

# Analysis of interactions between human immune system and a pathogenic virus

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**ABSTRACT.** In this paper we present a mathematical model for studying the interactions between human immune system and a pathogenic virus, such as Covid-19. A mathematical analysis based on dynamical systems theory is performed. More exactly, we model the interactions between the immune system and the virus by a modified predator-prey method. Several conclusions emerge from this study, and the main two of them are the followings: 1) a deficiency in the concentration of a single type of white blood cells in the early stages of virus proliferation may lead to the virus victory, and 2) if the number of at least one type of white blood cells can be increased beyond the normal threshold by medical interventions in the early stages of virus infection, then the immune system has a better chance to win against the virus.

## 1. INTRODUCTION

The immune system contains the main mechanisms and fighters to protect our bodies from an uncountable number of pathogenic invaders (microbes), such as bacteria, viruses, parasites and fungi [5]. While these minuscule invaders are invisible to the naked eye, they can have a tremendous impact on the organisms they enter, with consequences varying from mild flu-like discomfort to permanent dysfunctionalities of some organs and death.

The main fighters of the immune system with the pathogenic intruders are the white blood cells, which move through blood and tissues throughout body to find evil invaders. The cells are created in bone marrow and are part of the lymphatic system. There are five classes of white blood cells, namely: neutrophils 62%, eosinophils (acidophiles) 2.3%, basophils 0.4%, lymphocytes 30%, and monocytes 5.3%. Two classes of them, *neutrophils* [17] and *lymphocytes* [14], are by far the most numerous and together constitute about 92% of the total white blood cells. The typical lifetime of white blood cells varies from hours to days [7], [20].

In this work we aim to propose a mathematical model to study the interactions between a pathogenic virus and the human immune system represented by white blood cells. The approach we use is based on a modified predator-prey methodology [1], [2], [4], [15] used in population dynamics. We need to change some initial hypotheses used in classical predator-prey models to take into account the types of interactions occurring between the virus and white blood cells. While typically in classical predator-prey models [3], [12], known also as Lotka–Volterra models, a prey does not attack and kill a predator, and preys increase indefinitely in the absence of predators, we need to change these two premises to correspond to the reality of the interactions we want to model. More exactly, in our case, the two antagonist combatants are at the same time predators and preys, and, in addition, the preys do not increase indefinitely in the absence of predators but stabilize around a threshold. Several predator-prey models have been discussed in [11] to study

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interactions between host immunity and parasite growth. A model based on four differential equations to describe interactions between an invading pathogen and the innate immune system characterized by plasma cells, antibody concentrations and a health factor, was presented in [22]. The potential use of viruses in treating cancer has been studied in [23]. A bio-mathematical model to describe the interactions between influenza A virus and local tissues such as respiratory tract, has been recently considered in [21].

Compartmental models in epidemiology represent other techniques of mathematical modeling of infectious diseases [18]. Such models divide in more compartments the population to be studied, such that all individuals from the same compartment have the same characteristics. Typically, the models are based on a system of differential equations (often of predator-prey type) describing the evolution of the number of individuals in each compartment. A model with three compartments, susceptible, infectious and recovered individuals, is known as SIR model. There are many SIR models used in epidemiology such as [6], [8], [9], [10], [16] among others.

The paper is organized as follows. In the section two following the Introduction, we propose and study a three-dimensional (3D) model, with two friendly species fighting the same combatant enemy, a pathogenic virus. Since neutrophils and lymphocytes are the most abundant among the white blood cells, the two friendly species may represent these cells. In the next section we take into account all five types of immune cells and present a six-dimensional (6D) model. In section four we propose a control function to the 3D system and study the new model. Section five presents a model for the case when the immune system is affected by autoimmune diseases. Some conclusions arising from the studied models are presented at the end of the work.

## 2. THE 3D MODEL

Denote by  $x(t)$  and  $y(t)$  the number of cells at time  $t$  of specie 1, respectively, 2 attacking jointly a virus. For example,  $x(t)$  represents neutrophils while  $y(t)$  lymphocytes. Denote by  $z(t)$  the number of viruses of the same type which exist in a body at time  $t$ . Consider the time as being continuous,  $t \geq 0$ . Thus,  $\dot{x}(t)$ ,  $\dot{y}(t)$  and  $\dot{z}(t)$  are the rates of changes of these three quantities in a short unity of time;  $\dot{x}(t) = \frac{dx}{dt}$ . Our model is based on the following hypotheses.

H1. In the absence of virus, the two quantities of cells  $x(t)$  and  $y(t)$  increase up to a threshold value. This hypothesis is based on the fact that the total white cells in a healthy blood is between  $4 \times 10^9/L$  and  $1.1 \times 10^{10}/L$ . Thus, in the first stage, we consider the evolution laws of  $x(t)$  and  $y(t)$  of the form  $\dot{x} = a_1x - b_1x^2$  and  $\dot{y} = a_2y - b_2y^2$ , with  $a_{1,2} > 0$  and  $b_{1,2} > 0$ . One can check that, the general solution  $x(t)$  of the equation in  $\dot{x}$  with  $x(0) = x_0$  satisfies  $x(t) \rightarrow \frac{a_1}{b_1}$  for  $t \rightarrow \infty$  and all  $x_0 > 0$ . Notice that in the absence of the term  $-b_1x^2$ ,  $x(t)$  would increase exponentially. Similarly,  $y(t) \rightarrow \frac{a_2}{b_2}$  for  $t \rightarrow \infty$  and  $y_0 > 0$ . Thus,  $\frac{a_1}{b_1}$  is the threshold value for  $x(t)$  while  $\frac{a_2}{b_2}$  for  $y(t)$ .

H2. Typically, in a healthy body (without autoimmune diseases), the two classes of white blood cells do not attack each other. Thus, they are destroyed only due to viruses and, as such, a term  $-c_1xz$  should be added to the first equation in  $\dot{x}$ , respectively,  $-c_2yz$  to the equation in  $\dot{y}$ .

H3. In the absence of the immune system the virus would multiply indefinitely and exponentially,  $z$  satisfying the law  $\dot{z} = p_3z$ . What diminishes the number of viruses are the two classes of white cells, thus, a term of the form  $-p_1xz - p_2yz$  should be added to the law of  $\dot{z}$ .

These three hypotheses lead us to the following three-dimensional differential system with nine parameters, given by

$$(2.1) \quad \dot{x} = a_1x - b_1x^2 - c_1xz, \quad \dot{y} = a_2y - b_2y^2 - c_2yz, \quad \dot{z} = p_3z - p_1xz - p_2yz,$$

where the coefficients  $a_1, b_1, c_1, \dots, p_3$  are all positive. The model has medical relevance when  $x \geq 0, y \geq 0$  and  $z \geq 0$ , that is, when the system's solutions lie in the set  $\Sigma_+^0 = \{(x, y, z) \in \mathbb{R}^3, x \geq 0, y \geq 0, z \geq 0\}$ . An important observation on the behavior of the solutions with respect to  $\Sigma_+^0$  is given in the next remark.

