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Article

A Comparative Study of Three Mathematical Models for the Interaction between the Human Immune System and a Virus

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Abstract: In this paper it will be considered three deterministic models for the study of the interaction between the human immune system and a virus: the logistic model, the Gompertz model, and the generalized logistic model (or Richards model). A qualitative analysis of this models 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. Also, we will compare this models in order to understanding which is more appropriate to models the interaction between the human immune system and a virus. It will be obtained some natural medical interpretations which are available for all three models and can be useful to the medical community.

Keywords: mathematical models; systems of ordinary differential equations; dynamical systems; stability

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 [1]. 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) [2].

In this paper, we consider the interaction between the human body immune system and a pathogenic invader (virus, microbe, bacteria, parasites or fungi) and we try to find an appropriate deterministic mathematical model in order to study the fight of the immune system with the invader [3], [4]. These kinds of ordinary differential equations systems represent a class of Kolmogorov systems and they are widely used in the mathematical models for the dynamics of population, like predator-prey models or different models for the spread of diseases or for the growth of tumors [5], [6], [7], [8], [9].

We will denote by $x_1(t)$ the level in time of the immune system (antibodies level) and by $v(t)$ the level of the virus, more exactly $v(t)$ represent the number of viruses cells which exist in a body at time t. As soon as he noticed the presence of the virus in the body, the immune system will fight with the virus (e.g. the present corona-virus, Covid-19) in order to stop his multiplication and eliminate it. Consider the time as being continuous, $t \geq 0$. Thus, $\dot{x}_1(t)$ and $\dot{v}(t)$ are the rates of changes of these two quantities in a short unity of time, $\dot{x}_1(t) = \frac{dx_1}{dt}$, $\dot{v}(t) = \frac{dv}{dt}$. Following the ideas of G. Moza from [10], this model is based on the following three hypotheses:

Hypothesis 1. In the absence of the virus, the quantity of antibodies $x_1(t)$ can be present in the human body up to a threshold value K_1. 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 that the evolution law of $x_1(t)$ is the following:

$$\dot{x}_1 = a_1 x_1 - b_1 x_1^2$$

with $a_1 > 0$ and $b_1 > 0$. Taking into account that the solution of the prevoius equation with the initial condition $x_1(0) = x_{10}$ is

$$x_1(t) = \frac{K_1}{1 + \left(\frac{K_1}{x_{10}} - 1\right) e^{-a_1 t}}$$

one can observe that $x_1(t) \to K_1$ for $t \to \infty$, where $K_1 = \frac{a_1}{b_1}$ is the threshold value.

If the term $-b_1 x_1^2$ is missing, then $x_1(t)$ increase exponentially when $t \to \infty$, because in this case ($b_1 = 0$) the general solution of the equation in x_1 will be $x_1(t) = a_1 x_{10} e^{t a_1}$. Else, if $b_1 > 0$, then we have that the maximum threshold value of antibodies level x_1 is $\frac{a_1}{b_1} = K_1$.

Hypothesis 2. Normally, in an healthy body without autoimmune diseases, the antibodies of the immunity system do not attack other normal cells of the body. Thus, they are can be destroyed only due to viruses and, as such, a term in the form $-c_1 x_1 v$ should be added to each equation in $x_1(t)$, where $v(t)$ is the number of virus's cells which exists in the human body at time t.

Hypothesis 3. In the absence of the immune system of the body the virus would multiplicate indefinitely and exponentially, $v(t)$ satisfying the law $\dot{v} = p_2 v$. But, of course, in the presence of the immune system the number of virus's cells will decrease and consequently, we must add the terms $-p_1 x_1 v$ to the evolution law of $v(t)$.

If we will denote the variable v by x_2, then we can conclude that these hypotheses lead us to the following two-dimensional first order differential system with five parameters, given by

$$\begin{cases} \dot{x}_1 & = & a_1 x_1 - b_1 x_1^2 - c_1 x_1 x_2 \\ \dot{x}_2 & = & p_2 x_2 - p_1 x_1 x_2 \end{cases} \tag{1}$$

with $a_1 > 0$, $b_1 > 0$, $c_1 > 0$, $p_1 > 0$ and $p_2 > 0$.

Is obviously that the model has a medical relevance when $x_i \geq 0$, $i = 1, 2$. Therefore the solutions of the system lie in the set

$$\Sigma_+^0 = \left\{ (x_1, x_2) \in \mathbf{R}^2 \mid x_i \geq 0,\ i = 1, 2 \right\}.$$

Moreover, the lines $\{x_i = 0\}$ are invariant manifolds with respect to the flow of the system, i.e. any orbit starting from a point which belongs to $\Sigma_+ = \{(x_1, x_2) \in \mathbf{R}^2 \mid x_i > 0,\ i = 1, 2\}$ remains in Σ_+. So, the orbits cannot cross any of these two invariant lines 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.

