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SINGULAR AND NON-SINGULAR OPTIMAL STRATEGIES FOR PSORIASIS CONTROL MODEL

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Abstract. We consider a mathematical model of a psoriasis treatment, which is described by a nonlinear system of differential equations. Its phase variables are the concentrations of T-lymphocytes, keratinocytes, and dendritic cells (tissues macrophages). Such properties of this system as invariance and permanence are discussed. The existence of equilibria with nonnegative coordinates and finding the conditions for their local asymptotic stability are studied. Then, a scalar bounded control reflecting medication intake is included into this model, and already for the obtained control model on a given time interval the problem of minimizing the concentration of keratinocytes at the terminal time is considered. For its analysis the Pontryagin maximum principle is used. The relationships are established between parameters of the control model, under which the corresponding optimal control is either bang-bang type on the entire time interval, or, in addition to bang-bang type, it contains a singular arc. The order of such a singular arc is determined, the fulfillment of the necessary optimality condition for it is discussed, the forms of a concatenation of singular arc and bang-bang type of the optimal control are found. Also we establish that it is a chattering control. The obtained results are confirmed by numerical calculations, and the corresponding conclusions are presented.

1. Introduction

Psoriasis is a chronic disease affecting about 2% of the world's population. Psoriasis rarely poses a threat to life, but without any doubt, it causes a significant decrease in its quality, which in turn negatively affects the social adaptation, employment and career growth. In addition, psoriasis is often accompanied by stress, depression, anxiety and leads to abuse of psychoactive drugs. A patient suffering from moderate or severe psoriasis has an increased risk of mortality at a younger age because of concomitant diseases, such as diabetes, metabolic syndrome, malignant neoplasms. There is also a relationship between psoriasis and cardiovascular disease.

Psoriasis is an autoimmune disease with symptoms of chronic skin inflammation. In psoriasis skin cells grow very quickly leading to the appearance of red dry and scaly rashes ([18]). The outermost layer of skin consists mainly of keratinocytes, which are the type of cells considered important for psoriasis. This is due to the

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fact that they were observed in psoriatic skin in states of hyperproliferation and abnormally differentiation. Also, the adaptive immune system plays a significant role in psoriasis, because it is related to the presence of immune cells, such as T-lymphocytes and dendritic cells (tissues macrophages), in psoriatic skin lesions. The interaction of these three types of cells triggers a number of mechanisms leading ultimately to the development of the inflammatory process and the formation of psoriatic skin lesions ([12, 16, 17]). Adequate treatment of psoriasis is a very difficult task, and there is no medicine leading to complete cure.

The study of psoriasis depends on the availability of normal and psoriatic human skin and several preclinical models were developed ([4]). In addition to experimental studies, computational and mathematical models were created that can explain the hyperproliferation and abnormally differentiation of keratinocytes, the role of T-lymphocytes and dendritic cells in psoriasis, the morphology of the normal and psoriatic epidermis. In [20], based on the general approaches employed, existing models are divided into two groups: (i) agent-based models ([9, 10, 29, 33, 37]), and (ii) ordinary differential equation-based models ([3, 7, 14, 19, 20, 23, 24, 27, 28, 32, 36]). Also, we allocate separately the computational model for studying the spatio-temporal dynamics of epidermis homeostasis under normal and pathological conditions proposed in [39]. This model unites a kinetic model of the central transition pathway of keratinocyte proliferation, differentiation and apoptosis and an agent-based model that propagates cell movements and generates the stratified epidermis.

It is important in a psoriasis treatment to apply strategies, which are the best in one sense or another. Turning to the language of mathematical models, this means that in such a model a control is introduced and an objective function is added to it. As a result, an optimization problem arises, to which the optimal control theory can be applied. For the mathematical models of a psoriasis treatment the corresponding optimal control problems were considered and solved in [2, 5, 25], where numerically were found optimal strategies of treatment that minimized the cumulative concentration of keratinocytes and the cost of treatment. While the obtained results are very interesting, the presence of a square of the control under the integral of the objective function makes the optimal control problem numerically simplistic but prohibits the attainment of the optimal analytical solution. Before solving an optimal control problem numerically, it would be beneficial to investigate the problem analytically in order to reveal some features and properties of its optimal solutions. Therefore, in this paper we will consider the control model proposed in [25] with a different objective function.

This paper is organized as follows. In Section 2, on a given time interval a nonlinear control model of a psoriasis treatment, which is a system of three differential equations describing relationships between the concentrations of T-lymphocytes, keratinocytes, and dendritic cells (tissues macrophages) is considered. The scalar bounded control, also included in the model, reflects medication intake. Such properties of its solutions as positiveness, boundedness, and continuation on a given time interval are discussed. Section 3 is devoted to the study of the corresponding uncontrolled model, that is, the original model, in which control is a constant. For it, the invariant set is found, the existence of equilibria with non-negative coordinates is investigated. The permanence of the uncontrolled model is justified in Section 4. In

Section 5, the local asymptotic stability of equilibria, as well as sufficient conditions, which provide it, are studied. The results of Sections 3 and 5 refine similar results obtained earlier in [25]. For the original control model in Section 6, the problem of minimizing the concentration of keratinocytes at the end of the time interval is stated. The relevance of such a problem, as well as the existence in it of an optimal solution consisting of the optimal control and the corresponding optimal solutions of the system of differential equations, are discussed. To analyze the optimal solution in Section 7, the Pontryagin maximum principle is used. The corresponding adjoint system, the maximum condition for the optimal control, and the condition for the constancy of the Hamiltonian on the optimal solution are written. Then, the system of differential equations for the switching function describing the behavior of this control and its corresponding auxiliary functions are obtained. In Section 8, this system of equations allows us to investigate the type of the optimal control: this function has only a bang-bang type, or in addition to the portions of the bang-bang type, it also contains singular arc. The relationships between the parameters of the original control model are found under which the optimal control is of one type or another. When a singular arc arises, we discuss its order, the fulfillment of the corresponding necessary optimality condition for it, as well as possible forms of a concatenation of singular arc and bang-bang type of the optimal control. As a result, we have the chattering phenomenon for the optimal control. In Section 9, the obtained results are illustrated by numerical calculations. Section 10 contains our conclusions.

2. Mathematical model of psoriasis

Let us consider on a given time interval $[0,T]$ the following nonlinear control system of differential equations:

$$\begin{cases} \dot{l}(t) = \sigma - \delta l(t)m(t) - \gamma_1 u(t)l(t)k(t) - \mu l(t), \\ \dot{k}(t) = (\beta + \delta)l(t)m(t) + \gamma_2 u(t)l(t)k(t) - \lambda k(t), \\ \dot{m}(t) = \rho - \beta l(t)m(t) - \nu m(t), \\ l(0) = l_0,\ k(0) = k_0,\ m(0) = m_0;\ l_0, k_0, m_0 > 0, \end{cases} \tag{2.1}$$

which describes the interaction of different types of human cells during the drug therapy of psoriasis. Here, $l(t)$, $k(t)$, $m(t)$ are the phase variables of system (2.1) specifying the concentrations of T-lymphocytes, keratinocytes and dendritic cells (tissue microphages), respectively; l_0, k_0, m_0 are their initial conditions. Next, σ and ρ are the appropriate rates of influx of T-lymphocytes and dendritic cells; μ, λ, and ν are the per capita removal rates of T-lymphocytes, keratinocytes and dendritic cells, respectively. Moreover, δ is the rate of activation of T-lymphocytes by dendritic cells and β is the rate of activation of dendritic cells by T-lymphocytes; $(\beta + \delta)$ is the proportion at which keratinocytes are stimulated by T-lymphocytes and dendritic cells. Finally, γ_1 is the rate of activation of keratinocytes by T-lymphocytes and γ_2 is the rate of growth of keratinocytes due to T-lymphocytes as well.

In system (2.1) the function $u(t)$ is the control with the following restrictions:

$$0 < u_{\min} \leq u(t) \leq 1. \tag{2.2}$$

Control $u(t)$ is responsible for the medication dosage, which reduces the interaction of T-lymphocytes and epidermoidal keratinocytes. The set of admissible controls $\Omega(T)$ is formed by all Lebesgue measurable functions $u(t)$, which for almost all $t \in [0,T]$ satisfy restrictions (2.2).

We define the following positive constants:

$$\kappa_{\min} = \min\{\mu; \lambda; \nu\}, \quad \kappa_{\max} = \max\{\mu; \lambda; \nu\},$$
$$D_0 = \rho\left(1 + \delta\beta^{-1}\right)\gamma_1 + \sigma\gamma_2, \quad D_* = \left(\sigma + \beta^{-1}\alpha\rho\right)\gamma_2,$$

and using them we set the constant:

$$M_0 = \gamma_2 l_0 + \gamma_1 k_0 + \gamma_1\left(1 + \delta\beta^{-1}\right)m_0 + \kappa_{\min}^{-1} D_0.$$

Now, we introduce a set:

$$\Lambda_0 = \Big\{(l,m,k) : l > 0,\ m > 0,\ k > 0,$$
$$\gamma_2 l + \gamma_1 k + \gamma_1\left(1 + \delta\beta^{-1}\right)m < M_0\Big\}.$$

The boundedness, positiveness and continuation of the solutions for system (2.1) is established by the following lemma.

Lemma 2.1. *Let the inclusion*

$$(l_0, m_0, k_0) \in \Lambda_0 \tag{2.3}$$

hold. Then, for any admissible control $u(t)$, the corresponding absolutely continuous solutions $l(t)$, $k(t)$, $m(t)$ for system (2.1) *are defined on the entire interval* $[0,T]$ *and satisfy the inclusion:*

$$(l(t), m(t), k(t)) \in \Lambda_0, \quad t \in (0,T]. \tag{2.4}$$

Proof. Let $u(t)$ be an arbitrary admissible control. Then, the corresponding absolutely continuous solutions $l(t)$, $k(t)$, $m(t)$ for system (2.1) are defined on the interval $[0, t_0)$, which is the maximum possible interval for the existence of these solutions.

From system (2.1) we find the Cauchy problems:

$$\begin{cases} \dot{l}(t) = -(\delta m(t) + \gamma_1 u(t)k(t) + \mu)l(t) + \sigma, \\ l(0) = l_0 > 0, \end{cases}$$
$$\begin{cases} \dot{m}(t) = -(\beta l(t) + \nu)m(t) + \rho, \\ m(0) = m_0 > 0. \end{cases}$$

In these Cauchy problems the initial conditions are positive, and the corresponding differential equations are linear non-autonomous equations with positive inhomogeneities. Therefore, we immediately conclude that the inequalities:

$$l(t) > 0, \quad m(t) > 0, \quad t \in [0, t_0) \tag{2.5}$$

are valid. Also, from system (2.1) we have the Cauchy problem:

$$\begin{cases} \dot{k}(t) = (\gamma_2 u(t)l(t) - \lambda)k(t) + (\beta + \delta)l(t)m(t), \\ k(0) = k_0 > 0. \end{cases}$$

As in the previous Cauchy problems, the initial condition is positive in this Cauchy problem, and the differential equation is also a linear non-autonomous equation with positive inhomogeneity (see inequalities (2.5)). Hence, we find the inequality:

$$k(t) > 0, \quad t \in [0, t_0). \tag{2.6}$$

Thus, we have established the positivity of the solutions $l(t)$, $k(t)$, $m(t)$ on the interval $[0, t_0)$.

