Pure and Applied Functional Analysis
Volume 6, Number 2, 2021, 317–351

Yokohama Publishers
ISSN 2189-3764 ONLINE JOURNAL

OPTIMAL STRATEGIES FOR ACHIEVING IMMUNE BALANCE IN A MATHEMATICAL MODEL OF ALLERGY TREATMENT

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Abstract. Allergy is immune disorder that changes the code in action of T-helper cells. It is known that people showing allergy symptoms have a predominant concentration of inflammatory Th_2-cells than those without symptoms. Our aim is to create realistic control models of allergy and find possible way to prevent its symptoms by optimal treatment. Firstly, on a given time interval, we considered and investigated a system of differential equations describing interaction between naive T-helper cells, Th_1- and Th_2-cells, and of allergen. The model equilibria, their stability and bifurcation analysis are conducted. Secondly, three bounded controls reflecting the impact of drugs and other direct and indirect measures during anti-allergenic therapy are introduced into this system. The bounded controls may reflect the types of treatment related to a) the intake of antihistamine that suppresses the dominance of Th_2-cells by blocking histamine receptors, b) stimulation of Th_1-cells, c) isolation from the allergen or taking a drug inhibiting the release of histamine from mast cells. The objective of this study is to eliminate allergy symptoms by balancing $Th_1 - Th_2$ immune cells and to minimize the cost of the treatment. The results of analytical analysis and numerical calculations are presented. Optimal strategies leading to the minimization of the objective function and its interpretation and possible application to allergy treatment are discussed.

1. Introduction

It is unlikely that in our time you can find a person who has not heard anything about allergy. Unfortunately, in one form or another, this disease occurs very often. Allergy, as a disease, has always been, but since the mid-twentieth century, both the number of allergy sufferers and the spectrum of possible allergens have begun to increase rapidly. Today, up to 60% of the world's population suffer from various forms of allergy. At the same time, the incidence of allergy has not yet reached a maximum: only in the last three decades every ten years, the incidence of allergy has doubled.

Allergic diseases are hyperreactions of the body in response to the influence of certain environmental factors, which are considered as potentially dangerous, even if in fact they are not. Allergy is an increased sensitivity of the body to any substance that causes allergy. Individual allergens for different patients can be any compounds of sufficiently high molecular weight (especially those containing cyclic groups) of bacterial, viral, household, food, industrial, medicinal, pollen and other nature that are completely harmless to a healthy person. Reaction of the body to an allergen

2020 *Mathematics Subject Classification.* 49J15, 58E25, 92D30.
Key words and phrases. Mathematical model of allergy, nonlinear system of differential equations, optimal control problem, Pontryagin maximum principle.

can occur in the form of immediate and delayed hypersensitivity. The basis of allergy is the immune response (the release of the internal environment of the body from allergens), accompanied by damage to its tissues. The key role in the immune response belongs to naive T-helper cells ([17]). They are divided into different populations, the most important of which are:

- Th_1-cells. They participate in a "cell-mediated immunity", which usually deals with infections, viruses, and certain bacteria. These cells are the first line of defense of the human body from pathogens that enter the body's cells. They are characterized by the production of anti-inflammatory cytokines and are involved in the development of organ-specific autoimmune diseases.
- Th_2-cells. They are involved in a "humoral-mediated immunity" that deals with bacteria, toxins and allergens. These cells are responsible for stimulating the production of specific cells (antibodies) that specifically interact with extracellular pathogens. They play an important role in the immune responses to allergies, because they activate the production of IgE antibodies (immunoglobulin E), with the help of which allergic reactions are provoked ([20]).

In a well-functioning immune system, all T-helper cell populations work together to keep the immune system balanced. A certain population of cells may become more active in order to eliminate an external threat, then everything returns to its initial balanced state. A more detailed description of other populations of T-helper cells, as well as the interaction of Th_1- and Th_2-cells, is given in [16, 21–23, 27].

There are four types of allergic reactions ([31]). We will further focus on the consideration of only allergic reactions of the first type (IgE-dependent). Their course is characterized as follows. The first contact with the allergen leads to the differentiation of naive T-helper cells (for uniformity, T-cells) in the population of Th_1- and Th_2-cells, an increase in the activity of the Th_2-cell population against the background of a decrease in the activity of the Th_1-cell population (Th_2-dependent immune response). This activity of Th_2-cells is accompanied by the formation of a large number of IgE antibodies, which are fixed on mast cells. Repeated contact of the allergen with IgE on the surface of mast cells provokes their activation (degranulation) and a massive release of histamine, heparin, serotonin and other types of molecules (mediators of allergic reactions) that cause allergy symptoms and tissue damage around the site of contact with the allergen. Depending on which mediators predominate and how many are emitted, different manifestations of allergy develop: from itching and runny nose to allergic rhino-conjunctivitis, atopic dermatitis, bronchial asthma and even anaphylactic shock (Quincke edema).

The allergic reactions that we consider are diverse in their manifestations and severity of treatment, they are able to develop in different directions and involve various organs and tissues of the body.

The creation of effective and safe drugs and methods for treating allergic diseases is based on knowledge of the mechanisms that underlie the development of the considered allergic reactions, as well as the use of modern biotechnological approaches in the development of new drugs. In parallel with the study of the mechanisms of allergic reactions, a new generation of drugs are being developed, such that various forms of recombinant allergens or preparations of monoclonal antibodies against key

molecules of allergic reactions ([23, 25, 33]). Here, mathematical models, described by systems of differential and difference equations, play a large role. They allow a better understanding of the mechanisms of occurrence and course of the allergic reactions. Related to this, scientific publications can be divided into the following two groups:

- they describe mathematically only the interaction of naive T-cells, Th_1- and Th_2-cells with a pathogen (allergen). Here we highlight publications [1–3, 7, 10, 26, 32, 34, 35].
- they describe full immune response of the body to pathogens (allergens). Moreover, the interaction of naive T-cells, Th_1- and Th_2-cells is part of a complex process of such a response. Here we note publications [5,6,13,14,18].

Introduction into a mathematical model of allergy of bounded control functions leads to a control model of allergic disease. Consideration of such controls as intensities or doses of drugs and as the effect of various indirect measures allows us to evaluate their impact on the treatment of this disease. Finally, the formulation of a suitable optimal control problem for such a model and the use then of the Pontryagin maximum principle as a necessary optimality condition for analysis of the corresponding optimal solutions makes it possible to find the optimal allergy treatment strategies.

Based on these considerations, in this paper we take as a basis the simplest mathematical model of the interaction of populations of naive T-cells, Th_1- and Th_2-cells with allergens, presented in [1,10,26,32]. Its detailed description in the form of a system of differential equations, as well as a new normalization of the corresponding phase variables and parameters, is given in Section 2. The properties of the phase variables are presented in Section 3. Section 4 contains a detailed analysis of the stability of equilibria of the system, as well as their bifurcation analysis. Numerical calculations demonstrating the behavior of the phase variables of this system and performed using MAPLE-15 software for specific values of the parameters, as well as their detailed discussion are presented in Section 5. Section 6 describes the construction of a control mathematical model and the optimal control problem corresponding to it. The introduced bounded control functions reflect the possible impacts on the allergic disease of drugs and various indirect measures. The objective function, which is to be minimized, within the framework of the optimal control problem sets the balance between populations of Th_1- and Th_2-cells, and also takes into account the cost of the used drugs and indirect measures for the entire period of allergy treatment. This section also shows the application of the Pontryagin maximum principle to this problem as a necessary optimality condition. This allows to analytically establish important properties of the corresponding optimal controls. Section 7 contains the results of numerical calculations performed using BOCOP-2.0.5 software, which show the behavior of optimal solutions of the optimal control problem. Finally, Section 8 presents our discussion and conclusions.

2. Description of the model

To create a control mathematical model of allergy treatment, we used the model proposed in [1, 10, 26, 32] as the basis. It is described by a system of six differential

equations:

$$
\begin{cases}
\dfrac{d\widetilde{H}_0}{d\tau}(\tau) = \sigma - \beta_1 \widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{C}_1(\tau) - \beta_2 \widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{C}_2(\tau) - \gamma \widetilde{H}_0(\tau), \\
\dfrac{d\widetilde{H}_1}{d\tau}(\tau) = \rho\beta_1 \widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{C}_1(\tau) - \gamma \widetilde{H}_1(\tau), \\
\dfrac{d\widetilde{H}_2}{d\tau}(\tau) = \rho\beta_2 \widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{C}_2(\tau)\Big(1 + r_1\widetilde{C}_1(\tau)\Big)^{-1} - \gamma \widetilde{H}_2(\tau), \\
\dfrac{d\widetilde{C}_1}{d\tau}(\tau) = \alpha_1 \widetilde{H}_1(\tau)\Big(1 + r_2\widetilde{C}_2(\tau)\Big)^{-1} - \delta \widetilde{C}_1(\tau), \\
\dfrac{d\widetilde{C}_2}{d\tau}(\tau) = \alpha_2 \widetilde{H}_2(\tau) - \delta \widetilde{C}_2(\tau), \\
\dfrac{d\widetilde{A}}{d\tau}(\tau) = \epsilon - \eta\widetilde{A}(\tau)\Big(\widetilde{H}_1(\tau) + \widetilde{H}_2(\tau)\Big) - \kappa\widetilde{A}(\tau).
\end{cases}
\tag{2.1}
$$

These equations establish the interaction between the respective concentrations $\widetilde{H}_0(\tau)$, $\widetilde{H}_1(\tau)$, $\widetilde{H}_2(\tau)$, $\widetilde{C}_1(\tau)$, $\widetilde{C}_2(\tau)$, $\widetilde{A}(\tau)$ per unit volume of naive T-cells, Th_1- and Th_2-cells, cytokines secreted by these cells and allergens. As we already know, Th_1- and Th_2-cells produce different cytokines. It is important for us that we do not distinguish different cytokines secreted by Th_1-cells denoting the concentration of all of them by $\widetilde{C}_1(\tau)$. In a similar way we denote the concentration of the cytokines secreted by Th_2-cells as $\widetilde{C}_2(\tau)$.

In system (2.1), naive T-cells are produced with a rate σ and decay with the same characteristic time γ^{-1} as the Th_1- and Th_2-cells. Stimulated naive T-cells disappear from the population of such cells; their concentrations in the second and third equations are proportional to the appropriate products $\widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{C}_1(\tau)$ and $\widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{C}_2(\tau)(1 + r_1\widetilde{C}_1(\tau))^{-1}$, where the last factors reflect the autocrine effect of the cytokines secreted by the corresponding Th_1- and Th_2-cells. The parameters β_1 and β_2 define the differences in the activation of Th_1- and Th_2-cells by allergens, respectively. The value ρ determines a proliferation rate of these cells.

Cytokines decay with a characteristic time δ^{-1} which is small compared to γ^{-1}. They are produced at the rates α_1 and α_2 by the respective populations of Th_1- and Th_2-cells. The cross-suppression is described by factors of the form $(1+\text{const}\cdot x)^{-1}$, where x defines the concentration of suppressive cytokines. It is easy to see that such factors tend to 1 for low concentrations. Since the cytokines secreted by Th_2-cells suppress the production of the cytokines secreted by Th_1-cells whereas the cytokines secreted by Th_1-cells suppress the proliferation of Th_2-cells, there is an asymmetry in the equations for $\widetilde{H}_1(\tau)$ and $\widetilde{C}_1(\tau)$ on one side and equations for $\widetilde{H}_2(\tau)$ and $\widetilde{C}_2(\tau)$ on the other side.

Concentration $\widetilde{A}(\tau)$ of allergens is supplied at the rate ϵ and is eliminated proportional to the concentrations of Th_1- and Th_2-cells. Also,we assume that allergens decay with a characteristic time κ^{-1}.

The life-time of cytokines is short compared to that of naive T-cells, Th_1- and Th_2-cells ($\delta^{-1} \ll \gamma^{-1}$). Therefore, cytokines relax fast to a quasi-stationary state dictated by Th_1- and Th_2-cells. Hence, from the fourth and fifth equations of

system (2.1) we obtain the equalities:

$$\widetilde{C}_1(\tau) = \alpha_1\delta^{-1}\widetilde{H}_1(\tau)\left(1+\alpha_2 r_2\delta^{-1}\widetilde{H}_2(\tau)\right)^{-1},$$
$$\widetilde{C}_2(\tau) = \alpha_2\delta^{-1}\widetilde{H}_2(\tau).$$

After substitution of these expressions into the remaining equations of system (2.1), we obtain the system of differential equations:

$$\begin{cases} \dfrac{d\widetilde{H}_0}{d\tau}(\tau) = \sigma - \alpha_1\beta_1\delta^{-1}\widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{H}_1(\tau)\left(1+\alpha_2 r_2\delta^{-1}\widetilde{H}_2(\tau)\right)^{-1} \\ \qquad\qquad - \alpha_2\beta_2\delta^{-1}\widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{H}_2(\tau) - \gamma\widetilde{H}_0(\tau), \\ \dfrac{d\widetilde{H}_1}{d\tau}(\tau) = \rho\alpha_1\beta_1\delta^{-1}\widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{H}_1(\tau)\left(1+\alpha_2 r_2\delta^{-1}\widetilde{H}_2(\tau)\right)^{-1} - \gamma\widetilde{H}_1(\tau), \\ \dfrac{d\widetilde{H}_2}{d\tau}(\tau) = \rho\alpha_2\beta_2\delta^{-1}\widetilde{H}_0(\tau)\widetilde{A}(\tau)\widetilde{H}_2(\tau) \\ \qquad\qquad \times\left(1+\alpha_1 r_1\delta^{-1}\widetilde{H}_1(\tau)\left(1+\alpha_2 r_2\delta^{-1}\widetilde{H}_2(\tau)\right)^{-1}\right)^{-1} - \gamma\widetilde{H}_2(\tau), \\ \dfrac{d\widetilde{A}}{d\tau}(\tau) = \epsilon - \eta\widetilde{A}(\tau)\left(\widetilde{H}_1(\tau)+\widetilde{H}_2(\tau)\right) - \kappa\widetilde{A}(\tau). \end{cases} \tag{2.2}$$

Measuring the time in units of γ^{-1}, that is $\tau = \gamma^{-1}t$, and rescaling the variables as

$$\widetilde{H}_0 = \gamma\eta^{-1}H_0, \quad \widetilde{H}_1 = \gamma\eta^{-1}H_1, \quad \widetilde{H}_2 = \gamma\eta^{-1}H_2, \quad \widetilde{A} = \delta\eta A, \tag{2.3}$$

and introducing the constants:

$$\begin{aligned} &\alpha = \sigma\eta\gamma^{-2}, \quad \chi = \epsilon(\gamma\delta\eta)^{-1}, \quad \theta_1 = \alpha_1\beta_1, \quad \theta_2 = \alpha_2\beta_2, \\ &\mu_1 = \alpha_1 r_1\gamma(\delta\eta)^{-1}, \quad \mu_2 = \alpha_2 r_2\gamma(\delta\eta)^{-1}, \quad \nu = \kappa\gamma^{-1}, \end{aligned} \tag{2.4}$$

we rewrite system (2.2) as follows

$$\begin{cases} H_0'(t) = \alpha - \theta_1 H_0(t)A(t)H_1(t)\Big(1+\mu_2 H_2(t)\Big)^{-1} \\ \qquad\qquad - \theta_2 H_0(t)A(t)H_2(t) - H_0(t), \\ H_1'(t) = \rho\theta_1 H_0(t)A(t)H_1(t)\Big(1+\mu_2 H_2(t)\Big)^{-1} - H_1(t), \\ H_2'(t) = \rho\theta_2 H_0(t)A(t)H_2(t)\Big(1+\mu_2 H_2(t)\Big)\Big(1+\mu_1 H_1(t)+\mu_2 H_2(t)\Big)^{-1} \\ \qquad\qquad - H_2(t), \\ A'(t) = \chi - \Big(H_1(t)+H_2(t)+\nu\Big)A(t). \end{cases} \tag{2.5}$$

In this system, the values α, ρ, χ, ν, θ_1, θ_2, μ_1, μ_2 are the given positive parameters. In addition, we assume that ν satisfies the inequality:

$$\alpha\rho\chi\min\{\theta_1;\theta_2\} > \nu. \tag{2.6}$$

We also note that formulas (2.3) and (2.4) differ from similar expressions presented in [10, 26].