This deterministic mathematical model of the interaction between the immune system and a pathogenic invader is based on the logistic differential equation

$$\dot{x} = ax - bx^2$$

or, in the form

$$\dot{x} = ax\left(1 - \frac{x}{K}\right), \text{ where } K = \frac{a}{b}$$

Next, using the same hypothesis we can obtain another two models based on Gompertz equation

$$\dot{x} = ax(\ln K - \ln x)$$

and generalized logistic equation (Richards equation)

$$\dot{x} = ax\left(1 - \left(\frac{x}{K}\right)^{\nu}\right), \text{ where } \nu > 0\,.$$

The graphs of the solutions of these ordinary differential equations belongs to the so called S-shaped curves. See the figure 1. It can remark that only the logistic curve is symmetric with respect to his inflection point 0.5. The Gompertz curve has the inflection point lower, and the generalized logistic curve can have the inflection point over 0.5 or up to 0.5, depending on the parameter ν.

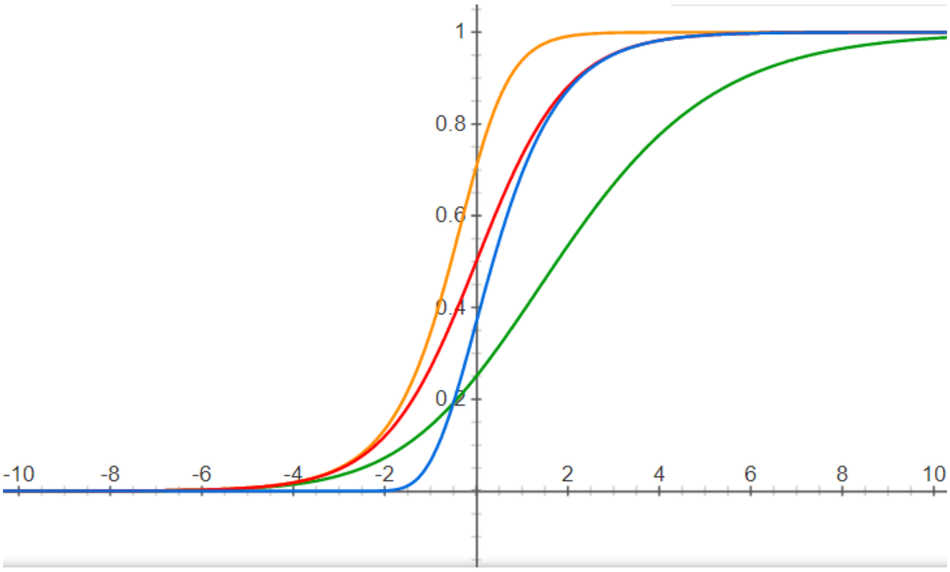

Figure 1. Graphs for the logistic model, $y = \frac{1}{1+e^{-x}}$, the Gompertz model, $y = e^{-e^{-x}}$, the generalized logistic model with $\nu = 2$, $y = \frac{1}{(1+e^{-2x})^{1/2}}$, and with $\nu = \frac{1}{2}$, $y = \frac{1}{\left(1+e^{-(1/2)x}\right)^2}$.

2. The logistic model

The logistic function was introduced in a series of three papers by Belgian mathematician Pierre-François Verhulst between 1838 and 1847, who devised it as a model of population growth by adjusting the exponential growth model (see the papers [11], [12], [13]).

2.1. A short presentation

The logistic equation is the following first order differential equation:

$$\dot{x} = ax - bx^2 \tag{2}$$

or, equivalently,

$$\dot{x} = ax\left(1 - \frac{x}{K}\right) \tag{3}$$

where $K = \frac{a}{b}$ is **the carrying capacity** and a is **the inherent growth rate** of the modelled population ($a > 0, b > 0$).

The solution of this differential equation with initial condition $x_0 = x(0)$ is **the logistic function**

$$x(t) = \frac{K}{1 + \left(\frac{K}{x_0} - 1\right)e^{-at}} \tag{4}$$

There are two equilibrium point for the dynamical system given by the logistic equation, namely $x_1 = 0$ and $x_2 = K$.

Since $F(x) = ax\left(1 - \frac{x}{K}\right)$ and $\frac{dF}{dx}(x) = a\left(1 - \frac{2x}{K}\right)$, it follows that $\frac{dF}{dx}(0) = a > 0$ and $\frac{dF}{dx}(K) = -a < 0$, i.e. $x_1 = 0$ is a repeller and $x_2 = K$ is an attractor.

2.2. *The interaction between the immune system and a virus by logistic model*

We consider the following system of two differential equations:

$$\begin{cases} \dot{x}_1 &= a_1x_1 - b_1x_1^2 - c_1x_1x_2 \\ \dot{x}_2 &= p_2x_2 - p_1x_1x_2 \end{cases}, \tag{5}$$

where $x_1 > 0$ represent the antibodies level of the immune system and $x_2 = v \geq 0$ means the concentration of the virus in the body. Here $K_1 = \frac{a_1}{b_1}$ is the carrying capacity of the antibodies, a_1 is his inherent growth rate, p_2 is the inherent growth rate of the virus and c_1, p_1 represent the interaction between antibodies and virus. All parameters a_i, b_i, c_i, p_i are strictly positive.

