \\ &= -\gamma_1 T_2^*(t) N_A^*(t) \psi_2^*(t) + \gamma_3 N_A^*(t) K^*(t) \psi_4^*(t) + \nu N_A^*(t), \end{aligned}$$

are the switching functions, because they determine the behavior of the corresponding optimal controls $u_1^*(t)$ and $u_2^*(t)$ with respect to (5.2) and (5.3). Due to the established in Lemma 4.1 positiveness of the functions $T_1^*(t)$ and $N_A^*(t)$, the switching functions $\Phi_{u_1}(t)$ and $\Phi_{u_2}(t)$ vanish, and also take negative and positive values at the same time as the corresponding functions $L_{u_1}(t)$ and $L_{u_2}(t)$, which are given by the formulas:

$$\begin{aligned} L_{u_1}(t) &= N_A^*(t)\psi_3^*(t) + \chi\gamma_2^{-1}, \\ L_{u_2}(t) &= -\gamma_1 T_2^*(t)\psi_2^*(t) + \gamma_3 K^*(t)\psi_4^*(t) + \nu. \end{aligned} \tag{5.4}$$

Since these functions are more simply arranged, we will consider them further as switching functions for the corresponding optimal controls $u_1^*(t)$ and $u_2^*(t)$, and instead of the formulas (5.2) and (5.3) we will use the following relations:

$$u_1^*(t) = \begin{cases} u_1^{\min} & , \text{ if } \quad L_{u_1}(t) < 0, \\ \text{any } u_1 \in \left[u_1^{\min}, 1\right] & , \text{ if } \quad L_{u_1}(t) = 0, \\ 1 & , \text{ if } \quad L_{u_1}(t) > 0, \end{cases} \tag{5.5}$$

$$u_2^*(t) = \begin{cases} u_2^{\min} & , \text{ if } \quad L_{u_2}(t) < 0, \\ \text{any } u_2 \in \left[u_2^{\min}, 1\right] & , \text{ if } \quad L_{u_2}(t) = 0, \\ 1 & , \text{ if } \quad L_{u_2}(t) > 0. \end{cases} \tag{5.6}$$

Let us now analyze together the formulas (5.4) and (5.5), (5.6). Their analysis shows how the switching functions $L_{u_1}(t)$ and $L_{u_2}(t)$ can behave, and hence the corresponding optimal controls $u_1^*(t)$ and $u_2^*(t)$. Since $L_{u_1}(t)$ and $L_{u_2}(t)$ are absolutely continuous functions, the controls $u_1^*(t)$ and $u_2^*(t)$ can have a bang-bang form and switch between the corresponding values $u_i^{\min}$ and 1, $i = 1, 2$. This will happen if, when passing time t, at which functions $L_{u_1}(t)$ and $L_{u_2}(t)$ vanish, the sign change of these functions occurs. Such values t are the moments of switching of the optimal controls $u_1^*(t)$ and $u_2^*(t)$. Besides the bang-bang type sections, the controls $u_1^*(t)$ and $u_2^*(t)$ can also contain singular sections that contain singular regimens [14, 15, 20]. This happens when the corresponding switching functions $L_{u_1}(t)$ and $L_{u_2}(t)$ vanish on some subintervals of the interval $[0, \Theta]$. The following considerations are devoted to a detailed study of the possible existence of singular regimens for the optimal controls $u_1^*(t)$ and $u_2^*(t)$.

6. Useful Transformations and Important Assumption

In order to simplify the adjoint system (5.1), as well as the formulas for the switching functions $L_{u_1}(t)$ and $L_{u_2}(t)$, we introduce new adjoint variables by the formulas:

$$\phi_1^*(t) = T_1^*(t)\psi_1^*(t), \quad \phi_2^*(t) = T_2^*(t)\psi_2^*(t),$$
$$\phi_3^*(t) = N_A^*(t)\psi_3^*(t), \quad \phi_4^*(t) = -K^*(t)\psi_4^*(t).$$

Then the switching $L_{u_1}(t)$ and $L_{u_2}(t)$ are transformed to:

$$L_{u_1}(t) = \phi_3^*(t) + \chi\gamma_2^{-1}, \quad L_{u_2}(t) = -\gamma_1\phi_2^*(t) - \gamma_3\phi_4^*(t) + \nu. \tag{6.1}$$