**Remark 2.1.** The planes of coordinates  $\{x = 0\}, \{y = 0\}$  and  $\{z = 0\}$  are invariant with respect to the flow of (2.1), thus, any orbit starting in the positive octant

$$\Sigma_+ = \{(x, y, z) \in \mathbb{R}^3, x > 0, y > 0, z > 0\}$$

remains in  $\Sigma_+$  in forward time. The orbits cannot cross any of the three invariant planes. Therefore, the study of the system where it has medical relevance is well-defined, in the sense that, any orbit starting in the zone with medical relevance does not enter the zone of medical irrelevance and vice versa.

**2.1. Local analysis.** The system has seven equilibrium points as it follows:  $h_1 = (0, 0, 0)$ ,  $h_2 = (0, \frac{a_2}{b_2}, 0)$ ,  $h_3 = (\frac{a_1}{b_1}, 0, 0)$ ,  $h_4 = (\frac{a_1}{b_1}, \frac{a_2}{b_2}, 0)$ ,  $h_5 = (0, \frac{p_3}{p_2}, \frac{1}{c_2}(a_2 - \frac{b_2}{p_2}p_3))$ ,  $h_6 = (\frac{p_3}{p_1}, 0, \frac{1}{c_1}(a_1 - \frac{b_1}{p_1}p_3))$ , respectively,  $h_7 = (x_7, y_7, z_7)$ , where  $x_7 = \frac{1}{b_1}(a_1 - c_1z_7)$ ,  $y_7 = \frac{1}{b_2}(a_2 - c_2z_7)$  and  $z_7 = \frac{b_1b_2}{b_2c_1p_1 + b_1c_2p_2}(\frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2 - p_3)$ .

The point  $h_5 \in \Sigma_+^0$  if  $a_2p_2 - b_2p_3 \geq 0$ ,  $h_6$  if  $a_1p_1 - b_1p_3 \geq 0$ , respectively,  $h_7 \in \Sigma_+^0$  if  $x_7 \geq 0, y_7 \geq 0$  and  $z_7 \geq 0$ . We notice that, with the exception of  $z_7$ , all the points lie on one or more of the invariant planes of coordinates. Denote further by  $\Delta_5 = p_3(p_3b_2^2 + 4a_2p_2^2 - 4p_3b_2p_2)$  and  $\Delta_6 = p_3(p_3b_1^2 + 4a_1p_1^2 - 4b_1p_1p_3)$ .

	$h_1$	$h_2$	$h_3$	$h_4$	$h_5$	$h_6$
$\lambda_1^{h_i}$	$a_1$	$a_1$	$-a_1$	$-a_1$	$a_1 - a_2\frac{c_1}{c_2} + b_2\frac{c_1}{c_2p_2}p_3$	$a_2 - \frac{a_1}{c_1}c_2 + \frac{b_1}{c_1}\frac{c_2}{p_1}p_3$
$\lambda_2^{h_i}$	$a_2$	$-a_2$	$a_2$	$-a_2$	$\frac{1}{2p_2}(\sqrt{\Delta_5} - b_2p_3)$	$\frac{1}{2p_1}(\sqrt{\Delta_6} - b_1p_3)$
$\lambda_3^{h_i}$	$p_3$	$p_3 - \frac{a_2}{b_2}p_2$	$p_3 - \frac{a_1}{b_1}p_1$	$k_1$	$\frac{1}{2p_2}(-\sqrt{\Delta_5} - b_2p_3)$	$\frac{1}{2p_1}(-\sqrt{\Delta_6} - b_1p_3)$
type	$r$	$s$	$s$	$a, s$	$s$	$s$

TABLE 1. The eigenvalues and types of the first six equilibrium points of system (2.1); the abbreviations  $r, s$  and  $a$  stand for repeller, saddle and attractor, respectively,  $i = 1, \dots, 6$ ;  $k_1 = p_3 - \frac{a_1}{b_1}p_1 - \frac{a_2}{b_2}p_2$ .

**Remark 2.2.** The equilibria  $h_5$  and  $h_6$  are saddles on  $\Sigma_+^0$ , since  $\lambda_2^{h_5}\lambda_3^{h_5} = -\frac{p_3}{p_2}(a_2p_2 - b_2p_3) < 0$  and  $\lambda_2^{h_6}\lambda_3^{h_6} = -\frac{p_3}{p_1}(a_1p_1 - b_1p_3) < 0$ .

For the local behavior of the system around the seventh equilibrium  $h_7$ , we have the next theorem.

**Theorem 2.1.** The following assertions are true.

- 1) The equilibrium point  $h_7$  is a saddle whenever it lies on  $\Sigma_+$ .
- 2) The system does not undergo a fold-Hopf or Hopf bifurcation at  $h_7$  on  $\Sigma_+$ .
- 3) The equilibrium  $h_7$  bifurcates from  $h_4$  along the surface  $S = \{(p_1, p_2, p_3), p_3 = \frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2\}$  by a transcritical bifurcation.

*Proof.* The characteristic polynomial at  $(x_7, y_7, z_7)$  is

$$(2.2) \quad P(\lambda) = \lambda^3 + m_2\lambda^2 + m_1\lambda + m_0,$$

where  $m_2 = m_{20} + m_{10}$ ,  $m_1 = m_{20}m_{10} - z_7 \left( \frac{c_1 p_1}{b_1} m_{20} + \frac{c_2 p_2}{b_2} m_{10} \right)$ ,

$$(2.3) \quad m_0 = -z_7 \frac{b_2 c_1 p_1 + b_1 c_2 p_2}{b_1 b_2} m_{20} m_{10},$$

$$m_{20} = \frac{b_1(p_2(a_1 c_2 - a_2 c_1) + b_2 c_1 p_3)}{b_2 c_1 p_1 + b_1 c_2 p_2} \text{ and } m_{10} = \frac{b_2(-p_1(a_1 c_2 - a_2 c_1) + b_1 c_2 p_3)}{b_2 c_1 p_1 + b_1 c_2 p_2}.$$

1) Assume  $h_7 \in \Sigma_+$  is an attractor, thus, the polynomial  $P(\lambda)$  has all roots with negative real part. But, from Routh-Hurwitz conditions, this is equivalent to  $m_2 > 0$ ,  $m_0 > 0$  and  $m_2 m_1 > m_0$ . It follows from (2.3) that, on  $\Sigma_+$ ,  $m_0 > 0$  iff  $m_{20} m_{10} < 0$ . On the other hand,

$$(2.4) \quad m_2 m_1 - m_0 = -\frac{b_1 c_2 p_2 m_{10}^2 + b_2 c_1 p_1 m_{20}^2}{b_1 b_2} z_7 + m_{10} m_{20} (m_{10} + m_{20}).$$

Thus  $m_2 m_1 - m_0 < 0$  since  $m_{10} + m_{20} > 0$  from  $m_2 > 0$ , which is a contradiction.