Now, we show the boundedness of these solutions. Let us consider the function:

$$V(l, k, m) = \gamma_2 l + \gamma_1 k + \gamma_1 \left(1 + \delta\beta^{-1}\right) m,$$

and calculate for the solutions $l(t)$, $k(t)$, $m(t)$ its derivative by virtue of the system (2.1). We have the expression:

$$\begin{aligned}\frac{dV}{dt}(l(t), k(t), m(t)) &= D_0 - \delta\gamma_2 l(t)m(t)\\ &\quad - \left(\mu\gamma_2 l(t) + \lambda\gamma_1 k(t) + \nu\gamma_1 \left(1 + \delta\beta^{-1}\right) m(t)\right),\end{aligned}$$

which, by (2.5), leads to the inequality:

$$\frac{dV}{dt}(l(t), k(t), m(t)) + \kappa_{\min} V(l(t), k(t), m(t)) < D_0.$$

Hence, we obtain the relationship:

$$\frac{d}{dt}\Big(V(l(t), k(t), m(t))\mathrm{e}^{\kappa_{\min} t}\Big) < D_0 \mathrm{e}^{\kappa_{\min} t}, \ \ t \in (0, t_0).$$

Integrating it on the interval $[0, t]$, we find a chain of inequalities:

$$\begin{aligned}V(l(t), k(t), m(t)) &< V(l_0, k_0, m_0)\mathrm{e}^{-\kappa_{\min} t} + \kappa_{\min}^{-1} D_0\Big(1 - \mathrm{e}^{-\kappa_{\min} t}\Big)\\ &< V(l_0, k_0, m_0) + \kappa_{\min}^{-1} D_0, \ \ t \in (0, t_0).\end{aligned}$$

Using the definition of the function $V(l, k, m)$ and inclusion (2.3), we obtain the inequality:

$$\gamma_2 l(t) + \gamma_1 k(t) + \gamma_1 \left(1 + \delta\beta^{-1}\right) m(t) < M_0, \ \ t \in [0, t_0). \tag{2.7}$$

Consequently, we have obtained the required boundedness of the solutions $l(t)$, $k(t)$, $m(t)$ on the interval $[0, t_0)$.

If the interval $[0, T]$ is contained in $[0, t_0)$, then the required fact is true. If the interval $[0, t_0) \subset [0, T]$, then, by the proven restrictions (2.5)–(2.7) and Theorem 3.1 ([13],Chapter 2), the solutions $l(t)$, $k(t)$, $m(t)$ are continued for the entire interval $[0, T]$. Thus, the inclusion (2.4) is established. The proof is complete. □

Let us introduce the constant:

$$\alpha = \gamma_2^{-1}((\beta + \gamma)\gamma_1 - \delta\gamma_2),$$

which implies that

$$\alpha + \delta = \gamma_1\gamma_2^{-1}(\beta + \delta) > 0. \tag{2.8}$$

We suppose that in subsequent arguments the following condition holds.

Condition 2.2. *Let the constant α be different from zero.*

3. Investigation of equilibria

Let us consider system (2.1) as the uncontrolled system:

$$\begin{cases} \dot{l}(t) = \sigma - \delta l(t)m(t) - \gamma_1 u l(t)k(t) - \mu l(t), \\ \dot{k}(t) = (\beta+\delta)l(t)m(t) + \gamma_2 u l(t)k(t) - \lambda k(t), \\ \dot{m}(t) = \rho - \beta l(t)m(t) - \nu m(t), \end{cases} \tag{3.1}$$

in which control $u \in [u_{\min}, 1]$ is a constant. It follows from the proof of Lemma 2.1 that any solutions $l(t)$, $k(t)$, $m(t)$ for this system with positive initial conditions:

$$l(0) = l_0, \quad k(0) = k_0, \quad m(0) = m_0 \tag{3.2}$$

are defined and bounded on the interval $[0, +\infty)$.

Now, we introduce a set:

$$\Lambda = \Big\{(l,m,k) : l > 0,\ m > 0,\ k > 0,\\ \gamma_2 l + \gamma_1 k + \gamma_1\left(1 + \delta\beta^{-1}\right) m < \kappa_{\min}^{-1} D_0\Big\}.$$

The following lemma is valid for it.

Lemma 3.1. *Set* Λ *is an invariant set of system* (3.1).

Proof. We consider arbitrary solutions $l(t)$, $k(t)$, $m(t)$ for system (3.1), initial conditions (3.2) of which satisfy the inclusion:

$$(l_0, k_0, m_0) \in \Lambda. \tag{3.3}$$

Analyzing the proof of Lemma 2.1, we see that these solutions are positive for all t and only the inequality:

$$\gamma_2 l(t) + \gamma_1 k(t) + \gamma_1\left(1 + \delta\beta^{-1}\right) m(t) < \kappa_{\min}^{-1} D_0 \tag{3.4}$$

requires a justification.

In Lemma 2.1, the following inequality was established:

$$V(l(t), k(t), m(t)) < V(l_0, k_0, m_0)\mathrm{e}^{-\kappa_{\min} t} + \kappa_{\min}^{-1} D_0\Big(1 - \mathrm{e}^{-\kappa_{\min} t}\Big). \tag{3.5}$$

Inclusion (3.3) implies the inequality $V(l_0, k_0, m_0) < \kappa_{\min}^{-1} D_0$. Then, by relationship (3.5), we find the inequality $V(l(t), k(t), m(t)) < \kappa_{\min}^{-1} D_0$, which means the validity of the required inequality (3.4). The proof is complete. □

The result, presented in Lemma 3.1, can be strengthened and reformulated as follows.

Corollary 3.2. *The closure of the set* Λ *is an invariant set of system* (3.1).

Now, let us investigate for system (3.1) the existence of equilibria $(l_\star, k_\star, m_\star)$, coordinates of which are non-negative. These investigations refine the results previously obtained in [25].

For this, we consider the following system of equations:

$$\begin{cases} \sigma - \delta l m - \gamma_1 u l k - \mu l = 0, \\ (\beta+\delta) l m + \gamma_2 u l k - \lambda k = 0, \\ \rho - \beta l m - \nu m = 0, \end{cases} \tag{3.6}$$

and study its solutions $(l_\star, k_\star, m_\star)$ that interest us.

We immediately note the absence of solutions $(l_\star, k_\star, m_\star)$ having at least one zero component. Hence, further we are looking for equilibria $(l_\star, k_\star, m_\star)$ for system (3.1), coordinates of which satisfy the restrictions:

$$l_\star > 0, \quad k_\star > 0, \quad m_\star > 0. \tag{3.7}$$

Now, we define for all $m \in \left[0, \nu^{-1}\rho\right]$ the following quadratic functions:

$$g_1(m) = \alpha\nu m^2 - (\sigma\beta + \nu\mu + \alpha\rho)m + \mu\rho,$$
$$g_2(m) = \delta\nu m^2 - (\sigma\beta + \nu\mu - \delta\rho)m - \mu\rho.$$

From the relationships:

$$g_1(0) = \mu\rho > 0, \quad g_1\left(\nu^{-1}\rho\right) = -\nu^{-1}\rho\sigma\beta < 0,$$
$$g_2(0) = -\mu\rho < 0, \quad g_2\left(\nu^{-1}\rho\right) = \nu^{-1}\rho\sigma\beta > 0,$$

we conclude that each of the quadratic functions $g_1(m)$, $g_2(m)$ has exactly one zero on the interval $\left(0, \nu^{-1}\rho\right)$, respectively:

$$g_1\left(m_1^0\right) = 0, \quad g_2\left(m_2^0\right) = 0. \tag{3.8}$$

Moreover, the following relationships hold:

$$g_1(m) \begin{cases} > 0 & \text{, if } \ 0 \le m < m_1^0, \\ = 0 & \text{, if } \ m = m_1^0, \\ < 0 & \text{, if } \ m_1^0 < m \le \nu^{-1}\rho, \end{cases} \tag{3.9}$$

$$g_2(m) \begin{cases} < 0 & \text{, if } \ 0 \le m < m_2^0, \\ = 0 & \text{, if } \ m = m_2^0, \\ > 0 & \text{, if } \ m_2^0 < m \le \nu^{-1}\rho. \end{cases} \tag{3.10}$$

Next, we show that the zeros m_1^0, m_2^0 are related by the inequality:

$$m_1^0 < m_2^0. \tag{3.11}$$

For this, using the definitions of the functions $g_1(m)$, $g_2(m)$, inequality (2.8), and the second equality in (3.8), we evaluate the sign of $g_2\left(m_1^0\right)$. As a result, we have the relationships:

$$g_2\left(m_1^0\right) = -\nu(\alpha + \delta)m_1^0(\nu^{-1}\rho - m_1^0) < 0 = g_2\left(m_2^0\right),$$

which, by formula (3.10), imply the validity of inequality (3.11).

Now, let us transform the equations of the system (3.6). First, we express the variable l from its third equation. We have the formula:

$$l = \frac{\rho - \nu m}{\beta m}. \tag{3.12}$$

Then, we multiply the first equation of system (3.6) by γ_2, and the second equation by γ_1 and add them. Next, in the resulting expression we substitute formula (3.12). After performing necessary transformations, we have the formula:

$$k = -\frac{\gamma_2}{\gamma_1} \cdot \frac{g_1(m)}{\lambda\beta m}. \tag{3.13}$$

From the analysis of inequalities (3.7), formulas (3.12) and (3.13), and also relationship (3.9), we find the interval $\left(m_1^0, \nu^{-1}\rho\right)$ of variation of the variable m.

Now, we substitute formulas (3.12) and (3.13) into the first equation of system (3.6). After performing necessary transformations in the resulting expression, we find the equation:

$$u\gamma_2(\nu m - \rho)g_1(m) - \lambda\beta m g_2(m) = 0, \quad m \in \left(m_1^0, \nu^{-1}\rho\right). \tag{3.14}$$

Thus, the problem of finding equilibria $(l_\star, k_\star, m_\star)$ for system (3.1), coordinates of which satisfy restrictions (3.7), is reduced to the problem of determining roots $m_\star$ of equation (3.14) on the interval $\left(m_1^0, \nu^{-1}\rho\right)$.

Next, let us rewrite equation (3.14) in a more convenient equivalent form:

$$F(m) = \frac{u\gamma_2(\nu m - \rho)}{\lambda\beta m} = \frac{g_2(m)}{g_1(m)} = G(m), \tag{3.15}$$

and study the existence of its roots on the interval $\left(m_1^0, \nu^{-1}\rho\right)$.

First, we consider the function $F(m)$, which we rewrite in a more convenient form:

$$F(m) = u\gamma_2\left(\frac{\nu}{\lambda\beta} - \frac{\rho}{\lambda\beta m}\right).$$

This function has the following properties:

$$\begin{gathered} F\left(m_1^0\right) < 0, \quad F\left(\nu^{-1}\rho\right) = 0, \\ \dot{F}(m) = \frac{u\gamma_2\rho}{\lambda\beta m^2} > 0, \quad \ddot{F}(m) = -\frac{2u\gamma_2\rho}{\lambda\beta m^3} < 0. \end{gathered} \tag{3.16}$$

From the analysis of relationships (3.16) we conclude that the function $F(m)$ is concave and increases from a certain negative value to zero. Hence, it is negative everywhere on the interval $\left[m_1^0, \nu^{-1}\rho\right)$.