Evaluating the derivatives $\phi_i^{*\prime}(t)$ of the new adjoint variables $\phi_i^*(t)$ with the use of the corresponding equations of the system (4.4) and the adjoint system (5.1), and also by adding the corresponding initial conditions, we find new adjoint system:

$$\begin{cases} \phi_1^{*\prime} = \left(\dfrac{a_1}{T_1^*} + r_1T_1^*\right)\phi_1^* + \alpha_2T_1^*\phi_2^* - \gamma_2u_1^*T_1^*\phi_3^* + \delta_1T_1^*\phi_4^* + \chi\,(1-u_1^*)\,T_1^*, \\ \phi_2^{*\prime} = \alpha_1T_2^*\phi_1^* + \left(\dfrac{a_2}{T_2^*} + r_2T_2^*\right)\phi_2^* - \delta_2T_2^*\phi_4^*, \\ \phi_3^{*\prime} = \gamma_1u_2^*N_A^*\phi_2^* + \left(\dfrac{b}{N_A^*} + r_3N_A^*\right)\phi_3^* + \gamma_3u_2^*N_A^*\phi_4^* + \nu\,(1-u_2^*)\,N_A^*, \\ \phi_4^{*\prime} = \dfrac{c}{K^*}\phi_4^*, \\ \phi_1^*(\Theta) = 0,\ \phi_2^*(\Theta) = 0,\ \phi_3^*(\Theta) = -\sigma N_A^*(\Theta),\ \phi_4^*(\Theta) = K^*(\Theta). \end{cases} \tag{6.2}$$

We now obtain differential equations for the switching functions $L_{u_1}(t)$ and $L_{u_2}(t)$. Using the definitions of these functions from (6.1), as well as the third equation system (6.2), we first find the differential equation for the switching function $L_{u_1}(t)$:

$$\begin{aligned} L'_{u_1}(t) = {} & \left(\frac{b}{N_A^*(t)} + r_3N_A^*(t)\right)L_{u_1}(t) - u_2^*(t)N_A^*(t)L_{u_2}(t) \\ & - \gamma_2^{-1}\left((\chi r_3 - \nu\gamma_2)N_A^*(t) + \frac{\chi b}{N_A^*(t)}\right). \end{aligned} \tag{6.3}$$

Using the definition of function $L_{u_2}(t)$ from (6.1), as well as the second and fourth equations of system (6.2) obtain differential equation for the switching function $L_{u_2}(t)$:

$$L'_{u_2}(t) = \left(\frac{a_2}{T_2^*(t)} + r_2T_2^*(t)\right)L_{u_2}(t) + F(t), \tag{6.4}$$

where the auxiliary function $F(t)$ is defined by the formula:

$$\begin{aligned} F(t) = - {} & \alpha_1\gamma_1T_2^*(t)\phi_1^*(t) \\ & + \left(\gamma_3\frac{a_2}{T_2^*(t)} + (\gamma_1\delta_2 + \gamma_3r_2)\,T_2^*(t) - \gamma_3\frac{c}{K^*(t)}\right)\phi_4^*(t) - \nu\left(\frac{a_2}{T_2^*(t)} + r_2T_2^*(t)\right). \end{aligned}$$

Now we find differential equations for the function $F(t)$. First, we will evaluate the derivative $F'(t)$ of this function and obtain the formula:

$$F' = -\alpha_1\gamma_1 T_2^{*\prime}\phi_1^* - \alpha_1\gamma_1 T_2^*\phi_1^{*\prime} + \left(-\left(\gamma_3\frac{a_2}{(T_2^*)^2} - (\gamma_1\delta_2 + \gamma_3 r_2)\right)T_2^{*\prime} + \gamma_3\frac{c}{(K^*)^2}K^{*\prime}\right)\phi_4^*$$
$$+\left(\gamma_3\frac{a_2}{T_2^*} + (\gamma_1\delta_2 + \gamma_3 r_2)T_2^* - \gamma_3\frac{c}{K^*}\right)\phi_4^{*\prime} + \nu\left(\frac{a_2}{(T_2^*)^2} - r_2\right)T_2^{*\prime}.$$

Let us substitute into this formula the equations for the functions $T_2^*(t)$ and $K^*(t)$ from system (4.4), as well as equations for the functions $\phi_1^*(t)$ and $\phi_4^*(t)$ from system (6.2). After which, in the resulting expression, we give similar terms and select the functions $L_{u_1}(t)$, $L_{u_2}(t)$ and $F(t)$. As a result, we find the required differential equation:

$$\begin{aligned} F'(t) = {} & P(T_1^*(t), T_2^*(t), N_A^*(t), u_2^*(t))\,F(t) + \alpha_1 T_1^*(t)T_2^*(t)\Big(\gamma_1\gamma_2 u_1^*(t)L_{u_1}(t) + \alpha_2 L_{u_2}(t)\Big) \\ & + Q(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), u_2^*(t))\,\phi_4^*(t) + R(T_1^*(t), T_2^*(t), N_A^*(t), u_2^*(t)), \end{aligned} \tag{6.5}$$

where $P(T_1, T_2, N_A, u_2)$, $Q(T_1, T_2, N_A, K, u_2)$ and $R(T_1, T_2, N_A, u_2)$ are defined by the formulas:

$$\begin{aligned} P(T_1, T_2, N_A, u_2) = {} & \left(\frac{a_1}{T_1} + r_1 T_1\right) + \left(\frac{a_2}{T_2} + r_2(1 - T_2) - \alpha_2 T_1 - \gamma_1 u_2 N_A - \mu_2\right), \\ Q(T_1, T_2, N_A, K, u_2) = {} & \frac{c}{K}\left(\gamma_3\frac{a_2}{T_2} + \Big((\gamma_1 - \gamma_3)\delta_2 + \gamma_3 r_2\Big)T_2 + \gamma_3\delta_1 T_1 - \gamma_3\mu_4\right) \\ & - \gamma_3\left(2\frac{a_2}{T_2} - \frac{c}{K}\right)\left(\frac{a_2}{T_2} + r_2(1 - T_2) - \alpha_2 T_1 - \mu_2\right) \\ & - \left(\frac{a_1}{T_1} + r_1 T_1\right)\left(\gamma_3\frac{a_2}{T_2} + (\gamma_1\delta_2 + \gamma_3 r_2)T_2 - \gamma_3\frac{c}{K}\right) \\ & - \alpha_1(\gamma_1\delta_1 - \gamma_3\alpha_2)T_1T_2 + u_2 N_A\left(2\gamma_1\gamma_3\frac{a_2}{T_2} + \gamma_3(\gamma_3 - \gamma_1)\frac{c}{K}\right), \\ R(T_1, T_2, N_A, u_2) = {} & 2\nu\frac{a_2}{T_2}\left(\frac{a_2}{T_2} + r_2(1 - T_2) - \alpha_2 T_1 - \gamma_1 u_2 N_A - \mu_2\right) \\ & + \nu\left(\frac{a_1}{T_1} + r_1 T_1\right)\left(\frac{a_2}{T_2} + r_2 T_2\right) - \alpha_1(\chi\gamma_1 + \nu\alpha_2)T_1T_2. \end{aligned}$$

Also, the lower estimate for the adjoint variable $\phi_4^*(t)$ will be important for us. The following lemma is true.

Lemma 6.1. *For function $\phi_4^*(t)$ the following inequality is valid:*

$$\phi_4^*(t) > K^{\min} e^{-\frac{c}{K^{\min}}\Theta}, \quad t \in [0, \Theta]. \tag{6.6}$$

Proof. Integrating the last differential equation of the system (6.2) with the corresponding initial condition, we find the formula:

$$\phi_4^*(t) = K^*(\Theta)e^{-c\int_t^{\Theta}\frac{d\xi}{K^*(\xi)}}, \quad t \in [0, \Theta].$$

Using the lower bound from Lemma 4.1 for the function $K^*(t)$, we immediately obtain inequality (6.6). □

Finally, we formulate the additional assumption under which we will carry out the subsequent reasoning.

Assumption. Let the following inequalities hold for the parameters of the minimization problem (4.4)–(4.6):

$$\gamma_3 > \gamma_1, \quad \nu \leq \gamma_3 K^{\min} e^{-\frac{c}{K^{\min}}\Theta}. \tag{6.7}$$

Note that due to the formulas (2.5), the first inequality in (6.7) is equivalent to the inequality $\beta_2 > \beta_1$, which, as follows from [19], is satisfied.

This assumption leads to the following lemma.

Lemma 6.2. *For all values $t \in [0, \Theta]$ the inequality is true:*

$$\left(2\gamma_1\gamma_3\frac{a_2}{T_2^*(t)} + \gamma_3(\gamma_3 - \gamma_1)\frac{c}{K^*(t)}\right)\phi_4^*(t) - 2\nu\gamma_1\frac{a_2}{T_2^*(t)} > 0. \tag{6.8}$$

Proof. Let us transform the left side of the inequality (6.8) as follows

$$\left(2\gamma_1\gamma_3\frac{a_2}{T_2^*(t)} + \gamma_3(\gamma_3 - \gamma_1)\frac{c}{K^*(t)}\right)\phi_4^*(t) - 2\nu\gamma_1\frac{a_2}{T_2^*(t)}$$
$$= 2\gamma_1\gamma_3\frac{a_2}{T_2^*(t)}\left(\phi_4^*(t) - \nu\gamma_3^{-1}\right) + \gamma_3(\gamma_3 - \gamma_1)\frac{c}{K^*(t)}\phi_4^*(t).$$

Due to the inequalities (6.6) and (6.7), both terms on the right-hand side of the last equality are positive. This ensures that inequality (6.8) is satisfied. □

7. Singular Regimens of the Optimal Controls

Let us now study the possible types of singular regimens that may arise for the optimal controls $u_1^*(t)$ and $u_2^*(t)$. There are the following three cases.