Assume further that  $h_7 \in \Sigma_+$  is a repeller with  $\lambda_i^{h_7} > 0, i = 1, 2, 3$ . Then  $\lambda_1^{h_7} \lambda_2^{h_7} \lambda_3^{h_7} = -m_0 > 0$ , thus,  $m_{20} m_{10} > 0$  by (2.3). When  $a_1 c_2 - a_2 c_1 \geq 0$  then  $m_{20} > 0$ , thus,  $m_{10} > 0$ . It follows that  $\lambda_1^{h_7} + \lambda_2^{h_7} + \lambda_3^{h_7} = -(m_{20} + m_{10}) < 0$ , which contradicts  $\lambda_i^{h_7} > 0$ . Similarly, if  $a_1 c_2 - a_2 c_1 < 0$  then  $m_{10} > 0$ , which, by  $m_{20} m_{10} > 0$ , yields  $m_{20} > 0$ , leading to the same contradiction. Thus,  $h_7$  is not a repeller. From 1) and 2) we conclude that  $h_7$  is a saddle whenever  $h_7 \in \Sigma_+$ .

2) If  $\lambda = 0$  is a root of  $P(\lambda)$  then, by (2.3),  $z_7 = 0$  or  $m_{20} m_{10} = 0$ . In the first case, this occurs on the invariant manifold  $S$  when  $h_7$  collides to  $h_4$ , having the eigenvalues  $-a_1, -a_2$  and  $0$ , thus, a fold-Hopf bifurcation cannot occur. In the definition of  $S$  we assume the two thresholds  $a_1/b_1$  and  $a_2/b_2$  are fixed.

In the second case,  $m_{20} m_{10} = 0$ , we assume first  $a_1 c_2 - a_2 c_1 > 0$ . Then  $m_{10} = 0$ , which yields  $p_3 = \frac{a_1 c_2 - a_2 c_1}{b_1 c_2} p_1$ , thus,  $h_7 = h_6$  and  $\Delta_6 > 0$ . In the second case  $a_1 c_2 - a_2 c_1 < 0$ , we get  $m_{20} = 0$ ,  $p_3 = -\frac{a_1 c_2 - a_2 c_1}{b_2 c_1} p_2$  and  $h_7 = h_5$  with  $\Delta_5 > 0$ . Thus,  $i\omega$  is not a root of  $P(\lambda)$  for  $\omega \neq 0$  in either of the two cases, which confirms that a fold-Hopf bifurcation cannot arise. Notice that  $m_{20} m_{10} \neq 0$  if  $a_1 c_2 - a_2 c_1 = 0$ .

Assume further  $\lambda_1^{h_7} < 0$  and  $\pm i\omega, \omega > 0$ , are the eigenvalues of  $h_7 \in \Sigma_+$  for some values of the parameters. Then  $\lambda_1^{h_7} \omega^2 = -m_0 < 0$ , which, by (2.3), leads to  $m_{20} m_{10} < 0$ . On the other hand, the complex value  $i\omega$  is a root of the polynomial  $P(\lambda)$  if and only if  $\omega^2 = m_1 > 0$  and  $m_2 m_1 - m_0 = 0$ , that is,  $\lambda_1^{h_7} = -m_2 < 0$ . Thus,  $m_{20} + m_{10} > 0$  and, by (2.4),  $m_2 m_1 - m_0 < 0$ , which is a contradiction to  $m_2 m_1 - m_0 = 0$ . Thus, a Hopf bifurcation cannot occur at  $h_7 \in \Sigma_+$ . The proof for  $\lambda_1^{h_7} > 0$  is similar, since  $m_{20} m_{10} > 0$  and  $m_{20} + m_{10} < 0$  in this case.

3) It is clear that  $h_7$  coincides to  $h_4$  on  $S$ ; notice that  $p_{1,2} > 0$ . In order to show that a transcritical bifurcation takes place on  $S$ , we apply Sotomayor's theorem from [19]. To this end, assume  $\frac{a_1}{b_1}, \frac{a_2}{b_2}, p_1, p_2$  are fixed (constants) while  $p_3$  vary, and denote by  $\mu = p_3 - k$ , where  $k = \frac{a_1}{b_1} p_1 + \frac{a_2}{b_2} p_2$ . Denote by  $u = \begin{pmatrix} x & y & z \end{pmatrix}^T$  and  $F = \begin{pmatrix} f & g & h \end{pmatrix}^T$ , and write the system (2.1) in the form

$$(2.5) \quad \dot{u} = F(u, \mu),$$

where  $f = a_1x - b_1x^2 - c_1xz$ ,  $g = a_2y - b_2y^2 - c_2yz$  and  $h = (\mu + k)z - p_1xz - p_2yz$ ;  $T$  stands for the transpose, that is,  $(x \ y \ z)^T = \begin{pmatrix} x \\ y \\ z \end{pmatrix}$ . Denote by  $u_0 = h_4$  and  $\mu_0 = 0$ , re-

spectively,  $F_\mu = \left( \frac{\partial f}{\partial \mu} \ \frac{\partial g}{\partial \mu} \ \frac{\partial h}{\partial \mu} \right)^T$  and  $D(u, \mu)$  the Jacobian matrix of (2.5). Then 0 is an eigenvalue both for  $D(u_0, \mu_0)$  and  $D^T(u_0, \mu_0)$ , with the corresponding eigenvectors  $v = \left( -\frac{1}{b_1}c_1 \ -\frac{1}{b_2}c_2 \ 1 \right)^T$  for  $D(u_0, \mu_0)$ , respectively,  $w = (0 \ 0 \ 1)^T$  for  $D^T(u_0, \mu_0)$ .

The first condition  $w^T F_\mu(u_0, \mu_0) = 0$  of the transcritical bifurcation is readily satisfied. Denoting by  $DF_\mu$  the Jacobian matrix of the vector field  $F_\mu = (0 \ 0 \ z)^T$ , it follows that  $w^T [DF_\mu(u_0, \mu_0)v] = 1 \neq 0$ . To prove the last condition, denote by  $D^2F(v, v) = (d^2f(v, v) \ d^2g(v, v) \ d^2h(v, v))^T$ ;  $d^2f(v, v)$  is the differential of second order applied at the pair  $(v, v)$ , that is,  $d^2f(v, v) = -2b_1v_1^2 - 2c_1v_1v_3$ , where  $v = (v_1 \ v_2 \ v_3)^T$ . At  $(u_0, \mu_0)$ , we obtain

$$w^T [D^2F(x_0, \mu_0)(v, v)] = 2\frac{c_1}{b_1}p_1 + 2\frac{c_2}{b_2}p_2 \neq 0,$$

which completes the proof. □

**Remark 2.3.** Two more transcritical bifurcations arise in the system (2.1) on the surfaces  $S_1 = \left\{ p_3 = \frac{a_1c_2 - a_2c_1}{b_1c_2}p_1, a_1c_2 > a_2c_1 \right\}$ , respectively,  $S_2 = \left\{ p_3 = -\frac{a_1c_2 - a_2c_1}{b_2c_1}p_2, a_1c_2 < a_2c_1 \right\}$ . More exactly,  $h_7$  collides to  $h_6$  on  $S_1$ , respectively,  $h_5$  on  $S_2$ .