Now, we consider the function $G(m)$. It has the following properties:

$$G\left(m_1^0\right) = +\infty, \quad G\left(m_2^0\right) = 0, \quad G\left(\nu^{-1}\rho\right) = -1, \tag{3.17}$$

$$\dot{G}(m) = -\frac{(\alpha+\delta)\left(\nu(\sigma\beta+\nu\mu)m^2 - 2\nu\mu\rho m + \mu\rho^2\right)}{(g_1(m))^2}. \tag{3.18}$$

The vertex of the parabola, which is determined by the quadratic function in the numerator of the fraction in formula (3.18), is given by the relationship:

$$m_G = \frac{\mu\rho}{\sigma\beta + \nu\mu} \in \left(0, \nu^{-1}\rho\right).$$

Direct calculations show that the value of this quadratic function for $m = m_G$ is positive. Consequently, it takes positive values everywhere on the interval $\left(0, \nu^{-1}\rho\right)$, and hence on the interval $\left(m_1^0, \nu^{-1}\rho\right)$. Using (2.8) in formula (3.18), we find that $\dot{G}(m) < 0$ for all $m \in \left(m_1^0, \nu^{-1}\rho\right)$. From the analysis of relationships (3.17) we conclude that the function $G(m)$ decreases from a positive infinity to a certain negative value and vanishes for $m = m_2^0$.

The established properties of the functions $F(m)$ and $G(m)$ lead us to the conclusion that equation (3.15), and hence the equation (3.14), has a single root

$m_\star \in \left(m_2^0, \nu^{-1}\rho\right)$. In turn, this fact means that system (3.1) has a single equilibrium $(l_\star, k_\star, m_\star)$ for control $u \in [u_{\min}, 1]$, the coordinates of which satisfy the restrictions (3.7). Moreover, based on formulas (3.12) and (3.13), for these coordinates we have the following relationships:

$$l_\star = \frac{\rho - \nu m_\star}{\beta m_\star}\,, \quad k_\star = -\frac{\gamma_2}{\gamma_1} \cdot \frac{g_1(m_\star)}{\lambda \beta m_\star}\,, \quad m_\star \in \left(m_2^0, \nu^{-1}\rho\right). \tag{3.19}$$

Thus, we have established the validity of the following lemma.

Lemma 3.3. *For each value of control $u \in [u_{\min}, 1]$ the uncontrolled system* (3.1) *has a unique equilibrium $(l_\star, k_\star, m_\star)$, the coordinates of which are positive and satisfy the relationships* (3.19).

Now, let us consider the equations of system (3.6) to which the coordinates of the equilibrium $(l_\star, k_\star, m_\star)$ satisfy. We multiply the first equation by γ_2, the second equation by γ_1, the third equation by $\gamma_1\left(1 + \delta\beta^{-1}\right)$. Then, we add them. As a result, we obtain the expression:

$$0 = D_0 - \delta\gamma_2 l_\star m_\star - \left(\mu\gamma_2 l_\star + \lambda\gamma_1 k_\star + \nu\gamma_1\left(1 + \delta\beta^{-1}\right) m_\star\right),$$

from which, by inequalities (3.7), we find a chain of inequalities:

$$D_0 > D_0 - \delta\gamma_2 l_\star m_\star \geq \kappa\left(\gamma_2 l_\star + \gamma_1 k_\star + \gamma_1\left(1 + \delta\beta^{-1}\right) m_\star\right). \tag{3.20}$$

As a consequence of inequalities (3.7) and (3.20), we have the validity of the following lemma.

Lemma 3.4. *For the equilibrium $(l_\star, k_\star, m_\star)$ the inclusion $(l_\star, k_\star, m_\star) \in \Lambda$ is true.*

4. Permanence of the uncontrolled system

Let us show the permanence of system (3.1) for $\alpha > 0$. For such value of α we introduce a set:

$$\Pi = \Big\{(l, m, k) : 0 \leq l \leq \mu^{-1}\sigma,\ k \geq 0,\ (\nu\mu + \sigma\rho)^{-1}\mu\rho \leq m \leq \nu^{-1}\rho,$$
$$\kappa_{\max}^{-1} D_* \leq \gamma_2 l + \gamma_1 k + \beta^{-1}\alpha\gamma_2 m \leq \kappa_{\min}^{-1} D_*\Big\}.$$

It is easy to see that for considered value of α the inclusion $\Pi \subseteq \bar{\Lambda}$ holds. Here $\bar{\Lambda}$ is the closure of the set Λ. This inclusion means that the set Π is less than $\bar{\Lambda}$.

First, we establish that Π is an invariant set for system (3.1). Let us consider again arbitrary solutions $l(t)$, $k(t)$, $m(t)$ for this system, defined on the interval $[0, +\infty)$, initial conditions (3.2) of which satisfy the inclusion $(l_0, k_0, m_0) \in \Pi$. The non-negative invariance of system (3.1) follows from Corollary 3.2. Therefore, the restrictions $l(t) \geq 0$ and $k(t) \geq 0$ are valid.

Next, let us consider the third equation of system (3.1). It implies the inequality:

$$\dot{m}(t) \leq \rho - \nu m(t).$$

Integrating it on the interval $[0, t]$ with the corresponding initial condition $m(0) = m_0$, we find the inequality:

$$m(t) \leq m_0 \mathrm{e}^{-\nu t} + \nu^{-1}\rho\left(1 - \mathrm{e}^{-\nu t}\right),$$

which yields the required restriction $m(t) \leq \nu^{-1}\rho$.

Then, we consider the first equation of this system. It also implies inequality:

$$\dot{l}(t) \leq \sigma - \mu l(t).$$

Integrating it on the interval $[0, t]$ with the corresponding initial condition $l(0) = l_0$, we obtain the inequality:

$$l(t) \leq l_0 \mathrm{e}^{-\mu t} + \mu^{-1}\sigma \left(1 - \mathrm{e}^{-\mu t}\right),$$

from which the desired restriction $l(t) \leq \mu^{-1}\sigma$ follows.

Now, we return to the study of the third equation. Using the restrictions found on the previous two stages, we have the inequality:

$$\dot{m}(t) \geq \rho - \mu^{-1}(\sigma\beta + \nu\mu)m(t).$$

Again integrating it on the interval $[0, t]$ with the corresponding initial condition $m(0) = m_0$, we find the inequality:

$$m(t) \geq m_0 \mathrm{e}^{-\mu^{-1}(\sigma\beta+\nu\mu)t} + (\sigma\beta + \nu\mu)^{-1}\mu\rho \left(1 - \mathrm{e}^{-\mu^{-1}(\sigma\beta+\nu\mu)t}\right),$$

which yields the required restriction $m(t) \geq (\sigma\beta + \nu\mu)^{-1}\mu\rho$.

Finally, let us establish the last restriction in the definition of the set Π. To do this, we introduce a function:

$$W(l, k, m) = \gamma_2 l + \gamma_1 k + \beta^{-1}\alpha\gamma_2 m,$$

and, as in Lemma 2.1, calculate for the solutions $l(t)$, $k(t)$, $m(t)$ its derivative by virtue of the system (3.1). We have the expression:

$$\frac{dW}{dt}(l(t), k(t), m(t)) = D_* - \left(\mu\gamma_2 l(t) + \lambda\gamma_1 k(t) + \nu\beta^{-1}\alpha\gamma_2 m(t)\right).$$

Using the defined above constants $\kappa_{\min}$ and $\kappa_{\max}$, we rewrite the last equality as follows:

$$\begin{aligned} D_* - \kappa_{\max} W(l(t), k(t), m(t)) \leq \frac{dW}{dt}&(l(t), k(t), m(t)) \\ &\leq D_* - \kappa_{\max} W(l(t), k(t), m(t)). \end{aligned}$$

Integrating this expression on the interval $[0, t]$ with the corresponding initial condition $W(l(0), k(0), m(0)) = W(l_0, k_0, m_0)$, we obtain the inequalities:

$$\begin{aligned} W(l(t), k(t), m(t)) &\leq W(l_0, k_0, m_0)\mathrm{e}^{-\kappa_{\min} t} + \kappa_{\min}^{-1} D_* \left(1 - \mathrm{e}^{-\kappa_{\min} t}\right), \\ W(l(t), k(t), m(t)) &\geq W(l_0, k_0, m_0)\mathrm{e}^{-\kappa_{\max} t} + \kappa_{\max}^{-1} D_* \left(1 - \mathrm{e}^{-\kappa_{\max} t}\right), \end{aligned}$$

which, by the definition of the function $W(l, k, m)$, imply the desired restriction:

$$\kappa_{\max}^{-1} D_* \leq \gamma_2 l(t) + \gamma_1 k(t) + \beta^{-1}\alpha\gamma_2 m(t) \leq \kappa_{\min}^{-1} D_*.$$

Thus, the invariance of the set Π is established.

Following [34], system (3.1) is permanent if all its solutions $l(t)$, $k(t)$, $m(t)$ with nonnegative initial conditions (3.2) finally come into the set Π and stay in it. The second property is actually justified, because we have just shown the invariance of this set. The first property is provided by the definition of the set Π and the following relationships:

$$
\begin{aligned}
&\dot{m}(t)\Big|_{m=(\sigma\beta+\nu\mu)^{-1}\mu\rho} \geq 0, \quad \dot{m}(t)\Big|_{m=\nu^{-1}\rho} \leq 0,\\
&\dot{l}(t)\Big|_{l=0} > 0, \quad \dot{l}(t)\Big|_{l=\mu^{-1}\sigma} \leq 0, \quad \dot{k}(t)\Big|_{k=0} \geq 0,\\
&\gamma_2\dot{l}(t) + \gamma_1\dot{k}(t) + \beta^{-1}\alpha\gamma_2\dot{m}(t)\Big|_{\gamma_2 l+\gamma_1 k+\beta^{-1}\alpha\gamma_2 m=\kappa_{\max}^{-1}D_*} \geq 0,\\
&\gamma_2\dot{l}(t) + \gamma_1\dot{k}(t) + \beta^{-1}\alpha\gamma_2\dot{m}(t)\Big|_{\gamma_2 l+\gamma_1 k+\beta^{-1}\alpha\gamma_2 m=\kappa_{\min}^{-1}D_*} \leq 0.
\end{aligned}
\tag{4.1}
$$

Moreover, inequalities like (4.1) will also hold for points outside the set Π. They show the motion of the phase point $(l(t), k(t), m(t))$ to this set.

Thus, for $\alpha > 0$ the permanence of system (3.1) is established. We note that similar results for other systems, also related to psoriasis, are presented in [5, 6].

Finally, the analysis of the equations for system (3.6), to which the coordinates of the equilibrium $(l_\star, k_\star, m_\star)$ satisfy, gives the important property of the set Π similar to that stated in Lemma 3.4. Namely, it contains the equilibrium $(l_\star, k_\star, m_\star)$.