Case 1. Let there be an interval $\Delta_0 \subset [0, \Theta]$ on which the following identities hold simultaneously:

$$L_{u_1}(t) \equiv 0, \quad L_{u_2}(t) \equiv 0. \tag{7.1}$$

This means that singular regimens can occur simultaneously for both optimal controls $u_1^*(t)$ and $u_2^*(t)$.

From (7.1), the equalities follow:

$$L'_{u_1}(t) = 0, \quad L'_{u_2}(t) = 0. \tag{7.2}$$

Both relationships in (7.1) and the first relationship in (7.2) used in equation (6.3) lead us to the equality:

$$(\chi r_3 - \nu\gamma_2)\left(N_A^*(t)\right)^2 + \chi b = 0, \quad t \in \Delta_0. \tag{7.3}$$

It is easy to see that the following two situations are possible.

If $\chi r_3 - \nu\gamma_2 \geq 0$, then equality (7.3) is contradictory. This means there is no singular regimen under which the identities (7.1) hold.

If $\chi r_3 - \nu\gamma_2 < 0$, then equation (7.3) implies the formula:

$$N_A^{\text{sing}} = \sqrt{\frac{\chi b}{|\chi r_3 - \nu\gamma_2|}}, \quad t \in \Delta_0. \tag{7.4}$$

This means that in the singular regimen under consideration, if it exists, the density of activated NK-cells is constant. Note that quantity N_A^{sing} must satisfy $N_A^{\text{sing}} < \widetilde{N}_A^{\max}$, which follows from

Lemma 4.1. Otherwise, there is no such singular regimen. Substituting the formula (7.4) into the third equation of system (4.4), we find the relationship:

$$u_1^{\text{sing}}(t) = -\frac{b + r_3 N_A^{\text{sing}}\left(1 - N_A^{\text{sing}}\right) - \mu_3 N_A^{\text{sing}}}{\gamma_2 T_1^*(t) N_A^{\text{sing}}}\,. \tag{7.5}$$

Moreover, if $u_1^{\text{sing}}(t)$ satisfies the inclusion $u_1^{\text{sing}}(t) \in \left(u_1^{\min}, 1\right)$ on Δ_0, then (7.5) determines the optimal control $u_1^*(t)$ on the considered singular regimen. Otherwise, this singular regimen is absent.

To find a possible form of the optimal control $u_2^*(t)$ on the interval Δ_0, we use both relationships in (7.1) and the second relationship in (7.2). Substituting them into the equation (6.4), we find the identity $F(t) \equiv 0$, which immediately leads us to the equality $F'(t) = 0$. Invoking these relationships together with the relationships (7.1) into the equation (6.5), as well as taking into account the linearity in the control u_2 functions $P(T_1,T_2,N_A,u_2)$, $Q(T_1,T_2,N_A,K,u_2)$ and $R(T_1,T_2,N_A,u_2)$, we get the formula:

$$u_2^{\text{sing}}(t) = -\frac{\Psi_0\left(T_1^*(t), T_2^*(t), N_A^{\text{sing}}, K^*(t), \phi_4^*(t)\right)}{N_A^{\text{sing}}\Pi\left(T_2^*(t), K^*(t), \phi_4^*(t)\right)}\,, \tag{7.6}$$

where function $\Psi_0(T_1,T_2,N_A,K,\phi_4)$ consists of the terms of the functions $P(T_1,T_2,N_A,u_2)$, $Q(T_1,T_2,N_A,K,u_2)\,\phi_4$ and $R(T_1,T_2,N_A,u_2)$, that do not contain control u_2; also here

$$\Pi(T_2,K,\phi_4) = \left(2\gamma_1\gamma_3\frac{a_2}{T_2} + \gamma_3(\gamma_3 - \gamma_1)\frac{c}{K}\right)\phi_4 - 2\nu\gamma_1\frac{a_2}{T_2}\,.$$

Note that, due to Lemma 6.2, the function $\Pi(T_2^*(t), K^*(t), \phi_4^*(t))$ in formula (7.6) is positive on the interval Δ_0. Moreover, if $u_2^{\text{sing}}(t)$ satisfies on this interval the inclusion $u_2^{\text{sing}}(t) \in \left(u_2^{\min}, 1\right)$, then formula (7.6) defines the optimal control $u_2^*(t)$ on the singular regimen under consideration. Otherwise there is no such singular regimen.

Let us now check the necessary optimality condition for the singular regimen under which identities (7.1) are valid. To do this, we will use the Goch condition from [15].