Finally, based on the physical meaning of phase variables of system (2.5), we add to it the following initial conditions:

$$H_0(0) = H_0^0 \geq 0,\ H_1(0) = H_1^0 \geq 0,\ H_2(0) = H_2^0 \geq 0,\ A(0) = A_0 \geq 0. \tag{2.7}$$

In [1,10,26,32], there are no studies of the properties of solutions for system (2.5) with initial conditions (2.7). Therefore, the next section fills this significant gap and presents the properties of such solutions.

3. Properties of solutions of the model

Let us analyze the properties of the solutions to system (2.5). Their nonnegativity and boundedness would indicate that the system behaves biologically correctly or it is a biological well-behaved system.

The following lemma ensures the non-negativity of the components of solutions for system (2.5) with initial conditions (2.7).

Lemma 3.1. *All components $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ are non-negative for all $t > 0$.*

Proof. Let the components $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ of an arbitrary solution for system (2.5), (2.7) be defined on some interval $[0, t_0)$. Then, the equations of system (2.5) can be rewritten as

$$\begin{aligned}
H_0'(t) &= \alpha - \left\{\theta_1 A(t) H_1(t)\Big(1 + \mu_2 H_2(t)\Big)^{-1} + \theta_2 A(t) H_2(t) + 1\right\} H_0(t) \\
&= \alpha - g_0(t) H_0(t), \\
H_1'(t) &= \left\{\rho\theta_1 H_0(t) A(t)\Big(1 + \mu_2 H_2(t)\Big)^{-1} - 1\right\} H_1(t) = g_1(t) H_1(t), \\
H_2'(t) &= \left\{\rho\theta_2 H_0(t) A(t)\Big(1 + \mu_2 H_2(t)\Big)\Big(1 + \mu_1 H_1(t) + \mu_2 H_2(t)\Big)^{-1} - 1\right\} H_2(t) \\
&= g_2(t) H_2(t), \\
A'(t) &= \chi - \Big\{H_1(t) + H_2(t) + \nu\Big\} A(t) = \chi - g_3(t) A(t),
\end{aligned}$$

where the functions $g_0(t)$, $g_1(t)$, $g_2(t)$, and $g_3(t)$ denote the corresponding expressions in braces. These new equations can be considered as the linear non-autonomous differential equations of the first order with the corresponding non-negative initial conditions (2.7) and positive heterogeneities for the first and fourth equations and without such heterogeneities for the second and third equations. Then, their solutions $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ are non-negative for all $t \in (0, t_0)$. This can be easily verified, for example, by direct integration of each differential equation using the constant variation method ([11]).

Hence, the non-negativity of the components $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ of an arbitrary solution for system (2.5), (2.7) on the interval $(0, t_0)$ is justified. □

We note that the non-negative octant $\mathbb{R}^4_+$ is an invariant region of system (2.5).

It is also important to show that all state variables of system (2.5) are bounded for all t. This will ensure that the studied model is well-posed and realistic to represent

the considered cell populations. The following lemma gives us the boundedness of the solutions of system (2.5).

Lemma 3.2. *All non-negative solutions of system* (2.5) *enter the region* $\Lambda \subset \mathbb{R}^4_+$ *and are ultimately bounded.* Λ *is defined as*

$$\Lambda = \Big\{(H_0, H_1, H_2, A)^\top \in \mathbb{R}^4_+ : 0 \le H_0 \le \alpha,\ H_1 \ge 0,\ H_2 \ge 0,$$
$$0 \le A \le \nu^{-1}\chi,\ \rho H_0 + H_1 + H_2 \le \alpha\rho\Big\},$$

where the symbol $^\top$ *denotes the transpose.*

Proof. Let us consider the first equation of system (2.5). Using Lemma 3.1, we have the inequality:

$$H_0'(t) \le \alpha - H_0(t). \tag{3.1}$$

By applying Theorem 4.1 ([11]), we obtain the inequality:

$$0 \le H_0(t) \le \alpha - (\alpha - H_0(0))\, e^{-t}, \quad t > 0,$$

from which it follows $H_0(t) \le \alpha$ if $H_0(0) \le \alpha$.

Similarly, by Lemma 3.1, from the fourth equation of system (2.5) we find the inequality:

$$A'(t) \le \chi - \nu A(t). \tag{3.2}$$

The same theorem leads us to the inequality:

$$0 \le A(t) \le \nu^{-1}\chi - \big(\nu^{-1}\chi - A(0)\big)\, e^{-\nu t}, \quad t > 0,$$

which implies that $A(t) \le \nu^{-1}\chi$ if $A(0) \le \nu^{-1}\chi$.

Next, let us consider the auxiliary function $W(t) = \rho H_0(t) + H_1(t) + H_2(t)$ and then calculate its derivative using the corresponding equations of system (2.5). As a result, after necessary transformations, we find the inequality:

$$W'(t) \le \alpha\rho - W(t). \tag{3.3}$$

Theorem 4.1 ([11]) again gives us the inequality:

$$0 \le W(t) \le \alpha\rho - (\alpha\rho - W(0))\, e^{-t}, \quad t > 0,$$

from which we obtain $W(t) \le \alpha\rho$ if $W(0) \le \alpha\rho$. This means that $\rho H_0(t) + H_1(t) + H_2(t) \le \alpha\rho$, when $\rho H_0(0) + H_1(0) + H_2(0) \le \alpha\rho$.

Thus, all solutions $(H_0(t), H_1(t), H_2(t), A(t))^\top$ of system (2.5) that start in Λ, remain in this set for all $t > 0$. It means that Λ is an invariant set of this system. Moreover, the region Λ is bounded and hence all mentioned solutions are ultimately bounded as well.

Finally, all solutions $(H_0(t), H_1(t), H_2(t), A(t))^\top$ with non-negative initial conditions (2.7) finally come into the region Λ 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 region Λ and the following relationships:

$$\begin{aligned} &H_0'(t)\Big|_{H_0=\alpha} \le 0, \quad A'(t)\Big|_{A=\nu^{-1}\chi} \le 0, \\ &\rho H_0'(t) + H_1'(t) + H_2'(t)\Big|_{\rho H_0 + H_1 + H_2 = \alpha\rho} \le 0, \end{aligned} \tag{3.4}$$

result from inequalities (3.1)–(3.3). Moreover, inequalities like (3.4) will also hold for points outside the region Λ. They show the motion of the phase point $(H_0(t), H_1(t), H_2(t), A(t))^\top$ toward this set. This guarantees the boundedness of all solutions $(H_0(t), H_1(t), H_2(t), A(t))^\top$ of system (2.5) with non-negative initial conditions (2.7). □

4. Stability analysis

Here we will discuss the existence of possible equilibria in $\Lambda \subset \mathbb{R}^4_+$ and their stability analysis.

4.1. **Existence of the equilibria.** To find the possible equilibria, we consider the system of equations:

$$\begin{cases} \alpha - \Big(\theta_1 A H_1 \Big(1+\mu_2 H_2\Big)^{-1} + \theta_2 A H_2 + 1\Big) H_0 = 0, \\ \Big(\rho\theta_1 H_0 A \Big(1+\mu_2 H_2\Big)^{-1} - 1\Big) H_1 = 0, \\ \Big(\rho\theta_2 H_0 A \Big(1+\mu_2 H_2\Big)\Big(1+\mu_1 H_1+\mu_2 H_2\Big)^{-1} - 1\Big) H_2 = 0, \\ \chi - \Big(H_1 + H_2 + \nu\Big) A = 0, \end{cases} \tag{4.1}$$

that follows from system (2.5). Analyzing the second and third equations of this system, we see that, depending on the vanishing of the variables H_1 and H_2, the following four cases are possible.

Case 1. Let $H_1 = 0$ and $H_2 = 0$. Then, from the first and fourth equations of system (4.1), we find the corresponding values $H_0 = \alpha$ and $A = \nu^{-1}\chi$. Therefore, there is the equilibrium:

$$\Delta_0 = \big(\alpha, 0, 0, \nu^{-1}\chi\big)^\top,$$

which is located on the boundary of the region Λ.

Case 2. Let $H_1 = 0$ and $H_2 > 0$. Then, the first, third and forth equations of system (4.1) give us the equilibrium:

$$\Delta_1 = \left(\frac{\alpha\rho+\nu}{\rho(\chi\theta_2+1)}, 0, \frac{\alpha\rho\chi\theta_2-\nu}{\chi\theta_2+1}, \frac{\chi\theta_2+1}{\theta_2(\alpha\rho+\nu)}\right)^\top.$$

It is easy to see that inequality (2.6) guarantees the location of Δ_1 on the boundary of the region Λ.

Case 3. Let $H_1 > 0$ and $H_2 = 0$. Then, the first, second and forth equations of system (4.1) lead us to the equilibrium:

$$\Delta_2 = \left(\frac{\alpha\rho+\nu}{\rho(\chi\theta_1+1)}, \frac{\alpha\rho\chi\theta_1-\nu}{\chi\theta_1+1}, 0, \frac{\chi\theta_1+1}{\theta_1(\alpha\rho+\nu)}\right)^\top,$$

which, again due to inequality (2.6), is located on the boundary of the region Λ.

Case 4. Let $H_1 > 0$ and $H_2 > 0$. We introduce an auxiliary variable $z = \rho H_0 A \geq 0$. Then, the second equation of system (4.1) implies the expression:

$$H_2 = \mu_2^{-1}(\theta_1 z - 1), \tag{4.2}$$

when $z > \theta_1^{-1}$. The third equation of the same system leads us to equality:

$$H_1 = \mu_1^{-1}\theta_1 z(\theta_2 z - 1), \tag{4.3}$$

which is valid for $z > \theta_2^{-1}$. Therefore, the consequence arguments of this case we will carry out for $z > z_0$, where $z_0 = \min\{\theta_1^{-1}; \theta_2^{-1}\}$. Let us note that relationship (2.6) implies the inequality:

$$z_0 < z_1, \tag{4.4}$$

where $z_1 = \alpha\rho\chi\nu^{-1}$.

Next we substitute formulas (4.2) and (4.3) into the last equation of system (4.1). As a result, the following formula can be obtained:

$$A = \chi\left[\mu_1^{-1}\theta_1 z(\theta_2 z - 1) + \mu_2^{-1}(\theta_1 z - 1) + \nu\right]^{-1}. \tag{4.5}$$

Substituting (4.5) into the definition of the variable z, we find the expression:

$$H_0 = (\rho\chi)^{-1} z\left[\mu_1^{-1}\theta_1 z(\theta_2 z - 1) + \mu_2^{-1}(\theta_1 z - 1) + \nu\right]. \tag{4.6}$$

Now, let us write through the variable z the first equation of system (4.1). For this, we substitute formulas (4.2), (4.3) and (4.5), (4.6) into it. After the necessary transformations, the following equation can be found:

$$q(z) = h(z), \tag{4.7}$$

where the functions $q(z)$ and $h(z)$ are defined as

$$q(z) = \alpha\rho\chi z^{-1} - \nu,$$
$$h(z) = \mu_1^{-1}\theta_1(z + \chi)(\theta_2 z - 1) + \mu_2^{-1}(\chi\theta_2 + 1)(\theta_1 z - 1).$$

Next, we study the solvability of equation (4.7) for $z > z_0$.

For this, let us establish the properties of the functions $q(z)$ and $h(z)$. It is easy to see that the function $q(z)$ is a hyperbola for which the following limit relationships hold:

$$\lim_{z\to+0} q(z) = +\infty, \quad \lim_{z\to+\infty} q(z) = -\nu,$$

as well as the equality $q(z_1) = 0$. This equality and (4.4) imply the inequality $q(z_0) > 0$.

The function $h(z)$ is a parabola opened upwards for which we have the relationship:

$$h(0) = -\mu_1^{-1}\chi\theta_1 - \mu_2^{-1}(\chi\theta_2 + 1) < 0.$$

Its derivative $h'(z)$ is determine by the formula:

$$h'(z) = \mu_1^{-1}\theta_1(\theta_2 z - 1) + \mu_1^{-1}\theta_1\theta_2(z + \chi) + \mu_2^{-1}\theta_1(\chi\theta_2 + 1).$$

Now, let us look at all possible relations between the parameters θ_1 and θ_2. The following three situations occur.

(a) Let $\theta_1 = \theta_2 = \theta$, then $z_0 = \theta^{-1}$. It is easy to see that $h(z_0) = 0$ and $h'(z_0) > 0$. The properties of the functions $q(z)$ and $h(z)$ lead us to the conclusion that on the interval $[z_0, z_1]$ the function $q(z)$ decreases from the positive value $q(z_0)$ to a zero value at $z = z_1$, and the function $h(z)$, on the contrary, increases from a zero value at $z = z_0$ to the positive value

$h(z_1)$. Therefore, on the interval (z_0, z_1) there is a unique solution $z_\star$ for equation (4.7).

(b) Let $\theta_1 < \theta_2$, then $z_0 = \theta_1^{-1}$. It is easy to calculate that

$$h(z_0) = (\mu_1\theta_1)^{-1}(\chi\theta_1 + 1)(\theta_2 - \theta_1) > 0,$$
$$h'(z_0) = \mu_1^{-1}(\theta_2 - \theta_1) + \mu_1^{-1}\theta_2(\chi\theta_1 + 1) + \mu_2^{-1}\theta_1(\chi\theta_2 + 1) > 0.$$

Therefore, the properties of the functions $q(z)$ and $h(z)$ lead us to the following conclusion. On the interval $[z_0, z_1]$ the function $q(z)$ decreases from the positive value $q(z_0)$ to a zero value at $z = z_1$, and the function $h(z)$, on the contrary, increases from the positive value $h(z_0)$ to also the positive value $h(z_1)$. Moreover, equation (4.7) has for $z > z_0$ a unique solution $z_\star$ if the inequality:

$$q(z_0) > h(z_0) \tag{4.8}$$

holds, which due to the definitions of the functions $q(z)$, $h(z)$ and the value z_0 leads us to the inequality:

$$\theta_2 < f(\theta_1), \tag{4.9}$$

where the function $f(\theta_1)$ is given by the formula:

$$f(\theta_1) = \theta_1 + \mu_1\theta_1(\alpha\rho\chi\theta_1 - \nu)(\chi\theta_1 + 1)^{-1}.$$

It is easy to see that this function is increasing and convex.