5. Stability analysis of the equilibrium

Let us study the local stability of the found above equilibrium $(l_\star, k_\star, m_\star)$. For this, we linearize system (3.1) in a neighborhood of the point $(l_\star, k_\star, m_\star)$. As a result, we obtain the corresponding linear system, the matrix of which has the form:

$$
\begin{pmatrix}
-(\delta m_\star + u\gamma_1 k_\star + \mu) & -u\gamma_1 l_\star & -\delta l_\star\\
((\beta+\delta)m_\star + u\gamma_2 k_\star) & (u\gamma_2 l_\star - \lambda) & (\beta+\delta)l_\star\\
-\beta m_\star & 0 & -(\beta l_\star + \nu)
\end{pmatrix}.
\tag{5.1}
$$

We simplify some elements of this matrix. For this, we use the equations for system (3.6) to which the coordinates of the equilibrium $(l_\star, k_\star, m_\star)$ satisfy. The following equalities are true:

$$
\begin{aligned}
&\delta m_\star + u\gamma_1 k_\star + \mu = \frac{\sigma}{l_\star}, \quad (\beta+\delta)m_\star + u\gamma_2 k_\star = \frac{\lambda k_\star}{l_\star},\\
&u\gamma_2 l_\star - \lambda = -(\beta+\delta)\frac{l_\star m_\star}{k_\star}, \quad \beta l_\star + \nu = \frac{\rho}{m_\star}.
\end{aligned}
$$

Substituting them into the corresponding elements of matrix (5.1), we obtain the following matrix of the considered linear system:

$$
\begin{pmatrix}
-\frac{\sigma}{l_\star} & -u\gamma_1 l_\star & -\delta l_\star\\
\frac{\lambda k_\star}{l_\star} & -(\beta+\delta)\frac{l_\star m_\star}{k_\star} & (\beta+\delta)l_\star\\
-\beta m_\star & 0 & -\frac{\rho}{m_\star}
\end{pmatrix}.
$$

Using this matrix, we write the appropriate characteristic equation:

$$
\theta^3 + A_1\theta^2 + A_2\theta + A_3 = 0,
\tag{5.2}
$$

where the coefficients A_1, A_2, A_3 are defined by the following formulas:

$$A_1 = \left(\frac{\sigma}{l_\star} + \frac{\rho}{m_\star}\right) + (\beta+\delta)\frac{l_\star m_\star}{k_\star} > 0,$$

$$A_2 = \left(\frac{\sigma\rho}{l_\star m_\star} - \delta\beta l_\star m_\star\right) + (\beta+\delta)\frac{l_\star m_\star}{k_\star}\left(\frac{\sigma}{l_\star} + \frac{\rho}{m_\star}\right) + u\lambda\gamma_1 k_\star,$$

$$A_3 = (\beta+\delta)\frac{l_\star m_\star}{k_\star}\left(\frac{\sigma\rho}{l_\star m_\star} - \delta\beta l_\star m_\star\right) + u\lambda\gamma_1 k_\star\left(\frac{\rho}{m_\star} - \frac{\beta(\beta+\delta)(l_\star)^2 m_\star}{\lambda k_\star}\right).$$

According to the Lyapunov Theorem ([35]), the equilibrium $(l_\star, k_\star, m_\star)$ is locally asymptotically stable if all the roots of the characteristic equation (5.2) have negative real parts. In turn, by the Routh-Hurwitz stability criterion ([8]), this fact takes place if the coefficients A_1, A_2, A_3 of a cubic polynomial in (5.2) satisfy the inequalities:

$$A_3 > 0, \quad A_1A_2 - A_3 > 0. \tag{5.3}$$

Let us find a relationship under which these inequalities are satisfied. To do this, using the formulas of the coefficients A_1, A_2 and A_3, we write the expression $(A_1A_2 - A_3)$:

$$A_1A_2 - A_3 = \left(\frac{\sigma}{l_\star} + \frac{\rho}{m_\star}\right)\left[\left((\beta+\delta)\frac{l_\star m_\star}{k_\star}\right)^2 + \left(\frac{\sigma}{l_\star} + \frac{\rho}{m_\star}\right)\left((\beta+\delta)\frac{l_\star m_\star}{k_\star}\right)\right.$$
$$\left. + \left(\frac{\sigma\rho}{l_\star m_\star} - \delta\beta l_\star m_\star\right)\right] + u\lambda\gamma_1 k_\star\left(\frac{\sigma}{l_\star} + \frac{(\beta+\delta)l_\star m_\star}{\lambda k_\star}\cdot(\beta l_\star + \lambda)\right).$$

Analyzing the formulas of A_3 and $(A_1A_2 - A_3)$, we see that to achieve the desired result, the validity of the following inequality is sufficient:

$$\frac{\sigma\rho}{l_\star m_\star} - \delta\beta l_\star m_\star \geq 0. \tag{5.4}$$

Indeed, by this inequality and inequalities (3.7), the expression $(A_1A_2 - A_3)$ is positive. Thus, the second inequality in (5.3) is satisfied. Moreover, the first term in the formula of A_3 is nonnegative. Now, we study the second term. Since the factor in it is positive, it is sufficient to study only the expression in parentheses:

$$\frac{\rho}{m_\star} - \frac{\beta(\beta+\delta)(l_\star)^2 m_\star}{\lambda k_\star},$$

or, by the corresponding inequalities in (3.7), the expression:

$$\lambda\rho k_\star - \beta(\beta+\delta)(l_\star m_\star)^2.$$

Substituting here the formulas of $l_\star$ and $k_\star$ from (3.19), we find the expression:

$$-\frac{(\beta+\delta)m_\star(\nu m_\star - \rho)^2 + \rho\gamma_1^{-1}\gamma_2 g_1(m_\star)}{\beta m_\star}, \tag{5.5}$$

which further we will study.

Let us consider the following function:

$$H(m) = (\beta+\delta)m(\nu m - \rho)^2 + \rho\gamma_1^{-1}\gamma_2 g_1(m).$$

We study its behavior on the interval $\left[m_1^0, \nu^{-1}\rho\right]$.

Using the first equality in (3.8), we find the relationship:

$$H\left(m_1^0\right) = (\beta+\delta)m_1^0\left(\nu m_1^0-\rho\right)^2 > 0. \tag{5.6}$$

Applying formula (3.9), we obtain the relationship:

$$H\left(\nu^{-1}\rho\right) = \rho\gamma_1^{-1}\gamma_2 g_1\left(\nu^{-1}\rho\right) < 0. \tag{5.7}$$

Finally, we estimate the sign of the value $H\left(m_2^0\right)$, where

$$H\left(m_2^0\right) = (\beta+\delta)m_2^0\left(\nu m_2^0-\rho\right)^2 + \rho\gamma_1^{-1}\gamma_2 g_1\left(m_2^0\right). \tag{5.8}$$

Adding the formulas of the functions $g_1(m)$ and $g_2(m)$, we have the equality:

$$g_1(m)+g_2(m) = (\alpha+\delta)m(\nu m-\rho),$$

from which, by the second equality in (3.8), we obtain the value:

$$g_1\left(m_2^0\right) = (\alpha+\delta)m_2^0\left(\nu m_2^0-\rho\right). \tag{5.9}$$

We substitute (5.9) into formula (5.8). After converting the resulting expression with using (2.8), we find the relationship:

$$H\left(m_2^0\right) = \nu(\beta+\delta)\left(m_2^0\right)^2\left(\nu m_2^0-\rho\right) < 0. \tag{5.10}$$

Since $H(m)$ is a cubic polynomial satisfying the limit relationships:

$$\lim_{m\to-\infty} H(m) = -\infty, \quad \lim_{m\to+\infty} H(m) = +\infty,$$

then inequality (3.11) and relationships (5.6), (5.7) and (5.10) imply the following inequality:

$$H(m) < 0, \quad m \in \left[m_2^0, \nu^{-1}\rho\right].$$

In turn, this inequality means the positivity of expression (5.5), and therefore the positivity of the value A_3. Thus, inequalities (5.3) are satisfied. Hence, the equilibrium $(l_\star, k_\star, m_\star)$ is locally asymptotically stable if inequality (5.4) holds.

Let us find the relationship between parameters of system (3.1), under which inequality (5.4) is true. For this, we substitute the first formula from (3.19) into (5.4). We obtain the inequality:

$$(\rho-\nu m_\star)^2 \le \frac{\sigma\rho\beta}{\delta}. \tag{5.11}$$

By the third relationship in (3.19), inequality (5.11) will be satisfied if the following inequality holds:

$$\frac{\beta}{\delta} \ge \frac{\rho}{\sigma}. \tag{5.12}$$

Thus, if inequality (5.12) is satisfied, the equilibrium $(l_\star, k_\star, m_\star)$ is asymptotically stable. This fact is demonstrated in Figure 1 by means of the image of the velocity field of system (3.1) with the following values of its parameters:

$$\begin{array}{lllll} \sigma=15.0 & \rho=3.6 & \beta=0.4 & \delta=0.005 & u=0.5 \\ \mu=0.01 & \lambda=0.9 & \nu=0.02 & \gamma_1=0.8 & \gamma_2=0.05 \end{array}$$

Also, we note that Figure 1 simultaneously shows the permanence of system (3.1), because the inequality $\alpha > 0$ is valid for the considered values of its parameters.

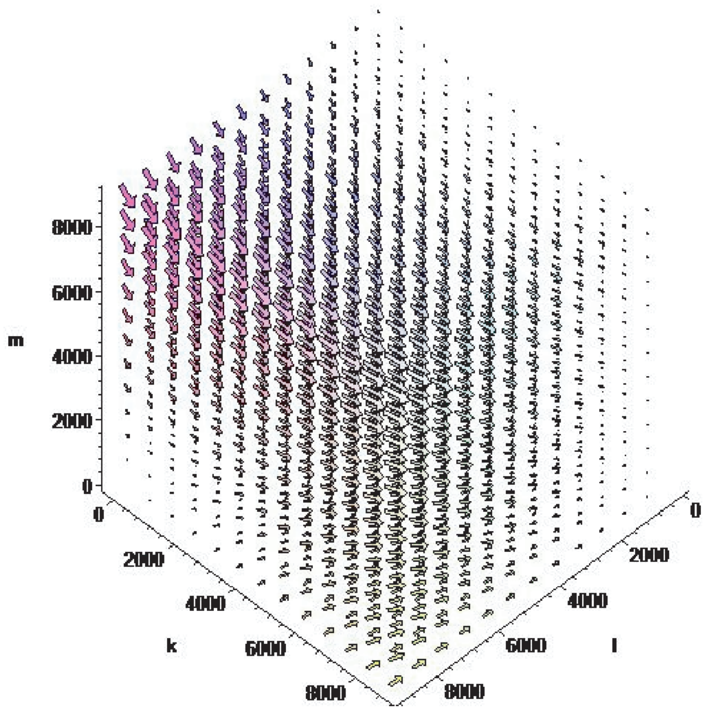

Figure 1. Velocity field of the uncontrolled system (3.1).

6. Optimal control problem

For system (2.1) on the set of admissible controls $\Omega(T)$ we consider the problem of minimization of the concentration of keratinocytes at the terminal time T:

$$J(u) = k(T) \to \min_{u(\cdot)\in\Omega(T)} . \tag{6.1}$$

We note that the optimal control problem (2.1), (6.1) differs from problems that are typically considered in the literature on the control of psoriasis models ([2, 5, 25]) in that the functional of (6.1) does not include an integral of the square of the control $u(t)$, which is responsible for the total cost of the drug dosage. In psoriasis therapy, in most cases, either a skin cream or an oral medication are used. Both prescribed medications have regular daily dosage and are not as harmful for patients as the drugs used in chemotherapy for cancer treatment ([31]). Therefore, the total cost of psoriasis treatment in the meaning of "harm" to a patient and that usually mathematically is described by an integral of the square of the control, can be ignored. Moreover, using the terminal functional in (6.1) instead of the corresponding integral functional (see [2, 25]), simplifies the subsequent analytical arguments.