First, we transform problem (4.4)–(4.6). Namely, we introduce a new phase variable $M(t)$ using the differential equation:

$$M'(t) = \chi(1 - u_1(t))\,T_1(t) + \nu(1 - u_2(t))\,N_A(t), \tag{7.7}$$

with the initial condition $M(0) = 0$. Then the minimization problem (4.4)–(4.6) with integro-terminal function becomes a minimization problem with a terminal objective function:

$$J(u_1,u_2) = K(\Theta) + \sigma N_A(\Theta) + M(\Theta). \tag{7.8}$$

By adding an equation (7.7) with an appropriate initial condition to system (4.4), let us rewrite the equations of the new system in vector form:

$$x'(t) = f(x(t)) + u_1(t)g_1(x(t)) + u_2(t)g_2(x(t)),$$

where the vector of phase variables x and the vector fields $f(x)$, $g_i(x)$, $i=1,2$ are defined the following formulas:

$$x=\begin{pmatrix}T_1\\T_2\\N_A\\K\\M\end{pmatrix},\quad f(x)=\begin{pmatrix}a_1+r_1T_1(1-T_1)-\alpha_1T_1T_2-\mu_1T_1\\a_2+r_2T_2(1-T_2)-\alpha_2T_1T_2-\mu_2T_2\\b+r_3N_A(1-N_A)-\mu_3N_A\\c+\delta_1T_1K-\delta_2T_2K-\mu_4K\\\chi T_1+\nu N_A\end{pmatrix},$$

$$g_1(x)=\begin{pmatrix}0\\0\\\gamma_2T_1N_A\\0\\-\chi T_1\end{pmatrix},\quad g_2(x)=\begin{pmatrix}0\\-\gamma_1T_2N_A\\0\\\gamma_3N_AK\\-\nu N_A\end{pmatrix}.$$

Compute the commutator $[g_1,g_2](x)$ of the vector fields $g_1(x)$ and $g_2(x)$ ([14]). Assuming that $Dg_1(x)$ and $Dg_2(x)$ are the corresponding Jacobi matrices for $g_1(x)$ and $g_2(x)$, we have the formula:

$$[g_1,g_2](x)=Dg_2(x)g_1(x)-Dg_1(x)g_2(x)$$

$$=\begin{pmatrix}0&0&0&0&0\\0&-\gamma_1N_A&-\gamma_1T_2&0&0\\0&0&0&0&0\\0&0&\gamma_3K&\gamma_3N_A&0\\0&0&-\nu&0&0\end{pmatrix}\begin{pmatrix}0\\0\\\gamma_2T_1N_A\\0\\-\chi T_1\end{pmatrix}$$

$$-\begin{pmatrix}0&0&0&0&0\\0&0&0&0&0\\\gamma_2N_A&0&\gamma_2T_1&0&0\\0&0&0&0&0\\-\chi&0&0&0&0\end{pmatrix}\begin{pmatrix}0\\-\gamma_1T_2N_A\\0\\\gamma_3N_AK\\-\nu N_A\end{pmatrix}=\begin{pmatrix}0\\-\gamma_1\gamma_2T_1T_2N_A\\0\\\gamma_2\gamma_3T_1N_AK\\-\nu\gamma_2T_1N_A\end{pmatrix}.$$

Then Goch condition is that the scalar product

$$\langle[g_1,g_2](x^*(t)),\eta^*(t)\rangle \tag{7.9}$$

functions $[g_1,g_2](x^*(t))$ and $\eta^*(t)$ identically vanish on the interval Δ_0. Here $x^*(t)$ is a vector of components of the optimal solution $(T_1^*(t),T_2^*(t),N_A^*(t),K^*(t),M^*(t))$ of the system corresponding to the minimization problem with terminal objective function (7.8), and $\eta^*(t)$ is the solution corresponding adjoint system arising as a result of applying to this problem the Pontryagin maximum principle. It is easy to see that the first four components of the adjoint variable $\eta^*(t)$ form a solution $\psi^*(t)$ of the adjoint system (5.1). Fifth component $\eta_5^*(t)$ satisfies the differential equation $\eta_5^{*\prime}=0$ with initial condition $\eta_5^*(\Theta)=-1$, and therefore is defined by the formula $\eta_5^*(t)=-1$. Considering all these considerations, we see that the expression (7.9) is converted to the form:

$$\begin{aligned}\langle[g_1,g_2](x^*(t)),\eta^*(t)\rangle=&-\gamma_1\gamma_2T_1^*(t)T_2^*(t)N_A^*(t)\psi_2^*(t)\\&+\gamma_2\gamma_3T_1^*(t)N_A^*(t)K^*(t)\psi_4^*(t)-\nu\gamma_2T_1^*(t)N_A^*(t).\end{aligned}$$

