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A 4-dimensional mathematical model for interaction between the human immune system and a virus

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Abstract

In the present study we introduce a deterministic mathematical model in order to study the interaction between the human immune system and a virus, like COVID 19. The mathematical analysis is based on the tools of dynamical systems theory, by modeling the interactions between the immune system and the virus, using a predator-prey method and following the ideas of G. Moza, from [1]. It will be obtained some conclusions with medical relevance and the main three of them are the followings: 1) A deficiency of a single type of immunity in the early stages of virus proliferation, may lead to a large virus multiplication and the human body can loses the fight against this virus; 2) If the level of all components of the immunity system are at the normal threshold from the first moment of the infection and the immune system kill the virus at higher rate than the rate of virus reproduction, then the human body has the ability to stop the multiplication of the virus and liquidate it, that means the virus will be destroyed; 3) If the level of at least one type of immunity can be increased beyond the normal threshold, by medical interventions (like vaccination) in the early stages of virus infection, then the immune system has a better chance to win the fight with the virus.

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Key words: population dynamics, predator-prey, covid-19, dynamical systems, stability, ODE.

Contents

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1 Introduction

According to the basic immunology treaties around the medical scientific world, from the structural point of view, the human immune system is formed by organs, cells and molecules. Tonsils and adenoids, thymus, lymph nodes, spleen, payer's patches, appendix, lymphatic vessels, bone marrow are the organs of the immune system. Lymphocytes (T-lymphocytes, B-lymphocytes, plasma cells, natural killer lymphocytes), monocytes, macrophage and granulocytes (neutrophils, eosinophils, basophils) are the cells of the immune system and antibodies, complements, cytokines, interleukines, interferons are the molecules of the human immune system.

The immune response is the collective and coordinated response to the introduction of foreign substances in an individual mediated by the cells and molecules of the immune system. The role of the immune system is to defense against microbes, to defense against the growth of tumor cells by kills of this tumor cells and to destroy of abnormal or dead cells (e.g. dead red or white blood cells, antigen-antibody complex).

The immunity is the resistance of the host body to pathogens and their toxic effects. Every human body has an nonspecific response (innate immunity) and a specific response (acquired immunity). The innate immunity relies on mechanisms already existing before microbe infects host and is the first line of defense, but has no memory for subsequent exposure and relies on non specific mechanisms. Instead, the adaptive acquired immunity develops following entry of microbe into the host and comes into action after innate immunity fails to get rid of microbe. She has memory to deal with subsequent exposure and acts through specific cells: T cells (i.e. cell mediated) and B cells (i.e. antibody mediated).

The immune system can be viewed as a system controlled by negative feedback. The central component of the system is represented by the lymphatic tissues, which include mature T (thymic) lymphocytes that have matured through development in the thymus and mature B lymphocytes that have matured in the bone marrow. Generally, this essential system of the human body has a primary immune response, short lasting and smaller in magnitude, and a secondary immune response, longer in duration and larger in magnitude, developing the so called "cell's memory", after the primary response. Failure of immune response can result in hypersensitivity and immunodeficiency.

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 and 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% ([2], [3], [4]). The typical lifetime of white blood cells varies from hours to days ([5], [6]). Because two classes of them, neutrophils and lymphocytes, represent about 92% of the total white blood cells, in the paper [1], Gheorghe Moza performed a complete study of the "fight" between the immune system and the pathogen agent (predator) by restriction of the interaction only with this two types of "bodyguards": neutrophils and lymphocytes. Of course, our approach can be extended to three kinds of white blood cells (neutrophils, lymphocytes and monocytes), which represent 97.3% of the total white blood cells and it will be obtain a similar study like in [1]. Moreover, we can also consider all five types of white blood cells ([1]), but the mathematical model of the resulting 6-dimensional dynamical system will be very complicated to study.

In this work we aim to propose a mathematical model to study the interaction between a virus and the human immune system represented by following three components: the innate immunity, the humoral immunity (after passing by infection or by vaccination) and the cellular immunity (only after passing by infection). Our approach is based on a modified predator-prey methodology ([7], [8], [9], [10], [11], [12]) used in population dynamics. It is need to change some initial hypotheses

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used in classical predator-prey models to take into account the types of interactions between the immune system and the virus (predator). Because in the classical predator-prey models ([13], [14], [15]), 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. So, in our study, the two 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 [16] to study 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 [17]. The potential use of viruses in treating cancer has been studied in [18]. A bio-mathematical model to describe the interactions between influenza A virus and local tissues such as respiratory tract, has been recently considered in [19]. A recent analysis of a systems biology model [20] proposes some methods to approach the fight against corona viruses.

Taking into account that the immunity system has three components (the innate immunity, the humoral immunity and the cellular immunity), in the second section we will consider a four-dimensional ($4D$) model with three friendly species fighting with the same combatant enemy, a pathogen agent. The local analysis of this model will be made in the third section with the mathematical tools of the dynamical system theory. Next, in the fourth section will be presented some very interesting medical interpretations about the behaviour of the modelled system around the fifteen equilibrium points. This system of ordinary differential equations represent a class of Kolmogorov systems ([21], [22], [23], [24]). This kind of systems is widely used in the mathematical models for the dynamics of population, like predator-prey models or different models for the spread of diseases ([25], [26], [27], [28], [29]). A qualitative analysis of this Lotka–Volterra type systems based on dynamical systems theory will be performed, by studying the local behavior of the equilibria and obtaining local dynamics properties from the linear stability point of view.

Finally, in the fifth section we will introduce two types of medical control for the $4D$ system, with three control functions each, in order to study the possibility to help the human immune system in the fight against the virus. The obtained results suggest us that by increasing of at least a category of immune system, by medical interventions, in the early stages of the virus infection, beyond its normal threshold, it is possible that the immune system will win the fight with the virus in spite of a very low level of another component.

2 The 4-dimensional mathematical model

Denote by $x_1(t)$, $x_2(t)$ and $x_3(t)$ the level of three types of immunity: the innate immunity, the humoral immunity and the cellular immunity. This three types of immunity fight jointly with the virus (like the present coronavirus, Covid-19) in order to stop the virus multiplication and eliminate it. The level of the virus we will denote by $v(t)$ and this represent the number of viruses cells of the this type which exist in a body at time t. Consider the time as being continuous, $t \geq 0$. Thus, $\dot{x}_1(t)$, $\dot{x}_2(t)$, $\dot{x}_3(t)$ and $\dot{v}(t)$ are the rates of changes of these four quantities in a short unity of time, $\dot{x}_i(t) = \frac{dx_i}{dt}$, $\dot{v}(t) = \frac{dv}{dt}$. Following the ideas from [1], this model is based on the following three hypotheses:

H1. In the absence of the virus, the three quantities $x_1(t)$, $x_2(t)$ and $x_3(t)$ can be present in the human body up to a threshold value. This hypothesis is based on the fact that the human body may have an innate immunity and also an humoral and cellular immunity, after a prior possible contact with the virus. Thus, in the first stage, before to a present contact with the virus $v(t)$, we consider

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that the evolution laws of $x_1(t)$, $x_2(t)$ and $x_3(t)$ are the followings:

$$(1) \qquad \begin{cases} \dot{x}_1 &= a_1x_1 - b_1x_1^2 \\ \dot{x}_2 &= a_2x_2 - b_2x_2^2 \\ \dot{x}_3 &= a_3x_3 - b_3x_3^2 \end{cases}$$

with $a_i > 0$ and $b_i > 0$, $i = 1, 2, 3$. Taking into account that the general solution of the equation $\dot{x}_i = a_ix_i - b_ix_i^2$ with the initial condition $x_i(0) = x_i^0$ is

$$x_i(t) = a_ix_i^0 \frac{e^{ta_i}}{a_i + b_ix_i^0\,(e^{ta_i} - 1)}\,, \quad t \geq 0$$

one can observe that $x_i(t) \to \frac{a_i}{b_i}$ for $t \to \infty$ and all x_i^0, $i = 1, 2, 3$.

If the term $-b_ix_i^2$ is missing, then $x_i(t)$ increase exponentially when $t \to \infty$, because in this case ($b_i = 0$) the general solution of the equation in x_i will be $x_i(t) = a_ix_i^0e^{ta_i}$. Else, if $b_i > 0$, then for each $i = 1, 2, 3$, we have that the maximum threshold value of the numbers of the blood white cells x_i is $\frac{a_i}{b_i}$.

H2. Normally, in an healthy body without autoimmune diseases, the three types of the immunity do not attack each other. Thus, they are destroyed only due to viruses and, as such, a term in the form $-c_ix_iv$ should be added to each equation in $x_i(t)$, where $v(t)$ is the number of viruses cells which exists in the human body at time t.

H3. In the absence of the immune system of the body the virus would multiplicate indefinitely and exponentially, $v(t)$ satisfying the law $\dot{v} = p_4v$. But, of course, in the presence of the immune system the number of viruses will decrease and consequently, we must add the terms $-p_ix_iv$, $i = 1, 2, 3$, to the evolution law of v.

If we will denote the fourth variable v by x_4, then we can conclude that these hypotheses lead us to the following four dimensional first order differential system with thirteen parameters, given by

$$(2) \qquad \begin{cases} \dot{x}_1 &= a_1x_1 - b_1x_1^2 - c_1x_1x_4 \\ \dot{x}_2 &= a_2x_2 - b_2x_2^2 - c_2x_2x_4 \\ \dot{x}_3 &= a_3x_3 - b_3x_3^2 - c_3x_3x_4 \\ \dot{x}_4 &= p_4x_4 - p_1x_1x_4 - p_2x_2x_4 - p_3x_3x_4 \end{cases}$$

with $a_i > 0$, $b_i > 0$, $c_i > 0$, $p_i > 0$, for all $i = 1, 2, 3, 4$.