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

$$A = \begin{pmatrix} a_1 - 2b_1x_1 - c_1x_2 & -c_1x_1 \\ -p_1x_2 & p_2 - p_1x_1 \end{pmatrix}$$

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

$$\begin{cases} x_1(a_1 - b_1x_1 - c_1x_2) = 0 \\ x_2(p_2 - p_1x_1) = 0 \end{cases}$$

we obtain the following three equlibria: $E_0(0,0)$ with eigenvalues $\lambda_1 = a_1$, $\lambda_2 = p_2$, $E_1\left(\frac{a_1}{b_1}, 0\right)$ with eigenvalues $\lambda_1 = -a_1$, $\lambda_2 = p_2 - p_1\frac{a_1}{b_1}$ and $E_2\left(\frac{p_2}{p_1}, \frac{1}{c_1}\left(a_1 - b_1\frac{p_2}{p_1}\right)\right)$, with eigenvalues

$$\lambda_{1,2} = \frac{1}{2p_1}\left(-b_1p_2 \pm \sqrt{b_1^2p_2^2 + 4p_2p_1^2\left(a_1 - b_1\frac{p_2}{p_1}\right)}\right).$$

Therefore, we have the following result:

Theorem 1. *a) The trivial equilibria $E_0(0,0)$ is always a repeller.*

b) The equilibria E_1 is an attractor if and only if $\frac{p_2}{p_1} < K_1 = \frac{a_1}{b_1}$. Else, E_1 is a saddle point.

c) The equilibria E_2 is a saddle point whenever it lies on Σ_+. Moreover, $E_2 \in \Sigma_+$ if and only if $\frac{p_2}{p_1} < K_1$, i.e. E_1 is an attractor.

d) The system does not undergo a Hopf bifurcation at E_2 on Σ_+.

e) E_2 collides with E_1 on the line $S : p_2 = p_1K_1$.

f) The equilibria E_2 bifurcates from the equilibria E_1 along the line $S = \{(p_1, p_2) | p_2 = p_1K_1\}$ by a transcritical bifurcation.

3. The Gompertz model

Taking into account that using the logistic equation there are a lot of mathematical models for describing the behavior in time of the epidemiological or ecological systems, further we will introduce a new mathematical model for studying the interactions between different kinds of species, by using the Gompertz model. This model was introduce by British mathematician Benjamin Gompertz in 1825 in order cu obtain a law of mortality and also, a demographic model (see the paper [14]). One hundred forty years later, in 1964 A.K. Laird used the Gompertz curve to fit data of growth of tumors [15].

3.1. A short presentation

The Gompertz equation is the following first order differential equation:

$$\dot{x} = ax \ln \frac{K}{x} \tag{6}$$

or, equivalently,

$$\dot{x} = ax(\ln K - \ln x) \tag{7}$$

where $K = \frac{a}{b}$ is **the carrying capacity** and a is **the inherent growth rate** of the modelled population ($a > 0$, $K > 0$).

The solution of this differential equation with initial condition $x_0 = x(0)$ is **the Gompertz function**

$$x(t) = Ke^{-\ln\left(\frac{K}{x_0}\right)e^{-at}} \tag{8}$$

There is only one equilibrium point for the dynamical system given by the Gompertz equation, namely $x_1 = K$.

Since $F(x) = ax(\ln K - \ln x)$ and $\frac{dF}{dx}(x) = a \ln \frac{K}{x} - a$, it follows that $\frac{dF}{dx}(K) = -a < 0$, i.e. $x_1 = K$ is an attractor.

3.2. The interaction between the immune system and a virus by Gompertz model

We consider the following system of two differential equations:

$$\begin{cases} \dot{x}_1 & = & a_1 x_1 \ln \frac{K_1}{x_1} - c_1 x_1 x_2 \\ \dot{x}_2 & = & p_2 x_2 - p_1 x_1 x_2 \end{cases} \tag{9}$$

where $x_1 > 0$ represent the antibodies level of the immune system and $x_2 = v \geq 0$ means the concentration of the virus in the body. Here $K_1 = \frac{a_1}{b_1}$ is the carrying capacity of the antibodies, a_1 is his inherent growth rate, p_2 is the inherent growth rate of the virus and c_1, p_1 are the interaction's coefficients between antibodies and virus. All parameters a_i, b_i, c_i, p_i are strictly positive.

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

$$A = \begin{pmatrix} a_1 \ln \frac{K_1}{x_1} - a_1 - c_1 x_2 & -c_1 x_1 \\ -p_1 x_2 & p_2 - p_1 x_1 \end{pmatrix}$$

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

$$\begin{cases} x_1 (a_1 \ln \frac{K_1}{x_1} - c_1 x_2) = 0 \\ x_2 (p_2 - p_1 x_1) = 0 \end{cases}$$

we obtain two equlibria: $E_1(K_1, 0)$, with eigenvalues $\lambda_1 = -a_1$, $\lambda_2 = p_2 - p_1 K_1$ and $E_2\left(\frac{p_2}{p_1}, \frac{a_1}{c_1} \ln\left(K_1 \frac{p_1}{p_2}\right)\right)$, which exists if and only if $K_1 \frac{p_1}{p_2} > 1$, i.e. $\frac{p_2}{p_1} < K_1$.