From the above analysis of the model, the following conclusions can be drawn, in terms of the relevance of the results for the fight between the immune system and a pathogenic virus.

1). Since  $h_1 = (0, 0, 0)$  is a repeller (unstable node) with its eigenvalues  $a_{1,2} > 0$  and  $p_3 > 0$ , any orbit  $\gamma(t) = (x(t), y(t), z(t))$  starting at a point  $u_0 = (x_0, y_0, z_0) \in \Sigma_+$  close to  $h_1$  will depart from it in forward time, which implies that  $z(t)$  may escape to infinity. Moreover, since a Hopf bifurcation is not possible at  $h_1$  (its eigenvalues are real), a stable limit cycle surrounding  $h_1$  does not arise by such a bifurcation. Therefore, *if the immune system is sufficiently weak when the virus starts to proliferate, the virus has a big chance to win.*

2). Let us look at  $h_2 = \left(0, \frac{a_2}{b_2}, 0\right)$ . Its eigenvalues are  $a_1, -a_2$  and  $p_3 - \frac{a_2}{b_2}p_2$ , thus, it is a saddle for either  $p_3 - \frac{a_2}{b_2}p_2 > 0$  or  $p_3 - \frac{a_2}{b_2}p_2 < 0$ . Any orbit  $\gamma(t)$  starting at a point  $u_0 \in \Sigma_+$  close to  $h_2$ ,  $u_0 \notin W_{h_2}^s$ , will depart from  $h_2$  in forward time, that is,  $z(t)$  may escape to infinity. A stable limit cycle around  $h_2$  cannot arise through a Hopf bifurcation since all eigenvalues are real. Therefore, if the white cells of type 1 (neutrophils in our model) are not in a normal quantity in the blood when the virus invades the body, the virus may win even though the quantity of white cells of type 2 (lymphocytes) is normal. *Thus, a deficiency in the quantity of a single type of white blood cells may lead to the virus victory.* For  $h_3 = \left(\frac{a_1}{b_1}, 0, 0\right)$  the results are similar.

3). Consider further  $h_4 = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, 0\right)$  with  $p_3 < \frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2$ , that is,  $h_4$  is an attractor, Fig.1 (left). In this case, any orbit  $\gamma(t)$  starting at a point  $u_0 \in \Sigma_+$  close to  $h_4$  will converge to  $h_4$  for  $t$  large, that is,  $z(t) \rightarrow 0$  for  $t \rightarrow \infty$ . Therefore, the model predicts that, *if the two types of white blood cells (neutrophils and lymphocytes) are in a sufficient number (i.e. normal concentrations) from the first moment they meet the virus, and if their joint actions kill the virus at a high rate, then the immune system wins.*

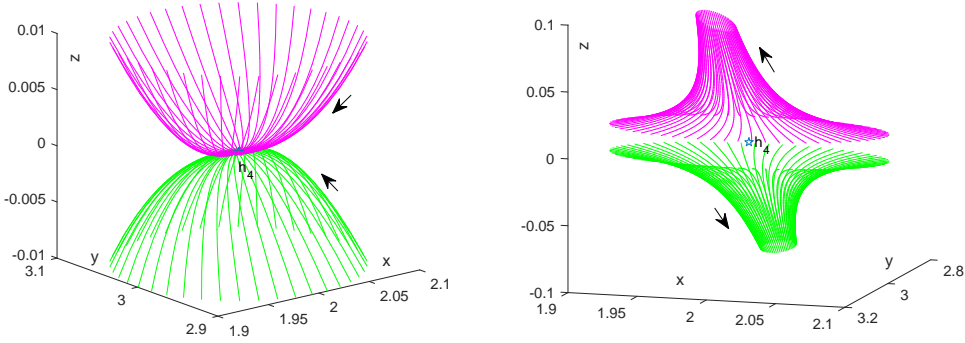


FIGURE 1. When  $b_1 = b_2 = 1$ ,  $a_1 = 2b_1$ ,  $a_2 = 3b_2$ ,  $c_1 = 1$ ,  $c_2 = 2$ ,  $p_1 = 1$ ,  $p_2 = 2$ , the steady state  $h_4$  attracts nearby orbits for  $p_3 = 3$  (left), respectively, repels for  $p_3 = 10$  (right).

On the other hand, if the joint destruction rate  $\frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2$  of the virus by the two white blood cells is not sufficiently strong to overcome the rate  $p_3$  of the virus proliferation, that is,  $h_4$  is a saddle with  $p_3 > \frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2$ , the virus may win since  $z(t)$  may escape to infinity, Fig.1 (right). A Hopf bifurcation leading to a stable limit cycle around  $h_2$  cannot arise since all eigenvalues are real.

4). Consider  $h_5$  with  $a_2p_2 > b_2p_3$ . The three eigenvalues of  $h_5$  are real,  $\lambda_i^{h_5} \in \mathbb{R}$ ,  $i = 1, 2, 3$ , since  $\Delta_5 = p_3(p_3b_2^2 + 4a_2p_2^2 - 4p_3b_2p_2) > b_2^2p_3^2 > 0$ . Thus, a Hopf bifurcation is not possible at  $h_5$ . Since  $h_5$  is a saddle,  $z(t)$  may escape to infinity, thus, the virus may win. For  $h_6$  the scenario is similar.

5). The model at the saddle  $h_7 \in \Sigma_+$  offers an interesting perspective. Notice first that  $x_7 < \frac{a_1}{b_1}$ ,  $y_7 < \frac{a_2}{b_2}$  and  $\frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2 > p_3$  if  $h_7 \in \Sigma_+$ . Since  $h_7$  is a saddle,  $z(t)$  of an orbit  $\gamma(t)$  starting close to  $h_7$  may escape to infinity. Thus, if the normal levels of the two types of white blood cells become at a moment considerably smaller than their normal concentrations, *the virus may win even though the immune system kills the virus at a rate higher than the rate of virus proliferation*. This case captures the possibility that the virus and the white blood cells increase in number at the same time, but the immune system does not have the ability to limitate the virus proliferation, which may win in the end.