Is obviously that the model has a medical relevance when $x_i \geq 0$, $i = 1, 2, 3, 4$. Therefore the solutions of the system lie in the set $\Sigma_+^0 = \left\{(x_1, x_2, x_2, x_4) \in \mathbf{R}^4 \mid x_i \geq 0,\, i = 1, 2, 3, 4\right\}$. Moreover, the hyperplanes $\{x_i = 0\}$ are invariant manifolds with respect to the flow of the system, that means any orbit starting from a point which belongs to $\Sigma_+ = \left\{(x_1, x_2, x_2, x_4) \in \mathbf{R}^4 \mid x_i > 0,\, i = 1, 2, 3, 4\right\}$ remains in Σ_+. So, the orbits cannot cross any of these four invariant hyperplanes and then the study of the system where it has a medical relevance is well-defined, in the sense that, an orbit starting from a zone with medical relevance does not enter in a zone with medical irrelevance and conversely.

3 The local analysis of the model

The Jacobi matrix at an equilibrium point (x_1, x_2, x_3, x_4) is

$$A = \begin{pmatrix} a_1 - 2b_1x_1 - c_1x_4 & 0 & 0 & -c_1x_1 \\ 0 & a_2 - 2b_2x_2 - c_2x_4 & 0 & -c_2x_2 \\ 0 & 0 & a_3 - 2b_3x_3 - c_3x_4 & -c_3x_3 \\ -p_1x_4 & -p_2x_4 & -p_3x_4 & p_4 - p_1x_1 - p_2x_2 - p_3x_3 \end{pmatrix}$$

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In order to find the equilibrium points, by analyzing the system,

$$\begin{cases} x_1\left(a_1 - b_1x_1 - c_1x_4\right) = 0 \\ x_2\left(a_2 - b_2x_2 - c_2x_4\right) = 0 \\ x_3\left(a_3 - b_3x_3 - c_3x_4\right) = 0 \\ x_4\left(p_4 - p_1x_1 - p_2x_2 - p_3x_3\right) = 0 \end{cases}$$

we obtain the following fifteen equilibrium points:
$E_0(0,0,0,0)$, $E_1^1(\frac{a_1}{b_1},0,0,0)$, $E_1^2(0,\frac{a_2}{b_2},0,0)$, $E_1^3(0,0,\frac{a_3}{b_3},0)$,
$E_2^{12}(\frac{a_1}{b_1},\frac{a_2}{b_2},0,0)$, $E_2^{13}(\frac{a_1}{b_1},0,\frac{a_3}{b_3},0)$, $E_2^{23}(0,\frac{a_2}{b_2},\frac{a_3}{b_3},0)$, $E_3(\frac{a_1}{b_1},\frac{a_2}{b_2},\frac{a_3}{b_3},0)$,
$E_4^1\left(\frac{p_4}{p_1},0,0,\frac{1}{c_1}(a_1 - b_1\frac{p_4}{p_1})\right)$, $E_4^2\left(0,\frac{p_4}{p_2},0,\frac{1}{c_2}(a_2 - b_2\frac{p_4}{p_2})\right)$, $E_4^3\left(0,0,\frac{p_4}{p_3},\frac{1}{c_3}(a_3 - b_3\frac{p_4}{p3})\right)$,
$E_5^{12}\left(\frac{1}{b_1}(a_1 - c_1v_5^{12}),\frac{1}{b_2}(a_2 - c_2v_5^{12}),0,v_5^{12}\right)$, where $v_5^{12} = \frac{1}{d_5^{12}}\left(p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} - p_4\right)$, $d_5^{12} = p_1\frac{c_1}{b_1} + p_2\frac{c_2}{b_2}$,
$E_5^{13}\left(\frac{1}{b_1}(a_1 - c_1v_5^{13}),0,\frac{1}{b_3}(a_3 - c_3v_5^{13}),v_5^{13}\right)$, where $v_5^{13} = \frac{1}{d_5^{13}}\left(p_1\frac{a_1}{b_1} + p_3\frac{a_3}{b_3} - p_4\right)$, $d_5^{13} = p_1\frac{c_1}{b_1} + p_3\frac{c_3}{b_3}$,
$E_5^{23}\left(0,\frac{1}{b_2}(a_2 - c_2v_5^{23}),\frac{1}{b_3}(a_3 - c_3v_5^{23}),v_5^{23}\right)$, where $v_5^{23} = \frac{1}{d_5^{23}}\left(p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4\right)$, $d_5^{23} = p_2\frac{c_2}{b_2} + p_3\frac{c_3}{b_3}$
and, finally $E_6(x_1,x_2,x_3,v_6)$, where $x_1 = \frac{1}{b_1}(a_1 - c_1v_6)$, $x_2 = \frac{1}{b_2}(a_2 - c_2v_6)$, $x_3 = \frac{1}{b_3}(a_3 - c_3v_6)$ and $v_6 = \frac{1}{d_6}\left(p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4\right)$, with $d_6 = p_1\frac{c_1}{b_1} + p_2\frac{c_2}{b_2} + p_3\frac{c_3}{b_3}$.

Next, it will be obtain the following results:

Theorem 1. *i) E_0 is an unstable node;*
ii) E_1^1, E_1^2 and E_1^3 are saddle points whenever belongs to Σ_+.
iii) E_2^{12}, E_2^{13} and E_2^{23} are saddle points whenever belongs to Σ_+.

Proof.

i) For $E_0(0,0,0,0)$ we have the Jacobian $A = \begin{pmatrix} a_1 & 0 & 0 & 0 \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 \end{pmatrix}$, with eigenvalues a_1, a_2, a_3, p_4. Then, this equilibria is a repeller, more exactly E_0 is an unstable node.

ii) For $E_1^1(\frac{a_1}{b_1},0,0,0)$ we have the Jacobian $A = \begin{pmatrix} -a_1 & 0 & 0 & -c_1\frac{a_1}{b_1} \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 - p_1\frac{a_1}{b_1} \end{pmatrix}$ with eigenvalues $-a_1$, a_2, a_3, $\frac{p_4b_1 - p_1a_1}{b_1} = p_4 - p_1\frac{a_1}{b_1}$ and then E_1^1 is a saddle point.

The same situation will be for $E_1^2(0,\frac{a_2}{b_2},0,0)$, with the Jacobian $A = \begin{pmatrix} a_1 & 0 & 0 & 0 \\ 0 & -a_2 & 0 & -c_2\frac{a_2}{b_2} \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 - p_2\frac{a_2}{b_2} \end{pmatrix}$

with eigenvalues a_1, $-a_2$, a_3, $\frac{p_4b_2 - p_2a_2}{b_2} = p_4 - p_2\frac{a_2}{b_2}$, and respectively, for $E_1^3(0,0,\frac{a_3}{b_3},0)$, with the Jacobian $A = \begin{pmatrix} a_1 & 0 & 0 & 0 \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & -a_3 & -c_3\frac{a_3}{b_3} \\ 0 & 0 & 0 & p_4 - p_3\frac{a_3}{b_3} \end{pmatrix}$, with eigenvalues a_1, a_2, $-a_3$, $\frac{p_4b_3 - p_3a_3}{b_3} = p_4 - p_3\frac{a_3}{b_3}$.

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iii) For $E_2^{12}(\frac{a_1}{b_1}, \frac{a_2}{b_2}, 0, 0)$ we have the Jacobian $A = \begin{pmatrix} -a_1 & 0 & 0 & -c_1\frac{a_1}{b_1} \\ 0 & -a_2 & 0 & -c_2\frac{a_2}{b_2} \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 - p_1\frac{a_1}{b_1} - p_2\frac{a_2}{b_2} \end{pmatrix}$,

with eigenvalues $-a_1$, $-a_2$, a_3, $\frac{p_4b_1b_2 - p_1a_1b_2 - p_2a_2b_1}{b_1b_2} = p_4 - p_1\frac{a_1}{b_1} - p_2\frac{a_2}{b_2}$. Then E_2^{12} is a saddle point.

The same situation will be also for $E_2^{13}(\frac{a_1}{b_1}, 0, \frac{a_3}{b_3}, 0)$ and $E_2^{23}(0, \frac{a_2}{b_2}, \frac{a_3}{b_3}, 0)$.

For E_2^{13} we have $A = \begin{pmatrix} -a_1 & 0 & 0 & -c_1\frac{a_1}{b_1} \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & -a_3 & -c_3\frac{a_3}{b_3} \\ 0 & 0 & 0 & p_4 - p_1\frac{a_1}{b_1} - p_3\frac{a_3}{b_3} \end{pmatrix}$ with eigenvalues $-a_1$, a_2, $-a_3$, $\frac{p_4b_1b_3 - p_1a_1b_3 - p_3a_3b_1}{b_1b_3} = p_4 - p_1\frac{a_1}{b_1} - p_3\frac{a_3}{b_3}$.