Else, if $\frac{p_2}{p_1} \geq K_1$, the equilibria E_2 don't exists, i.e. don't belongs to Σ_+.

For E_2 we obtain the eigenvalues $\lambda_{1,2} = -\frac{1}{2} a_1 \pm \frac{1}{2} \sqrt{\left(a_1^2 + 4 p_2 a_1 \ln K_1 \frac{p_1}{p_2}\right)}$.

Since $\lambda_1 + \lambda_2 = -a_1 < 0$ and $\lambda_1 \lambda_2 = -p_2 a_1 \ln\left(K_1 \frac{p_1}{p_2}\right) < 0$ it results that E_2 is a saddle point.

In conclusion, we have the following result:

Theorem 2. *a) The equilibria E_1 is an attractor if and only if $\frac{p_2}{p_1} < K_1$. Else, E_1 is a saddle point.*

b) The equilibria E_2 is a saddle point whenever it lies on Σ_+. Moreover, $E_2 \in \Sigma_+$ if and only if $\frac{p_2}{p_1} < K_1$, i.e. E_1 is an attractor.

c) The system does not undergo a Hopf bifurcation at E_2 on Σ_+.

d) E_2 collides with E_1 on the line $S : p_2 = p_1 K_1$.

e) The equilibria E_2 bifurcates from the equilibria E_1 along the line $S = \{(p_1, p_2) | p_2 = p_1 K_1\}$ by a transcritical bifurcation.

4. The generalized logistic model

The generalized logistic function, also known as Richards's function is an extension of the logistic function, allowing for more flexible S-shaped curves. This function is the solution of the Richards differential equation (RDE or generalized logistic differential equation), and RDE models many growth phenomena, arising in fields such as oncology and epidemiology. F. J. Richards proposed this growth function for the first time in 1959, in [16].

4.1. A short presentation

The generalized logistic equation (or Richards's differential equation or RDE) is the following first order differential equation:

$$\dot{x} = ax\left(1 - \left(\frac{x}{K}\right)^{\nu}\right) \tag{10}$$

where $K = \frac{a}{b}$ is **the carrying capacity**, a is **the inherent growth rate** of the modelled population and $\nu > 0$ ($a > 0, b > 0$).

The solution of this differential equation with initial condition $x_0 = x(0)$ is **the generalized logistic function** or **Richards function**

$$x(t) = \frac{K}{\left[1 + \left(\left(\frac{K}{x_0}\right)^{\nu} - 1\right) e^{-a\nu t}\right]^{\frac{1}{\nu}}} \tag{11}$$

There are two equilibrium points for the dynamical system given by the generalized logistic equation, namely $x_1 = 0$ and $x_2 = K$.

Since $F(x) = ax\left(1 - \left(\frac{x}{K}\right)^{\nu}\right)$ and $\frac{dF}{dx}(x) = a\left(1 - 2\left(\frac{x}{K}\right)^{\nu}\right)$, it follows that $\frac{dF}{dx}(0) = a > 0$ and $\frac{dF}{dx}(K) = -a < 0$, i.e. $x_1 = 0$ is a repeller and $x_2 = K$ is an attractor.

Let us remark that the classical logistic differential equation (3) is a particular case of the Richards differential equation (10), with $\nu = 1$. Moreover, the Gompertz equation (7) can be obtained from the generalized logistic equation (10) when $\nu \searrow 0$ provided that $a = O(\frac{1}{\nu})$. In fact, for $\nu > 0$, enough small, we can take $a = \frac{r}{\nu}$, with $r > 0$, and then the Richards equation $\dot{x} = ax\left(1 - \left(\frac{x}{K}\right)^{\nu}\right)$ becomes

$$\dot{x} = \frac{r}{\nu} x\left(1 - \left(\frac{x}{K}\right)^{\nu}\right) = rx\left(\frac{1 - e^{\nu \ln\left(\frac{x}{K}\right)}}{\nu}\right) = rx \ln\left(\frac{K}{x}\right)$$

if we taking into account that $\frac{1 - e^{\nu Y}}{\nu} = \frac{-\nu Y}{\nu} = -Y$ for $\nu > 0$ very small. Here, the terms of order greater than two from $e^{\nu Y} = \sum_{n=0}^{+\infty} \frac{(\nu Y)^n}{n!}$ was neglected, because v is very small.