**Remark 2.4.** From the analysis of the all seven equilibrium points, we notice that in a single case there are sufficient conditions to constraint and destroy the virus, namely, when  $h_4 \in \Sigma_+^0$  is an attractor with  $p_3 < \frac{a_1}{b_1}p_1 + \frac{a_2}{b_2}p_2$ .

### 3. THE 6D MODEL

In the same way we can model the interactions between the virus and the five types of white blood cells. The model in this case becomes

$$(3.6) \quad \begin{cases} \dot{x}_i = a_i x_i - b_i x_i^2 - c_i x_i v, & i = \overline{1, 5}, \\ \dot{v} = p_6 v - (p_1 x_1 + p_2 x_2 + p_3 x_3 + p_4 x_4 + p_5 x_5) v \end{cases} .$$

A first class of equilibrium points of the 6D model (3.6) which can be studied analytically are those with  $v = 0$ . They are the followings.

$h_1 = \bar{0} \in \mathbb{R}^6$  with eigenvalues  $a_i$  and  $p_6$ ,  $i = 1, \dots, 5$ . Thus, it is an unstable node.

$h_2 = \left(\frac{a_1}{b_1}, 0, 0, 0, 0\right)$  with eigenvalues  $-a_1, a_2, a_3, a_4, a_5, p_6 - \frac{a_1}{b_1}p_1$ . Thus,  $h_2$  is a saddle.

There are five equilibria of type  $h_2$ , all saddles, having  $v = 0$  and a single value  $x_i = \frac{a_i}{b_i}$

non-zero on the position  $i$ , where  $i = 1, \dots, 5$ . For example,  $h_{21} = \left(0, \frac{a_2}{b_2}, 0, 0, 0, 0\right)$  and so on.

$h_3 = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, 0, 0, 0, 0\right)$  with eigenvalues  $-a_1, -a_2, a_3, a_4, a_5, p_6 - \sum_{k=1}^2 \frac{a_k}{b_k} p_k$ . There are more equilibria of this type, all saddles, having  $v = 0$  and two values  $x_i = \frac{a_i}{b_i}$  non-zero while the other values  $x_i = 0$ . For example,  $h_{31} = \left(\frac{a_1}{b_1}, 0, \frac{a_3}{b_3}, 0, 0, 0\right)$  and so on.

$h_4 = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, \frac{a_3}{b_3}, 0, 0, 0\right)$  with eigenvalues  $-a_1, -a_2, -a_3, a_4, a_5, p_6 - \sum_{k=1}^3 \frac{a_k}{b_k} p_k$ . There are more equilibria of this type, all saddles. For example,  $h_{41} = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, 0, \frac{a_4}{b_4}, 0, 0\right)$ .

$h_5 = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, \frac{a_3}{b_3}, \frac{a_4}{b_4}, 0, 0\right)$  with eigenvalues  $-a_1, -a_2, -a_3, -a_4, a_5, p_6 - \sum_{k=1}^4 \frac{a_k}{b_k} p_k$ . Thus,  $h_5$  is a saddle along with other four equilibria of this type.

$h_6 = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, \frac{a_3}{b_3}, \frac{a_4}{b_4}, \frac{a_5}{b_5}, 0\right)$  with eigenvalues  $-a_1, -a_2, -a_3, -a_4, -a_5, \lambda_6^{h_6} = p_6 - \sum_{k=1}^5 \frac{a_k}{b_k} p_k$ . This equilibrium is unique of this type and can be an attractor or a saddle, depending on the sign of  $\lambda_6^{h_6}$ .

A second class of equilibrium points which still can be studied analytically are those with  $v \neq 0$  and a single  $x_i = \frac{p_6}{p_i} \neq 0, i = 1, \dots, 5$ . The first one is  $h_7 = \left(\frac{p_6}{p_1}, 0, 0, 0, 0, v_1\right)$ ,  $v_1 = \frac{1}{c_1} \left(a_1 - \frac{b_1}{p_1} p_6\right)$ , which has the eigenvalues  $a_2 - \frac{a_1}{c_1} c_2 + \frac{b_1}{c_1} \frac{c_2}{p_1} p_6, a_3 - \frac{a_1}{c_1} c_3 + \frac{b_1}{c_1} \frac{c_3}{p_1} p_6, a_4 - \frac{a_1}{c_1} c_4 + \frac{b_1}{c_1} \frac{c_4}{p_1} p_6, a_5 - \frac{a_1}{c_1} c_5 + \frac{b_1}{c_1} \frac{c_5}{p_1} p_6$  and  $\lambda_{5,6}^{h_7} = \frac{1}{2p_1} \left(-b_1 p_6 \pm \sqrt{\Delta_1}\right)$ , where  $\Delta_1 = b_1^2 p_6^2 + 4a_1 p_1^2 p_6 - 4b_1 p_1 p_6^2$ . We notice that  $\Delta_1 > 0$  and  $\lambda_5^{h_7} \lambda_6^{h_7} = -p_6 \frac{a_1 p_1 - b_1 p_6}{p_1} < 0$  whenever  $v_1 > 0$ , thus,  $h_7$  is a saddle on  $a_1 p_1 - b_1 p_6 > 0$ . There are four more saddles of this type, for example,  $h_{71} = \left(0, \frac{p_6}{p_2}, 0, 0, 0, v_2\right)$ , with  $v_2 = \frac{1}{c_2} \left(a_2 - \frac{b_2}{p_2} p_6\right)$ .

The system has four more classes of equilibrium points but their analytical study is intractable. They have the following forms.

$$h_8 = (x_1, x_2, 0, 0, 0, v_8), \text{ where } x_1 = \frac{1}{b_1} (a_1 - v_8 c_1), x_2 = \frac{1}{b_2} (a_2 - v_8 c_2),$$

$$v_8 = \frac{1}{d_8} \left(\frac{a_1}{b_1} p_1 + \frac{a_2}{b_2} p_2 - p_6\right) \text{ with } d_8 = \frac{c_1}{b_1} p_1 + \frac{c_2}{b_2} p_2.$$

$$h_9 = (x_1, x_2, x_3, 0, 0, v_9), \text{ where } x_1 = \frac{1}{b_1} (a_1 - v_9 c_1), x_2 = \frac{1}{b_2} (a_2 - v_9 c_2),$$

$$x_3 = \frac{1}{b_3} (a_3 - v_9 c_3), v_9 = \frac{1}{d_9} \left(\frac{a_1}{b_1} p_1 + \frac{a_2}{b_2} p_2 + \frac{a_3}{b_3} p_3 - p_6\right) \text{ with } d_9 = d_8 + \frac{c_3}{b_3} p_3.$$

$$h_{10} = (x_1, x_2, x_3, x_4, 0, v_{10}), \text{ where } x_1 = \frac{1}{b_1} (a_1 - v_{10} c_1), x_2 = \frac{1}{b_2} (a_2 - v_{10} c_2), x_3 = \frac{1}{b_3} (a_3 - v_{10} c_3), x_4 = \frac{1}{b_4} (a_4 - v_{10} c_4), v_{10} = \frac{1}{d_{10}} \left(\frac{a_1}{b_1} p_1 + \frac{a_2}{b_2} p_2 + \frac{a_3}{b_3} p_3 + \frac{a_4}{b_4} p_4 - p_6\right) \text{ with } d_{10} = d_9 + \frac{c_4}{b_4} p_4.$$