For E_2^{23} we have $A = \begin{pmatrix} a_1 & 0 & 0 & 0 \\ 0 & -a_2 & 0 & -c_2\frac{a_2}{b_2} \\ 0 & 0 & -a_3 & -c_3\frac{a_3}{b_3} \\ 0 & 0 & 0 & p_4 - p_2\frac{a_2}{b_2} - p_3\frac{a_3}{b_3} \end{pmatrix}$ with eigenvalues a_1, $-a_2$, $-a_3$, $\frac{p_4b_2b_3 - p_2a_2b_3 - p_3a_3b_2}{b_2b_3} = p_4 - p_2\frac{a_2}{b_2} - p_3\frac{a_3}{b_3}$. Q.E.D.

For the equilibria E_3 we have the following result:

Theorem 2. *E_3 is an attractor (stable node) if and only if $p_4 < p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3}$ and E_3 is a saddle point if and only if $p_4 > p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3}$.*

Proof.

At the equilibria E_3, with $x_1 = \frac{a_1}{b_1}$, $x_2 = \frac{a_2}{b_2}$, $x_3 = \frac{a_3}{b_3}$, $x_4 = 0$, we have

$$A = \begin{pmatrix} -a_1 & 0 & 0 & -c_1\frac{a_1}{b_1} \\ 0 & -a_2 & 0 & -c_2\frac{a_2}{b_2} \\ 0 & 0 & -a_3 & -c_3\frac{a_3}{b_3} \\ 0 & 0 & 0 & p_4 - p_1\frac{a_1}{b_1} - p_2\frac{a_2}{b_2} - p_3\frac{a_3}{b_3} \end{pmatrix}$$

with eigenvalues $\lambda_1 = -a_1$, $\lambda_2 = -a_2$, $\lambda_3 = -a_3$, $\lambda_4 = p_4 - p_1\frac{a_1}{b_1} - p_2\frac{a_2}{b_2} - p_3\frac{a_3}{b_3}$. Q.E.D.

Next, we have the following results:

Theorem 3. *i) E_4^1, E_4^2 and E_4^3 are saddle points whenever belongs to Σ_+.*
ii) E_5^{12}, E_5^{13} and E_5^{23} are saddle points whenever belongs to Σ_+.

Proof.

i) For $E_4^1\left(\frac{p_4}{p_1}, 0, 0, \frac{1}{c_1}(a_1 - b_1\frac{p_4}{p_1})\right)$ we have the Jacobian

$$A = \begin{pmatrix} -b_1\frac{p_4}{p_1} & 0 & 0 & -c_1\frac{p_4}{p_1} \\ 0 & a_2 - \frac{c_2}{c_1}\left(a_1 - b_1\frac{p_4}{p_1}\right) & 0 & 0 \\ 0 & 0 & a_3 - \frac{c_3}{c_1}\left(a_1 - b_1\frac{p_4}{p_1}\right) & 0 \\ -\frac{p_1}{c_1}\left(a_1 - b_1\frac{p_4}{p_1}\right) & -\frac{p_2}{c_1}\left(a_1 - b_1\frac{p_4}{p_1}\right) & -\frac{p_3}{c_1}\left(a_1 - b_1\frac{p_4}{p_1}\right) & 0 \end{pmatrix}$$

with eigenvalues $a_2 - \frac{c_2(p_1a_1 - p_4b_1)}{c_1p_1}$, $a_3 - \frac{c_3(p_1a_1 - p_4b_1)}{c_1p_1}$, $\frac{1}{2p_1}\left(-p_4b_1 + \sqrt{\Delta}\right)$, $\frac{1}{2p_1}\left(-p_4b_1 - \sqrt{\Delta}\right)$, where $\Delta = p_4^2b_1^2 - 4p_1p_4^2b_1 + 4p_4p_1^2a_1$.

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If E_4^1 is a proper equilibria (i.e. $\frac{1}{c_1}(a_1 - b_1\frac{p_4}{p_1}) > 0$), then $\Delta = p_4^2 b_1^2 + 4p_1p_4(p_1a_1 - p_4b_1) > 0$ and $\sqrt{\Delta} > p_4b_1$. So, it results that E_4^1 is a saddle point, because the last two eigenvalues has different signs.

Following a similarly analysis, $E_4^2\left(0, \frac{p_4}{p_2}, 0, \frac{1}{c_2}(a_2 - b_2\frac{p_4}{p_2})\right)$ and $E_4^3\left(0, 0, \frac{p_4}{p_3}, \frac{1}{c_3}(a_3 - b_3\frac{p_4}{p3})\right)$ are also saddle points whenever belongs to Σ_+.

ii) For $E_5^{12}\left(\frac{1}{b_1}(a_1 - c_1v_5^{12}), \frac{1}{b_2}(a_2 - c_2v_5^{12}), 0, v_5^{12}\right)$, where $v_5^{12} = \frac{1}{d_5^{12}}\left(p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} - p_4\right)$ and $d_5^{12} = p_1\frac{c_1}{b_1} + p_2\frac{c_2}{b_2}$, we have the Jacobian

$$A = \begin{pmatrix} -a_1 + c_1v_5^{12} & 0 & 0 & -\frac{c_1}{b_1}\left(a_1 - c_1v_5^{12}\right) \\ 0 & -a_2 + c_2v_5^{12} & 0 & -\frac{c_2}{b_2}\left(a_2 - c_2v_5^{12}\right) \\ 0 & 0 & a_3 - c_3v_5^{12} & 0 \\ -p_1v_5^{12} & -p_2v_5^{12} & -p_3v_5^{12} & 0 \end{pmatrix}$$

or

$$A = \begin{pmatrix} -b_1x_1 & 0 & 0 & -c_1x_1 \\ 0 & -b_2x_2 & 0 & -c_2x_2 \\ 0 & 0 & a_3 - c_3x_4 & 0 \\ -p_1x_4 & -p_2x_4 & -p_3x_4 & 0 \end{pmatrix}$$

The eigenvalues of this matrix is very complicated to find, but we observe an eigenvalue $\lambda_1 = -(c_3x_4 - a_3)$, where $x_1 = \frac{a_1p_2c_2 - c_1p_2a_2 + c_1p_4b_2}{p_1c_1b_2 + p_2c_2b_1}$, $x_2 = \frac{a_2p_1c_1 - c_2p_1a_1 + c_2p_4b_1}{p_1c_1b_2 + p_2c_2b_1}$, $x_3 = 0$, $x_4 = \frac{p_1a_1b_2 + p_2a_2b_1 - p_4b_1b_2}{p_1c_1b_2 + p_2c_2b_1}$.

The characteristic polynomial at E_5^{12} is $P_{E_5^{12}}(X) = X^4 + A_3X^3 + A_2X^2 + A_1X + A_0$, where

$$\begin{aligned} A_3 &= b_1x_1 + b_2x_2 + c_3x_4 - a_3 \\ A_2 &= b_1x_1c_3x_4 + b_2x_2c_3x_4 - p_1x_4c_1x_1 - p_2x_4c_2x_2 + b_1x_1b_2x_2 - b_2x_2a_3 - b_1x_1a_3 \\ A_1 &= -b_1x_1b_2x_2a_3 + b_1x_1b_2x_2c_3x_4 - b_1x_1p_2x_4c_2x_2 + p_2x_4c_2x_2a_3 - p_2x_4^2c_2x_2c_3 \\ &\quad -p_1x_4c_1x_1b_2x_2 + p_1x_4c_1x_1a_3 - p_1x_4^2c_1x_1c_3 \\ A_0 &= x_2x_1x_4\left(a_3 - c_3x_4\right)\left(b_1p_2c_2 + p_1c_1b_2\right) \end{aligned}$$

According to Routh–Hurwitz criterion for fourth order polynomials, $P(X) = X^4 + A_3X^3 + A_2X^2 + A_1X + A_0$ has all roots in the open left half plane (i.e. $\lambda_i < 0$ or Re $\lambda_i < 0$, for all i) if and only if $A_3 > 0$, $A_2A_3 - A_1 > 0$, $A_1A_2A_3 - A_0A_3^2 - A_1^2 > 0$ and $A_0 > 0$.

We are interested to study the equilibria $E_5^{12}(x_1, x_2, x_3, x_4)$ only if it has all components positive, that means $x_4 < \frac{a_1}{c_1}$, $x_4 < \frac{a_2}{c_2}$, $p_4 < p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2}$ and then we obtain $A_0 < 0$ if and only if $x_4 > \frac{a_3}{c_3}$ or $A_0 > 0$ if and only if $x_4 < \frac{a_3}{c_3}$.

If λ_i $(i = 1, 2, 3, 4)$ denote the eigenvalues at E_5^{12}, then, according with Viéte's relations, we have $\lambda_1\lambda_2\lambda_3\lambda_4 = A_0$. So, it can be said that E_5^{12} is a saddle point if $x_4 > \frac{a_3}{c_3}$.