(c) Let $\theta_1 > \theta_2$, then $z_0 = \theta_2^{-1}$. Again we calculate the values:

$$h(z_0) = (\mu_2\theta_2)^{-1}(\chi\theta_2 + 1)(\theta_1 - \theta_2) > 0,$$
$$h'(z_0) = \left(\mu_1^{-1} + \mu_2^{-1}\right)\theta_1(\chi\theta_2 + 1) > 0.$$

Therefore, we again carry out the corresponding arguments of the previous situation with the only difference that by the definition of the value z_0, inequality (4.8) implies the inequality:

$$\theta_1 < g(\theta_2), \tag{4.10}$$

where the function $g(\theta_2)$ is determined by the formula:

$$g(\theta_2) = \theta_2 + \mu_2\theta_2(\alpha\rho\chi\theta_2 - \nu)(\chi\theta_2 + 1)^{-1},$$

from which it is clear that this function is also increasing and convex.

Inequalities (4.9) and (4.10) imply the introduction in the positive quarter $\mathbb{R}^2_+$ of the coordinate system (θ_1, θ_2) the following sets:

$$A = \Big\{(\theta_1, \theta_2)^\top : \theta_1 > 0,\ \theta_2 > 0,\ \theta_2 > f(\theta_1)\Big\},$$
$$B = \Big\{(\theta_1, \theta_2)^\top : \theta_1 > 0,\ \theta_2 > 0,\ \theta_1 < g(\theta_2),\ \theta_2 < f(\theta_1)\Big\},$$
$$C = \Big\{(\theta_1, \theta_2)^\top : \theta_1 > 0,\ \theta_2 > 0,\ \theta_1 > g(\theta_2)\Big\}.$$

Their location is given on Figure 1. In addition, we select the curves $\theta_2 = f(\theta_1)$ and $\theta_1 = g(\theta_2)$ located in $\mathbb{R}^2_+$.

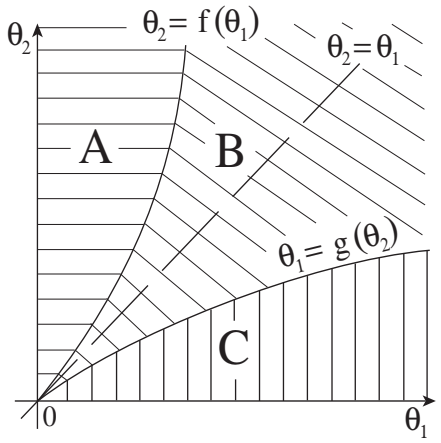

FIGURE 1. The location of sets A, B and C in the positive quadrant $\mathbb{R}^2_+$.

The considered situations (a)–(c) show that equation (4.7) for $z > z_0$ has a unique solution $z_\star \in (z_0, z_1)$, if only the point $(\theta_1, \theta_2)^\top$ is in the set B. If it is located in the sets A and C, or on the curves $\theta_2 = f(\theta_1)$ and $\theta_1 = g(\theta_2)$, the required solution is absent.

Then, for $(\theta_1, \theta_2)^\top \in B$ there exists the equilibrium:

$$\Delta_\star = (H_0^\star, H_1^\star, H_2^\star, A_\star)^\top,$$

which is located inside the region Λ. Here the values $H_0^\star$, $H_1^\star$, $H_2^\star$ and $A_\star$ are defined through the root $z_\star$ due to formulas (4.2), (4.3) and (4.5), (4.6). If the point $(\theta_1, \theta_2)^\top$ is in the sets A and C or on the curves $\theta_2 = f(\theta_1)$ and $\theta_1 = g(\theta_2)$, then this equilibrium does not exist.

We also note that the analysis of Case 4 is not presented in [10, 26].

4.2. **Local stability.** For local stability analysis we will evaluate the Jacobian matrix J at every equilibrium Δ_0, Δ_1, Δ_2 and $\Delta_\star$. Let us study each equilibrium separately.

• Let us consider the equilibrium Δ_0. The corresponding Jacobian matrix $J(\Delta_0)$ is written as follows

$$\begin{pmatrix} -1 & -\alpha\chi\theta_1\nu^{-1} & -\alpha\chi\theta_2\nu^{-1} & 0 \\ 0 & \nu^{-1}(\alpha\rho\chi\theta_1 - \nu) & 0 & 0 \\ 0 & 0 & \nu^{-1}(\alpha\rho\chi\theta_2 - \nu) & 0 \\ 0 & -\nu^{-1}\chi & -\nu^{-1}\chi & -\nu \end{pmatrix}.$$

The behavior of trajectories of system (2.5) near the equilibrium Δ_0 depends on the eigenvalues of this Jacobian matrix. It is easy to see that by (2.6) it has two positive eigenvalues $\nu^{-1}(\alpha\rho\chi\theta_1 - \nu)$ and $\nu^{-1}(\alpha\rho\chi\theta_2 - \nu)$, and also two negative eigenvalues (-1) and $(-\nu)$. Therefore, as follows from the results of § 5.8 ([28]), the equilibrium Δ_0 is unstable.

• Let us consider the equilibrium Δ_1. The corresponding Jacobian matrix $J(\Delta_1)$ has the form:

$$\begin{pmatrix} -\frac{\alpha\rho(\chi\theta_2+1)}{\alpha\rho+\nu} & -\frac{\theta_1(\chi\theta_2+1)}{\rho\theta_2[(\chi\theta_2+1)+\mu_2(\alpha\rho\chi\theta_2-\nu)]} & -\frac{1}{\rho} & -\frac{\theta_2(\alpha\rho+\nu)(\alpha\rho\chi\theta_2-\nu)}{\rho(\chi\theta_2+1)^2} \\ 0 & \left(\frac{\theta_1(\chi\theta_2+1)}{\theta_2[(\chi\theta_2+1)+\mu_2(\alpha\rho\chi\theta_2-\nu)]}-1\right) & 0 & 0 \\ \frac{\rho(\alpha\rho\chi\theta_2-\nu)}{\alpha\rho+\nu} & -\frac{\mu_1(\alpha\rho\chi\theta_2-\nu)}{\chi\theta_2+1} & 0 & \frac{\theta_2(\alpha\rho+\nu)(\alpha\rho\chi\theta_2-\nu)}{(\chi\theta_2+1)^2} \\ 0 & -\frac{\chi\theta_2+1}{\theta_2(\alpha\rho+\nu)} & -\frac{\chi\theta_2+1}{\theta_2(\alpha\rho+\nu)} & -\frac{\chi\theta_2(\alpha\rho+\nu)}{\chi\theta_2+1} \end{pmatrix}.$$

Again, the behavior of trajectories of system (2.5) near the equilibrium Δ_1 depends on the eigenvalues of this Jacobian matrix, which, as it is easy to see, after the necessary transformations satisfy the equation:

$$\begin{aligned} &\left[\lambda-\left(\frac{\theta_1(\chi\theta_2+1)}{\theta_2\left[(\chi\theta_2+1)+\mu_2(\alpha\rho\chi\theta_2-\nu)\right]}-1\right)\right] \\ &\times\Big[\lambda^3+\left(\frac{\chi\theta_2(\alpha\rho+\nu)}{\chi\theta_2+1}+\frac{\alpha\rho(\chi\theta_2+1)}{\alpha\rho+\nu}\right)\lambda^2 \\ &\quad+\left(\alpha\rho\chi\theta_2+\frac{\alpha\rho\chi\theta_2-\nu}{\chi\theta_2+1}+\frac{\alpha\rho\chi\theta_2-\nu}{\alpha\rho+\nu}\right)\lambda+(\alpha\rho\chi\theta_2-\nu)\Big]=0. \end{aligned} \tag{4.11}$$

Analyzing this equation we see that due to the definition of the function $\theta_1 = g(\theta_2)$, one eigenvalue is given by the formula:

$$\lambda=\frac{\chi\theta_2+1}{\theta_2\left[(\chi\theta_2+1)+\mu_2(\alpha\rho\chi\theta_2-\nu)\right]}(\theta_1-g(\theta_2)), \tag{4.12}$$

and the other three eigenvalues are the roots of the cubic equation:

$$\begin{aligned} &\lambda^3+\left(\frac{\chi\theta_2(\alpha\rho+\nu)}{\chi\theta_2+1}+\frac{\alpha\rho(\chi\theta_2+1)}{\alpha\rho+\nu}\right)\lambda^2 \\ &\quad+\left(\alpha\rho\chi\theta_2+\frac{\alpha\rho\chi\theta_2-\nu}{\chi\theta_2+1}+\frac{\alpha\rho\chi\theta_2-\nu}{\alpha\rho+\nu}\right)\lambda+(\alpha\rho\chi\theta_2-\nu)=0, \end{aligned} \tag{4.13}$$

in which by (2.6) all coefficients are positive. Moreover, the determinant of the matrix:

$$\begin{pmatrix} \left(\frac{\chi\theta_2(\alpha\rho+\nu)}{\chi\theta_2+1}+\frac{\alpha\rho(\chi\theta_2+1)}{\alpha\rho+\nu}\right) & 1 \\ (\alpha\rho\chi\theta_2-\nu) & \left(\alpha\rho\chi\theta_2+\frac{\alpha\rho\chi\theta_2-\nu}{\chi\theta_2+1}+\frac{\alpha\rho\chi\theta_2-\nu}{\alpha\rho+\nu}\right) \end{pmatrix}$$

constructed from the coefficients of equation (4.13), is also positive. When this fact is proven, the following equality is useful:

$$\begin{aligned} \alpha\rho\chi\theta_2-\nu=&\frac{\alpha\rho(\chi\theta_2+1)}{\alpha\rho+\nu}\cdot\frac{\alpha\rho\chi\theta_2-\nu}{\chi\theta_2+1}+\frac{\chi\theta_2(\alpha\rho+\nu)}{\chi\theta_2+1}\cdot\frac{\alpha\rho\chi\theta_2-\nu}{\alpha\rho+\nu} \\ &-\frac{\alpha\rho\chi\theta_2-\nu}{\chi\theta_2+1}\cdot\frac{\alpha\rho\chi\theta_2-\nu}{\alpha\rho+\nu}. \end{aligned}$$

Then, due to the Routh-Hurwitz criterion ([9]), all the roots of equation (4.13) have negative real parts. Therefore, by virtue of formula (4.12), the local asymptotic stability or instability of the equilibrium Δ_1 depends on where the point $(\theta_1,\theta_2)^\top$ is in $\mathbb{R}^2_+$. If it is in the set A or B, or on the curve $\theta_2 = f(\theta_1)$, then the equilibrium Δ_1 is locally asymptotically stable, and if the point $(\theta_1,\theta_2)^\top$ falls into the set C,

then this equilibrium is unstable. Finally, if $(\theta_1,\theta_2)^\top$ is on the curve $\theta_1 = g(\theta_2)$, then the eigenvalue given by formula (4.12) becomes zero and nothing can be said about the stability of the equilibrium Δ_1. More detailed studies are needed.

• Let us consider the equilibrium Δ_2. The corresponding Jacobian matrix $J(\Delta_2)$ is written as follows

$$\begin{pmatrix} -\frac{\alpha\rho(\chi\theta_1+1)}{\alpha\rho+\nu} & -\frac{1}{\rho} & \left(\frac{\mu_2(\alpha\rho\chi\theta_1-\nu)}{\rho(\chi\theta_1+1)} - \frac{\theta_2}{\rho\theta_1}\right) & -\frac{\theta_1(\alpha\rho+\nu)(\alpha\rho\chi\theta_1-\nu)}{\rho(\chi\theta_1+1)^2} \\ \frac{\rho(\alpha\rho\chi\theta_1-\nu)}{\alpha\rho+\nu} & 0 & -\frac{\mu_2(\alpha\rho\chi\theta_1-\nu)}{\chi\theta_1+1} & \frac{\theta_1(\alpha\rho+\nu)(\alpha\rho\chi\theta_1-\nu)}{(\chi\theta_1+1)^2} \\ 0 & 0 & \left(\frac{\theta_2(\chi\theta_1+1)}{\theta_1[(\chi\theta_1+1)+\mu_1(\alpha\rho\chi\theta_1-\nu)]} - 1\right) & 0 \\ 0 & -\frac{\chi\theta_1+1}{\theta_1(\alpha\rho+\nu)} & -\frac{\chi\theta_1+1}{\theta_1(\alpha\rho+\nu)} & -\frac{\chi\theta_1(\alpha\rho+\nu)}{\chi\theta_1+1} \end{pmatrix}.$$

Again, the behavior of trajectories of system (2.5) near the equilibrium Δ_2 depends on the eigenvalues of this Jacobian matrix, which, as it is easy to see, after the necessary transformations satisfy the equation:

$$\begin{aligned} &\left[\lambda - \left(\frac{\theta_2(\chi\theta_1+1)}{\theta_1\left[(\chi\theta_1+1)+\mu_1(\alpha\rho\chi\theta_1-\nu)\right]} - 1\right)\right] \\ &\times\Big[\lambda^3 + \left(\frac{\chi\theta_1(\alpha\rho+\nu)}{\chi\theta_1+1} + \frac{\alpha\rho(\chi\theta_1+1)}{\alpha\rho+\nu}\right)\lambda^2 \\ &\quad + \left(\alpha\rho\chi\theta_1 + \frac{\alpha\rho\chi\theta_1-\nu}{\chi\theta_1+1} + \frac{\alpha\rho\chi\theta_1-\nu}{\alpha\rho+\nu}\right)\lambda + (\alpha\rho\chi\theta_1-\nu)\Big] = 0. \end{aligned} \tag{4.14}$$

Analyzing this equation we see that it is similar to equation (4.11). Then, due to the definition of the function $\theta_2 = f(\theta_1)$, one eigenvalue is given by the formula:

$$\lambda = \frac{\chi\theta_1+1}{\theta_1\left[(\chi\theta_1+1)+\mu_1(\alpha\rho\chi\theta_1-\nu)\right]}(\theta_2 - f(\theta_1)), \tag{4.15}$$

and the remaining three eigenvalues satisfy a cubic equation similar to (4.13). Therefore, all the arguments made earlier are true here. According to them, the local asymptotic stability or instability of the equilibrium Δ_2 depends, by virtue of formula (4.15), on where the point $(\theta_1,\theta_2)^\top$ is in $\mathbb{R}^2_+$. If it is in the set B or C, or on the curve $\theta_1 = g(\theta_2)$, then the equilibrium Δ_2 is locally asymptotically stable, and if the point $(\theta_1,\theta_2)^\top$ falls into the set A, then the equilibrium Δ_2 is unstable. Finally, if $(\theta_1,\theta_2)^\top$ is on the curve $\theta_2 = f(\theta_1)$, then the eigenvalue determined by formula (4.15) becomes zero and nothing can be said about stability. More detailed studies are needed.