4.2. The interaction between the immune system and a virus by generalized logistic model

We consider the following system of two differential equations:

$$\begin{cases} \dot{x}_1 & = & a_1 x_1 \left(1 - \left(\frac{x_1}{K_1}\right)^{\nu}\right) - c_1 x_1 x_2 \\ \dot{x}_2 & = & p_2 x_2 - p_1 x_1 x_2 \end{cases}, \tag{12}$$

where $x_1 > 0$ represent the antibodies level of the immune system and $x_2 = v \geq 0$ means the concentration of the virus in the body. Here $K_1 = \frac{a_1}{b_1}$ is the carrying capacity of the antibodies, a_1 is his inherent growth rate, p_2 is the inherent growth rate of the virus and c_1, p_1 are the interaction's coefficients between antibodies and virus. All parameters a_i, b_i, c_i, p_i and $\nu \in (0,1)$ are strictly positive.

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

$$A = \begin{pmatrix} a_1 - a_1(1+\nu)\left(\frac{x_1}{K_1}\right)^{\nu} - c_1x_2 & -c_1x_1 \\ -p_1x_2 & p_2 - p_1x_1 \end{pmatrix}.$$

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

$$\begin{cases} x_1\left(a_1\left(1 - \left(\frac{x_1}{K_1}\right)^{\nu}\right) - c_1x_2\right) = 0 \\ x_2(p_2 - p_1x_1) = 0 \end{cases}$$

we obtain the following three equilibria: $E_0(0,0)$ with eigenvalues $\lambda_1 = a_1$, $\lambda_2 = p_2$, $E_1(K_1, 0)$ with eigenvalues $\lambda_1 = -a_1\nu$, $\lambda_2 = p_2 - p_1K_1$ and $E_2\left(\frac{p_2}{p_1}, \frac{a_1}{c_1}\left(1 - \left(\frac{p_2}{p_1K_1}\right)^{\nu}\right)\right)$ with eigenvalues $\lambda_{1,2} = -\frac{1}{2}a_1\nu\left(\frac{p_2}{p_1K_1}\right)^{\nu} \pm \frac{1}{2}\sqrt{a_1^2\nu^2\left(\frac{p_2}{p_1K_1}\right)^{2\nu} + 4p_2a_1 - 4p_2a_1\left(\frac{p_2}{p_1K_1}\right)^{\nu}}$.

For E_2, since $\lambda_1 + \lambda_2 = -a_1\nu e^{\nu \ln \frac{p_2}{p_1K_1}} < 0$ and $\lambda_1\lambda_2 = -p_2a_1\left(1 - \left(\frac{p_2}{p_1K_1}\right)^{\nu}\right) < 0$, it follow that E_2 is a saddle point, whenever belongs to Σ_+.

Then, we have the result:

Theorem 3. *a) The trivial equilibria* $E_0(0,0)$ *is always a repeller.*

b) The equilibria E_1 *is an attractor if and only if* $\frac{p_2}{p_1} < K_1$*. Else,* E_1 *is a saddle point.*

c) The equilibria E_2 *is a saddle point whenever it lies on* Σ_+*. Moreover,* $E_2 \in \Sigma_+$ *if and only if* $\frac{p_2}{p_1} < K_1$*, i.e.* E_1 *is an attractor.*

d) The system does not undergo a Hopf bifurcation at E_2 *on* Σ_+*.*

e) E_2 *collides with* E_1 *on the line* $S : p_2 = p_1K_1$*.*

f) The equilibria E_2 *bifurcates from the equilibria* E_1 *along the line* $S = \{(p_1, p_2) | p_2 = p_1K_1\}$ *by a transcritical bifurcation.*

5. Generalizations for $n \geq 3$

If we consider a mathematical model with interaction between two, three (or more) types of human body immunities (or antibodies) and a virus, then we can consider similarly a system with three, four (or more) differential equations using logistic model, Gompertz model or generalized logistic model.

For the three dimensional model build by the logistic model complete results can be found in the paper of G. Moza, [10]. For the extended four dimensional model the results can be found in [17]. For three dimensional system there are at most 7 equilibrium points among which only one can be an attractor. The rest of equilibria are saddle points (if exists), with the exception of the trivial equilibrium (the origin O) which is repeller. More precisely, the equilibrium $(K_1, K_2, 0)$ is an attractor iff $p_3 < p_1K_1 + p_2K_2$, where K_1, K_2 are the threshold values of the antibodies [10]. Similar results was obtained in [17] for the four dimensional model, but the number of the discovered equilibrium points are larger, up to fifteen equilibria. A generalization for higher dimensions can be discussed, but the number of equilibria becomes huge. E.g., for six dimension it will be obtained up to 63 points of equilibrium [17].

However, if we consider the Gompertz model with two, three (or more) types of human body immunities (or antibodies) and a virus, then the number of equilibria remains constant and the obtained results doesn't dependent of the number of variables of the system, from the qualitative point of view.

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For $n = 3$ we consider the following system of three differential equations:

$$\left\{\begin{array}{lcl} \dot{x}_1 & = & a_1 x_1 \ln \frac{K_1}{x_1} - c_1 x_1 x_3 \\ \dot{x}_2 & = & a_2 x_2 \ln \frac{K_2}{x_2} - c_2 x_2 x_3 \\ \dot{x}_3 & = & p_3 x_3 - p_1 x_1 x_3 - p_2 x_2 x_3 \end{array}\right. , \tag{13}$$

where $x_1, x_2 > 0$ and $x_3 = v \geq 0$.