Invoking here the new adjoint variables $\phi_2^*(t)$ and $\phi_4^*(t)$, as well as the switching function $L_{u_2}(t)$ from (5.4), we conclude that there is a chain of equalities:

$$\langle [g_1, g_2]\,(x^*(t)), \eta^*(t)\rangle = \gamma_2 T_1^*(t) N_A^*(t)\,(-\gamma_1\phi_2^*(t) - \gamma_3\phi_4^*(t) + \nu) = \gamma_2 T_1^*(t) N_A^*(t) L_{u_2}(t),$$

which due to the second relationship (7.1) is identically equal to zero on the interval Δ_0. This means that the necessary condition for the optimality of the singular regimen under consideration (the Goch condition) is satisfied, and therefore such a singular regimen is possible.
Case 2. Let there be an interval $\Delta_1 \subset [0,\Theta]$ on which the identity is true:

$$L_{u_1}(t) \equiv 0, \tag{7.10}$$

and the switching function $L_{u_2}(t)$ does not vanish. This means that only the optimal control $u_1^*(t)$ can have a singular regimen. The control $u_2^*(t)$ on the interval Δ_1 is a bang-bang function that takes the values $u_2^{\min}$ and 1. The equality follows from the formula (7.10):

$$L'_{u_1}(t) = 0. \tag{7.11}$$

The relationships (7.10) and (7.11) used in the equation (6.3) lead to the expression:

$$-u_2^*(t)N_A^*(t)L_{u_2}(t) - \gamma_2^{-1}\left((\chi r_3 - \nu\gamma_2)\,N_A^*(t) + \frac{\chi b}{N_A^*(t)}\right) = 0,\ \ t \in \Delta_1. \tag{7.12}$$

An analysis of this equality shows that it is inconsistent for $\chi r_3 - \nu\gamma_2 \geq 0$ and $u_2^*(t) = 1, t \in \Delta_1$. Hence, under these restrictions, the considered singular regimen is absent. Under other constraints, to find a possible type of optimal control $u_1^*(t)$ on the interval Δ_1, we differentiate the relationship (7.12). Substituting the third equation of the system (4.4) in the resulting expression and the equation (6.4), after necessary transformations, we find the relationship:

$$\begin{aligned}
&-\gamma_2 u_1^*(t) T_1^*(t)\left[u_2^*(t)N_A^*(t)L_{u_2}(t) + \gamma_2^{-1}\left((\chi r_3 - \nu\gamma_2)\,N_A^*(t) - \frac{\chi b}{N_A^*(t)}\right)\right] \\
&-\left(\frac{b}{N_A^*(t)} + r_3\,(1 - N_A^*(t)) - \mu_3\right) \\
&\times\left[u_2^*(t)N_A^*(t)L_{u_2}(t) + \gamma_2^{-1}\left((\chi r_3 - \nu\gamma_2)\,N_A^*(t) - \frac{\chi b}{N_A^*(t)}\right)\right] \\
&-u_2^*(t)N_A^*(t)\left[\left(\frac{a_2}{T_2^*(t)} + r_2 T_2^*(t)\right)L_{u_2}(t) + F(t)\right] = 0, \quad t \in \Delta_1.
\end{aligned}$$

Taking into account the formula (7.12) in it, we get the expression:

$$\begin{aligned}
&2\chi b u_1^*(t)\frac{T_1^*(t)}{N_A^*(t)} + 2\gamma_2^{-1}\frac{\chi b}{N_A^*(t)}\left(\frac{b}{N_A^*(t)} + r_3\,(1 - N_A^*(t)) - \mu_3\right) \\
&\quad - u_2^*(t)N_A^*(t)\left[\left(\frac{a_2}{T_2^*(t)} + r_2 T_2^*(t)\right)L_{u_2}(t) + F(t)\right] = 0, \quad t \in \Delta_1,
\end{aligned} \tag{7.13}$$

which leads to the formula:

$$u_1^{\text{sing}}(t) = -\frac{\Psi_1\,(T_2^*(t), N_A^*(t), L_{u_2}(t), F(t), u_2^*(t))}{2\chi b T_1^*(t)/N_A^*(t)}\,, \tag{7.14}$$

where

$$\Psi_1(T_2, N_A, L_{u_2}, F, u_2) = -2\gamma_2^{-1}\frac{\chi b}{N_A}\left(\frac{b}{N_A} + r_3(1-N_A) - \mu_3\right) + u_2 N_A\left[\left(\frac{a_2}{T_2} + r_2 T_2\right)L_{u_2} + F\right].$$

Moreover, if the function $u_1^{\text{sing}}(t)$ satisfies on the interval Δ_1 the inclusion $u_1^{\text{sing}}(t) \in (u_1^{\min}, 1)$, then the formula (7.14) defines the optimal control $u_1^*(t)$ on the considered singular regimen. Otherwise, this singular regimen is absent.