If $x_4 = \frac{a_3}{c_3}$ (i.e. $A_0 = 0$), then $x_1 = \frac{1}{b_1}\left(a_1 - c_1\frac{a_3}{c_3}\right)$, $x_2 = \frac{1}{b_2}\left(a_2 - c_2\frac{a_3}{c_3}\right)$ and it results

$A_3 = b_1x_1 + b_2x_2 + c_3x_4 - a_3 = \left(a_1 - c_1\frac{a_3}{c_3}\right) + \left(a_2 - c_2\frac{a_3}{c_3}\right) > 0,$

$A_2 = b_1x_1c_3x_4 + b_2x_2c_3x_4 - p_1x_4c_1x_1 - p_2x_4c_2x_2 + b_1x_1b_2x_2 - b_2x_2a_3 - b_1x_1a_3$

$= -p_1\frac{a_3}{c_3}\frac{c_1}{b_1}\left(a_1 - c_1\frac{a_3}{c_3}\right) - p_2\frac{a_3}{c_3}\frac{c_2}{b_2}\left(a_2 - c_2\frac{a_3}{c_3}\right) + \left(a_1 - c_1\frac{a_3}{c_3}\right)\left(a_2 - c_2\frac{a_3}{c_3}\right)$

and

$A_1 = -b_1x_1b_2x_2a_3 + b_1x_1b_2x_2c_3x_4 - b_1x_1p_2x_4c_2x_2 + p_2x_4c_2x_2a_3 - p_2x_4^2c_2x_2c_3$

$-p_1x_4c_1x_1b_2x_2 + p_1x_4c_1x_1a_3 - p_1x_4^2c_1x_1c_3$

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$= -\left(a_1 - c_1\frac{a_3}{c_3}\right)p_2\frac{a_3}{c_3}\frac{c_2}{b_2}\left(a_2 - c_2\frac{a_3}{c_3}\right) - p_1\frac{a_3}{c_3}\frac{c_1}{b_1}\left(a_1 - c_1\frac{a_3}{c_3}\right)\left(a_2 - c_2\frac{a_3}{c_3}\right) < 0,$
due to the positivity of the first two components of E_5^{12}.

So, since the eigenvalues of the characteristic polynomial at this nonhyperbolic equilibria E_5^{12} are $\lambda_1 = 0$ and λ_2, λ_2, λ_3 exactly the roots of the polynomial $Q(X) = X^3 + A_3X^2 + A_2X^1 + A_1$, it results that $\lambda_2 + \lambda_3 + \lambda_4 = -A_3 < 0$, $\lambda_2\lambda_3 + \lambda_3\lambda_4 + \lambda_4\lambda_2 = A_2$, $\lambda_2\lambda_3\lambda_4 = -A_1 > 0$ and

$\lambda_2^2+\lambda_3^2+\lambda_4^2 = (\lambda_2 + \lambda_3 + \lambda_4)^2 - 2(\lambda_2\lambda_3 + \lambda_3\lambda_4 + \lambda_4\lambda_2) = A_3^2 - 2A_2 = \left(a_1 - c_1\frac{a_3}{c_3} + a_2 - c_2\frac{a_3}{c_3}\right)^2 -$
$2\left(-p_1\frac{a_3}{c_3}\frac{c_1}{b_1}\left(a_1 - c_1\frac{a_3}{c_3}\right) - p_2\frac{a_3}{c_3}\frac{c_2}{b_2}\left(a_2 - c_2\frac{a_3}{c_3}\right) + \left(a_1 - c_1\frac{a_3}{c_3}\right)\left(a_2 - c_2\frac{a_3}{c_3}\right)\right) =$
$\left(a_1 - c_1\frac{a_3}{c_3}\right)^2 + \left(a_2 - c_2\frac{a_3}{c_3}\right)^2 + 2p_1\frac{a_3}{c_3}\frac{c_1}{b_1}\left(a_1 - c_1\frac{a_3}{c_3}\right) + 2p_2\frac{a_3}{c_3}\frac{c_2}{b_2}\left(a_2 - c_2\frac{a_3}{c_3}\right) > 0,$
due to the positivity of the first two components of E_5^{12}. Then λ_2, λ_2, λ_3 are real eigenvalues with different signs (two negative and one pozitive), that means that E_5^{12} is a saddle point, also in this case.

If $x_4 < \frac{a_3}{c_3}$ then $A_0 > 0$, but the sign of A_1, A_2, A_3 is very complicated to study because we have to many parameters. However, using the first root $\lambda_1 = -(c_3x_4 - a_3)$ of the characteristic polynomial at E_5^{12}, we have

$P_{E_5^{12}}(X) = X^4 + A_3X^3 + A_2X^2 + A_1X + A_0 = (X - \lambda_1)\left(X^3 + B_2X^2 + B_1X + B_0\right)$,
where $B_2 = A_3 + \lambda_1$, $B_1 = A_2 + \lambda_1B_2$, $B_0 = A_1 + \lambda_1B_1$ or $A_0 = -\lambda_1B_0$.

But, in his case $x_4 < \frac{a_3}{c_3}$, we have $\lambda_1 = -(c_3x_4 - a_3) > 0$ and then $B_0 < 0$, because $A_0 > 0$.
It follow $\lambda_2\lambda_3\lambda_4 = B_0 < 0$, that means that E_5^{12} is a saddle point, also in this case.

Then E_5^{12} is a saddle point whenever belongs to Σ_+.

Similarly, for $E_5^{13}\left(\frac{1}{b_1}(a_1 - c_1v_5^{13}), 0, \frac{1}{b_3}(a_3 - c_3v_5^{13}), v_5^{13}\right)$, where $v_5^{13} = \frac{1}{d_5^{13}}\left(p_1\frac{a_1}{b_1} + p_3\frac{a_3}{b_3} - p_4\right)$, $d_5^{13} = p_1\frac{c_1}{b_1} + p_3\frac{c_3}{b_3}$ and $E_5^{23}\left(0, \frac{1}{b_2}(a_2 - c_2v_5^{23}), \frac{1}{b_3}(a_3 - c_3v_5^{23}), v_5^{23}\right)$, where $v_5^{23} = \frac{1}{d_5^{23}}\left(p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4\right)$, $d_5^{23} = p_2\frac{c_2}{b_2} + p_3\frac{c_3}{b_3}$ we obtain that these two equilibria are also saddle points. Q.E.D.

Finally, for $E_6(x_1, x_2, x_3, x_4)$, where $x_1 = \frac{1}{b_1}(a_1 - c_1v_6)$, $x_2 = \frac{1}{b_2}(a_2 - c_2v_6)$, $x_3 = \frac{1}{b_3}(a_3 - c_3v_6)$ and $x_4 = v_6 = \frac{1}{d_6}\left(p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4\right)$, with $d_6 = p_1\frac{c_1}{b_1} + p_2\frac{c_2}{b_2} + p_3\frac{c_3}{b_3}$, we obtain the Jacobian

$$A = \begin{pmatrix} -b_1x_1 & 0 & 0 & -c_1x_1 \\ 0 & -b_2x_2 & 0 & -c_2x_2 \\ 0 & 0 & -b_3x_3 & -c_3x_3 \\ -p_1x_4 & -p_2x_4 & -p_3x_4 & 0 \end{pmatrix}$$

or

$$A = \begin{pmatrix} -a_1 + \frac{c_1}{d_6}t_6 & 0 & 0 & -\frac{c_1}{b_1}\left(a_1 - \frac{c_1}{d_6}t_6\right) \\ 0 & -a_2 + \frac{c_2}{d_6}t_6 & 0 & -\frac{c_2}{b_2}\left(a_2 - \frac{c_2}{d_6}t_6\right) \\ 0 & 0 & -a_3 + \frac{c_3}{d_6}t_6 & -\frac{c_3}{b_3}\left(a_3 - \frac{c_3}{d_6}t_6\right) \\ -\frac{p_1}{d_6}t_6 & -\frac{p_2}{d_6}t_6 & -\frac{p_3}{d_6}t_6 & 0 \end{pmatrix},$$

where $t_6 = p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4$.

The characteristic polynomial at E_6 is $P_{E_6}(X) = X^4 + A_3X^3 + A_2X^2 + A_1X + A_0$, where

$$\begin{aligned} A_3 &= b_1x_1 + b_2x_2 + b_3x_3 \\ A_2 &= b_1x_1b_2x_2 + b_1x_1b_3x_3 + b_2x_2b_3x_3 - (p_1c_1x_1 + p_2c_2x_2 + c_3x_3p_3)\,x_4 \\ A_1 &= x_1x_2x_3b_1b_2b_3 - x_2x_3x_4\,(p_2b_3c_2 + p_3b_2c_3) - x_1x_2x_4\,(p_1b_2c_1 + p_2b_1c_2) - x_1x_3x_4\,(p_3b_1c_3 + p_1b_3c_1) \\ A_0 &= -x_1x_2x_3x_4\,(p_3b_1b_2c_3 + p_1b_2b_3c_1 + b_1p_2b_3c_2) \end{aligned}$$

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According to Routh–Hurwitz criterion for fourth order polynomials, $P(X) = X^4 + A_3X^3 + A_2X^2 + A_1X + A_0$ has all roots in the open left half plane (i.e. $\lambda_i < 0$ or Re $\lambda_i < 0$, for all i) if and only if $A_3 > 0$, $A_2A_3 - A_1 > 0$, $A_1A_2A_3 - A_0A_3^2 - A_1^2 > 0$ and $A_0 > 0$.

Due to the fact that we are interested to study only proper equilibrium points, it result that $E_6(x_1, x_2, x_3, x_4)$ has all components positive, that means $a_1 - c_1x_4 > 0$, $a_2 - c_2x_4 > 0$, $a_3 - c_3x_4 > 0$, $p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4 > 0$ and then we obtain $A_3 > 0$, but $A_0 < 0$.

Moreover, we have the next theorem.