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

$$A = \begin{pmatrix} a_1 \ln \frac{K_1}{x_1} - a_1 - c_1 x_3 & 0 & -c_1 x_1 \\ 0 & a_2 \ln \frac{K_2}{x_2} - a_2 - c_2 x_3 & -c_2 x_2 \\ -p_1 x_3 & -p_2 x_3 & p_3 - p_1 x_1 - p_2 x_2 \end{pmatrix}$$

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

$$\left\{\begin{array}{r} x_1(a_1 \ln \frac{K_1}{x_1} - c_1 x_3) = 0 \\ x_2(a_2 \ln \frac{K_2}{x_2} - c_2 x_3) = 0 \\ x_3(p_3 - p_1 x_1 - p_2 x_2) = 0 \end{array}\right.$$

we obtain the following two equilibria:

$E_1(K_1, K_2, 0)$ with eigenvalues $\lambda_1 = -a_1$, $\lambda_2 = -a_2$, $\lambda_3 = p_3 - p_1 K_1 - p_2 K_2$ and $E_2(x_1^*, x_2^*, x_3^*)$ which exists iff $p_3 - p_1 K_1 - p_2 K_2 < 0$ (i.e. E_1 is an attractor), where x_1^*, x_2^*, x_3^* are stricly positive real numbers which satisfy $\frac{a_i}{c_i} \ln \frac{K_i}{x_i^*} = x_3^*$ or $x_i^* = K_i e^{-x_3^* \frac{c_i}{a_i}}$ $(i = 1, 2)$ and $p_1 x_1^* + p_2 x_2^* = p_3$.

The characteristic polynomial at E_2 is

$$P(\lambda) = \lambda^3 + (a_1 + a_2)\lambda^2 + (a_1 a_2 - x_3^*(c_2 x_2^* p_2 + p_1 c_1 x_1^*))\lambda - x_3^*(a_1 c_2 x_2^* p_2 + p_1 c_1 x_1^* a_2) .$$

Tacking into account that $\alpha_2 = a_1 + a_2 > 0$, $\alpha_1 = \left(a_1 a_2 - x_3^*\left(c_2 x_2^* p_2 + p_1 c_1 x_1^*\right)\right)$, $\alpha_0 = -x_3^*\left(a_1 c_2 x_2^* p_2 + v p_1 c_1 x_1^* a_2\right) < 0$, and $\alpha_2 \alpha_1 - \alpha_0 = a_1 a_2 (a_1 + a_2) - x_3^*\left(p_1 c_1 x_1^* a_1 + c_2 x_2^* p_2 a_2\right)$, following the Hurwitz criterion, it results that E_2 is not an attractor!

Moreover, because we have $\lambda_1 + \lambda_2 + \lambda_3 = -(a_1 + a_2) < 0$, $\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_3\lambda_1 = \left(a_1 a_2 - x_3^*\left(c_2 x_2^* p_2 + p_1 c_1 x_1^*\right)\right)$, $\lambda_1\lambda_2\lambda_3 = x_3^*\left(a_1 c_2 x_2^* p_2 + p_1 c_1 x_1^* a_2\right) > 0$ and $\lambda_1^2 + \lambda_2^2 + \lambda_3^2 = (a_1 + a_2)^2 - 2\left(a_1 a_2 - x_3^*\left(c_2 x_2^* p_2 + p_1 c_1 x_1^*\right)\right) = a_1^2 + a_2^2 + 2 c_2 x_2^* p_2 x_3^* + 2 p_1 x_3^* c_1 x_1^* > 0$, it results that E_2 is a saddle point whenever exists.

Next, we obtain the result:

Theorem 4. *a) The equilibria $E_1(K_1, K_2, 0)$ is an attractor if and only if $p_3 - p_1 K_1 - p_2 K_2 < 0$. Else, $E_1(K_1, K_2, 0)$ is a saddle point.*

b) The equilibria E_2 is a saddle point whenever it lies on Σ_+. Moreover, $E_2 \in \Sigma_+$ if and only if $p_3 - p_1 K_1 - p_2 K_2 < 0$, i.e. E_1 is an attractor.

c) The system does not undergo a fold-Hopf bifurcation at E_2.

d) E_2 collides with E_1 on the surface $S : p_1 x_1 + p_2 x_2 = p_3$.

e) The equilibria E_2 bifurcates from E_1 along the surface

$$S = \{(p_1, p_2, p_3) | p_3 = p_1 K_1 + p_2 K_2\}$$

by a transcritical bifurcation.