Let us now check the necessary condition for the optimality of the singular regimen, under which identity (7.10) is valid. To do this, we use the Kelly condition from [20]. We will find on the interval Δ_1 derivative

$$\frac{\partial}{\partial u_1}\left(L''_{u_1}(t)\right)$$

while simultaneously fulfilling the relationships (7.10)–(7.12). Analyzing expression (7.13), we conclude that the formula holds:

$$\frac{\partial}{\partial u_1}\left(L''_{u_1}(t)\right) = 2\chi b\frac{T_1^*(t)}{N_A^*(t)} > 0, \quad t \in \Delta_1.$$

This means that the Kelly condition is satisfied and, moreover, in a strengthened form. Therefore, due to [14, 15], the optimal control $u_1^*(t)$ on the interval Δ_1 there may be a first-order singular regimen that concatenates with non-singular bang-bang sections of this control.

Case 3. Let there be an interval $\Delta_2 \subset [0, \Theta]$ on which place identity:

$$L_{u_2}(t) \equiv 0, \tag{7.15}$$

and the switching function $L_{u_1}(t)$ does not vanish identically. This means that the singular regimen can arise only for the optimal control $u_2^*(t)$. Control $u_1^*(t)$ on the interval Δ_2 is a bang-bang function and takes the values $u_1^{\min}$ and 1. From formula (7.15) the equality follows:

$$L'_{u_2}(t) = 0. \tag{7.16}$$

The relationships (7.14) and (7.15) used in the equation (6.4) lead to identity:

$$F(t) \equiv 0, \quad t \in \Delta_2, \tag{7.17}$$

from which follows the equality:

$$F'(t) = 0, \quad t \in \Delta_2. \tag{7.18}$$

Using the relationships (7.15), (7.17) and (7.18) in the equation (6.5), we find the expression:

$$\begin{aligned} &u_2^*(t)N_A^*(t)\Pi(T_2^*(t), K^*(t), \phi_4^*(t)) + \alpha_1\gamma_1\gamma_2 u_1^*(t)T_1^*(t)T_2^*(t)L_{u_1}(t) \\ &\quad + \Psi_0(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), \phi_4^*(t)) = 0, \quad t \in \Delta_2, \end{aligned} \tag{7.19}$$

where functions $\Pi(T_2, K, \phi_4)$ and $\Psi_0(T_1, T_2, N_A, K, \phi_4)$ were defined under consideration of Case 1. From relationship (7.19) we obtain the formula:

$$u_2^{\text{sing}}(t) = -\frac{\Psi_2(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), L_{u_1}(t), \phi_4^*(t), u_1^*(t))}{N_A^*(t)\Pi\left(T_2^*(t), K^*(t), \phi_4^*(t)\right)}, \tag{7.20}$$

where

$$\begin{aligned} &\Psi_2(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), L_{u_1}(t), \phi_4^*(t), u_1^*(t)) \\ &\quad = \alpha_1\gamma_1\gamma_2 u_1^*(t)T_1^*(t)T_2^*(t)L_{u_1}(t) + \Psi_0(T_1^*(t), T_2^*(t), N_A^*(t), K^*(t), \phi_4^*(t)). \end{aligned}$$

Note that, by Lemma 6.2, the function $\Pi\left(T_2^*(t), K^*(t), \phi_4^*(t)\right)$ in formula (7.20), as in Case 1, is positive on the interval Δ_2. Moreover, if the function $u_2^{\text{sing}}(t)$ satisfies the inclusion $u_2^{\text{sing}}(t) \in \left(u_2^{\min}, 1\right)$ on this interval, then formula (7.20) defines the optimal control $u_2^*(t)$ on the considered singular regimen. Otherwise, there is no such singular regimen.

Let us now check the necessary optimality condition for the singular regimen under which the identity (7.15) is true. To do this, we again apply the Kelly condition from [20]. Let's find on interval Δ_2 the derivative

$$\frac{\partial}{\partial u_2}\left(L''_{u_2}(t)\right)$$

while simultaneously fulfilling the relationships (7.15)–(7.18). Analyzing expression (7.19), we come to the conclusion that the formula takes place:

$$\frac{\partial}{\partial u_2}\left(L''_{u_2}(t)\right) = N_A^*(t)\Pi\left(T_2^*(t), K^*(t), \phi_4^*(t)\right) > 0, \quad t \in \Delta_2.$$

Therefore, as in Case 2, the Kelly condition is satisfied and, moreover, in a stronger form. Hence, again due to [14, 15], the optimal control $u_2^*(t)$ on the interval Δ_2 can have a singular first-order regimen, which is concatenated with non-singular bang-bang sections of this control.

Thus, we make the final conclusion that on some interval

- singular regimens may arise for the optimal controls $u_1^*(t)$ and $u_2^*(t)$ simultaneously;
- a singular regimen can only be in the optimal control $u_1^*(t)$, and the control $u_2^*(t)$ is a bang-bang function;
- a singular regimen can only be in the optimal control $u_2^*(t)$, and the control $u_1^*(t)$ is a bang-bang function.