• Let us consider the equilibrium $\Delta_\star$. Using the equations of system (4.1), we write the corresponding Jacobian matrix $J(\Delta_\star)$ in terms of the values $H_0^\star$, $H_1^\star$, $H_2^\star$, $A_\star$ as follows

$$\begin{pmatrix} -\frac{\alpha}{H_0^\star} & -\frac{1}{\rho} & \left(\frac{\mu_2 H_1^\star}{\rho^2\theta_1 H_0^\star A_\star} - \theta_2 H_0^\star A_\star\right) & -\frac{\alpha - H_0^\star}{A_\star} \\ \frac{H_1^\star}{H_0^\star} & 0 & -\frac{\mu_2 H_1^\star}{\rho\theta_1 H_0^\star A_\star} & \frac{H_1^\star}{A_\star} \\ \frac{H_2^\star}{H_0^\star} & -\frac{\mu_1 H_2^\star}{\rho^2\theta_1\theta_2(H_0^\star A_\star)^2} & \frac{\mu_1\mu_2 H_1^\star H_2^\star}{\rho^3\theta_1^2\theta_2(H_0^\star A_\star)^3} & \frac{H_2^\star}{A_\star} \\ 0 & -A_\star & -A_\star & -\frac{\chi}{A_\star} \end{pmatrix}.$$

As with the previous equilibria, the behavior of trajectories of system (2.5) near the equilibrium $\Delta_\star$, when it exists, depends on the eigenvalues of this Jacobian matrix,

which are the roots of the corresponding characteristic equation:

$$\lambda^4 - d_1\lambda^3 + d_2\lambda^2 - d_3\lambda + d_4 = 0, \tag{4.16}$$

where d_1 is the trace of the matrix $J(\Delta_\star)$, and d_4 is its determinant. The coefficients d_2 and d_3 are found by the corresponding formulas through the elements of the matrix $J(\Delta_\star)$ ([9]). We note that the equations (4.11) and (4.14) are also characteristic equations for the corresponding matrices $J(\Delta_1)$ and $J(\Delta_2)$.

Now we evaluate the determinant of the matrix $J(\Delta_\star)$. To do this, we first extract the values $H_1^\star$, $H_2^\star$, $(-A_\star)$ from its second, third, and fourth rows, respectively. Then, from its first and last columns, the corresponding values $(H_0^\star)^{-1}$ and $A_\star^{-1}$ are extracted as well. As a result, we have the determinant:

$$d_4 = -H_1^\star H_2^\star (H_0^\star)^{-1}$$

$$\times \begin{bmatrix} -\alpha & -\frac{1}{\rho} & \left(\frac{\mu_2 H_1^\star}{\rho^2\theta_1 H_0^\star A_\star} - \theta_2 H_0^\star A_\star\right) & -(\alpha - H_0^\star) \\ 1 & 0 & -\frac{\mu_2}{\rho\theta_1 H_0^\star A_\star} & 1 \\ 1 & -\frac{\mu_1}{\rho^2\theta_1\theta_2(H_0^\star A_\star)^2} & \frac{\mu_1\mu_2 H_1^\star}{\rho^3\theta_1^2\theta_2(H_0^\star A_\star)^3} & 1 \\ 0 & 1 & 1 & \frac{\chi}{A_\star} \end{bmatrix}.$$

Now, we subtract the first column from the last column in it, and then decompose the resulting determinant on the last column. After the necessary transformations, we have the expression:

$$\begin{aligned} d_4 = &- H_1^\star H_2^\star \left[\left(\frac{\mu_1}{\rho^2\theta_1\theta_2(H_0^\star A_\star)^2} + \frac{\mu_2}{\rho\theta_1 H_0^\star A_\star} + \frac{\mu_1\mu_2 H_1^\star}{\rho^3\theta_1^2\theta_2(H_0^\star A_\star)^3} \right) \right. \\ &\left. + \frac{\chi}{H_0^\star A_\star} \left(\frac{\mu_1 + 1}{\rho^2\theta_1 H_0^\star A_\star} + \frac{\alpha\mu_1\mu_2}{\rho^3\theta_1^2\theta_2(H_0^\star A_\star)^3} \right) \right], \end{aligned}$$

which is negative. Therefore, the characteristic equation (4.16) has at least one positive root. Then, according to the results of § 5.8 ([28]), the equilibrium $\Delta_\star$ is unstable, when it exists.

Finally, we summarize all the previously obtained results in Table 1.

	$(\theta_1,\theta_2)^\top \in A$	$\theta_2 = f(\theta_1)$	$(\theta_1,\theta_2)^\top \in B$	$\theta_1 = g(\theta_2)$	$(\theta_1,\theta_2) \in C$
Δ_0	unstable	unstable	unstable	unstable	unstable
Δ_1	local asymptotically stable	local asymptotically stable	local asymptotically stable	it is necessary further investigations	unstable
Δ_2	unstable	it is necessary further investigations	local asymptotically stable	local asymptotically stable	local asymptotically stable
$\Delta_\star$	does not exist	does not exist	unstable	does not exist	does not exist

TABLE 1. Final results on the stability of equilibria.

4.3. **Bifurcation analysis.** Bifurcation can be observed in the behavior of the equilibria Δ_1, Δ_2 and $\Delta_\star$, when the point $(\theta_1, \theta_2)^\top$ moves in the positive quadrant $\mathbb{R}^2_+$ between the regions A, B and C. The above analysis of the existence of the root $z_\star$ for equation (4.7) on the interval (z_0, z_1) can be supplemented by a natural possibility $z_\star = z_0$. Moreover, if $\theta_1 > \theta_2$, then it is obvious that $z_\star = \theta_2^{-1}$. Formulas (4.2), (4.3) and (4.5), (4.6) show that the point $(\theta_1, \theta_2)^\top$ falls on the curve $\theta_1 = g(\theta_2)$, and the equilibrium $\Delta_\star$ coincides with Δ_1. Otherwise, when $\theta_1 < \theta_2$, then $z_\star = \theta_1^{-1}$. These formulas lead us to the conclusion that the point $(\theta_1, \theta_2)^\top$ is on the curve $\theta_2 = f(\theta_1)$, and the equilibrium $\Delta_\star$ coincides with Δ_2.

Bifurcation is observed when the point $(\theta_1, \theta_2)^\top$ being in the region B, where the equilibrium $\Delta_\star$ exists and is unstable, and Δ_1, Δ_2 are simultaneously locally asymptotically stable, moves, for example, to the boundary between the regions B and C (see Figure 1). Then, the equilibrium $\Delta_\star$ also moves to Δ_1 and coincides with it as soon as the point $(\theta_1, \theta_2)^\top$ falls on the curve $\theta_1 = g(\theta_2)$. In this case, the equilibrium Δ_1 ceases to be locally asymptotically stable and becomes unstable, when the point $(\theta_1, \theta_2)^\top$ appears in the region C. A similar behavior is observed when this point moves toward the boundary $\theta_2 = f(\theta_1)$ between the regions A and B (see Figure 1). Then the equilibrium $\Delta_\star$ again moves to Δ_2 and coincides with it as soon as the point $(\theta_1, \theta_2)^\top$ appears on the curve $\theta_2 = f(\theta_1)$. In this case, the equilibrium Δ_2 ceases to be locally asymptotically stable and becomes unstable, when this point is in the region A.

5. Numerical results for uncontrolled system

Let us add to system (2.5) the positive initial conditions:

$$H_0(0) = H_0^0 > 0,\ H_1(0) = H_1^0 > 0,\ H_2(0) = H_2^0 > 0,\ A(0) = A_0 > 0, \tag{5.1}$$

and then we will consider it on a given time interval $[0, T]$.

Then, the continuation of the solution to system (2.5) with the initial conditions (5.1) and the bounds of change of its components are established by the following lemma.

Lemma 5.1. *The solution* $(H_0(t), H_1(t), H_2(t), A(t))^\top$ *for system* (2.5) *with initial conditions* (5.1) *is defined on the entire interval* $[0, T]$ *and on which its components satisfy the inequalities:*

$$\begin{aligned} &0 < H_0(t) < H_0^{\max},\ \ 0 < H_1(t) < H_1^{\max}, \\ &0 < H_2(t) < H_2^{\max},\ \ 0 < A(t) < A_{\max}, \end{aligned} \tag{5.2}$$

where

$$\begin{aligned} &H_0^{\max} = H_0^0 + \alpha T, \quad A_{\max} = A_0 + \chi T, \\ &H_1^{\max} = H_1^0 e^{\rho\theta_1 H_0^{\max} A_{\max} T}, \quad H_2^{\max} = H_2^0 e^{\rho\theta_2 H_0^{\max} A_{\max} T}. \end{aligned}$$

Proof. Let the solution $(H_0(t), H_1(t), H_2(t), A(t))^\top$ be defined on some interval $[0, t_1)$, which is the maximum possible interval of its existence. Then, the positivity of the components $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ is justified as in Lemma 3.1. The right bounds in the first and last inequalities from (5.2) follow from differential inequalities (3.1), (3.2) and their subsequent integration with the corresponding

initial conditions from (5.1). For the second and third inequalities from (5.2), the following differential inequalities can be written:

$$H_1'(t) < \rho\theta_1 H_0^{\max} A_{\max} H_1(t), \quad H_2'(t) < \rho\theta_2 H_0^{\max} A_{\max} H_2(t).$$

Integrating them with the corresponding initial conditions from (5.1), we find the right bounds in the second and third inequalities from (5.2).

Thus, we substantiated the validity of inequalities (5.2) on the maximum possible interval $[0, t_1)$ of existence of the solution $(H_0(t), H_1(t), H_2(t), A(t))^\top$. If $t_1 > T$, then the required fact is established. If $t_1 \leq T$, then this fact follows from inequalities (5.2) and the possibility of continuation of the solution $(H_0(t), H_1(t), H_2(t), A(t))^\top$ for the entire interval $[0, T]$ ([11]). □

Figures 2–7 show the graphs of the components $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ of the solution $(H_0(t), H_1(t), H_2(t), A(t))^\top$ obtained by numerically integrating the system (2.5) with the initial conditions (5.1). We wrote a computer program in MAPLE-15 for the following values of the parameters:

$$\begin{array}{llll} \alpha = 10.0 & \rho = 8.0 & \nu = 0.001 & \chi \in \{0.1; 1.0; 5.0\} \\ \mu_1 = 0.2 & \mu_2 = 0.1 & \theta_1 = 1.0 & \theta_2 = 1.02 \qquad T = 30 \\ H_0^0 = 10.0 & H_1^0 = 10.0 & H_2^0 = 20.0 & A_0 \in \{0.05; 15.0\} \end{array}$$

These parameter's values were adopted from [1, 26, 32].

It is easy to check that $\theta_1 = 1.0$ and $\theta_2 = 1.02$ belong to the region B, i.e. $(\theta_1, \theta_2)^\top \in B$. Hence, theoretically we can observe either Δ_1 or Δ_2 equilibria that both are asymptotically stable in this region. Figures 2–4 correspond to the high initial concentration of the allergen $A_0 = 15.0$ and Figures 5–7 to a relatively small concentration of the allergen, $A_0 = 0.05$. In the presented graphs, we also emphasized the importance of the allergen influx rate on the solutions of the system. Thus Figures 2 and 5 show the graphs of $H_0(t)$, $H_1(t)$, $H_2(t)$ and $A(t)$ for $\chi = 0.1$ (the lowest influx rate), Figures 3 and 6 for $\chi = 1.0$ (an average influx rate) and Figures 4 and 7 for $\chi = 5.0$ (the highest influx rate). The concentration of the allergen is shown in blue in a separate graph on the right for each case.

Please note that for the selected initial conditions, the system trajectory is approaching only its equilibrium Δ_1. This equilibrium point is characterized by zero value for the second component, H_1. However, the allergen concentration does not ever become zero, but is given by the formula of $(\chi\theta_2 + 1)/(\theta_2(\alpha\rho + \nu))$. For example, for $\chi = 0.1$ and $A_0 = 15.0$ (Figure 2) it should be close to 0.0134, while for $\chi = 5.0$ and $A_0 = 15.0$ (Figure 4) it should approach the value of 0.075, which are, of course, hard to see in the graphs compared to the initial value of the allergen (15.0). The dynamics of the allergen and its nonzero equilibrium value is clearly seen in Figures 5–7 at the small initial value of the allergen ($A_0 = 0.05$) and different influx rates. Thus, in Figure 5 for the influx rate of the allergen $\chi = 0.1$, we can see that the concentration of the allergen is approaching the value of 0.0135, that also can be approximated by the same formula above.

Figures 2–4 correspond to the value $A_0 = 15.0$, and Figures 5–7 relate to the value $A_0 = 0.05$. Figures 2 and 5 show the graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ for $\chi = 0.1$, Figures 3 and 6 give the graphs of the same functions for $\chi = 1.0$, and finally, Figures 4 and 7 depict the graphs of such functions for $\chi = 5.0$.

On each such figure, on the left there are the graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$, and on the right there is the graph of the function $A(t)$: $H_0(t)$ is shown as a red curve, $H_1(t)$ as blue and $H_2(t)$ as a green curves, $A(t)$ is shown in blue.

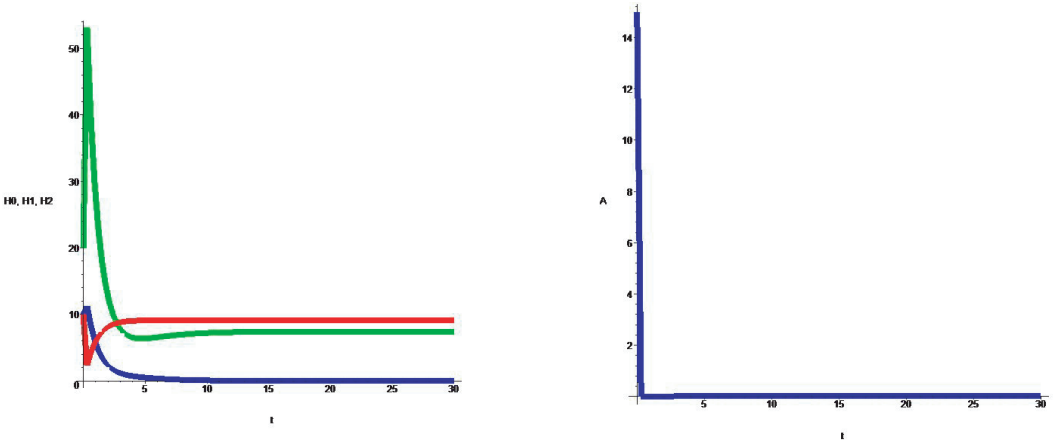

FIGURE 2. Graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$ (left) and $A(t)$ (right) for $\chi = 0.1$ and $A_0 = 15.0$.