The existence in problem (2.1), (6.1) of the optimal control $u_*(t)$ and the corresponding optimal solutions $l_*(t)$, $k_*(t)$, $m_*(t)$ follows from Lemma 2.1 and Theorem 4 ([15],Chapter 4).

Using results from [2, 23, 25, 26], we assume that in subsequent arguments the following condition is true.

Condition 6.1. *Let the inequalities be valid:*

$$\gamma_1 \neq \gamma_2, \quad \lambda > \mu, \quad \lambda > \nu. \tag{6.2}$$

7. Pontryagin maximum principle

For the analysis of the optimal control $u_*(t)$ and corresponding to it optimal solutions $l_*(t)$, $k_*(t)$, $m_*(t)$ we will apply the Pontryagin maximum principle ([22]). First, we define the Hamiltonian:

$$\begin{aligned}\widetilde{H}(l,k,m,u,\psi_1,\psi_2,\psi_3) &= (\sigma - \delta lm - \gamma_1 ulk - \mu l)\psi_1 \\ &\quad + ((\beta+\delta)lm + \gamma_2 ulk - \lambda k)\,\psi_2 + (\rho - \beta lm - \nu m)\psi_3,\end{aligned}$$

where ψ_1, ψ_2, ψ_3 are the adjoint variables. Second, we evaluate all required partial derivatives:

$$\begin{aligned}\widetilde{H}'_l(l,k,m,u,\psi_1,\psi_2,\psi_3) &= uk(\gamma_2\psi_2 - \gamma_1\psi_1) \\ &\quad - m(\delta\psi_1 - (\beta+\delta)\psi_2 + \beta\psi_3) - \mu\psi_1,\\ \widetilde{H}'_k(l,k,m,u,\psi_1,\psi_2,\psi_3) &= ul(\gamma_2\psi_2 - \gamma_1\psi_1) - \lambda\psi_2,\\ \widetilde{H}'_m(l,k,m,u,\psi_1,\psi_2,\psi_3) &= -l(\delta\psi_1 - (\beta+\delta)\psi_2 + \beta\psi_3) - \nu\psi_3,\\ \widetilde{H}'_u(l,k,m,u,\psi_1,\psi_2,\psi_3) &= lk(\gamma_2\psi_2 - \gamma_1\psi_1).\end{aligned}$$

Next, by the Pontryagin maximum principle, for optimal control $u_*(t)$ and optimal solutions $l_*(t)$, $k_*(t)$, $m_*(t)$ there exists the vector-function $\psi_*(t) = (\psi_1^*(t), \psi_2^*(t), \psi_3^*(t))$, such that:

- $\psi_*(t)$ is the nontrivial solution of the adjoint system:

$$\begin{cases} \dot{\psi}_1^*(t) = -u_*(t)k_*(t)(\gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t)) \\ \qquad\qquad +m_*(t)(\delta\psi_1^*(t) - (\beta+\delta)\psi_2^*(t) + \beta\psi_3^*(t)) + \mu\psi_1^*(t), \\ \dot{\psi}_2^*(t) = -u_*(t)l_*(t)(\gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t)) + \lambda\psi_2^*(t), \\ \dot{\psi}_3^*(t) = l_*(t)(\delta\psi_1^*(t) - (\beta+\delta)\psi_2^*(t) + \beta\psi_3^*(t)) + \nu\psi_3^*(t), \\ \psi_1^*(T) = 0,\ \psi_2^*(T) = -1,\ \psi_3^*(T) = 0. \end{cases} \tag{7.1}$$

- the control $u_*(t)$ maximizes the Hamiltonian

$$\widetilde{H}(l_*(t), k_*(t), m_*(t), u, \psi_1^*(t), \psi_2^*(t), \psi_3^*(t))$$

with respect to $u \in [u_{\min}, 1]$ for almost all $t \in [0,T]$, and therefore the following relationship holds:

$$u_*(t) = \begin{cases} 1 & ,\ \text{if} \quad L(t) > 0, \\ \forall u \in [u_{\min}, 1] & ,\ \text{if} \quad L(t) = 0, \\ u_{\min} & ,\ \text{if} \quad L(t) < 0, \end{cases} \tag{7.2}$$

where, by Lemma 2.1, the function $L(t) = \gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t)$ is the switching function, which defines the type of the optimal control $u_*(t)$ according to formula (7.2).

- the Hamiltonian

$$\widetilde{H}(l_*(t), k_*(t), m_*(t), u_*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t)) \tag{7.3}$$

is constant on the entire interval $[0, T]$.

Let us introduce the following functions:

$$
\begin{aligned}
a(t) &= (\alpha + \delta)m_*(t) + u_*(t)\left(\gamma_1 k_*(t) - \gamma_2 l_*(t)\right) + \lambda, \\
b(t) &= (\alpha + \delta)\gamma_1^{-1} m_*(t)\left(\alpha m_*(t) - \beta l_*(t) + (\lambda - \mu)\right) \\
&\quad + u_*(t)k_*(t)\left(\alpha m_*(t) + (\lambda - \mu)\right), \\
c(t) &= (m_*(t))^{-1}\left(\alpha(m_*(t))^2 + (\lambda - \mu)m_*(t) - \rho\right), \\
d(t) &= (m_*(t))^{-1}\left(\alpha(\lambda - \nu)(m_*(t))^2 + \lambda(\lambda - \mu)m_*(t) - \rho(\lambda - \mu)\right), \\
e(t) &= (\alpha + \delta)\gamma_1^{-1} m_*(t) + u_*(t)k_*(t).
\end{aligned} \tag{7.4}
$$

Also, we define the auxiliary function:

$$
P(t) = -m_*(t)(\beta\psi_3^*(t) - \alpha\psi_1^*(t)) + (\lambda - \mu)\psi_1^*(t).
$$

Then, using the equations and initial conditions of systems (2.1) and (7.1), we obtain the system of differential equations for the switching function $L(t)$ and the functions $P(t)$ and $\psi_1^*(t)$:

$$
\begin{cases}
\dot{L}(t) = a(t)L(t) + \gamma_1 P(t), \quad t \in [0, T], \\
\dot{P}(t) = -b(t)L(t) - c(t)P(t) + d(t)\psi_1^*(t), \\
\dot{\psi}_1^*(t) = -e(t)L(t) - P(t) + \lambda\psi_1^*(t), \\
L(T) = -\gamma_2, \ P(T) = 0, \ \psi_1^*(T) = 0.
\end{cases} \tag{7.5}
$$

By the first initial condition of system (7.5) and the continuity of the switching function $L(t)$, the following lemma can be stated.

Lemma 7.1. *There exists such a value $t_0 \in [0, T)$ that for all $t \in (t_0, T]$ the switching function $L(t)$ is negative.*

Corollary 7.2. *From Lemma 7.1 and formula (7.2) it follows that*

$$
u_*(t) = u_{\min}, \quad t \in (t_0, T].
$$

Now, let us rewrite the constancy of the Hamiltonian on the optimal solution (7.3) in terms of the functions $L(t)$, $P(t)$ and $\psi_1^*(t)$ as follows:

$$
\begin{aligned}
&\dot{k}_*(t)L(t) - \frac{\gamma_2 \dot{m}_*(t)}{\beta m_*(t)}P(t) \\
&\quad + \left(\gamma_2 \dot{l}_*(t) + \gamma_1 \dot{k}_*(t) + \frac{\gamma_2 \dot{m}_*(t)}{\beta m_*(t)}(\alpha m_*(t) + (\lambda - \mu))\right)\psi_1^*(t) \\
&\quad = -\gamma_2 \dot{k}_*(T), \quad t \in [0, T).
\end{aligned} \tag{7.6}
$$

Finally, formula (7.2) shows us the possible types of the optimal control $u_*(t)$. It can have a bang-bang type, and switches only between the values $u_{\min}$ and 1. Such type occurs, when at all points where the switching function $L(t)$ vanishes, its derivative $\dot{L}(t)$ is not zero. Or, in addition to the portions of a bang-bang type the control $u_*(t)$ can also contain a singular arc (see [30, 38]). This arises, when the switching function $L(t)$ vanishes identically over some open subinterval of the interval $[0, T]$. The next section relates to finding the relationships between the parameters of system (2.1) under which the optimal control $u_*(t)$ is of one type or another.

8. Investigation of a singular arc

Let us study the existence of a singular arc at the optimal control $u_*(t)$. According to [30, 38], this means that can the switching function $L(t)$ become zero identically on some interval $\Delta \subset [0, T]$? We will examine this question in detail.

Let us assume that it is possible. Then, the following equality holds:

$$L(t) = 0, \quad t \in \Delta. \tag{8.1}$$

We use the first equation of the system (7.5) for finding on the interval Δ the first derivative of the function $L(t)$, and then set it equal to zero:

$$\frac{dL}{dt}(t)\Big|_{L(t)=0} = 0.$$

This relationship implies the equality:

$$P(t) = 0, \quad t \in \Delta. \tag{8.2}$$

Now, using the second equation of this system, we find the second derivative of the function $L(t)$, and again equate it to zero:

$$\frac{d^2L}{dt^2}(t)\Big|_{L(t)=0,\ L^{(1)}(t)=0} = 0.$$

This expression implies the equality:

$$d(t)\psi_1^*(t) = 0, \quad t \in \Delta. \tag{8.3}$$

Equality to zero of the function $\psi_1^*(t)$ on the interval Δ together with equalities (8.1) and (8.2) lead to the conclusion that the vector-function $\psi_*(t) = (\psi_1^*(t), \psi_2^*(t), \psi_3^*(t))$ is trivial on this interval, and hence also on the entire interval $[0, T]$. This fact is contradictory. Hence, the function $\psi_1^*(t)$ does not vanish at any point of the interval Δ, and therefore we have the equality:

$$d(t) = 0, \quad t \in \Delta. \tag{8.4}$$

By the formula of the function $d(t)$ from (7.4), we see that the analysis of equality (8.4) is related to the behavior of the quadratic function:

$$f(m) = \alpha(\lambda - \nu)m^2 + \lambda(\lambda - \mu)m - \rho(\lambda - \mu).$$

Its discriminant has the form:

$$D_f = \lambda^2(\lambda - \mu)^2 + 4\alpha\rho(\lambda - \nu)(\lambda - \mu).$$

Using inequalities (6.2), we see that depending on the values of α and D_f, the following cases are possible.

Case (a) If $\alpha < 0$ and $D_f < 0$, then the function $f(m)$ takes negative values for all $m > 0$, and equality (8.4) is impossible. Hence, the switching function $L(t)$ cannot be zero on any subinterval of the interval $[0, T]$. Therefore, the optimal control $u_*(t)$ does not have a singular arc. By formula (7.2), we see that it is bang-bang control taking the values $\{u_{\min}; 1\}$ on the interval $[0, T]$. Next, we can estimate the number of zeros of the function $L(t)$ and consequently find the estimate of the number of switchings of the control $u_*(t)$. In more detail these questions are considered in [11].