Finally, there is a single equilibrium of the form  $h_{11} = (x_1, x_2, x_3, x_4, x_5, v_{11})$ , where  $x_1 = \frac{1}{b_1} (a_1 - v_{11} c_1), x_2 = \frac{1}{b_2} (a_2 - v_{11} c_2), x_3 = \frac{1}{b_3} (a_3 - v_{11} c_3), x_4 = \frac{1}{b_4} (a_4 - v_{11} c_4), x_5 = \frac{1}{b_5} (a_5 - v_{11} c_5), v_{11} = \frac{1}{d_{11}} \left(\frac{a_1}{b_1} p_1 + \frac{a_2}{b_2} p_2 + \frac{a_3}{b_3} p_3 + \frac{a_4}{b_4} p_4 + \frac{a_5}{b_5} p_5 - p_6\right)$  and  $d_{11} = d_{10} + \frac{c_5}{b_5} p_5$ .

**Remark 3.5.** Of the equilibrium points of the first two classes described above for the 6D system, only the attractor  $h_6$  predicts that the immune system may win. The conclusion in this case is similar to the one for the 3D system described at 3).

We expect the equilibrium points of the remaining classes for the 6D system to be all unstable (saddles or repellers), whenever their coordinates are positive, thus, they do not reveal different scenarios. We base our hypothesis on the existing similarities between the 3D and 6D systems. However, since the analytical analysis in the remaining cases is difficult, this remains an open problem.

4. THE 3D MODEL WITH CONTROL

In the 3D and 6D models presented above, we modeled the interactions between virus and immune system by considering their natural developments, without external interventions as, for example, drug administration or additional means for increasing the production of white blood cells.

We aim to model in this section the case when the interactions depend also on external factors. To this end, a control function  $u(t)$  to one of the first two equations related to the immune system is proposed, having linear terms in  $u$  and nonlinear terms in  $xy$ , in the form of a 4D differential system given by:

$$(4.7) \quad \dot{x} = a_1x + u - b_1x^2 - c_1xz, \quad \dot{y} = a_2y - b_2y^2 - c_2yz, \quad \dot{z} = p_3z - p_1xz - p_2yz, \quad \dot{u} = \beta u - \alpha xy,$$

where  $\alpha$  and  $\beta$  are real numbers. The system has seven equilibrium points:  $q_1 = (0, 0, 0, 0)$ ,  $q_2 = \left(\frac{a_1}{b_1}, 0, 0, 0\right)$ ,  $q_3 = \left(0, \frac{a_2}{b_2}, 0, 0\right)$ ,  $q_4 = \left(0, \frac{p_3}{p_2}, \frac{1}{c_2} \left(a_2 - b_2 \frac{p_3}{p_2}\right), 0\right)$ ,  $q_5 = \left(\frac{p_3}{p_1}, 0, \frac{1}{c_1} \left(a_1 - b_1 \frac{p_3}{p_1}\right), 0\right)$ ,  $q_6 = (x_6, y_6, 0, u_6)$ , where  $y_6 = \frac{a_2}{b_2}$ ,  $x_6 = \frac{1}{b_1} \left(a_1 + \frac{\alpha}{\beta} y_6\right)$ ,  $u_6 = \frac{\alpha}{\beta} x_6 y_6$ , respectively,  $q_7 = (x_7, y_7, z_7, u_7)$ , with  $x_7 = \frac{1}{p_1} (p_3 - y_7 p_2)$ ,  $y_7 = \frac{1}{b_2} (a_2 - z_7 c_2)$ ,  $z_7 = \frac{1}{n_7} (\alpha a_2 p_1 + \beta a_1 b_2 p_1 + \beta a_2 b_1 p_2 - \beta b_1 b_2 p_3)$  and  $u_7 = \frac{\alpha}{\beta} x_7 y_7$ , with  $n_7 = \alpha c_2 p_1 + \beta b_2 c_1 p_1 + \beta b_1 c_2 p_2$ .

The eigenvalues of the first six points  $q_i$  can be determined analytically and are given in the next table. The equilibria  $q_1, q_2, q_4$  and  $q_5$  are unstable (repellers or saddles), while  $q_3$  and  $q_6$  can be attractors;  $\lambda_1^{q_4} \lambda_2^{q_4} = -\left(a_2 - b_2 \frac{p_3}{p_2}\right) p_3 < 0$  since  $z_4 = \frac{1}{c_2} \left(a_2 - b_2 \frac{p_3}{p_2}\right) > 0$ , while  $\lambda_3^{q_5} \lambda_4^{q_5} = -p_3 \left(a_1 - b_1 \frac{p_3}{p_1}\right) < 0$  since  $z_5 > 0$ .

**Remark 4.6.** Numerical simulations show that  $q_7$  is a saddle for a large spectrum of the parameters. In particular, if  $n_7 < 0$  and  $\alpha > 0$ , one can show  $\lambda_1^{q_7} \lambda_2^{q_7} \lambda_3^{q_7} \lambda_4^{q_7} < -2y_7^2 z_7 \alpha c_2 p_2 < 0$ , thus,  $q_7$  is a saddle. It remains an open problem to determine the type and stability of  $q_7$  in all cases.

The equilibrium  $q_3$  is an attractor if  $p_3 < \frac{a_2}{b_2} p_2$ ,  $\lambda_3^{q_3} \lambda_4^{q_3} = \frac{1}{b_2} (\alpha a_2 + \beta a_1 b_2) > 0$  and  $\lambda_3^{q_3} + \lambda_4^{q_3} = a_1 + \beta < 0$ , while  $q_6$  is an attractor if  $\lambda_2^{q_6} < 0$ ,  $\lambda_3^{q_6} \lambda_4^{q_6} = -\frac{1}{b_2} (\alpha a_2 + \beta a_1 b_2) > 0$  and  $\lambda_3^{q_6} + \lambda_4^{q_6} = -\frac{1}{\beta b_2} (2\alpha a_2 - \beta^2 b_2 + \beta a_1 b_2) < 0$ .