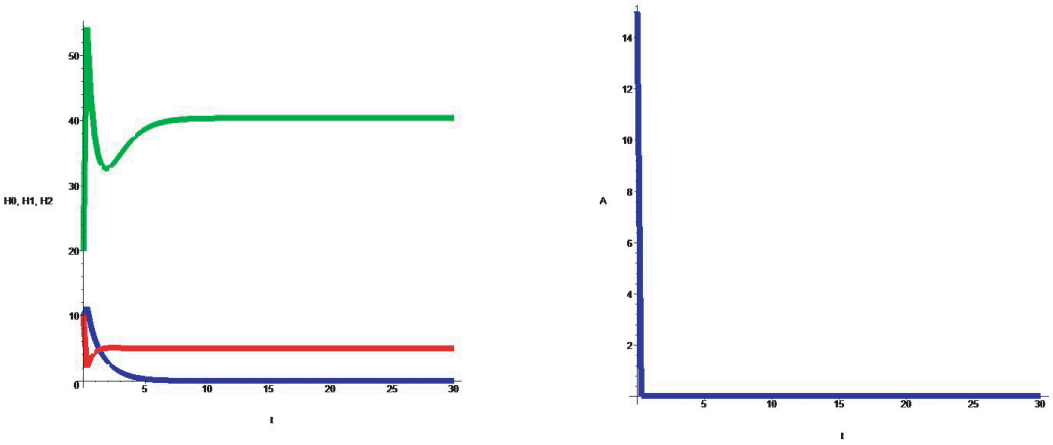

FIGURE 3. Graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$ (left) and $A(t)$ (right) for $\chi = 1.0$ and $A_0 = 15.0$.

Analyzing the graphs presented in Figures 2–7, we can make the following conclusions:

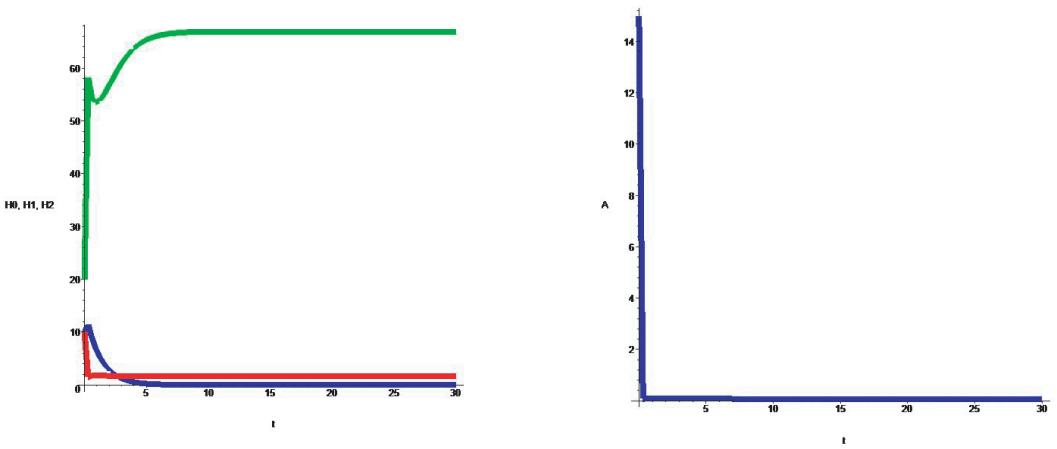

FIGURE 4. Graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$ (left) and $A(t)$ (right) for $\chi = 5.0$ and $A_0 = 15.0$.

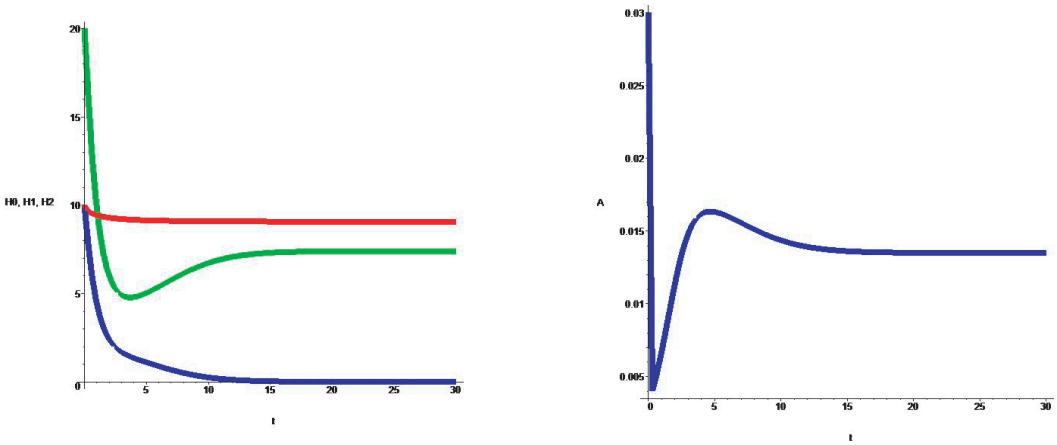

FIGURE 5. Graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$ (left) and $A(t)$ (right) for $\chi = 0.1$ and $A_0 = 0.05$.

- with an increase of the influx rate χ of the allergen, the values of $H_2(t)$ become larger, and the values of $H_1(t)$ smaller. Thus, the absolute value of the difference between $H_2(t)$ and $H_1(t)$ increases. (This is clearly seen on the left in Figures 2–4 ($A_0 = 15.0$), or in Figures 5–7 ($A_0 = 0.05$)).
- with an increase of the influx rate χ of the allergen, $H_0(t)$, $H_1(t)$ and $H_2(t)$ move to their saturation states more quickly.
- allergen concentration $A(t)$ drops to a very small but non-zero value, reaching a state of equilibrium. At the same time, with an increase of the influx rate χ of allergens, this saturation is achieved faster.

Therefore, the "organism" modeled by system (2.5) reacts differently to allergen's invasion and, depending on the initial concentration of the allergen and its influx rate, exhibits slightly different dynamics. However, eventually the system does approach its asymptotically stable equilibrium that does not represent "healthy" state. Instead it moves the system into unhealthy, allergic state.

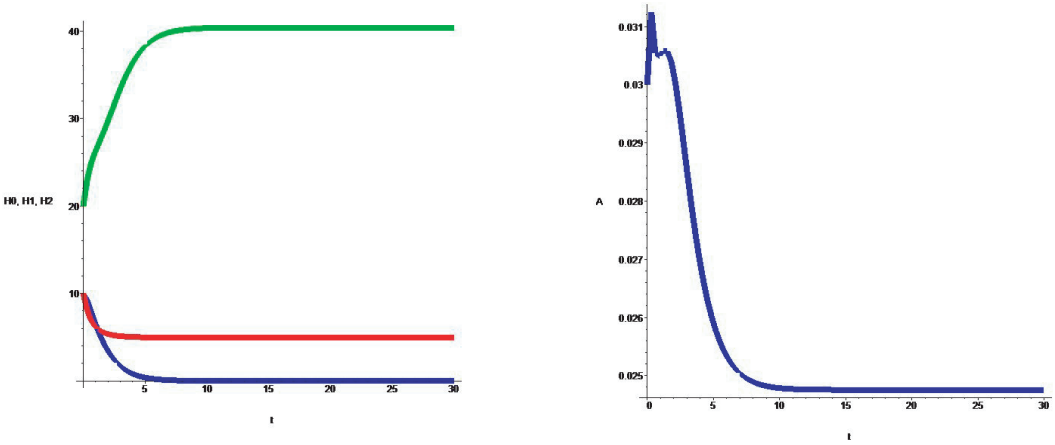

FIGURE 6. Graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$ (left) and $A(t)$ (right) for $\chi = 1.0$ and $A_0 = 0.05$.

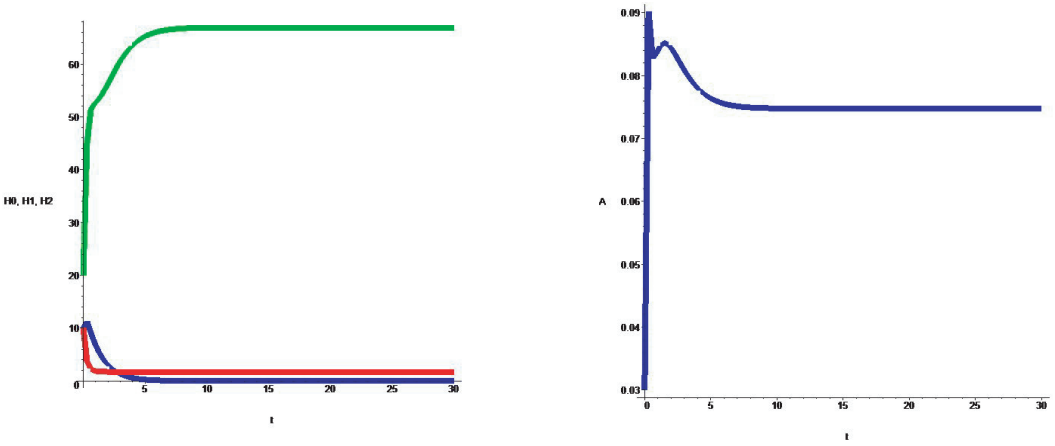

FIGURE 7. Graphs of the functions $H_0(t)$, $H_1(t)$, $H_2(t)$ (left) and $A(t)$ (right) for $\chi = 5.0$ and $A_0 = 0.05$.

6. Optimal control problem and its analysis

As it was noted in the Introduction, during allergy, Th_2-cells dominate over Th_1-cells. Recovering means the transition of these cells to a state, in which a balance is established between Th_1- and Th_2-cells, that is, in some sense, $H_1(t) \approx H_2(t)$.

The numerical calculations from Section 5 showed that even if the influx rate χ of the allergen is small, the immune system cannot recover by itself. Moreover, neither equilibrium Δ_1 nor Δ_2 is suitable for healthy immune state. Therefore, external intervention is necessary, for example, with medication and other indirect measures of impact. And then, the question arises about the effective (optimal) schedule for drug administration together with other indirect impacts.

6.1. **Statement of the optimal control problem.** Taking into account all the above, we will introduce into system (2.5), (5.1) control functions that will reflect the effect of drugs and other indirect impacts on allergy symptoms. During allergy, the mentioned balance between Th_1- and Th_2-cells can be restored again by the following acts:

- suppression of Th_2-cells or decrease in the concentration of Th_2-cells through drugs;
- stimulation of Th_1-cells that means an increase in the concentration of Th_1-cells with drugs;
- reducing the influx rate of allergens that means to reduce their concentration due to indirect impacts or drugs.

These acts carried out by introducing into system (2.5), (5.1) the appropriate control functions of time $u(t)$, $v(t)$ and $w(t)$ satisfying the restrictions:

$$0 \le u(t) \le u_{\max} < 1, \;\; 0 \le v(t) \le v_{\max} < 1, \;\; 0 \le w(t) \le w_{\max} < 1. \tag{6.1}$$

As a result, we obtain the control system of differential equations:

$$\begin{cases} H_0'(t) = \alpha - \theta_1(1+v(t))H_0(t)A(t)H_1(t)\Big(1+\mu_2 H_2(t)\Big)^{-1} \\ \qquad\qquad - \theta_2(1-u(t))H_0(t)A(t)H_2(t) - H_0(t), \\ H_1'(t) = \rho\theta_1(1+v(t))H_0(t)A(t)H_1(t)\Big(1+\mu_2 H_2(t)\Big)^{-1} - H_1(t), \\ H_2'(t) = \rho\theta_2(1-u(t))H_0(t)A(t)H_2(t)\Big(1+\mu_2 H_2(t)\Big) \\ \qquad\qquad \times \Big(1+\mu_1 H_1(t)+\mu_2 H_2(t)\Big)^{-1} - H_2(t), \\ A'(t) = \chi(1-w(t)) - \Big(H_1(t)+H_2(t)+\nu\Big)A(t), \\ H_0(0) = H_0^0,\; H_1(0) = H_1^0,\; H_2(0) = H_2^0,\; A(0) = A_0, \end{cases} \tag{6.2}$$

which we will consider on a given time interval $[0, T]$. Here the values H_0^0, H_1^0, H_2^0 and A_0 are positive. Controls $u(t)$ and $v(t)$ are included in the first three equations of this system, where the corresponding coefficients α_2, β_2 and α_1, β_1 determine the production rates of Th_2- and Th_1-cells (see formulas in (2.4)). Control $w(t)$ is included only in the last equation of system (6.2). We note that when $u(t) \equiv 0$, $v(t) \equiv 0$ and $w(t) \equiv 0$, this system is the original uncontrolled system (2.5).

The set of admissible controls $\Omega(T)$ is all possible triples of Lebesgue measurable functions $(u(t), v(t), w(t))$, which for almost all $t \in [0, T]$ satisfy inequalities (6.1).

It is easy to see that for each solution $(H_0(t), H_1(t), H_2(t), A(t))^\top$ for system (6.2) corresponding to the triple $(u(t), v(t), w(t))$ of the admissible controls, Lemma 5.1 holds. This allows us on the set $\Omega(T)$ to consider for system (6.2) the problem of

minimizing the following objective function:

$$
\begin{aligned}
J(u(\cdot), v(\cdot), w(\cdot)) = 0.5 \int_0^T \Big(H_1(t) - H_2(t)\Big)^2 dt \\
+ 0.5 \int_0^T \Big(au^2(t) + bv^2(t) + cw^2(t)\Big) dt,
\end{aligned} \tag{6.3}
$$

where a, b, c are the positive weighting coefficients. We note that in (6.3) the first term reflects the balance between Th_1- and Th_2-cells, and the second term gives the total cost of allergy treatment.

The boundedness of the components $H_0(t)$, $H_1(t)$, $H_2(t)$, $A(t)$ of the solution $(H_0(t), H_1(t), H_2(t), A(t))^\top$ (see (5.2)) and Theorem 4 ([15], Chapter 4) ensures the existence of the optimal solution in the minimization problem (6.3), which consists of:

- the optimal controls $u_*(t)$, $v_*(t)$ and $w_*(t)$,
- the corresponding components $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$, $A_*(t)$ of the optimal solution $(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t))^\top$ to system (6.2) for these controls.

6.2. **Pontryagin maximum principle.** For the analysis of the controls $u_*(t)$, $v_*(t)$, $w_*(t)$ and the corresponding solution $(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t))^\top$ we apply the Pontryagin maximum principle ([24]).