Case (b) If $\alpha > 0$, then $D_f > 0$. Equation (8.4) has only one positive root $m^0_{\rm sing}$:

$$m^0_{\rm sing} = \frac{-\lambda(\lambda-\mu) + \sqrt{\lambda^2(\lambda-\mu)^2 + 4\alpha\rho(\lambda-\nu)(\lambda-\mu)}}{2\alpha(\lambda-\nu)}.$$

Case (c) If $\alpha < 0$ and $D_f > 0$, then equation (8.4) has two positive roots $m^1_{\rm sing}$, $m^2_{\rm sing}$ and $m^1_{\rm sing} < m^2_{\rm sing}$:

$$m^1_{\rm sing} = \frac{-\lambda(\lambda-\mu) + \sqrt{\lambda^2(\lambda-\mu)^2 + 4\alpha\rho(\lambda-\nu)(\lambda-\mu)}}{2\alpha(\lambda-\nu)},$$
$$m^2_{\rm sing} = \frac{-\lambda(\lambda-\mu) - \sqrt{\lambda^2(\lambda-\mu)^2 + 4\alpha\rho(\lambda-\nu)(\lambda-\mu)}}{2\alpha(\lambda-\nu)}.$$

For simplification of consequent arguments let the following condition be valid.

Condition 8.1. *We exclude from consideration the case when $\alpha < 0$ the equality $D_f = 0$ holds.*

Next, as we see, the second derivative of the switching function $L(t)$ leads to expression (8.3), which does not contain the control $u_*(t)$. This means that in Cases (b) and (c) the order q of the singular arc is greater than one (see [30, 38]).

Further, in Cases (b) and (c), we take on the interval Δ the third derivative of the switching function $L(t)$, and then equate it to zero:

$$\frac{d^3L}{dt^3}(t)\Big|_{L(t)=0,\ L^{(1)}(t)=0,\ L^{(2)}(t)=0} = 0.$$

This formula implies the differentiation of equality (8.3) on the interval Δ. The use of equality (8.4) in the resulting expression leads to the relationship:

$$(2\alpha(\lambda-\nu)m_{\rm sing} + \lambda(\lambda-\mu))\dot{m}_*(t)\psi^*_1(t) = 0, \quad t \in \Delta. \tag{8.5}$$

This expression implies that everywhere on the interval Δ the following equality holds:

$$\dot{m}_*(t) = 0, \tag{8.6}$$

which, first, allows us to find the value $l_{\rm sing}$ for variable l on the singular arc:

$$l_{\rm sing} = \frac{\rho - \nu m_{\rm sing}}{\beta m_{\rm sing}} = Const. \tag{8.7}$$

Here, $m_{\rm sing}$ is the value of variable m on the singular arc as well. For Case (b) such value is the value $m^0_{\rm sing}$, for Case (c) one of the values $m^1_{\rm sing}$, $m^2_{\rm sing}$. Secondly, the positivity of the value $l_{\rm sing}$ leads to the restriction on the value $m_{\rm sing}$:

$$m_{\rm sing} \in \left(0, \nu^{-1}\rho\right). \tag{8.8}$$

Finally, we evaluate on the interval Δ the fourth derivative of the switching function $L(t)$, and then equate it to zero:

$$\frac{d^4L}{dt^4}(t)\Big|_{L(t)=0,\ L^{(1)}(t)=0,\ L^{(2)}(t)=0,\ L^{(3)}(t)=0} = 0.$$

This formula implies the differentiation of equality (8.5) on the interval Δ. By equality (8.6) in the resulting expression, we obtain the relationship:

$$-\beta m_{\text{sing}}(2\alpha(\lambda-\nu)m_{\text{sing}}+\lambda(\lambda-\mu))\dot{l}_*(t)\psi_1^*(t)=0, \quad t\in\Delta, \tag{8.9}$$

or in a more detailed form:

$$\begin{aligned}&-\beta m_{\text{sing}}(2\alpha(\lambda-\nu)m_{\text{sing}}+\lambda(\lambda-\mu))\\&\times(\sigma-\delta l_{\text{sing}}m_{\text{sing}}-\gamma_1 u_{\text{sing}}(t)l_{\text{sing}}k_{\text{sing}}(t)-\mu l_{\text{sing}})\,\psi_1^*(t)=0,\end{aligned}$$

where $u_{\text{sing}}(t)$ is control and $k_{\text{sing}}(t)$ is the value of variable k on the singular arc.

From the analysis of this formula we can make the following conclusions. First, the order q of the singular arc equals two. Secondly, the necessary condition of the optimality of the singular arc (Kelly-Cope-Moyer condition ([38])) has the type:

$$(2\alpha(\lambda-\nu)m_{\text{sing}}+\lambda(\lambda-\mu))\,\psi_1^*(t)\le 0, \quad t\in\Delta.$$

As we have already noted, on the interval Δ the function $\psi_1^*(t)$ is sign-definite, that is, it takes either only positive or only negative values. Hence, the Kelly-Cope-Moyer condition is either valid in a strengthened form:

$$(2\alpha(\lambda-\nu)m_{\text{sing}}+\lambda(\lambda-\mu))\,\psi_1^*(t)<0, \quad t\in\Delta, \tag{8.10}$$

or it is not valid at all, i.e.:

$$(2\alpha(\lambda-\nu)m_{\text{sing}}+\lambda(\lambda-\mu))\,\psi_1^*(t)>0, \quad t\in\Delta. \tag{8.11}$$

Third, expression (8.9) implies that everywhere on the interval Δ the following equality holds:

$$\dot{l}_*(t)=0, \tag{8.12}$$

which allows us to find the formula for the control $u_{\text{sing}}(t)$ and function $k_{\text{sing}}(t)$:

$$u_{\text{sing}}(t)k_{\text{sing}}(t)=\frac{\sigma-\delta l_{\text{sing}}m_{\text{sing}}-\mu l_{\text{sing}}}{\gamma_1 l_{\text{sing}}}=Const. \tag{8.13}$$

Formula (8.7) and the defined above function $g_2(m)$ make it possible to rewrite equality (8.13) as follows:

$$u_{\text{sing}}(t)k_{\text{sing}}(t)=\frac{g_2(m_{\text{sing}})}{\gamma_1(\rho-\nu m_{\text{sing}})}=Const, \quad t\in\Delta. \tag{8.14}$$

The positivity of the product on the left-hand side of this formula, as well as relationships (3.10) and (8.8), yields the following inclusion:

$$m_{\text{sing}}\in\left(m_2^0,\nu^{-1}\rho\right), \tag{8.15}$$

which is a necessary condition for the existence of the singular arc.

Let us analyze inclusion (8.15) for considered above Cases (b) and (c).

Case (b) If $\alpha>0$, then one of the following situations is possible:

- the value $m_{\text{sing}}^0\notin\left(m_2^0,\nu^{-1}\rho\right)$. Therefore, the singular arc is not possible. Optimal control $u_*(t)$ is bang-bang taking only values $\{u_{\min};1\}$.
- the value $m_{\text{sing}}^0\in\left(m_2^0,\nu^{-1}\rho\right)$. Then, this value becomes the value m_{sing} of variable m on the interval Δ.

Case (c) If $\alpha<0$ and $D_f>0$, then one of the following situations is possible:

• none of the values m_{sing}^1, m_{sing}^2 do not belong to the interval $\big(m_2^0, \nu^{-1}\rho\big)$. Therefore, the singular arc is not possible. Optimal control $u_*(t)$ is bang-bang taking only values $\{u_{\min}; 1\}$.
• only one of the values m_{sing}^1, m_{sing}^2 belongs to the interval $\big(m_2^0, \nu^{-1}\rho\big)$. Then, this value becomes the value m_{sing} of variable m on the interval Δ.
• both values m_{sing}^1, m_{sing}^2 belong to the interval $\big(m_2^0, \nu^{-1}\rho\big)$. Since the expressions $(2\alpha(\lambda-\nu)m_{\text{sing}}^{1,2} + \lambda(\lambda-\mu))$ are opposite in sign:

$$2\alpha(\lambda-\nu)m_{\text{sing}}^1 + \lambda(\lambda-\mu) > 0, \quad 2\alpha(\lambda-\nu)m_{\text{sing}}^2 + \lambda(\lambda-\mu) < 0,$$

and the function $\psi_1^*(t)$ is sign-definite, then for one of them inequality (8.10) will be satisfied, and for the other inequality (8.11). It means that only one of them satisfies the necessary condition of the optimality of the singular arc (Kelly-Cope-Moyer condition). Namely, this value becomes the value m_{sing} of variable m on the interval Δ.

Now, let us return to formula (8.14) and discuss how to find the function $k_{\text{sing}}(t)$. We substitute formula (8.14) into the second equation of the system (2.1), and then transform the resulting expression with using formula (8.7) and the defined above functions $g_1(m)$ and $g_2(m)$. As a result, we obtain a linear autonomous nonhomogeneous differential equation:

$$\dot{k}_{\text{sing}}(t) = -\lambda k_{\text{sing}}(t) - \frac{\gamma_2}{\gamma_1} \cdot \frac{g_1(m_{\text{sing}})}{\beta m_{\text{sing}}}\,, \quad t \in \Delta. \tag{8.16}$$

Adding to the equation (8.16) an initial condition, which can be taken as the value of the function $k_{\text{sing}}(t)$ at a time moment where the singular and non-singular portions of the optimal solution $k_*(t)$ are concatenated, and then integrating the resulting Cauchy problem, we find the function $k_{\text{sing}}(t)$ on the interval Δ.

Now, let us discuss formula (7.6) of the constancy of the Hamiltonian on the optimal solution. On the interval Δ it can be written as follows:

$$\gamma_1 \dot{k}_{\text{sing}}(t)\psi_1^*(t) = -\gamma_2 \dot{k}_*(T). \tag{8.17}$$

Depending on the value of $\dot{k}_*(T)$, the following two cases are possible.

• If $\dot{k}_*(T) = 0$, then formula (8.17) leads to the equality:

$$\dot{k}_{\text{sing}}(t) = 0, \quad t \in \Delta. \tag{8.18}$$

By relationships (8.14) and (8.16), we find the following formulas:

$$k_{\text{sing}} = -\frac{\gamma_2}{\gamma_1} \cdot \frac{g_1(m_{\text{sing}})}{\lambda\beta m_{\text{sing}}} = Const,$$
$$u_{\text{sing}} = -\frac{\lambda\beta m_{\text{sing}}}{\gamma_2(\rho - \nu m_{\text{sing}})} \cdot \frac{g_2(m_{\text{sing}})}{g_1(m_{\text{sing}})} = Const.$$

By the inclusion $u_{\text{sing}} \in [u_{\min}, 1]$, the control $u_*(t) = u_{\text{sing}}$ is admissible on the interval Δ. Since the coordinates of the point $(l_{\text{sing}}, k_{\text{sing}}, m_{\text{sing}})$ were found from equalities (8.6), (8.12) and (8.18), then it coincides with the equilibrium $(l_\star, k_\star, m_\star)$ related to the control $u = u_{\text{sing}}$ and studied in Section 3. Corollary 7.2 shows that the singular arc of the optimal control $u_*(t)$ is concatenated with non-singular portion, where it is a bang-bang control. Let $\tau \in (0, T)$ be the time moment, when such portions are concatenated. Then, as it follows from [31], when $u_{\text{sing}} \in (u_{\min}, 1)$, the non-singular portion contains at least the countable number of switchings of control $u_*(t)$, accumulating to the point τ. This behavior of the optimal control $u_*(t)$ on non-singular portions is called a chattering phenomenon and will be observed on both sides of the interval Δ.