For $n = 4$ we consider the following system of four differential equations:

$$\left\{\begin{array}{lcl} \dot{x}_1 & = & a_1 x_1 \ln \frac{K_1}{x_1} - c_1 x_1 x_4 \\ \dot{x}_2 & = & a_2 x_2 \ln \frac{K_2}{x_2} - c_2 x_2 x_4 \\ \dot{x}_3 & = & a_3 x_3 \ln \frac{K_3}{x_3} - c_3 x_3 x_4 \\ \dot{x}_4 & = & p_4 x_4 - p_1 x_1 x_4 - p_2 x_2 x_4 - p_3 x_3 x_4 \end{array}\right. , \tag{14}$$

where $x_1, x_2, x_3 > 0$ and $x_4 = v \geq 0$.

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

$$\begin{pmatrix} a_1 \ln \frac{K_1}{x_1} - a_1 - c_1 x_4 & 0 & 0 & -c_1 x_1 \\ 0 & a_2 \ln \frac{K_2}{x_2} - a_2 - c_2 x_4 & 0 & -c_2 x_2 \\ 0 & 0 & a_3 \ln \frac{K_3}{x_3} - a_3 - c_3 x_4 & -c_3 x_3 \\ -p_1 x_4 & -p_2 x_4 & -p_3 x_4 & p_4 - p_1 x_1 - p_2 x_2 - p_3 x_3 \end{pmatrix}$$

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

$$\begin{cases} x_1 (a_1 \ln \frac{K_1}{x_1} - c_1 x_4) = 0 \\ x_2 (a_2 \ln \frac{K_2}{x_2} - c_2 x_4) = 0 \\ x_3 (a_3 \ln \frac{K_3}{x_3} - c_3 x_4) = 0 \\ x_4 (p_4 - p_1 x_1 - p_2 x_2 - p_3 x_3) = 0 \end{cases}$$

we obtain the following two equilibria: $E_1(K_1, K_2, K_3, 0)$ with eigenvalues $\lambda_1 = -a_1$, $\lambda_2 = -a_2$, $\lambda_3 = -a_3$, $\lambda_4 = p_4 - p_1 K_1 - p_2 K_2 - p_3 K_3$, and $E_2(x_1^*, x_2^*, x_3^*, x_4^*)$ which exists if and only if $p_4 - p_1 K_1 - p_2 K_2 - p_3 K_3 < 0$ (i.e. E_1 is an attractor), where x_1^*, x_2^*, x_3^*, x_4^* are strictly positive real numbers which satisfy $\frac{a_i}{c_i} \ln \frac{K_i}{x_i^*} = x_4^*$ or $x_i^* = K_i e^{-x_4^* \frac{c_i}{a_i}}$ $(i = 1, 2, 3)$ and $p_1 x_1^* + p_2 x_2^* + p_3 x_3^* = p_4$.

The characteristic polynomial at E_2 is $P(\lambda) = \lambda^4 + \alpha_3 \lambda^3 + \alpha_2 \lambda^2 + \alpha_1 \lambda + \alpha_0$, where $\alpha_3 = a_1 + a_2 + a_3$, $\alpha_2 = a_1 a_2 + a_2 a_3 + a_3 a_1 - x_4^* (x_1^* c_1 p_1 + x_2^* c_2 p_2 + x_3^* c_3 p_3)$,
$\alpha_1 = a_1 a_2 a_3 - x_4^* [x_1^* c_1 p_1 (a_2 + a_3) + x_2^* c_2 p_2 (a_1 + a_3) + x_3^* c_3 p_3 (a_1 + a_2)]$, and
$\alpha_0 = -x_4^* (x_1^* c_1 p_1 a_2 a_3 + x_2^* c_2 p_2 a_1 a_3 + x_3^* c_3 p_3 a_1 a_2) = \det A$.

Following the relations of Viète for $P(\lambda)$, we have $\lambda_1 \lambda_2 \lambda_3 \lambda_4 = \alpha_0 < 0$ and $\lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 = -\alpha_3 < 0$ and then it results that E_2 is a saddle point, whenever exists.

Moreover, the characteristic polynomial at E_2 has at least two real eigenvalues with different signs. So, we have the result:

Theorem 5. *a) The equilibria $E_1(K_1, K_2, K_3, 0)$ is an attractor if and only if $p_4 - p_1 K_1 - p_2 K_2 - p_3 K_3 < 0$. Else, $E_1(K_1, K_2, K_3, 0)$ is a saddle point.*

b) The equilibria E_2 is a saddle point whenever it lies on Σ_+. Moreover, $E_2 \in \Sigma_+$ if and only if $p_4 - p_1 K_1 - p_2 K_2 - p_3 K_3 < 0$, i.e. E_1 is an attractor.

c) The system does not undergo a Hopf-Hopf bifurcation at E_2.

d) E_2 collides with E_1 on the hypersurface $S : p_4 = p_1 x_1 + p_2 x_2 + p_3 x_3$.

e) The equilibria E_2 bifurcates from E_1 along the hypersurface

$$S = \{(p_1, p_2, p_3, p_4) | p_4 = p_1 x_1 + p_2 x_2 + p_3 x_3\}$$

by a transcritical bifurcation.