First, we will perform all the necessary auxiliary actions:

- First, we rewrite system (6.2) as

$$
\begin{cases}
H_0'(t) = H_0(t) f_0(H_0(t), H_1(t), H_2(t), A(t), u(t), v(t)) \\
\qquad = H_0(t)\Big(\alpha H_0^{-1}(t) - \theta_1(1+v(t))A(t)H_1(t)\Big(1+\mu_2 H_2(t)\Big)^{-1} \\
\qquad\qquad - \theta_2(1-u(t))A(t)H_2(t) - 1\Big), \\
H_1'(t) = H_1(t) f_1(H_0(t), H_1(t), H_2(t), A(t), v(t)) \\
\qquad = H_1(t)\Big(\rho\theta_1(1+v(t))H_0(t)A(t)\Big(1+\mu_2 H_2(t)\Big)^{-1} - 1\Big), \\
H_2'(t) = H_2(t) f_2(H_0(t), H_1(t), H_2(t), A(t), u(t)) \\
\qquad = H_2(t)\Big(\rho\theta_2(1-u(t))H_0(t)A(t)\Big(1+\mu_2 H_2(t)\Big) \\
\qquad\qquad \times \Big(1+\mu_1 H_1(t) + \mu_2 H_2(t)\Big)^{-1} - 1\Big), \\
A'(t) = A(t) f_3(H_1(t), H_2(t), A(t), w(t)) \\
\qquad = A(t)\Big(\chi(1-w(t))A^{-1}(t) - H_1(t) - H_2(t) - \nu\Big), \\
H_0(0) = H_0^0,\ H_1(0) = H_1^0,\ H_2(0) = H_2^0,\ A(0) = A_0.
\end{cases} \tag{6.4}
$$

• Second, using this system, we define the Hamiltonian:

$$Q(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = f_0\left(H_0,H_1,H_2,A,u,v\right)H_0\psi_0 + f_1\left(H_0,H_1,H_2,A,v\right)H_1\psi_1 + f_2\left(H_0,H_1,H_2,A,u\right)H_2\psi_2 + f_3\left(H_1,H_2,A,w\right)A\psi_3 - 0.5\Big((H_1-H_2)^2+au^2+bv^2+cw^2\Big),$$

where ψ_0, ψ_1, ψ_2, ψ_3 are the adjoint variables.

• Third, we evaluate all the required partial derivatives of the Hamiltonian with respect to variables H_0, H_1, H_2, A:

$$Q'_{H_0}(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = f_0\left(H_0,H_1,H_2,A,u,v\right)\psi_0 + \frac{\partial f_0}{\partial H_0}\left(H_0,H_1,H_2,A,u,v\right)H_0\psi_0 + \frac{\partial f_1}{\partial H_0}\left(H_0,H_1,H_2,A,v\right)H_1\psi_1 + \frac{\partial f_2}{\partial H_0}\left(H_0,H_1,H_2,A,u\right)H_2\psi_2,$$

$$Q'_{H_1}(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = f_1\left(H_0,H_1,H_2,A,v\right)\psi_1 + \frac{\partial f_0}{\partial H_1}\left(H_0,H_1,H_2,A,u,v\right)H_0\psi_0 + \frac{\partial f_1}{\partial H_1}\left(H_0,H_1,H_2,A,v\right)H_1\psi_1 + \frac{\partial f_2}{\partial H_1}\left(H_0,H_1,H_2,A,u\right)H_2\psi_2 + \frac{\partial f_3}{\partial H_1}\left(H_1,H_2,A,w\right)A\psi_3 - \left(H_1-H_2\right),$$

$$Q'_{H_2}(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = f_2\left(H_0,H_1,H_2,A,u\right)\psi_2 + \frac{\partial f_0}{\partial H_2}\left(H_0,H_1,H_2,A,u,v\right)H_0\psi_0 + \frac{\partial f_1}{\partial H_2}\left(H_0,H_1,H_2,A,v\right)H_1\psi_1 + \frac{\partial f_2}{\partial H_2}\left(H_0,H_1,H_2,A,u\right)H_2\psi_2 + \frac{\partial f_3}{\partial H_2}\left(H_1,H_2,A,w\right)A\psi_3 + \left(H_1-H_2\right),$$

$$Q'_{A}(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = f_3\left(H_1,H_2,A,w\right)\psi_3 + \frac{\partial f_0}{\partial A}\left(H_0,H_1,H_2,A,u,v\right)H_0\psi_0 + \frac{\partial f_1}{\partial A}\left(H_0,H_1,H_2,A,v\right)H_1\psi_1 + \frac{\partial f_2}{\partial A}\left(H_0,H_1,H_2,A,u\right)H_2\psi_2 + \frac{\partial f_3}{\partial A}\left(H_1,H_2,A,w\right)A\psi_3,$$

and also with respect to controls u, v and w:

$$Q'_u(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = \frac{\partial f_0}{\partial u}(H_0,H_1,H_2,A,u,v)H_0\psi_0 + \frac{\partial f_2}{\partial u}(H_0,H_1,H_2,A,u)H_2\psi_2 - au,$$

$$Q'_v(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = \frac{\partial f_0}{\partial v}(H_0,H_1,H_2,A,u,v)H_0\psi_0 + \frac{\partial f_1}{\partial v}(H_0,H_1,H_2,A,v)H_1\psi_1 - bv,$$

$$Q'_w(H_0,H_1,H_2,A,u,v,w,\psi_0,\psi_1,\psi_2,\psi_3) = \frac{\partial f_3}{\partial w}(H_1,H_2,A,w)A\psi_3 - cw.$$

Then, by the Pontryagin maximum principle, for optimal controls $u_*(t)$, $v_*(t)$, $w_*(t)$ and the corresponding optimal solution $(H_0^*(t),H_1^*(t),H_2^*(t),A_*(t))^\top$, there exists the vector-function $\psi_*(t) = (\psi_0^*(t),\psi_1^*(t),\psi_2^*(t),\psi_3^*(t))^\top$, such that:

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

(6.5)
$$
\begin{cases}
\psi_0^{*\prime}(t) = -Q'_{H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t), w_*(t), \psi_0^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t)) \\
\qquad = -f_0\,(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\,\psi_0^*(t) \\
\qquad\quad - \dfrac{\partial f_0}{\partial H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t)) H_0^*(t)\psi_0^*(t) \\
\qquad\quad - \dfrac{\partial f_1}{\partial H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t)) H_1^*(t)\psi_1^*(t) \\
\qquad\quad - \dfrac{\partial f_2}{\partial H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t)) H_2^*(t)\psi_2^*(t), \\
\psi_1^{*\prime}(t) = -Q'_{H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t), w_*(t), \psi_0^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t)) \\
\qquad = -f_1\,(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t))\,\psi_1^*(t) \\
\qquad\quad - \dfrac{\partial f_0}{\partial H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t)) H_0^*(t)\psi_0^*(t) \\
\qquad\quad - \dfrac{\partial f_1}{\partial H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t)) H_1^*(t)\psi_1^*(t) \\
\qquad\quad - \dfrac{\partial f_2}{\partial H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t)) H_2^*(t)\psi_2^*(t) \\
\qquad\quad - \dfrac{\partial f_3}{\partial H_1}(H_1^*(t), H_2^*(t), A_*(t), w_*(t)) A_*(t)\psi_3^*(t) + (T_1^*(t) - T_2^*(t)), \\
\psi_2^{*\prime}(t) = -Q'_{H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t), w_*(t), \psi_0^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t)) \\
\qquad = -f_2\,(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t))\,\psi_2^*(t) \\
\qquad\quad - \dfrac{\partial f_0}{\partial H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t)) H_0^*(t)\psi_0^*(t) \\
\qquad\quad - \dfrac{\partial f_1}{\partial H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t)) H_1^*(t)\psi_1^*(t) \\
\qquad\quad - \dfrac{\partial f_2}{\partial H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t)) H_2^*(t)\psi_2^*(t) \\
\qquad\quad - \dfrac{\partial f_3}{\partial H_2}(H_1^*(t), H_2^*(t), A_*(t), w_*(t)) A_*(t)\psi_3^*(t) - (T_1^*(t) - T_2^*(t)), \\
\psi_3^{*\prime}(t) = -Q'_A(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t), w_*(t), \psi_0^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t)) \\
\qquad = -f_3\,(H_1^*(t), H_2^*(t), A_*(t), w_*(t))\,\psi_3^*(t) \\
\qquad\quad - \dfrac{\partial f_0}{\partial A}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t)) H_0^*(t)\psi_0^*(t) \\
\qquad\quad - \dfrac{\partial f_1}{\partial A}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t)) H_1^*(t)\psi_1^*(t) \\
\qquad\quad - \dfrac{\partial f_2}{\partial A}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t)) H_2^*(t)\psi_2^*(t) \\
\qquad\quad - \dfrac{\partial f_3}{\partial A}(H_1^*(t), H_2^*(t), A_*(t), w_*(t)) A_*(t)\psi_3^*(t), \\
\psi_0^*(T) = 0,\ \psi_1^*(T) = 0,\ \psi_2^*(T) = 0,\ \psi_3^*(T) = 0;
\end{cases}
$$

• the controls $u_*(t)$, $v_*(t)$ and $w_*(t)$ maximize the Hamiltonian

$$
Q(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u, v, w, \psi_0^*(t), \psi_1^*(t), \psi_2^*(t), \psi_3^*(t)) \tag{6.6}
$$

with respect to $u \in [0, u_{\max}]$, $v \in [0, v_{\max}]$ and $w \in [0, w_{\max}]$ for almost all $t \in [0, T]$, and therefore the following relationships hold:

$$u_*(t) = \begin{cases} u_{\max} & , \text{ if } \quad \xi_u(t) \geq u_{\max}, \\ \xi_u(t) & , \text{ if } \quad 0 < \xi_u(t) < u_{\max}, \\ 0 & , \text{ if } \quad \xi_u(t) \leq 0, \end{cases} \tag{6.7}$$

$$v_*(t) = \begin{cases} v_{\max} & , \text{ if } \quad \xi_v(t) \geq v_{\max}, \\ \xi_v(t) & , \text{ if } \quad 0 < \xi_v(t) < v_{\max}, \\ 0 & , \text{ if } \quad \xi_v(t) \leq 0, \end{cases} \tag{6.8}$$

$$w_*(t) = \begin{cases} w_{\max} & , \text{ if } \quad \xi_w(t) \geq w_{\max}, \\ \xi_w(t) & , \text{ if } \quad 0 < \xi_w(t) < w_{\max}, \\ 0 & , \text{ if } \quad \xi_w(t) \leq 0, \end{cases} \tag{6.9}$$

where

$$\begin{aligned} \xi_u(t) &= a^{-1} \left(\frac{\partial f_0}{\partial u}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t)) H_0^*(t) \psi_0^*(t) \right. \\ &\quad \left. + \frac{\partial f_2}{\partial u}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t)) H_2^*(t) \psi_2^*(t) \right), \\ \xi_v(t) &= b^{-1} \left(\frac{\partial f_0}{\partial v}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t)) H_0^*(t) \psi_0^*(t) \right. \\ &\quad \left. + \frac{\partial f_1}{\partial v}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t)) H_1^*(t) \psi_1^*(t) \right), \\ \xi_w(t) &= c^{-1} \quad \frac{\partial f_3}{\partial w}(H_1^*(t), H_2^*(t), A_*(t), w_*(t)) A_*(t) \psi_3^*(t) \end{aligned} \tag{6.10}$$

are the so-called the indicator functions ([29]), which determine the behavior of the corresponding optimal controls $u_*(t)$, $v_*(t)$ and $w_*(t)$ according to formulas (6.7)–(6.9).

To simplify consequent arguments, we introduce new adjoint variables $\phi_0^*(t)$, $\phi_1^*(t)$, $\phi_2^*(t)$, $\phi_3^*(t)$ by the following formulas:

$$\begin{aligned} \phi_0^*(t) &= H_0^*(t)\psi_0^*(t), \quad \phi_1^*(t) = H_1^*(t)\psi_1^*(t), \\ \phi_2^*(t) &= H_2^*(t)\psi_2^*(t), \quad \phi_3^*(t) = A_*(t)\psi_3^*(t). \end{aligned}$$

Then using systems (6.4) and (6.5), after necessary calculations, we find the new

adjoint system:

(6.11)
$$
\begin{cases}
\phi_0^{*\prime}(t) = -\dfrac{\partial f_0}{\partial H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\phi_0^*(t) \\
\qquad\qquad -\dfrac{\partial f_1}{\partial H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t))\phi_1^*(t) \\
\qquad\qquad -\dfrac{\partial f_2}{\partial H_0}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t))\phi_2^*(t), \\
\phi_1^{*\prime}(t) = -\dfrac{\partial f_0}{\partial H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\phi_0^*(t) \\
[3pt] \quad -\dfrac{\partial f_1}{\partial H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t))\phi_1^*(t) \\
\qquad\qquad -\dfrac{\partial f_2}{\partial H_1}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t))\phi_2^*(t) \\
\qquad\qquad -\dfrac{\partial f_3}{\partial H_1}(H_1^*(t), H_2^*(t), A_*(t), w_*(t))\phi_3^*(t) + H_1^*(t)(H_1^*(t) - H_2^*(t)), \\
\phi_2^{*\prime}(t) = -\dfrac{\partial f_0}{\partial H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\phi_0^*(t) \\
\qquad\qquad -\dfrac{\partial f_1}{\partial H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t))\phi_1^*(t) \\
\qquad\qquad -\dfrac{\partial f_2}{\partial H_2}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t))\phi_2^*(t) \\
\qquad\qquad -\dfrac{\partial f_3}{\partial H_2}(H_1^*(t), H_2^*(t), A_*(t), w_*(t))\phi_3^*(t) - H_2^*(t)(H_1^*(t) - H_2^*(t)), \\
\phi_3^{*\prime}(t) = -\dfrac{\partial f_0}{\partial A}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\phi_0^*(t) \\
\qquad\qquad -\dfrac{\partial f_1}{\partial A}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t))\phi_1^*(t) \\
\qquad\qquad -\dfrac{\partial f_2}{\partial A}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t))\phi_2^*(t) \\
\qquad\qquad -\dfrac{\partial f_3}{\partial A}(T_1^*(t), T_2^*(t), A_*(t), w_*(t))\phi_3^*(t), \\
\phi_0^*(T) = 0,\ \phi_1^*(T) = 0,\ \phi_2^*(T) = 0,\ \phi_3^*(T) = 0.
\end{cases}
$$

At the same time, formulas (6.10) for indicator functions $\xi_u(t)$, $\xi_v(t)$ and $\xi_w(t)$ are

rewritten in the form:

$$\xi_u(t) = a^{-1}\left(\frac{\partial f_0}{\partial u}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\phi_0^*(t) + \frac{\partial f_2}{\partial u}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t))\phi_2^*(t)\right),$$

$$\xi_v(t) = b^{-1}\left(\frac{\partial f_0}{\partial v}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), u_*(t), v_*(t))\phi_0^*(t) + \frac{\partial f_1}{\partial v}(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t), v_*(t))\phi_1^*(t)\right), \tag{6.12}$$

$$\xi_w(t) = c^{-1}\ \frac{\partial f_3}{\partial w}(H_1^*(t), H_2^*(t), A_*(t), w_*(t))\phi_3^*(t)\ .$$

Study of relationships (6.7)–(6.9) show that for all values of $t \in [0, T]$, the maximum of Hamiltonian (6.6) is reached with unique values $u = u_*(t)$, $v = v_*(t)$, $w = w_*(t)$. Therefore, Theorem 6.1 in [8] implies the continuity of control $u_*(t)$, $v_*(t)$ and $w_*(t)$. Adding to this result the analysis of the adjoint system (6.11), formulas (6.12), and again relationships (6.7)–(6.9) leads us to the validity of the following theorems.