8. Results of Numerical Calculations and Their Discussion

Here we demonstrate the results of a numerical solution of minimization problem (4.4)–(4.6). For numerical calculations, we used the following parameters values of system (4.4) and its initial conditions, the values of constraints on controls from (4.5) and the weight coefficients of the objective function (4.6):

$$\begin{array}{llll} a_1 = 0.0333 & a_2 = 0.04 & b = 0.0333 & c = 0.01 \\ \mu_1 = 0.035 & \mu_2 = 0.01 & \mu_3 = 0.02 & \mu_4 = 0.035 \\ \alpha_1 = 0.003 & \alpha_2 = 0.006 & \delta_1 \in [0.12, 0.5] & \delta_2 = 0.36 \\ r_1 = 0.01 & r_2 = 0.01 & r_3 = 0.002 & \\ \gamma_1 = 0.000375 & \gamma_2 = 0.075 & \gamma_3 \in [0.15, 1.5] & \\ u_1^{\min} = 0.01 & u_2^{\min} = 0.01 & \sigma = 1.0 & \Theta = 30.0 \end{array} \tag{8.1}$$

Most of these values are taken from [19]. Numerical calculations were carried out using the BOCOP environment ([2]). Note that the density of keratinocytes $K(t)$ was also scaled as $K(t) \to K(t)10^{-2}$, which actually consisted in the corresponding proportional decrease in the value of the parameter c. In addition, some of the parameter values in (8.1) were chosen in such a way as to ensure the existence and stability of the already mentioned equilibrium position of system (2.7), which consists in the simultaneous fulfillment of the inequalities:

$$r_1 r_2 - \alpha_1\alpha_2 > 0, \quad (r_1 r_2 - \alpha_1\alpha_2) r_3 > \alpha_1\gamma_1\gamma_2, \tag{8.2}$$

as well as other hypothetical restrictions on the parameter values of this system. Otherwise, there was an unlimited and uncontrolled increase in the density of keratinocytes $K(t)$, which had no biological sense. Finally, the initial conditions T_1^0, T_2^0, N_A^0, K^0, as well as the values of the weight coefficients χ and ν were varied in the range from very small values to unity.

Recall that the controls $u_1(t)$ and $u_2(t)$ in the minimization problem (4.4)–(4.6) are auxiliary. They are introduced into the system (4.4) to simplify the subsequent analysis (Section 4). The corresponding physical (original) controls $\widetilde{u}_1(t)$ and $\widetilde{u}_2(t)$ are related to the controls $u_1(t)$ and $u_2(t)$ by the formulas:

$$\widetilde{u}_1(t) = 1 - u_1(t), \quad \widetilde{u}_2(t) = 1 - u_2(t).$$

Therefore, if the auxiliary optimal control $u_1^*(t)$ has a maximum value 1, then the corresponding physical optimal control $\widetilde{u}_1^*(t)$ takes the minimum value 0 and vice versa. A similar remark is also valid for the auxiliary optimal control $u_2^*(t)$ and for the corresponding physical optimal control $\widetilde{u}_2^*(t)$.

As a result, numerical calculations have shown that the physical optimal control $\widetilde{u}_1^*(t)$ is a piecewise constant function with one or two switchings of the forms:

$$\widetilde{u}_1^*(t) = \begin{cases} 0 & , \text{ if } \quad 0 \le t \le \tau^*, \\ \widetilde{u}_1^{\max} & , \text{ if } \quad \tau^* < t \le \Theta, \end{cases}$$

$$\widetilde{u}_1^*(t) = \begin{cases} 0 & , \text{ if } \quad 0 \le t \le \tau_1^*, \\ \widetilde{u}_1^{\max} & , \text{ if } \quad \tau_1^* < t \le \tau_2^*, \\ 0 & , \text{ if } \quad \tau_2^* < t \le \Theta, \end{cases}$$

where τ^* and τ_i^*, $i = 1,2$ are the corresponding switchings. The physical optimal control $\widetilde{u}_2^*(t)$ is a constant function taking the value $\widetilde{u}_2^{\max}$ over the entire time interval $[0,\Theta]$.

Unfortunately, due to the large number of parameters in system (4.4), as well as due to complex and nonlinear dependencies between these parameters, initial conditions, and weight coefficients in relationships (3.3), (6.7), (7.3), and (8.2), we were unable to find the singular regimens in the minimization problem (4.4)–(4.6) numerically. However, the numerical detection of these singular regimens, as well as the application of our theoretical results to the treatment of real patients with psoriasis, will be prospects for our future research.

Acknowledgements

We are grateful to Professor P.K. Roy from Jadavpur University, Kolkata, India for helpful and insightful comments and suggestions on psoriasis model building.

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