	$\lambda_1^{q_i}$	$\lambda_2^{q_i}$	$\lambda_3^{q_i}$	$\lambda_4^{q_i}$
$q_1$	$\beta$	$a_1$	$a_2$	$p_3$
$q_2$	$\beta$	$-a_1$	$a_2$	$p_3 - \frac{a_1}{b_1} p_1$
$q_3$	$-a_2$	$p_3 - \frac{a_2}{b_2} p_2$	$\frac{1}{2} (a_1 + \beta + \sqrt{l_1})$	$\frac{1}{2} (a_1 + \beta - \sqrt{l_1})$
$q_4$	$\frac{1}{2p_2} (-b_2 p_3 + \sqrt{l_2})$	$\frac{1}{2p_2} (-b_2 p_3 - \sqrt{l_2})$	$\frac{1}{2c_2 p_2} (l_3 + \sqrt{l_4})$	$\frac{1}{2c_2 p_2} (l_3 - \sqrt{l_4})$
$q_5$	$\beta$	$a_2 - \frac{a_1}{c_1} c_2 + \frac{b_1}{c_1} \frac{c_2}{p_1} p_3$	$\frac{1}{2p_1} (-b_1 p_3 + \sqrt{l_5})$	$\frac{1}{2p_1} (-b_1 p_3 - \sqrt{l_5})$
$q_6$	$-a_2$	$k_2$	$\frac{1}{2\beta b_2} (l_6 + \sqrt{l_7})$	$\frac{1}{2\beta b_2} (l_6 - \sqrt{l_7})$

TABLE 2. The eigenvalues of the first six equilibrium points of the controlled system (4.7);  $k_2 = p_3 - \frac{a_1}{b_1} p_1 - \frac{a_2}{b_2} p_2 - \frac{\alpha}{\beta} \frac{a_2}{b_1 b_2} p_1$ .

where  $l_1 = (\beta - a_1)^2 - 4\alpha \frac{a_2}{b_2}$ ,  $l_2 = p_3 (4a_2 p_2^2 + b_2^2 p_3 - 4b_2 p_2 p_3)$ ,  $l_3 = b_2 c_1 p_3 + p_2 (\beta c_2 + a_1 c_2 - a_2 c_1)$ ,  $l_4 = (\beta c_2 - a_1 c_2 + a_2 c_1)^2 p_2^2 - 2p_3 (2\alpha c_2^2 + a_2 b_2 c_1^2 + \beta b_2 c_1 c_2 - a_1 b_2 c_1 c_2) + b_2^2 c_1^2 p_3^2$ ,



$$l_5 = p_3 (4a_1p_1^2 + b_1^2p_3 - 4b_1p_1p_3), l_6 = -2\alpha a_2 + \beta^2b_2 - \beta a_1b_2 \text{ and } l_7 = (2\alpha a_2 + \beta a_1b_2)^2 + \beta^3b_2^2(\beta + 2a_1).$$

The control function  $u$  proposed in this section changes the local behavior of the 3D uncontrolled system (2.1) around the saddle  $h_2 = (0, \frac{\alpha_2}{b_2}, 0)$ , by transforming  $h_2$  in the attractor  $q_3 = (0, \frac{\alpha_2}{b_2}, 0, 0)$  in the new 4D system (4.7) with control, for some values of the parameters.

**Remark 4.7.** 1) The existence of the attractors  $q_3$  and  $q_6$  supports the idea that the virus can be better destroyed by external interventions on the immune system.

2) The attractor  $q_3$  shows that, if the second threshold  $\frac{\alpha_2}{b_2}$  is sufficiently high, then the immune system may win even though the initial level of immune cells of type 1 is very low when meeting the virus.

3) Since  $x_6 = \frac{\alpha_1}{b_1} + \frac{\alpha}{b_1\beta} \frac{\alpha_2}{b_2}$  in the attractor  $q_6$ , it follows that the control  $u$  stabilizes the long term behavior of (4.7) to various values around the two thresholds  $\frac{\alpha_1}{b_1}$  and  $\frac{\alpha_2}{b_2}$ .

### 5. A MODEL WITH AUTOIMMUNE DISEASE

Assume in this section that the immune system is affected by autoimmune diseases. In other words, the white blood cells attack each other. Therefore, the cells  $x(t)$  perish at a rate of  $-xzc_1 - xyd_1$ , while  $y(t)$  at a rate of  $-yzc_2 - xyd_2$ . These hypotheses lead to the system

$$(5.8) \quad \dot{x} = x(a_1 - xb_1 - zc_1 - yd_1), \dot{y} = y(a_2 - yb_2 - zc_2 - xd_2), \dot{z} = z(p_3 - xp_1 - yp_2),$$

which will be analyzed in what follows. The equilibrium points of the new system (5.8) are:

$$P_1(0, 0, 0), P_2\left(0, \frac{\alpha_2}{b_2}, 0\right), P_3\left(\frac{\alpha_1}{b_1}, 0, 0\right), P_4\left(0, \frac{p_3}{p_2}, \frac{1}{c_2}\left(a_2 - \frac{p_3}{p_2}b_2\right)\right), \\ P_5\left(\frac{p_3}{p_1}, 0, \frac{1}{c_1}\left(a_1 - \frac{p_3}{p_1}b_1\right)\right), P_6\left(\frac{a_1b_2 - a_2d_1}{b_1b_2 - d_1d_2}, \frac{a_2b_1 - a_1d_2}{b_1b_2 - d_1d_2}, 0\right) \text{ and } P_7(x_7, y_7, z_7), \text{ where } x_7 = \frac{N_1}{N_2}, \\ y_7 = \frac{p_3 - x_7p_1}{p_2} \text{ and } z_7 = \frac{1}{c_2}\left(x_7b_2\frac{p_1}{p_2} - x_7d_2 + a_2 - \frac{b_2}{p_2}p_3\right), \text{ respectively, } N_1 = a_1c_2p_2 - a_2c_1p_2 + b_2c_1p_3 - c_2d_1p_3 \text{ and } N_2 = b_2c_1p_1 + b_1c_2p_2 - c_2d_1p_1 - c_1d_2p_2.$$

$P_1$  is a repeller with eigenvalues  $a_{1,2}$  and  $p_3$ , while,  $P_2$  can be a saddle or an attractor, with eigenvalues  $-a_2, a_1 - \frac{\alpha_2}{b_2}d_1$  and  $p_3 - \frac{\alpha_2}{b_2}p_2$ . If  $p_3 < \frac{\alpha_2}{b_2}p_2$  and  $d_1 > \frac{\alpha_1}{a_2}b_2$ ,  $P_2$  is an attractor, thus, an immune disease may not affect the ability of the immune system to defeat the virus; an orbit starting close to  $P_2$  converges to  $P_2$ , that is,  $z(t) \rightarrow 0$  as  $t$  increases. A similar scenario occurs for  $P_3$ , whose eigenvalues are  $-a_1, a_2 - \frac{\alpha_1}{b_1}d_2$  and  $p_3 - \frac{\alpha_1}{b_1}p_1$ .