Finally, of course, we can write a generalized result available for any $n \geq 3$:

Theorem 6. *a) $E_1(K_1, \ldots, K_{n-1}, 0)$ is an attractor if and only if $p_n < \sum\limits_{i=1}^{n-1} p_i K_i$. Else, E_1 is a saddle point.*

b) The equilibria E_2 is a saddle point whenever it lies on Σ_+, i.e. E_1 is an attractor.

Let us remark that the coordinates of the second equilibria $E_2(x_1^*, \ldots, x_{n-1}^*, x_n^*)$ are strictly positive real numbers x_i which satisfy $x_i^* = K_i e^{-x_n^* \frac{c_i}{a_i}}$ $(i = \overline{1, n-1})$ and $p_1 x_1^* + \cdots + p_{n-1} x_{n-1}^* = p_n$. Moreover, $x_i^* < K_i$, for all $i = \overline{1, n-1}$.

Obviously, if we want to use the generalized logistic model (Richards model) for the interaction between two, three or more types of human body immunities (or antibodies) and a virus, then the results will be similarly, but the computations are very complicated. This study can be done in a future work.

6. Conclusions

Tacking into account that our body has at least three types of immunity (the innate immunity, the humoral immunity and the cellular immunity) and this three types of immunity fight jointly with the pathogenic invader (virus, bacteria, parasite or fungi) in order to stop his multiplication and eliminate it, in this work I presented a study about the interactions between the antibodies, the cells and the organs of immune system and others complex human body's mechanisms (like the complement system of the body) and a pathogenic agent, such as Covid-2019. It was used a mathematical approach based on a first order system of differential equations for modeling the interactions, and tools from dynamical systems theory for the analysis of the models, following ideas from [10] and [17]. The study reveals the importance of the antibodies in the fight against the virus. Several conclusions relevant for the medical world arise from our study, as it follows.

1. If the immune system is sufficiently weak when the virus starts to proliferate (e.g., in the neighborhood of the trivial equilibria, the origin O), that is, the level of the antibodies is very small, but also the virus concentration is very small, then the virus has a big chance to win. This fact happens in the neighborhood of the origin O, because O is a repeller (for logistic and generalized logistic models) and then any orbit $\gamma(t)$ starting at a point $\mathbf{x}_0 \in \Sigma_+$ close to O will depart from O for t large, that means $v(t)$ may escape to infinity when t is large. Therefore, a serious deficiency in the level of the immunity in the early stages of virus proliferation, may lead to the virus's victory.

2. If the immunity system is within his normal level (at the carrying capacity) from the first moment he discover the virus and if the immune system is in a healthy condition to kill the virus at a high rate ($K_1 > \frac{p_2}{p_1}$), then the immune system has the best chance to win the battle with the virus. See the case of the first equilibrium point $E_1(K_1, 0)$, when is an attractor. Indeed, any orbit $\gamma(t)$ starting at a point $\mathbf{x}_0 \in \Sigma_+$ close to $E_1(K_1, 0)$, will converge to E_1 for t large, that is $v(t)$ tends to 0 for t large.

3. If the levels of the immunity become at a moment during the battle with the virus is considerably smaller than their normal concentrations ($x_1 < K_1$), then the virus may win even though the immune system kills the virus at a rate higher than the rate of virus proliferation ($K_1 > \frac{p_2}{p_1}$). This is the case of second equilibrium point $E_2(x_1, v)$, $x_1 = \frac{p_2}{p1}$, $v > 0$, which is a saddle point, whenever exists. More exactly, any orbit $\gamma(t)$ starting at a point $\mathbf{x}_0 \in \Sigma_+$ close to E_2, $\mathbf{x}_0 \notin W^s_{E_2}$, will depart from E_2 for t large, that means $v(t)$ may escape to infinity when t is large. A stable limit cycle around E_2 cannot arise through a Hopf bifurcation since all eigenvalues are real.

4. If the immunity system is within his normal level (at the carrying capacity) from the first moment when he discovered the virus, but the immune system is not able to eliminate the virus at a high rate ($K_1 < \frac{p_2}{p_1}$), then the immune system can lose the battle with the virus. This is exactly the situation when the first equilibrium point E_1 is a saddle point and then any orbit $\gamma(t)$ starting at a point $\mathbf{x}_0 \in \Sigma_+$ close to E_1, $\mathbf{x}_0 \notin W^s_{E_1}$, will depart from E_1 for t large, that means $v(t)$ may escape to infinity when t is large. A stable limit cycle around E_1 cannot arise through a Hopf bifurcation since all eigenvalues are real.

5. If the first equilibrium point $E_1(K_1, 0)$ (for which the level of the immunity is maximum, at the thresholds K_1, but the virus concentration is very, very low) is an attractor, then we can conclude that the immune system eliminate the virus for any orbit starting from a point belongs to an enough small neighborhood of E_1. But the virus has another opportunity, in the neighborhood of the second equilibrium point E_2, which is a saddle point, whenever exists. More that, this second equilibria exists if and only if the first equilibria is an attractor.

Although of the three models, only the logistic model has a symmetry with respect to the inflection point, these conclusions are available no matter what model is used: logistic, Gompertz or generalized logistic model (Richards model).

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

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