• If $\dot{k}_*(T) \neq 0$, then, as in the previous case, from formula (8.17) we conclude that $\dot{k}_{\text{sing}}(t) \neq 0$ for all $t \in \Delta$. It means that the function $k_{\text{sing}}(t)$ is either increasing or decreasing. By formula (8.14), the corresponding control $u_{\text{sing}}(t)$ is, on the contrary, either a decreasing or an increasing function. The specific form of the function $k_{\text{sing}}(t)$ depends on the sign of value α, as well as the positivity or negativity of the function $\psi_1^*(t)$ on the interval Δ. When the inclusion $u_{\text{sing}}(t) \in (u_{\min}, 1)$ holds for all $t \in \Delta$, the behavior of the control $u_*(t)$ on non-singular portions is similar to the previous case.

Situations, when $u_{\text{sing}} \in \{u_{\min}; 1\}$ for the first case and $u_{\text{sing}}(\tau) \in \{u_{\min}; 1\}$ for the second case, are required more complicated and cumbersome arguments. Therefore, here they are not considered.

Finally, we note that the study of the singular arc conducted in this section differs from similar studies (see [30, 31], and references therein), which use the Lie brackets and the switching function

$$L_0(t) = l_*(t)k_*(t)(\gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t))$$

related to the derivative $\widetilde{H}'_u(l, k, m, u, \psi_1, \psi_2, \psi_3)$ from Section 7. The basis of our arguments is system (7.5) for the switching function $L(t)$ and the corresponding auxiliary functions $P(t)$ and $\psi_1^*(t)$. Conducting direct calculations shows that the results presented above and in [30, 31] are the same. Moreover, in our opinion, they are obtained in a more concise way.

9. Results of numerical calculations

Here we demonstrate the results of a numerical solution of the minimization problem (2.1), (6.1), namely, give the graphics of the optimal control $u_*(t)$ and the corresponding optimal solutions $l_*(t)$, $k_*(t)$, $m_*(t)$ for the two cases considered in the previous section: Case (a) and Case (b). In both cases the values of the parameters and initial conditions of system (2.1) and restrictions (2.2) are taken from [25]. Also, numerical calculations were made in Case (c), but there were no qualitative differences from the results obtained in Cases (a) and (b). Therefore, here we do not give them. In addition, we want to say that the numerical calculations in Case (a) supplement and confirm the theoretical results obtained earlier in [11].

It is important to note that the control $u(t)$ is auxiliary. It is introduced into system (2.1) to simplify analytical analysis. The corresponding physical control $v(t)$ in the same system is related to the control $u(t)$ by the formula $v(t) = 1 - u(t)$. Therefore, where the auxiliary optimal control $u_*(t)$ has a maximum value of 1, the appropriate physical optimal control $v_*(t)$ takes a minimum value of 0, and vice versa.

In Case (a), when $\alpha < 0$ and $D_f < 0$, for numerical calculations the following values of the parameters and initial conditions of the system (2.1) and restrictions (2.2) were used:

$$\begin{array}{llll} \sigma = 15.0 & \rho = 12.0 & \beta = 0.12 & \delta = 0.15 \\ \mu = 0.04 & \nu = 0.05 & \gamma_1 = 0.03 & \gamma_2 = 0.09 \\ u_{\min} = 0.3 & T = 100.0 & & \\ l_0 = 100.0 & k_0 = 40.0 & m_0 = 50.0 & \end{array}$$

These numerical calculations were conducted using "GPOPS–2.3" ([21]). The corresponding results are shown in Figures 2 and 3. Here J_* is the minimum value of the functional $J(u)$ from (6.1).

Physical optimal control $v_*(t)$ according to Figures 2 and 3 has one switching from the minimum value to the maximum value that describes the situation when, first there is the period of the psoriasis treatment with the lower intensity, and then, the switching occurs to the period of the treatment with the greatest intensity.

In Case (b), when $\alpha > 0$, for numerical calculations the following values of the parameters and initial conditions of the system (2.1) and restrictions (2.2) were used:

$$\begin{array}{llll} \sigma = 15.0 & \rho = 3.6 & \beta = 0.4 & \delta = 0.005 \\ \mu = 0.01 & \nu = 0.02 & \gamma_1 = 0.8 & \gamma_2 = 0.05 \\ u_{\min} = 0.3 & T = 100.0 & & \\ l_0 = 100.0 & k_0 = 40.0 & m_0 = 50.0 & \end{array}$$

These numerical calculations were conducted using "BOCOP–2.0.5" ([1]) and "GPOPS–2.3" ([21]). Simultaneous use of these softwares was necessary to verify their performance in the study of such a complex from the computational point of view of the phenomenon as chattering. As a result, they have proved themselves well, showing equal opportunities. The corresponding results of the numerical calculations are shown in Figures 4–7. Here J_* is the minimum value of the functional $J(u)$ from (6.1) as well.

Figures 4–7 show that the behavior of the physical optimal control $v_*(t)$ is qualitatively different from the previous one. This difference consists in the presence of a period of the psoriasis treatment with a smooth increase in the dose of used medication. To the beginning and the end of this period of the psoriasis treatment there are the periods with increasing number of switchings with lower intensity to greatest intensity and vice versa, which does not make much sense as a type of medical treatment. At the same time, the whole process of this treatment ends with the period with the greatest intensity.

Finally, we would like to emphasize that in all performed numerical calculations, the optimal concentration of keratinocytes $k_*(t)$ decreases to an acceptable level to the end T of the psoriasis treatment (see Figures 2–7).

10. Conclusion

Mathematical model of a psoriasis treatment described by a nonlinear system of three differential equations involving the concentrations of T-lymphocytes, keratinocytes, and dendritic cells (tissues macrophages) was considered. Its invariance and permanence, the existence of equilibria with nonnegative coordinates, and conditions for their local asymptotic stability were investigated and refined. Then, a control function as medication intake was introduced into this model, and such control model was considered on a given time interval. An optimal control problem of minimizing the release of keratinocytes at the end of the time interval was stated and studied using the Pontryagin maximum principle. The corresponding adjoint system, the maximum condition for the optimal control, and the condition for the constancy of the Hamiltonian on the optimal solution were written. Then, a system of differential equations for the switching function describing the behavior of this control and its corresponding auxiliary functions was obtained. This system of equations allowed us to determine the type of the optimal control: this function has only a bang-bang type, or in addition to the bang-bang type, it also contains singular arc. The relationships between the parameters of the original control model were found under which the optimal control is of one type or another. When a singular arc arose, its order, the fulfillment of the corresponding necessary optimality condition for it, as well as possible forms of a concatenation of singular arc and bang-bang type of the optimal control were discussed. The obtained results were illustrated by numerical calculations, and corresponding conclusions were made.

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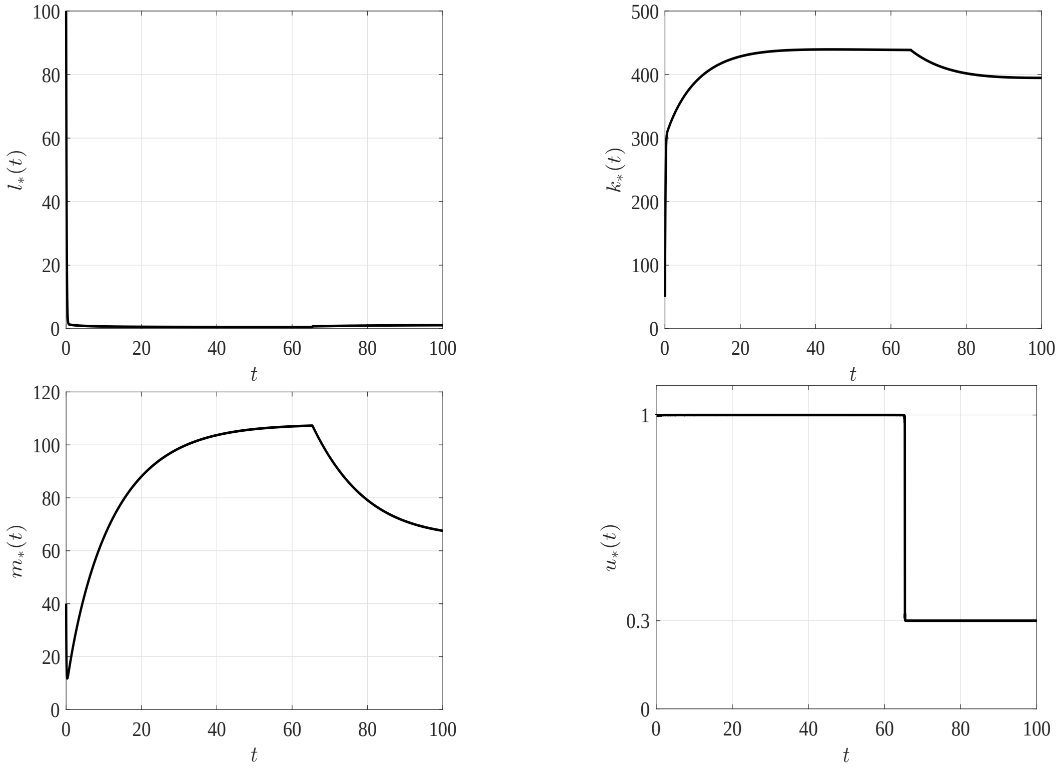

FIGURE 2. Optimal solutions and optimal control for $\lambda = 0.08$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$. $J_* = 394.7763$.

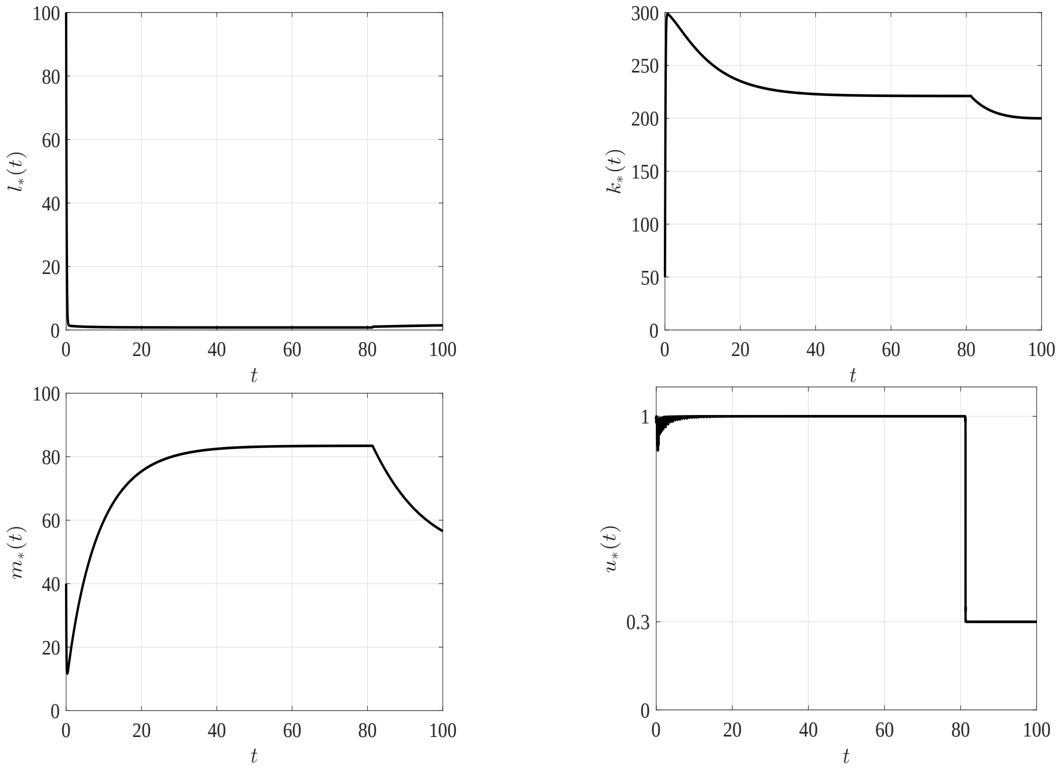

FIGURE 3. Optimal solutions and optimal control for $\lambda = 0.15$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$. $J_* = 200.0344$.