Theorem 4. *i) The equilibrium point E_6 is a saddle whenever belongs to Σ_+.*

ii) The system (2) does not undergo a Hopf-Hopf bifurcation at E_6 on Σ_+.

iii) The equilibria E_6 bifurcates from E_3 along the hyperplane

$$S = \{(p_1, p_2, p_3, p_4) | p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4 = 0\}$$

by a transcritical bifurcation.

iv) Three more transcritical bifurcations arise in the system (2) on the hyperplanes

$$S_{12} = \left\{(p_1, p_2, p_3, p_4) | p_1\left(\frac{a_1}{b_1} - \frac{a_3c_1}{b_1c_3}\right) + p_2\left(\frac{a_2}{b_2} - \frac{a_3c_2}{b_2c_3}\right) - p_4 = 0, a_1c_3 - a_3c_1 > 0, a_2c_3 - a_3c_2 > 0\right\},$$

$$S_{13} = \left\{(p_1, p_2, p_3, p_4) | p_1\left(\frac{a_1}{b_1} - \frac{a_2c_1}{b_1c_2}\right) + p_3\left(\frac{a_3}{b_3} - \frac{a_2c_3}{b_3c_2}\right) - p_4 = 0, a_1c_2 - a_2c_1 > 0, a_3c_2 - a_2c_3 > 0\right\},$$

$$S_{23} = \left\{(p_1, p_2, p_3, p_4) | p_2\left(\frac{a_2}{b_2} - \frac{a_1c_2}{b_2c_1}\right) + p_3\left(\frac{a_3}{b_3} - \frac{a_1c_3}{b_3c_1}\right) - p_4 = 0, a_2c_1 - a_1c_2 > 0, a_3c_1 - a_1c_3 > 0\right\}.$$

E_6 collides to E_5^{12} on S_{12}, E_6 collides to E_5^{13} on S_{13}, respectively, E_6 collides to E_5^{23} on S_{23}.

v) Moreover, there are three transcritical bifurcations arise in the system (2) on the 2-planes $\pi_1 = S_{12} \cap S_{13}$, $\pi_2 = S_{12} \cap S_{23}$ and $\pi_3 = S_{13} \cap S_{23}$. More precisely, E_6 collides to E_4^1 on π_1, E_6 collides to E_4^2 on π_2, respectively, E_6 collides to E_4^3 on π_3.

Proof.

i) If we suppose that E_6 is an attractor, then all roots of the characteristic polynomial at E_6 are in the open left half plane (i.e. $\lambda_i < 0$ or Re $\lambda_i < 0$, for all i) and then according to Routh–Hurwitz criterion we must have $A_3 > 0$, $A_2A_3 - A_1 > 0$, $A_1A_2A_3 - A_0A_3^2 - A_1^2 > 0$ and $A_0 > 0$. But $A_0 < 0$ and then E_6 cannot be an attractor. On the other hand, if we suppose that E_6 is a repeller, with $\lambda_i > 0$ for all i we obtain again a contradiction with $\lambda_1\lambda_2\lambda_3\lambda_4 = A_0 < 0$, according with the relations of Viéte. In conclusion, E_6 is not a repeller and we can conclude the E_6 is a saddle point whenever belongs to Σ_+.

ii) If we suppose that the characteristic polynomial at E_6 has the roots $\pm i\omega_1$, $\pm i\omega_2$, with $\omega_1 >$ and $\omega_2 >$, then $\lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 = 0$ and $\lambda_1\lambda_2\lambda_3\lambda_4 = \omega_1^2\omega_2^2 > 0$, what is in contradiction with the relations of Viéte ($A_3 > 0$ and $A_0 < 0$). Therefore the system (2) does not undergo a Hopf-Hopf bifurcation at E_6 on Σ_+.

iii) It is obviously that E_6 coincides with E_3 on the hyperplane S. In order to prove that a transcritical bifurcation takes places on S, we will apply Sotomayor's theorem ([22]).

For this purpose, we will assume that $\frac{a_i}{b_i}$, p_i, $i = 1, 2, 3$, are constants while p_4 vary. Let's take the parameter $\mu = p_4 - k$, where $k = \sum_{i=1}^{3} pi\frac{a_i}{b_i}$ and let's denote $u = (x_1\, x_2\, x_3\, x_4)^T$ $F = (F_1\, F_2\, F_3\, F_4)^T$,

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where T represent the transpose matrix, i.e. $(x_1, x_2, x_3, x_4)^T = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix}$.

Then the system (2) can be write in the form

$$\dot{u} = F(u, \mu), \tag{3}$$

where $F_1 = a_1x_1 - b_1x_1^2 - c_1x_1x_4$, $F_2 = a_2x_2 - b_2x_2^2 - c_2x_2x_4$, $F_3 = a_3x_3 - b_3x_3^2 - c_3x_3x_4$, $F_4 = (\mu + k)x_4 - p_1x_1x_4 - p_2x_2x_4 - p_3x_3x_4$.

Next, we denote $F_\mu = \left(\frac{\partial F_1}{\partial \mu} \frac{\partial F_2}{\partial \mu} \frac{\partial F_3}{\partial \mu} \frac{\partial F_4}{\partial \mu}\right)^T$ and $DF(u, \mu)$ the Jacobian matrix of F from (3) with respect to u. If we set $u_0 = E_3 = \left(\frac{a_1}{b_1}, \frac{a_2}{b_2}, \frac{a_3}{b_3}, 0\right)$ and $\mu_0 = 0$, then 0 is an eigenvalues both for $DF(u_0, \mu_0)$ and his transpose $DF^T(u, \mu)$, with the corresponding eigenvectors $v = \left(-\frac{c_1}{b_1}, -\frac{c_2}{b_2}, -\frac{c_3}{b_3}, 1\right)^T$ for $DF(u_0, \mu_0)$, respectively $w = (0, 0, 0, 1)^T$ for $DF^T(u_0, \mu_0)$.

The first condition of the transcritical bifurcation, $w^T F_\mu(u_0, \mu_0) = 0$ is obviously satisfied.

If we denote by DF_μ the Jacobi matrix of $F_\mu = (0\,0,\ ,0\,, x_4)^T$, then we have verified the condition, $w^T\left[DF_\mu(u_0, \mu_0)v\right] = 1 \neq 0$.

In order to prove the third condition, we denote the second differential of F at (u, u) by

$$D^2F(u, u) = \left(d^2F_1(u, u)\,, d^2F_2(u, u)\,, d^2F_3(u, u)\,, d^2F_4(u, u)\right)^T\,,$$

where $d^2F_i(u, u)$ is the differential of second order of F_i applied at the pair (u, u), $u = (x_1\,, x_2\,, x_3\,, x_4)^T$. Then $d^2F_i(u, u) = -2b_ix_i^2 - 2c_ix_ix_4$, for $i = 1, 2, 3$, $d^2F_4(u, u) = -2(p_1x_1 + p_2x_2 + p_3x_3)x_4$ and then at (u_0, μ_0) we have

$$w^T\left[D^2F(u_0, \mu_0)(v, v)\right] = 2\left(p_1\frac{c_1}{b_1} + p_2\frac{c_2}{b_2} + p_3\frac{c_3}{b_3}\right) \neq 0\,,$$

which means that was checked the last condition to have a transcritical bifurcation on S.

iv) We have similar treatments like above for each hyperplane.

v) Using the varying parameters μ_1, μ_2 for each 2-plane, we can check the Sotomayor's theorem conditions. Q.E.D.

4 Medical interpretations of the results

Taking into account that this four dimensional mathematical model has 15 equilibria and one is a repeller (unstable node), one is attractor or saddle and the rest of thirteen are saddle points, it would be very useful to present some medical interpretations of the behavior of the system near to each equilibrium points, following the ideas of Gheorghe Moza from [1].

Interpretation for the equilibria $E_0(0, 0, 0, 0)$.

Because E_0 is a repeller (unstable node) with strictly positive eigenvalues a_1, a_2, a_3, p_4, it results that any orbit $\mathbf{x}(t) = (x_1(t), x_2(t), x_3(t), x_4(t))$ starting at a point $\mathbf{x}_0 = (x_{10}, x_{20}, x_{30}, x_{40}) \in \Sigma_+$ close to E_0 will depart from it for t large, that is, $x_4(t)$ may escape to infinity. Moreover, since Hopf bifurcation is not possible at E_0 (its eigenvalues are real), a stable limit cycle surrounding E_0 does not arise by such a bifurcation. Taken together, these mean that, *if the human immune system is*

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sufficiently weak when the virus starts to proliferate in the body, then the virus can win the fight with the antibody cells, which from the theoretically point of view means the death of the human body. We emphasize the idea that the virus can gain (through uncontrolled growth), even if at first it was present in a negligible amount! But the levels of the innate immunity, the humoral immunity and the cellular immunity are extremely small in the vicinity of the origin.

Interpretation for $E_1^1(\frac{a_1}{b_1},0,0,0)$, $E_1^2(0,\frac{a_2}{b_2},0,0)$ and $E_1^3(0,0,\frac{a_3}{b_3},0)$.

If we consider the equilibrium point $E_1^1(\frac{a_1}{b_1},0,0,0)$, then its eigenvalues are $-a_1$, a_2, a_3, $p_4-p_1\frac{a_1}{b_1}$ and E_1^1 is a saddle point for either $p_4-p_1\frac{a_1}{b_1}>0$ or $p_4-p_1\frac{a_1}{b_1}<0$. Any orbit $\mathbf{x}(t)$ starting at a point $\mathbf{x}_0\in\Sigma_+$ close to E_1^1, $\mathbf{x}_0\notin W^s_{E_1^1}$, will depart from E_1^1 for t large, that is $x_4(t)$ may escape to infinity. A stable limit cycle around E_1^1 cannot arise through a Hopf bifurcation since all eigenvalues are real. This means that, if the humoral and cellular immunities are not at the normal level when the virus invades the human body, then the virus may win even though the level of the innate immunity is normal, even at the maximum threshold value $\frac{a_1}{b_1}$. Thus, *a deficiency of two types of immunities may lead to the virus victory. The virus can gain even if at first it was present in a negligible amount!*

For E_1^2 and E_1^3 the results are similar.