Not the same scenarios arise around  $P_4$  and  $P_5$ , since they are both saddles while lying in the first quadrant  $Q_1$ . Indeed, the eigenvalues of  $P_4$  are  $\lambda_{2,3}^{P_4} = -\frac{1}{2p_2}(b_2p_3 \pm \sqrt{\Delta_1})$  and  $\lambda_1^{P_4} = \frac{1}{c_2p_2}(a_1c_2p_2 - a_2c_1p_2 + b_2c_1p_3 - c_2d_1p_3)$ , where  $\Delta_1 = p_3(4a_2p_2^2 + b_2^2p_3 - 4b_2p_2p_3)$ . Since  $z_4 = a_2 - \frac{p_3}{p_2}b_2 > 0$ , it follows that

$$\lambda_2^{P_4}\lambda_3^{P_4} = -\frac{p_3}{p_2}(a_2p_2 - b_2p_3) < 0,$$

that is,  $P_4$  is a saddle. Similarly, the eigenvalues of  $P_5$  are  $\lambda_{2,3}^{P_5} = -\frac{1}{2p_1}(b_1p_3 \pm \sqrt{\Delta_2})$  and  $\lambda_1^{P_5} = \frac{1}{c_1p_1}(a_2c_1p_1 + b_1c_2p_3 - a_1c_2p_1 - c_1d_2p_3)$ , where  $\Delta_2 = p_3(4a_1p_1^2 + b_1^2p_3 - 4b_1p_1p_3)$ , such that,  $\lambda_2^{P_5}\lambda_3^{P_5} = -\frac{p_3}{p_1}(a_1p_1 - b_1p_3) < 0$ .

The eigenvalues of  $P_6$  are  $\lambda_1^{P_6} = p_3 - x_6 p_1 - y_6 p_2$  and  $\lambda_{2,3}^{P_6} = -\frac{1}{2}(x_6 b_1 + y_6 b_2) \pm \frac{1}{2}\sqrt{\Delta_3}$ , where  $\Delta_3 = (b_1 x_6 - b_2 y_6)^2 + 4d_1 d_2 x_6 y_6$ , respectively,  $x_6 = \frac{a_1 b_2 - a_2 d_1}{b_1 b_2 - d_1 d_2} > 0$  and  $y_6 = \frac{a_2 b_1 - a_1 d_2}{b_1 b_2 - d_1 d_2} > 0$ . Notice that

$$\lambda_2^{P_6} \lambda_3^{P_6} = x_6 y_6 (b_1 b_2 - d_1 d_2)$$

and  $\lambda_2^{P_6} + \lambda_3^{P_6} = -x_6 b_1 - y_6 b_2 < 0$ , thus,  $P_6$  is an attractor if  $b_1 b_2 < d_1 d_2$ , respectively, a saddle if  $b_1 b_2 > d_1 d_2$ , whenever  $P_6$  lies in the first quadrant  $Q_1$ . An orbit starting close to  $P_6$  attractor satisfies  $z(t) \rightarrow 0$  as  $t$  increases, thus, the immune system may win despite the autoimmune disease.

In order to study  $P_7$  when it lies in the first quadrant  $Q_1$ , we use its characteristic polynomial

$$P(\lambda) = \lambda^3 + m_2 \lambda^2 + m_1 \lambda + m_0,$$

where  $m_2 = x_7 b_1 + y_7 b_2$ ,  $m_1 = x_7 y_7 (b_1 b_2 - d_1 d_2) - z_7 (x_7 c_1 p_1 + y_7 c_2 p_2)$  and  $m_0 = -x_7 y_7 z_7 N_2$ . Denote by  $\lambda_i^{P_7}$  its roots, with  $i = 1, 2, 3$ .

Notice that  $m_2 > 0$  whenever  $P_7 \in Q_1$ . Since  $S_1 = \lambda_1^{P_7} + \lambda_2^{P_7} + \lambda_3^{P_7} = -m_2 < 0$ ,  $P_7$  cannot be a repeller but a saddle or an attractor on  $Q_1$ .

**Remark 5.8.**  $P_7$  is a saddle in  $Q_1$ , if 1)  $m_0 < 0$  or 2)  $m_0 > 0$  and  $b_1 b_2 < d_1 d_2$ .

Indeed, the proof for  $m_0 < 0$  follows from  $S_3 = \lambda_1^{P_7} \lambda_2^{P_7} \lambda_3^{P_7} = -m_0 > 0$  and  $S_1 < 0$ . To prove 2), we assume by contrary that  $P_7$  is an attractor. By Routh-Hurwitz conditions,  $P_7$  is an attractor if and only if  $m_0 > 0$  and  $m_2 m_1 > m_0$ , which, by  $m_2 > 0$ , yield  $m_1 > 0$ . But  $m_1 < 0$  if  $P_7 \in Q_1$  and  $b_1 b_2 < d_1 d_2$ , thus, a contradiction, and 2) follows.

If  $m_0 > 0$  and  $b_1 b_2 > d_1 d_2$ , numerical simulations show that  $P_7 \in Q_1$  is also a saddle. However, a full analytical proof remains open. It needs to determine the signs of  $m_1$  and  $M = m_2 m_1 - m_0$ , which can be written in the form

$$M = -c_1 x_7 z_7 (x_7 b_1 p_1 + y_7 d_2 p_2) - c_2 y_7 z_7 (x_7 d_1 p_1 + y_7 b_2 p_2) + y_7 x_7 (b_1 b_2 - d_1 d_2) (x_7 b_1 + y_7 b_2).$$

**Remark 5.9.** One can show that  $P_7$  is born from  $P_4$ ,  $P_5$  or  $P_6$  by a transcritical bifurcation.

From the above analysis of this section, it follows that, our model predicts that the immune system may win even though it is affected by autoimmune diseases.

## 6. CONCLUSIONS

We presented in this work a study on interactions between the white blood cells of immune system and a pathogenic virus, such as Covid-2019. We used a mathematical approach based on differential equations for modeling the interactions, and tools from dynamical systems theory to analyze the models. The study reveals the importance of the white blood cells in the fight against the virus. Several conclusions arising from our study are the followings:

1. If the immune system is sufficiently weak when the virus starts to proliferate, then the virus has a big chance to win.
2. A deficiency in the normal concentration of a single type of white blood cells in the early stages of virus proliferation, may lead to the virus victory.
3. If the levels of white blood cells become at a moment during the battle with the virus considerably smaller than their normal concentrations, the virus may win even though the immune system kills the virus at a rate higher than the rate of virus proliferation.
4. If the white blood cells are within their normal concentrations from the first moment they discover the virus and if the immune system is in a healthy condition to kill the virus at a high rate, then the immune system can win.

5. If the concentration of at least one type of white blood cells can be significantly increased beyond its normal threshold by medical interventions in the early stages of virus infection, then the immune system has a better chance to win. This conclusion reveals the possibility of winning against a virus by increasing the number of a single category of fighters.

6. The immune system may win even though it is affected by autoimmune diseases.

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