Theorem 6.1. *The optimal controls $u_*(t)$, $v_*(t)$ and $w_*(t)$ are continuous functions on the interval $[0, T]$, which satisfy the equalities:*

$$u_*(T) = 0, \quad v_*(T) = 0, \quad w_*(T) = 0.$$

Theorem 6.2. *Let the inequality $H_1^*(T) \neq H_2^*(T)$ hold. Then, there exists such a value $t_\star \in [0, T)$ that on the interval $(t_\star, T)$ the optimal controls $u_*(t)$ and $v_*(t)$ either simultaneously take the value 0, if $H_1^*(T) > H_2^*(T)$; or take positive values from the corresponding intervals $(0, u_{\max})$ and $(0, v_{\max})$, if $H_1^*(T) < H_2^*(T)$.*

Systems (6.4) and (6.11), relationships (6.7)–(6.9), together with formulas (6.12) form the boundary value problem for the maximum principle. The optimal controls $u_*(t)$, $v_*(t)$ and $w_*(t)$ satisfy this boundary value problem together with the corresponding optimal solution $(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t))^\top$. Moreover, arguing as in [12, 19, 30], it is possible to justify the uniqueness of these controls due to the boundedness of the state and adjoint variables and the Lipschitz properties of systems (6.4) and (6.11) defining these variables and relationships (6.7)–(6.9) that establish such controls.

7. Numerical results for the optimal control problem

The following values of the parameters and initial conditions for system (6.2) and the control restrictions from (6.1) were adopted from [1, 26, 32] and then used for numerical calculations in the optimal control problem (6.3):

$\alpha = 10.0$	$\rho = 8.0$	$\nu = 0.001$	$\chi \in \{0.1; 1.0; 5.0\}$
$\theta_1 = 1.0$	$\theta_2 = 1.02$	$\mu_1 = 0.2$	$\mu_2 = 0.1$
$a = 0.5$	$b = 0.5$	$c = 0.5$	$T = 30$
$u_{\max} = 0.8$	$v_{\max} = 0.8$	$w_{\max} = 0.8$	
$H_0^0 = 10.0$	$H_1^0 = 10.0$	$H_2^0 = 20.0$	$A_0 \in \{0.05; 15.0\}$

All numerical calculations were conducted using BOCOP-2.0.5. Their results are shown in the following figures.

BOCOP-2.0.5 ([4]) is an optimal control interface, implemented in MATLAB, for solving optimal control problems with general path and boundary constraints and free or fixed final time. By a time discretization, such problems are approximated by finite-dimensional optimization problems, which are then solved by well-known software IPOPT, using sparse exact derivatives computed by ADOL-C. IPOPT is the open-source software package for large-scale nonlinear optimization. In BOCOP-2.0.5, we set the number of time steps to 5000 and the tolerance to 10^{-14}, and we use the sixth-order Lobatto III C discretization rule (see for details [4]).

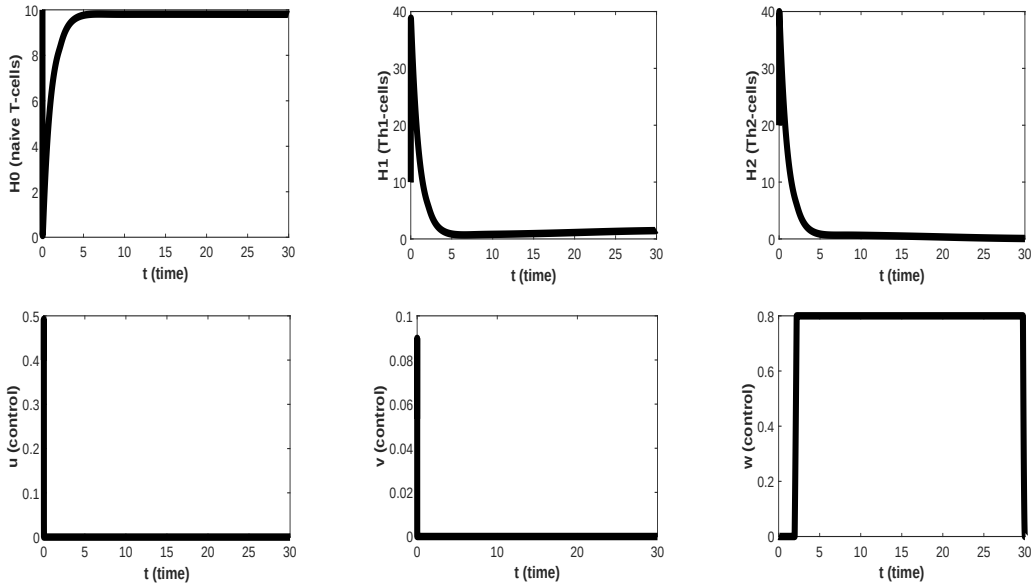

FIGURE 8. Optimal solution and optimal controls for $\chi = 0.1$ and $A_0 = 15.0$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

As it was previously noted, $(\theta_1, \theta_2)^\top \in B$, where θ_1 and θ_2 are the coefficients of the natural growth rates of Th_1- and Th_2-cells, respectively. The relationship chosen for the values of θ_1 and θ_2 ($\theta_2 > \theta_1$) implies that systems (2.5) and (6.2) model a potentially allergic symptomatic organism, in which Th_2-cells have higher growth rate than Th_1-cells.

Figures 8–10 correspond to the value $A_0 = 15.0$, and Figures 11–13 relate to the value $A_0 = 0.05$. Figures 8 and 11 show the graphs of the optimal solutions $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$ and the optimal controls $u_*(t)$, $v_*(t)$, $w_*(t)$ for $\chi = 0.1$, Figures 9 and 12 give the graphs of the optimal solutions and controls for $\chi = 1.0$, and finally, Figures 10 and 13 depict the graphs of such solutions and controls for $\chi = 5.0$. In each such figure, on the upper row there are the graphs of the solutions $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$ and on the lower row there are the graphs of the controls $u_*(t)$, $v_*(t)$, $w_*(t)$.

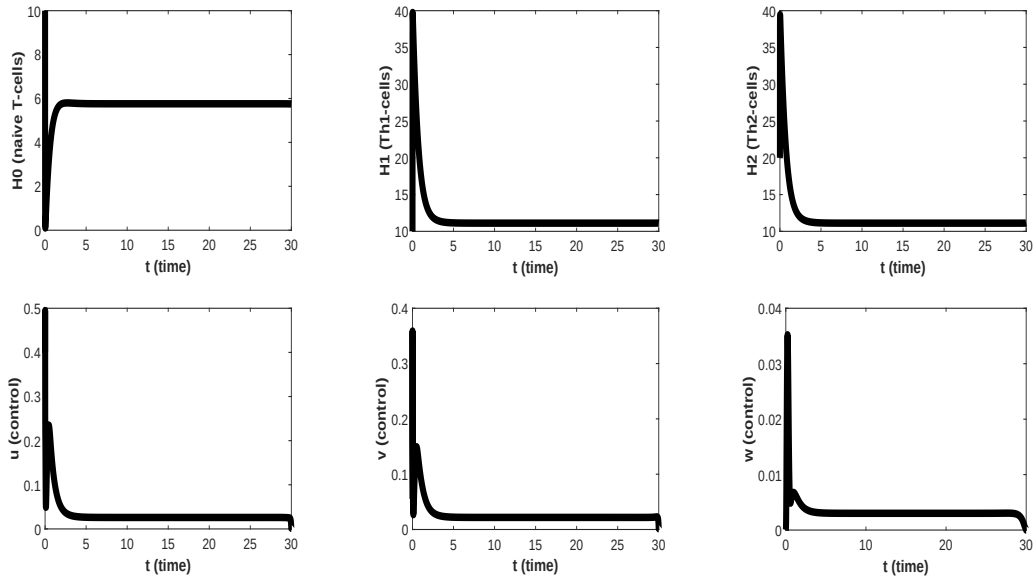

FIGURE 9. Optimal solution and optimal controls for $\chi = 1.0$ and $A_0 = 15.0$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

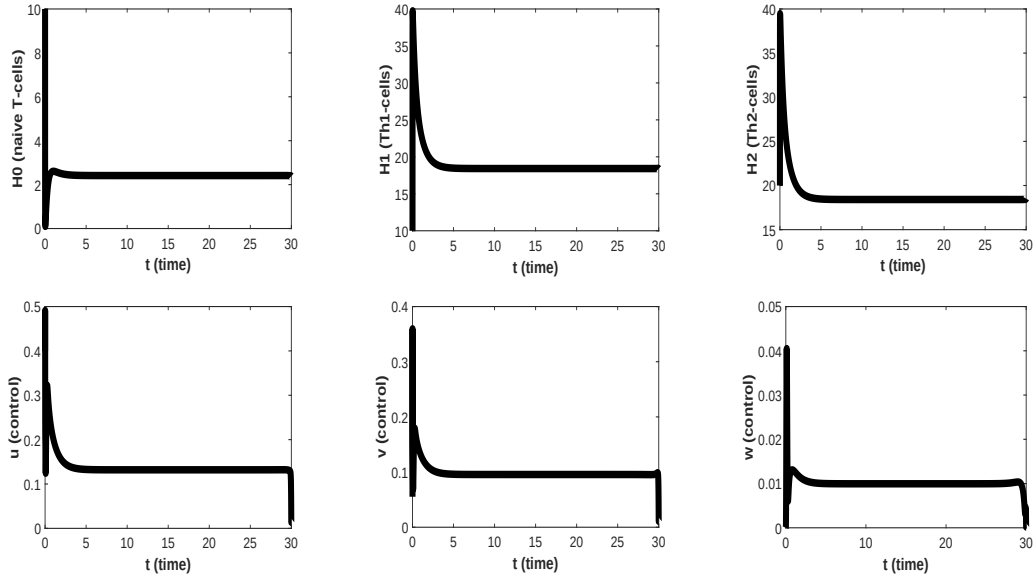

FIGURE 10. Optimal solution and optimal controls for $\chi = 5.0$ and $A_0 = 15.0$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

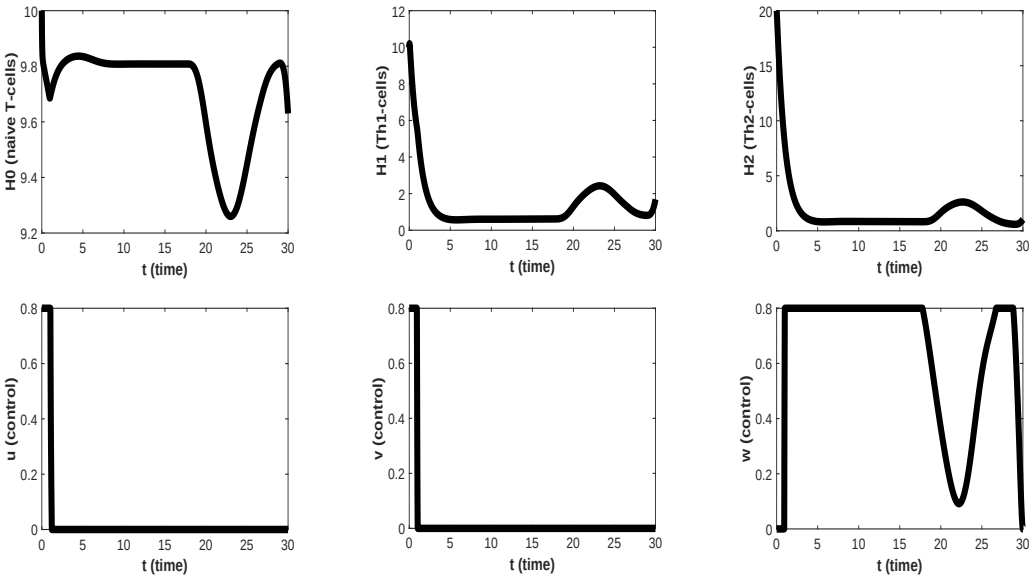

FIGURE 11. Optimal solution and optimal controls for $\chi = 0.1$ and $A_0 = 0.05$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

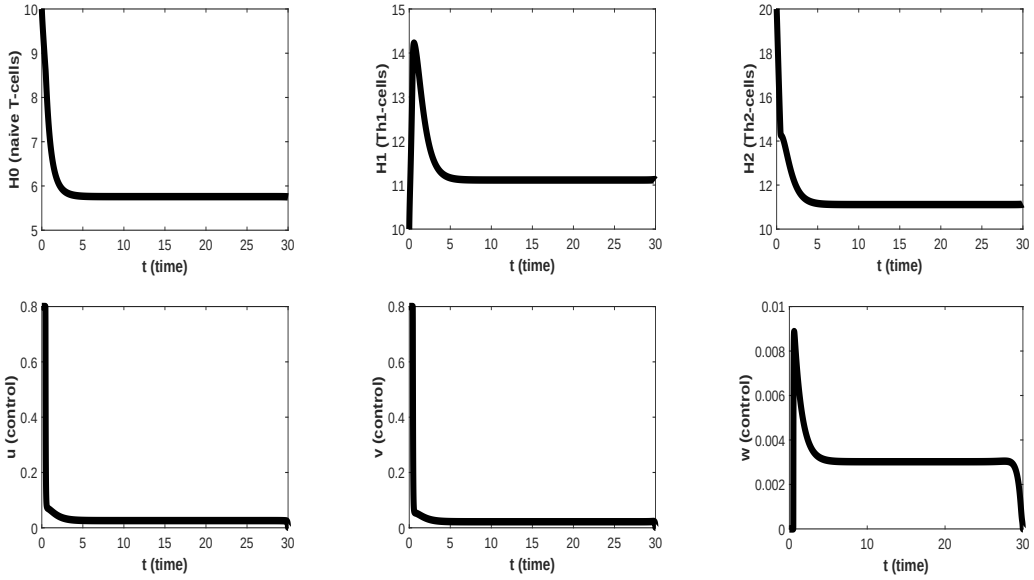

FIGURE 12. Optimal solution and optimal controls for $\chi = 1.0$ and $A_0 = 0.05$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