Interpretation for $E_2^{12}(\frac{a_1}{b_1},\frac{a_2}{b_2},0,0)$, $E_2^{13}(\frac{a_1}{b_1},0,\frac{a_3}{b_3},0)$ and $E_2^{23}(0,\frac{a_2}{b_2},\frac{a_3}{b_3},0)$.

If we consider the equilibrium point $E_2^{12}(\frac{a_1}{b_1},\frac{a_2}{b_2},0,0)$, then its eigenvalues are $-a_1$, $-a_2$, a_3, $p_4-p_1\frac{a_1}{b_1}-p_2\frac{a_2}{b_2}$ and E_1^1 is a saddle point for either $p_4-p_1\frac{a_1}{b_1}-p_2\frac{a_2}{b_2}>0$ or $p_4-p_1\frac{a_1}{b_1}-p_2\frac{a_2}{b_2}<0$. Any orbit $\mathbf{x}(t)$ starting at a point $\mathbf{x}_0\in\Sigma_+$ close to E_1^{12}, $\mathbf{x}_0\notin W^s_{E_1^{12}}$, will depart from E_1^{12} for t large, that is $x_4(t)$ may escape to infinity. A stable limit cycle around E_1^{12} cannot arise through a Hopf bifurcation since all eigenvalues are real. This means that, if the cellular immunity is not at the normal level when the virus invades the human body, then the virus may win even though the levels of innate and humoral immunities are normal, even at the maximum threshold value $\frac{a_1}{b_1}$ and, respectively $\frac{a_2}{b_2}$. Thus, *a deficiency in the quantity of a single type of immunities may lead to the virus victory. The virus can gain even if at first it was present in a negligible amount!*

For E_2^{13} and E_2^{23} the results are similar.

Interpretation for $E_3(\frac{a_1}{b_1},\frac{a_2}{b_2},\frac{a_3}{b_3},0)$.

If $p_4<p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}$, then E_3 is an attractor (stable node). It results that any orbit $\mathbf{x}(t)$ starting at a point $\mathbf{x}_0\in\Sigma_+$ close to E_3, will converge to $\left(\frac{a_1}{b_1},\frac{a_2}{b_2},\frac{a_3}{b_3},0\right)$ for t large, that means $x_4(t)$ tend to 0 when t tend to $+\infty$. In conclusion, this model shows us that, *if the innate immunity, the humoral immunity and the cellular immunity are at the normal levels (i.e. $\frac{a_i}{b_i}$, $i=1,2,3$) from the first moment they discover the virus and if their joint actions kill the virus at a higher rate than the rate of virus proliferation (i.e. $p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}>p_4$), then the immune system of the body has the ability to break the virus multiplication and liquidate it and the immune system wins the fight.* Else, if the joint destruction rate $p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}$ of the virus by the three immunities actions is not sufficiently strong to overcome rate p_4 of the virus proliferation ($p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}<p_4$, i.e. E_3 is a saddle point), then *the virus may win* since $x_4(t)$ may escape to infinity if an orbit $\mathbf{x}(t)$ start at a point $\mathbf{x}_0\in\Sigma_+$ close to E_3, but $\mathbf{x}_0\notin W^s_{E_3}$. Else, if $\mathbf{x}_0\in W^s_{E_3}$, then the quantity of virus $x_4(t)$ will converge to 0, for t large, and the virus is eliminate. Obviously, a Hopf bifurcation leading to a stable cycle around E_3 is not possible because all eigenvalues are real.

Interpretation for E_4^1, E_4^2 and E_4^3.

If $p_1\frac{a_1}{b_1}>p_4$, then $E_4^1\left(\frac{p_4}{p_1},0,0,\frac{1}{c_1}(a_1-b_1\frac{p_4}{p_1})\right)\in\Sigma_+$ and at this equilibria any Hopf bifurcation is not possible because all eigenvalues are real. Due to the different signs of them, E_4^1 is a saddle and then $x_4(t)$ may escape to infinity, that means *the virus may win.*

For E_4^2 and E_4^3 we have the same scenario.

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Interpretation for E_5^{12}, E_5^{13} and E_5^{23}.

For $E_5^{12}\left(\frac{1}{b_1}(a_1-c_1v_5^{12}),\frac{1}{b_2}(a_2-c_2v_5^{12}),0,v_5^{12}\right)$, where $v_5^{12}=\frac{1}{d_5^{12}}\left(p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}-p_4\right)$, $d_5^{12}=p_1\frac{c_1}{b_1}+p_2\frac{c_2}{b_2}$, if $p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}>p_4$, then $E_5^{12}\in\Sigma_+$ and at this equilibria any Hopf bifurcation is not possible because all eigenvalues are real. Due to the different signs of the eigenvalues, E_5^{12} is a saddle point and then $x_4(t)$ may escape to infinity, that means *the virus may win.*
For E_5^{13} and E_5^{23} the results are similar.

Interpretation for the interior equilibria E_6.

For $E_6(x_1,x_2,x_3,v_6)$, where $x_1=\frac{1}{b_1}(a_1-c_1v_6)$, $x_2=\frac{1}{b_2}(a_2-c_2v_6)$, $x_3=\frac{1}{b_3}(a_3-c_3v_6)$ and $v_6=\frac{1}{d_6}\left(p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}-p_4\right)$, with $d_6=p_1\frac{c_1}{b_1}+p_2\frac{c_2}{b_2}+p_3\frac{c_3}{b_3}$ we have that this equilibria is a saddle point always and then $x_4(t)$ may escape to infinity, that means *the virus may win*, also in this case. Since $E_6\in\Sigma_+$ if and only if $\frac{a_i}{c_i}>v_6>0$, for all $i=1,2,3$, we have that $x_i<\frac{a_i}{b_i}$, for all $i=1,2,3$ and $p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}>p_4$. Then we can conclude that if the levels of all three immunities (innate, humoral and cellular immunity) become at a moment considerably smaller than their normal levels, then 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 three immunities increase in number at the same time but the immune system does not have the ability to eliminate the virus proliferation. Therefore, the quantity of virus $x_4(t)$ may escape to infinity if an orbit $\mathbf{x}(t)$ start at a point $\mathbf{x}_0\in\Sigma_+$ close to E_6, but $\mathbf{x}_0\notin W^s_{E_6}$ or the quantity of virus $x_4(t)$ will converge to v_6, for t large, if $\mathbf{x}_0\in W^s_{E_6}$. A stable limit cycle around E_6 cannot arise through a Hopf bifurcation since all eigenvalues are real.

In conclusion, after this analysis we can say that only in a single case there are sufficient conditions to destroy completely the virus, namely, when $E_3\in\Sigma_+$ and $p_4<p_1\frac{a_1}{b_1}+p_2\frac{a_2}{b_2}+p_3\frac{a_3}{b_3}$, i.e. E_3 is an attractor proper equilibrium point. In the rest of the cases, the virus may win the fight with the human body immune system or, at best, the immune system manages to limit the proliferation of the virus.

5 The 4-dimensional model with two types of medical control

Like in [1], for the $4D$ model presented above, we studied the interaction between a virus and the immune body system by considering only natural developments, without external influences as, for example, drug administration or additional means for increasing of one of the components of the immunity system. In this section, following the ideas from Moza's paper [1], we intend to obtain a mathematical model for the case when the interaction depend also on external factors, like a good life style, drug or vitamins administration or even vaccination for increasing at least one of the kinds of the immunity.

5.1 First medical control

For this purpose, we will use three control functions, one in each of the three equations that model the behavior of immunity's categories, because usually an external intervention can be performed to strengthen the immune system, but not for for destroying or weakening the virus (the last equation).

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Therefore, taking into account of the system (2), we propose the following 4D differential system:

$$(4)\qquad \begin{cases} \dot{x}_1 &= a_1x_1 - b_1x_1^2 - c_1x_1x_4 + \alpha x_1x_2x_3 \\ \dot{x}_2 &= a_2x_2 - b_2x_2^2 - c_2x_2x_4 + \beta x_1x_2x_3 \\ \dot{x}_3 &= a_3x_3 - b_3x_3^2 - c_3x_3x_4 + \gamma x_1x_2x_3 \\ \dot{x}_4 &= p_4x_4 - p_1x_1x_4 - p_2x_2x_4 - p_3x_3x_4 \end{cases}$$

where α, β, γ are real constants and they are using only to improve the role of the immune system in the fight against the virus.

Very interesting is the fact that this system has also fifteen equilibria, like the $4D$ system without control. Moreover, only E_3 and E_6 has another coordinates and, also very complicated to find. The rest of thirteen equilibria has the same coordinates like for the uncontrolled system. However, the local behavior of the system around these equilibrium points will be very different from the uncontrolled case.