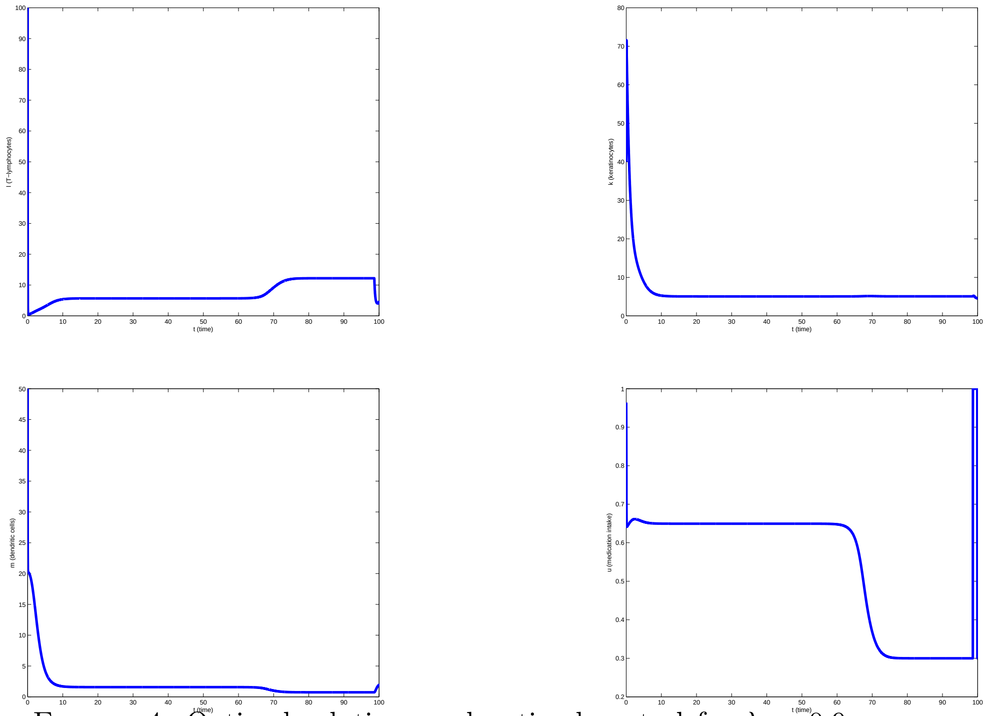

FIGURE 4. Optimal solutions and optimal control for $\lambda = 0.9$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$. $J_* = 4.55257$.

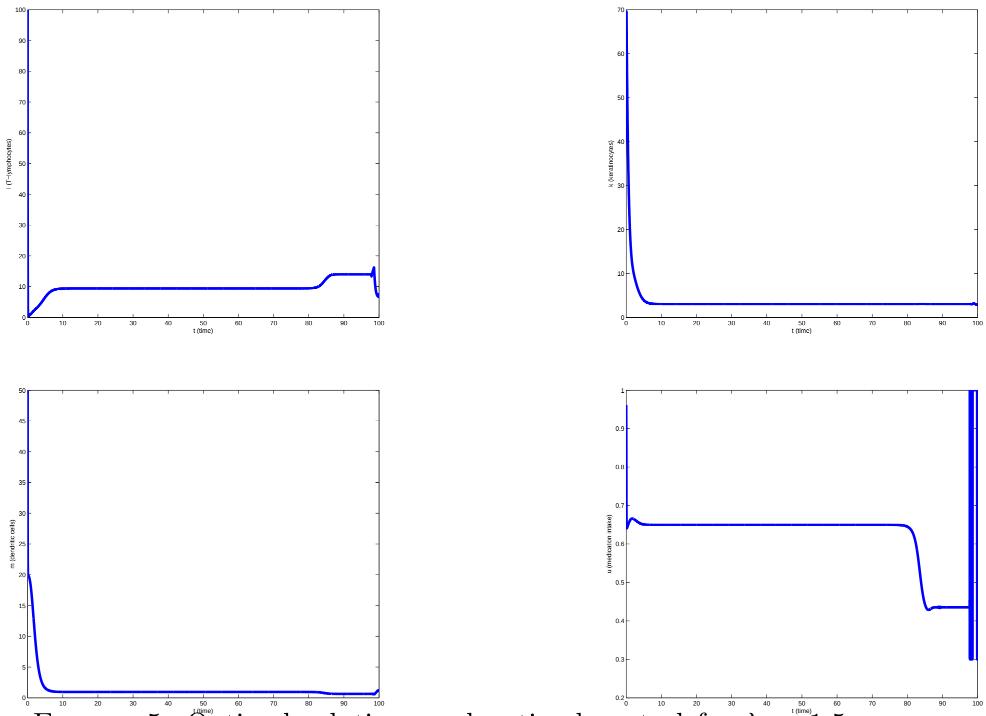

FIGURE 5. Optimal solutions and optimal control for $\lambda = 1.5$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$. $J_* = 2.86014$.

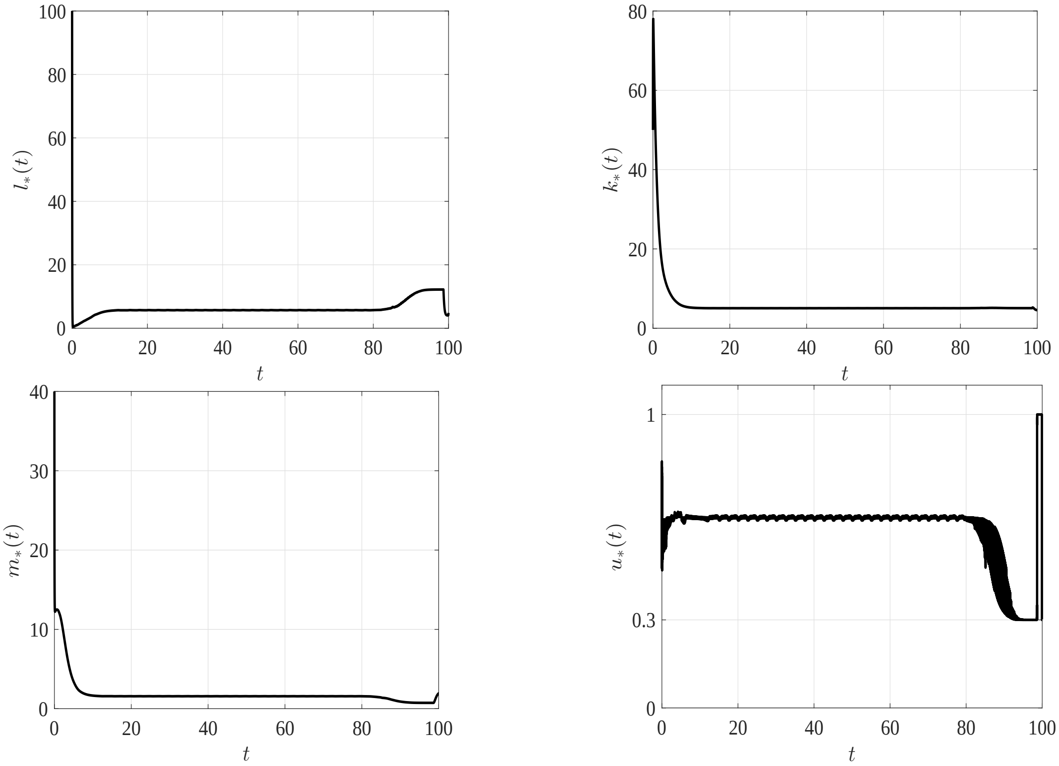

FIGURE 6. Optimal solutions and optimal control for $\lambda = 0.9$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$. $J_* = 4.5527$.

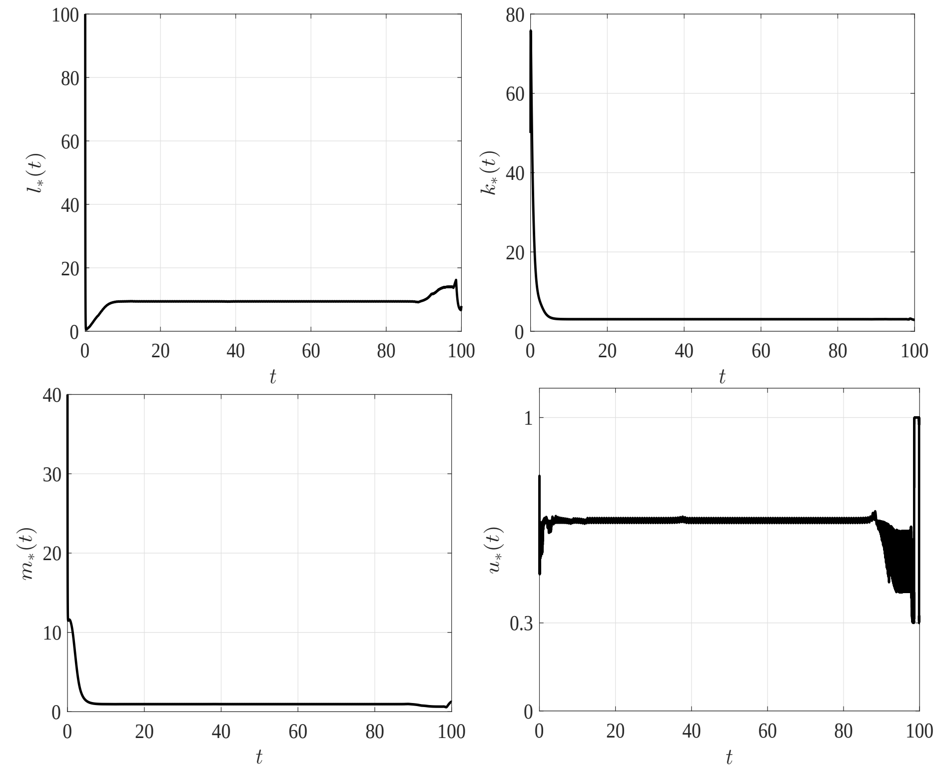

FIGURE 7. Optimal solutions and optimal control for $\lambda = 1.5$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$. $J_* = 2.8602$.