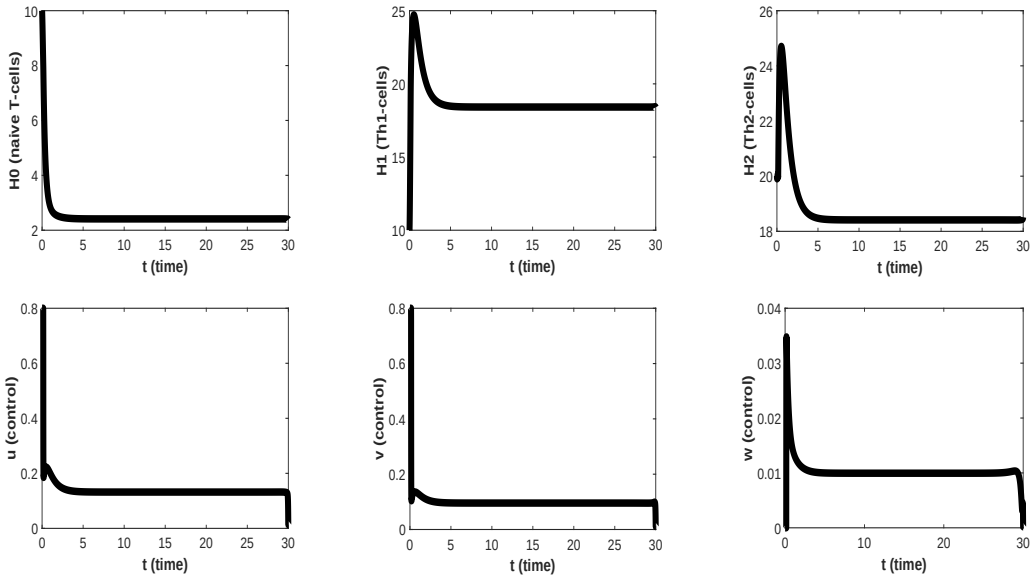

FIGURE 13. Optimal solution and optimal controls for $\chi = 5.0$ and $A_0 = 0.05$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

We also performed numerical calculations for the case when $\chi = 5.0$ and $\theta_1 = 1.0$, $\theta_2 = 1.52$. In this case, system (6.2) models an organism more sensitive to allergic reactions. It still means that $(\theta_1, \theta_2)^\top \in B$. Their results are shown in Figures 14 and 15. Figure 14 gives the graphs of the optimal solutions $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$ and the optimal controls $u_*(t)$, $v_*(t)$, $w_*(t)$ for $A_0 = 15.0$, Figure 15 depicts the graphs of the optimal solutions and controls for $A_0 = 0.05$. In each such figure, on the upper row there are the graphs of the solutions $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$ and on the lower row there are the graphs of the controls $u_*(t)$, $v_*(t)$, $w_*(t)$ as well.

By analyzing the graphs presented on Figures 8–15, we can make the following conclusions.

- Behavior of the components $H_1^*(t)$ and $H_2^*(t)$ of the optimal solution $(H_0^*(t), H_1^*(t), H_2^*(t), A_*(t))^\top$ corresponding to the concentrations of Th_1- and Th_2-cells is characterized by the starting spark that is gradually decreasing and leading to a stable, almost constant state lasted to the end of the treatment period $[0, T]$.
- Similar behavior is related to the optimal controls $u_*(t)$ and $v_*(t)$. In case of $A_0 = 0.05$ both controls $u_*(t)$ and $v_*(t)$ first take the maximum possible value of 0.8 and then decrease to the constant minimal value that is almost zero for the lower influx rates (0.1 and 1.0) and is higher (close to 0.2) for the influx rate of 5.0. In case of $A_0 = 15.0$, both optimal controls $u_*(t)$ and $v_*(t)$ start from some high values but these values are less than the maximal possible value of 0.8. In fact, while $u_*(t)$ starts at approximately 0.5 for all influx rates of the allergen, the optimal control $v_*(t)$ behaves differently for

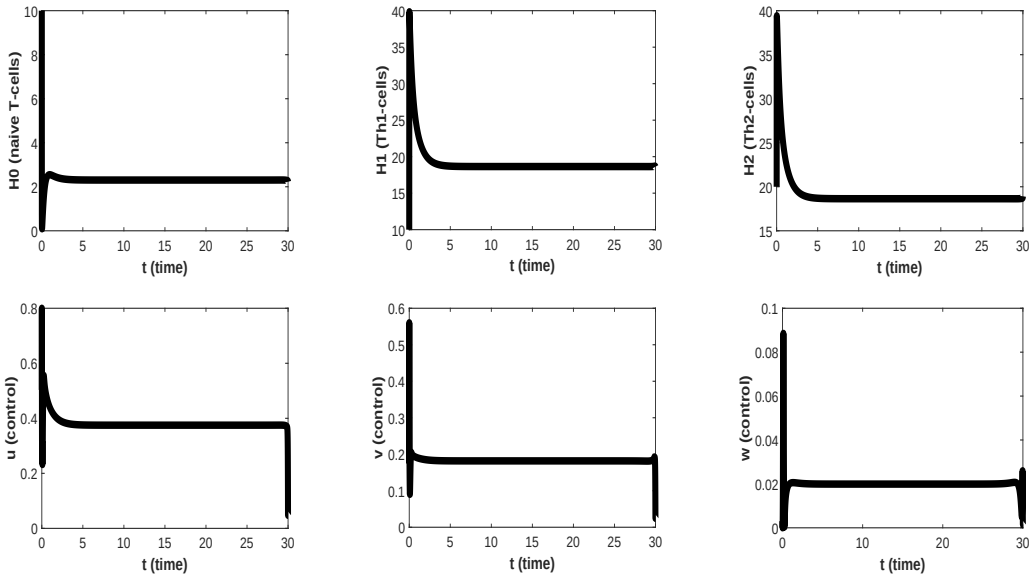

FIGURE 14. Optimal solutions and optimal controls for $\chi = 5.0$, $\theta_1 = 1.0$, $\theta_2 = 1.52$, $A_0 = 15.0$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

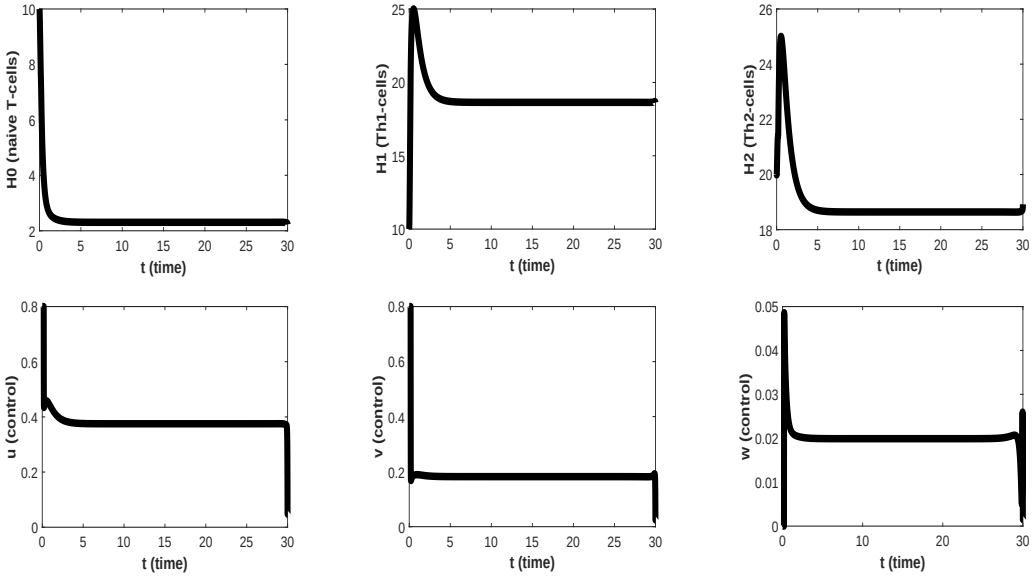

FIGURE 15. Optimal solutions and optimal controls for $\chi = 5.0$, $\theta_1 = 1.0$, $\theta_2 = 1.52$, $A_0 = 0.05$: upper row: $H_0^*(t)$, $H_1^*(t)$, $H_2^*(t)$; lower row: $u_*(t)$, $v_*(t)$, $w_*(t)$.

different influx rates. For example, $v_*(t)$ starts for 0.09 (that is much less than 0.8) for $\chi = 0.1$, and at values $0.3 - 0.35$ for higher influx rates and quickly goes to zero at $\chi = 0.1$ and to the minimal constant values of 0.3 and 0.1 for $\chi = 1$ and $\chi = 5$, respectively.

- For the behavior of the optimal control $w_*(t)$ (that is responsible for all direct (drugs of new generation) and indirect measures (escape the allergen, reduce possible interaction of the system with the allergen)) we can distinguish the following two cases:
  - **a)** average or high influx rate of the allergen. In this case the highest value of $w_*(t)$ is $0.01 - 0.04$ that is much less than 0.8, the upper boundary for this control. In Figures 9, 10 and 12–15 the optimal control $w_*(t)$ is very similar to the type of the optimal controls $u_*(t)$ and $v_*(t)$ and first it takes the high values and then quickly decreases to the lower, nonzero value.
  - **b)** low influx rate of the allergen, $\chi = 0.1$. This case is presented in Figures 8 and 11. If the initial concentration of the allergen is high ($A_0 = 15.0$), then all precautious measures must be taken almost immediately and then $w_*(t)$ optimal takes the maximum value over the entire time period. If the initial concentration of the allergen is low ($A_0 = 0.05$) in this case, $w_*(t)$ optimal almost immediately (after day 1) takes its maximum value of 0.8, that is kept the following 18 days, then it is gradually reduced to the value of 0.1 and then increases back to 0.8, is kept at that level for couple of days and then quickly goes to zero during the last day of the time interval.
- An increase of the ratio θ_2/θ_1 leads to an increase of the saturated level of the control $u_*(t)$ compared to that for the control $v_*(t)$.
- With an increase in the duration of the treatment period $[0, T]$, the behavior of the optimal controls and the components of the optimal solution corresponding to them do not qualitatively change.

8. Discussion and conclusions

In this paper, in order to construct a controllable mathematical model for treating allergic reactions of an immediate type, the model of interaction between populations of naive T-cells, Th_1- and Th_2-cells with an allergens, based on the works [1, 10, 26, 32], is investigated in detail. Sections 2 and 3 are devoted to the description of the system of differential equations defining this model, as well as the justification of the properties of the phase variables of this system. A detailed stability analysis of equilibria together with their bifurcation analysis is presented in Section 4. The behavior of phase variables at specific values of the model parameters is demonstrated in Section 5 using numerical calculations performed in MAPLE-15 software. We found that the "organism" modeled by system (2.5) reacts differently on the allergen's invasion and, depending on the initial concentration of the allergen and its influx rate, shows slightly different dynamics. However, eventually the system does approach its asymptotically stable equilibrium that does not represent "healthy" state. Instead it moves the system into unhealthy, allergic state. Naturally, this allergy state can be changed only by taking drugs that either suppress the activity

of Th_2-cells or activate Th_1-cells. Obviously, we can eliminate allergic state by removing the allergen. Mathematically we have to create a control model. Section 6 describes the construction of a control mathematical model and on its basis the formulation of the corresponding optimal control problem, as well as the application of the necessary optimality condition in the form of the Pontryagin maximum principle. This allows us to analytically establish important properties of optimal solutions to this problem. The results of numerical calculations using BOCOP-2.0.5 software and their analysis are given in Section 7.

In our model, the optimal controls $u_*(t)$ and $v_*(t)$ represent the optimal drug intake schedule for treating allergy symptoms under different initial conditions of the system, its tendency to develop an allergy ($\theta_2 > \theta_1$), the initial concentration of the allergen, A_0 and its influx rate, χ. Based on the analytical and numerical investigations, it looks like if an organism (person) is exposed to allergen, then first, both medications (that suppress activity of Th_2-cells and those that stimulate Th_1-cells) must be taken at their highest doses, and then the dose of both drugs should be drastically reduced to the minimum. In fact, this is exactly what many allergic people do: if they feel itching or other typical allergy symptoms, they usually take the maximum dose of antihistamine (benadryl) and steroid (prednisone) and then continue to take a less strong allergy medicine in a minimum dose, for a month.

Regarding the optimal control $w_*(t)$, in general, the strategy is similar to that for two other optimal controls. Since the highest value of the optimal control $w_*(t)$ for influx rate $\chi = 1.0$ or $\chi = 5.0$ is less than 0.04, then this control does not play a very important role in treating allergy. However, there are some difference in the optimal control $w_*(t)$ occurs when the influx rate of the allergen is very low, $\chi = 0.1$. In this case, the optimal control $w_*(t)$ takes its highest value of 0.8 for almost the entire time interval $[0, T]$. Thus, if the influx rate is 0.1, all three optimal controls $u_*(t)$, $v_*(t)$ and $w_*(t)$ are important to help with allergy symptoms. Assume that a person has an allergy to cats. Then Figures 8 and 11 can represent the cases when a person, potentially allergic to cats, moves in with her (his) friend who has a cat. Figure 8 represents the case when a person allergic to cats, stroked the cat and played with it and so gets right away a huge amount of allergen (say $A_0 = 15.0$), then began to have an allergy (coughing and sneezing). Hence, she (he) does not play with the cat anymore and even isolates from the cat in a different room. Figure 11 represents a case when an allergic person does not play with the cat or stroke it, but since the cat is present in the place, gets exposed to a lower allergen concentration of $A_0 = 0.05$. Assume that there is no cat around but there still some influx of the allergen in the area. In this case our recommendation would be to take highest dose of drug 1, maybe drug 2 and the maximum dose of drug 3 (control $w_*(t)$) and isolate yourself from the cat.

Thus, in the case of low allergen influx rate ($\chi = 0.1$), we found that the optimal strategy related to optimal control $w_*(t)$ is different from those at $\chi = 1.0$ and $\chi = 5.0$. This could be explained by cell interactive mechanisms reported in some immunology study. In fact, in [17] some studies show that immune cell interaction through signaling cytokines goes by mechanisms that depends on allergen influx rate and allergen concentration. Moreover, it was reported that high allergen concentrations sometimes make allergic reaction to go by a different scenario that

activate Th_1-cells instead with the use of IgG (immunoglobulin G) that do not lead to inflammation and allergy symptoms. They also reported that small allergen concentrations certainly activate Th_2-cells so as IgE (immunoglobulin E) that provokes degranulation of mast cells and causes acute allergic symptoms. Contrarily, IgG helps to switch the dominative action of Th_2-cells to Th_1-cells and slow down IgE phase of allergic reaction, and hence to reduce the inflammation and hyperactivity.

In this paper, it was established that if contact with the allergen cannot be eliminated, and there is no treatment leading to a full recovery from allergy, the optimal strategy is to take the highest doses of the antihistamine drugs right away and then continue it at lower doses for a month. Our future study can look at immune disorders as characteristic symptoms within a controllable subspace in which the T-cells, mast cells, IgE and IgG are deterministic components of an information transmission channel.

Acknowledgement

E. N. Khailov was funded by Russian Foundation for Basic Research according to the research project $18-51-45003$ IND_a.

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Manuscript received March 17 2020
revised July 27 2020

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