The Jacobi matrix at an equilibrium point (x_1, x_2, x_3, x_4) is

$$\begin{pmatrix} a_1 - 2b_1x_1 - c_1x_4 + \alpha x_2x_3 & \alpha x_1x_3 & \alpha x_1x_2 & -c_1x_1 \\ \beta x_2x_3 & a_2 - 2b_2x_2 - c_2x_4 + \beta x_1x_3 & \beta x_1x_2 & -c_2x_2 \\ \gamma x_2x_3 & \gamma x_1x_3 & a_3 - 2b_3x_3 - c_3x_4 + \gamma x_1x_2 & -c_3x_3 \\ -p_1x_4 & -p_2x_4 & -p_3x_4 & p_4 - \sum_{i=1}^{3} p_ix_i \end{pmatrix}$$

In order to find the equilibria, by analyzing the system,

$$(5)\qquad \begin{cases} x_1\left(a_1 - b_1x_1 - c_1x_4 + \alpha x_2x_3\right) = 0 \\ x_2\left(a_2 - b_2x_2 - c_2x_4 + \beta x_1x_3\right) = 0 \\ x_3\left(a_3 - b_3x_3 - c_3x_4 + \gamma x_1x_2\right) = 0 \\ x_4\left(p_4 - p_1x_1 - p_2x_2 - p_3x_3\right) = 0 \end{cases}$$

we obtain the following equlibria:

$E_0(0,0,0,0)$, $E_1^1(\frac{a_1}{b_1},0,0,0)$, $E_1^2(0,\frac{a_2}{b_2},0,0)$, $E_1^3(0,0,\frac{a_3}{b_3},0)$, $E_2^{12}(\frac{a_1}{b_1},\frac{a_2}{b_2},0,0)$, $E_2^{13}(\frac{a_1}{b_1},0,\frac{a_3}{b_3},0)$, $E_2^{23}(0,\frac{a_2}{b_2},\frac{a_3}{b_3},0)$, $E_3(x_1,x_2,x_3,0)$, where (x_1,x_2,x_3,x_4) is a solution of (5) with $x_i > 0$, $i = 1,2,3$ and $x_4 = 0$,

$E_4^1\left(\frac{p_4}{p_1},0,0,\frac{1}{c_1}(a_1 - b_1\frac{p_4}{p_1})\right)$, $E_4^2\left(0,\frac{p_4}{p_2},0,\frac{1}{c_2}(a_2 - b_2\frac{p_4}{p_2})\right)$, $E_4^3\left(0,0,\frac{p_4}{p_3},\frac{1}{c_3}(a_3 - b_3\frac{p_4}{p3})\right)$,

$E_5^{12}\left(\frac{1}{b_1}(a_1 - c_1v_5^{12}),\frac{1}{b_2}(a_2 - c_2v_5^{12}),0,v_5^{12}\right)$, where $v_5^{12} = \frac{1}{d_5^{12}}\left(p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} - p_4\right)$, $d_5^{12} = p_1\frac{c_1}{b_1} + p_2\frac{c_2}{b_2}$,

$E_5^{13}\left(\frac{1}{b_1}(a_1 - c_1v_5^{13}),0,\frac{1}{b_3}(a_3 - c_3v_5^{13}),v_5^{13}\right)$, where $v_5^{13} = \frac{1}{d_5^{13}}\left(p_1\frac{a_1}{b_1} + p_3\frac{a_3}{b_3} - p_4\right)$, $d_5^{13} = p_1\frac{c_1}{b_1} + p_3\frac{c_3}{b_3}$,

$E_5^{23}\left(0,\frac{1}{b_2}(a_2 - c_2v_5^{23}),\frac{1}{b_3}(a_3 - c_3v_5^{23}),v_5^{23}\right)$, where $v_5^{23} = \frac{1}{d_5^{23}}\left(p_2\frac{a_2}{b_2} + p_3\frac{a_3}{b_3} - p_4\right)$, $d_5^{23} = p_2\frac{c_2}{b_2} + p_3\frac{c_3}{b_3}$,

and finally $E_6(x_1,x_2,x_3,x_4)$, where (x_1,x_2,x_3,x_4) is a solution of (5) with $x_i > 0$, $i = 1,2,3,4$.

For $E_0(0,0,0,0)$ we have the Jacobian $A = \begin{pmatrix} a_1 & 0 & 0 & 0 \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 \end{pmatrix}$, with eigenvalues a_1, a_2, a_3, p_4 and then equilibria at the origin is a repeller, an unstable node.

For $E_1^1(\frac{a_1}{b_1},0,0,0)$ we have the Jacobian $A = \begin{pmatrix} -a_1 & 0 & 0 & -c_1\frac{a_1}{b_1} \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 - p_1\frac{a_1}{b_1} \end{pmatrix}$ with eigenvalues $-a_1$,

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a_2, a_3, $\frac{p_4b_1-p_1a_1}{b_1} = p_4 - p_1\frac{a_1}{b_1}$. Then E_1^1 is a saddle point like for the uncontrolled system. The same situation will be for E_1^2 and E_1^3.

For $E_2^{12}(\frac{a_1}{b_1}, \frac{a_2}{b_2}, 0, 0)$ we have the Jacobian $A = \begin{pmatrix} -a_1 & 0 & \alpha\frac{a_1}{b_1}\frac{a_2}{b_2} & -c_1\frac{a_1}{b_1} \\ 0 & -a_2 & \beta\frac{a_1}{b_1}\frac{a_2}{b_2} & -c_2\frac{a_2}{b_2} \\ 0 & 0 & a_3+\gamma\frac{a_1}{b_1}\frac{a_2}{b_2} & 0 \\ 0 & 0 & 0 & p_4 - p_1\frac{a_1}{b_1} - p_2\frac{a_2}{b_2} \end{pmatrix}$,

with eigenvalues: $-a_1$,$-a_2$, $\frac{a_3b_1b_2+\gamma a_1a_2}{b_1b_2}$, $p_4 - p_1\frac{a_1}{b_1} - p_2\frac{a_2}{b_2}$.

Then we obtain the result:

Theorem 5. *E_2^{12} is an attractor if and only if $p_4 < p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2}$ and $a_3b_1b_2 + \gamma a_1a_2 < 0$. Else, E_2^{12} is a saddle point.*

In conclusion, in spite of the missing of third type of the immunity, if the level of the first two types of immunity is higher that the rate of virus proliferation ($p_1\frac{a_1}{b_1} + p_2\frac{a_2}{b_2} > p_4$) and $\gamma < -a_3\frac{b_1b_2}{a_1a_2} < 0$, then the immune system may win the fight with the virus. This happens because any orbit starting at a point close to E_2^{12} will converge to E_2^{12} for t increasing very much. So, even though the initial level of the cellular immunity is very low when meeting the virus, the immune system may win the fight if the innate immunity and the humoral immunity will be increased beyond the normal threshold by medical interventions in the early stages of virus infection (i.e. $\gamma < -a_3\frac{b_1b_2}{a_1a_2} < 0$).

A similar scenario occurs for E_2^{13} and E_2^{23}, respectively for humoral immunity and, innate immunity.

Due to the complicated computations, for the equilibria E_3 and, also for E_4^i $(i = 1, 2, 3)$, E_5^{ij} $(1 \le i < j \le 3)$, E_6 is very difficult to obtain some analytical results and medical interpretations at this moment.

5.2 Second medical control

Further, we will use others three control functions and then let us consider the following $4D$ differential system:

$$(6) \qquad \begin{cases} \dot{x}_1 &= a_1x_1 - b_1x_1^2 - c_1x_1x_4 + \alpha x_1(x_2+x_3) \\ \dot{x}_2 &= a_2x_2 - b_2x_2^2 - c_2x_2x_4 + \beta x_2(x_3+x_1) \\ \dot{x}_3 &= a_3x_3 - b_3x_3^2 - c_3x_3x_4 + \gamma x_3(x_1+x_2) \\ \dot{x}_4 &= p_4x_4 - p_1x_1x_4 - p_2x_2x_4 - p_3x_3x_4 \end{cases}$$

where α, β, γ are also real constants and they are using only to improve the role of the immune system in the fight against the virus.

The Jacobi matrix at an equilibrium point (x_1, x_2, x_3, x_4) is

$$\begin{pmatrix} a_1 - 2b_1x_1 - c_1x_4 + \alpha x_2 + \alpha x_3 & \alpha x_1 & \alpha x_1 & -c_1x_1 \\ \beta x_2 & a_2 - 2b_2x_2 - c_2x_4 + \beta x_3 + \beta x_1 & \beta x_2 & -c_2x_2 \\ \gamma x_3 & \gamma x_3 & a_3 - 2b_3x_3 - c_3x_4 + \gamma x_1 + \gamma x_2 & -c_3x_3 \\ -p_1x_4 & -p_2x_4 & -p_3x_4 & p_4 - \sum_{i=1}^{3} p_ix_i \end{pmatrix}$$

In order to find the equilibria, by analyzing the system,

$$(7) \qquad \begin{cases} x_1\left(a_1 - b_1x_1 - c_1x_4 + \alpha x_2 + \alpha x_3\right) = 0 \\ x_2\left(a_2 - b_2x_2 - c_2x_4 + \beta x_1 + \beta x_3\right) = 0 \\ x_3\left(a_3 - b_3x_3 - c_3x_4 + \gamma x_1 + \gamma x_2\right) = 0 \\ x_4\left(p_4 - p_1x_1 - p_2x_2 - p_3x_3\right) = 0 \end{cases}$$

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we obtain the following equilibria:

$E_0(0,0,0,0)$, $E_1^1(\frac{a_1}{b_1},0,0,0)$, $E_1^2(0,\frac{a_2}{b_2},0,0)$, $E_1^3(0,0,\frac{a_3}{b_3},0)$,

The equilibria $E_2^{12}(x_1,x_2,0,0)$, $E_2^{13}(x_1,0,x_3,0)$, $E_2^{23}(0,x_2,x_3,0)$ may exist only under some conditions about the system (7).

$E_3(x_1,x_2,x_3,0)$ is the unique equilibria with $x_4=0$ if and only if $\det\begin{pmatrix} b_1 & -\alpha & -\alpha \\ -\beta & b_2 & -\beta \\ -\gamma & -\gamma & b_3 \end{pmatrix} = b_1b_2b_3 - 2\alpha\beta\gamma - b_1\beta\gamma - b_2\alpha\gamma - b_3\alpha\beta$ is not equal with 0 and $x_i>0$, $i=1,2,3$. Else, we can obtain an infinity of such equilibria or none.

Like for the previously controlled system (4), the study of the system's behaviour around of the rest of the equilibria of this second controlled system (6), is very hard to do!

It is about the following equilibria:

$E_4^1\left(\frac{p_4}{p_1},0,0,\frac{1}{c_1}(a_1-b_1\frac{p_4}{p_1})\right)$, $E_4^2\left(0,\frac{p_4}{p_2},0,\frac{1}{c_2}(a_2-b_2\frac{p_4}{p_2})\right)$, $E_4^3\left(0,0,\frac{p_4}{p_3},\frac{1}{c_3}(a_3-b_3\frac{p_4}{p3})\right)$,

E_5^{ij}, with $x_i>0$, $x_j>0$, $1\le i<j\le 3$, $x_k=0$, $k=1,2,3$, but different by i and j, $x_4>0$,

and $E_6(x_1,x_2,x_3,x_4)$, where $x_i>0$, $i=1,2,3,4$.

For $E_0(0,0,0,0)$ we have the Jacobian $A=\begin{pmatrix} a_1 & 0 & 0 & 0 \\ 0 & a_2 & 0 & 0 \\ 0 & 0 & a_3 & 0 \\ 0 & 0 & 0 & p_4 \end{pmatrix}$, with eigenvalues a_1, a_2, a_3, p_4.

Then equilibria at the origin is a repeller, an unstable node.

For $E_1^1(\frac{a_1}{b_1},0,0,0)$ we have the Jacobian $A=\begin{pmatrix} -a_1 & \alpha\frac{a_1}{b_1} & \alpha\frac{a_1}{b_1} & -c_1\frac{a_1}{b_1} \\ 0 & a_2+\beta\frac{a_1}{b_1} & 0 & 0 \\ 0 & 0 & a_3+\gamma\frac{a_1}{b_1} & 0 \\ 0 & 0 & 0 & p_4-p_1\frac{a_1}{b_1} \end{pmatrix}$ with

eigenvalues $-a_1$, $\frac{a_2b_1+\beta a_1}{b_1}$, $\frac{a_3b_1+\gamma a_1}{b_1}$, $p_4-p_1\frac{a_1}{b_1}$. Then we have the result:

Theorem 6. *E_1^1 is an attractor if and only if $\frac{a_1}{b_1}>\frac{p_4}{p_1}$ and $a_2b_1+\beta a_1<0$, $a_3b_1+\gamma a_1<0$. Else, E_1^1 is a saddle point.*

In conclusion, in spite of the missing of the second and third types of immunities (humoral immunity and cellular immunity), if the level of the first type of immunity (the innate immunity) is higher that the rate of virus proliferation ($p_1\frac{a_1}{b_1}>p_4$) and $\beta<-a_2\frac{b_1}{a_1}<0$, $\gamma<-a_3\frac{b_1}{a_1}<0$, then the immune system may win the fight with the virus. This happens because any orbit starting at a point close to E_1^1 will converge to E_1^1 for t increasing very much. So, even though the initial level of the last two categories of immunities is very, very low when meeting the virus, the immune system may win the fight if the level of the first category of immunity will be increased beyond the normal threshold by medical interventions in the early stages of virus infection (i.e. $\beta<-a_2\frac{b_1}{a_1}<0$, $\gamma<-a_3\frac{b_1}{a_1}<0$). A similar scenario occurs for E_1^2 and E_1^3, respectively for humoral immunity and cellular immunity.

Indeed, for $E_1^2(0,\frac{a_2}{b_2},0,0)$ we have the Jacobian

$$A=\begin{pmatrix} a_1+\alpha\frac{a_2}{b_2} & 0 & 0 & 0 \\ \beta\frac{a_2}{b_2} & -a_2 & \beta\frac{a_2}{b_2} & -c_2\frac{a_2}{b_2} \\ 0 & 0 & a_3+\gamma\frac{a_2}{b_2} & 0 \\ 0 & 0 & 0 & p_4-p_2\frac{a_2}{b_2} \end{pmatrix}$$

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with eigenvalues $\frac{a_1b_2+\alpha a_2}{b_2}$, $-a_2$, $\frac{a_3b_2+a_2\gamma}{b_2}$, $p_4-p_2\frac{a_2}{b_2}$ and for $E_1^3(0,0,\frac{a_3}{b_3},0)$ we have the Jacobian

$$A=\begin{pmatrix} a_1+\alpha\frac{a_3}{b_3} & 0 & 0 & 0 \\ 0 & a_2+\beta\frac{a_3}{b_3} & 0 & 0 \\ \gamma\frac{a_3}{b_3} & \gamma\frac{a_3}{b_3} & -a_3 & -c_3\frac{a_3}{b_3} \\ 0 & 0 & 0 & p_4-p_3\frac{a_3}{b_3} \end{pmatrix}$$

with eigenvalues $\frac{a_1b_3+\alpha a_3}{b_3}$, $\frac{a_2b_3+\beta a_3}{b_3}$,$-a_3$, $p_4-p_3\frac{a_3}{b_3}$.

The equilibria $E_2^{12}(\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta},\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta},0,0)$ don't exists if $\det\begin{pmatrix} b_1 & -\alpha & a_1 \\ -\beta & b_2 & a_2 \\ -\gamma & -\gamma & a_3 \end{pmatrix}$ is not equal with 0. But, if E_2^{12} exists, then his Jacobi matrix is to wide to write here, but we write the characteristic polynomial

$\left(X-\left(a_3+\gamma\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}+\gamma\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}\right)\right)\left(X-\left(p_4-p_1\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}-p_2\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}\right)\right)$
$\left(X^2+\frac{b_2a_2b_1+b_2\beta a_1+\alpha a_2b_1+a_1b_2b_1}{b_1b_2-\alpha\beta}X+\frac{a_1b_2a_2b_1+\alpha a_2^2b_1+a_1^2b_2\beta+\beta a_2\alpha a_1}{b_1b_2-\alpha\beta}\right)$.

Then E_2^{12} is an attractor if and only if $a_3+\gamma\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}+\gamma\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}<0$, $p_4-p_1\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}-p_2\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}<0$ and $\frac{b_1(a_1b_2+a_2\alpha)+b_2(a_2b_1+a_1\beta)}{b_1b_2-\alpha\beta}=b_1\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}+b_2\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}>0$, $\frac{(a_1b_2+a_2\alpha)(a_2b_1+\beta a_1)}{b_1b_2-\alpha\beta}>0$.

That means the immune system may win even though the initial level of the third immunity (cellular immunity) is very low when meeting the virus. This happens because any orbit starting at a point close to E_2^{12} will converge to E_2^{12} for t large, whenever E_2^{12} hold conditions to be an attractor. So, we obtain the following result:

Theorem 7. *If E_2^{12} is a proper equilibria, then the equilibria E_2^{12} is an attractor if and only if $\gamma<-a_3\left(\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}+\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}\right)^{-1}$, $p_4<p_1\frac{a_1b_2+a_2\alpha}{b_1b_2-\alpha\beta}+p_2\frac{a_2b_1+a_1\beta}{b_1b_2-\alpha\beta}<0$ and $a_2b_1+\beta a_1>0$ ($\beta>-a_2\frac{b_1}{a_1}$), $a_1b_2+\alpha a_2>0$ ($\alpha>-a_1\frac{b_2}{a_2}$). Else, E_2^{12} is a saddle point.*

A similar scenario occurs for E_2^{13} and E_2^{23}, respectively for humoral immunity and, innate immunity.

Due to the complicated computation, for the equilibria E_3 and, also for E_4^i $(i=1,2,3)$, E_5^{ij} $(1\leq i<j\leq 3)$, E_6 is very difficult to obtain some analytical results.

6 Conclusions

In this work I presented a study on interaction between the human body immune system and a pathogenic virus, such as COVID 19. We used a mathematical approach based on a first order system of differential equations for modeling the interaction, and tools from dynamical systems theory for the analysis of the models. The study reveals the importance of all three kinds of the immunity (innate, humoral and cellular) in the fight against the virus. Several conclusions relevant for the medical world arise from this study, as it follows.

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 quantity of a single type of immunity in the early stages of virus proliferation, may lead to the virus victory.

3. If the levels of the immunities become at a moment during the battle with the virus considerably smaller than their normal concentrations, then 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 levels of the immunities 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 has a better chance to win the battle with the virus.

5. If the concentration of at least one type of the immunities can be 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 last conclusion is extremely important, since, it reveals the possibility of winning the fight against a virus by increasing the level for at least a category of immunity. In our opinion, this natural idea should be further exploited in medical studies.

The results we obtained in this work tell the medical community to work more on methods for strengthening the immune system to win battles with pathogenic agents.

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