Ciencias Matemáticas, Vol. 34, No. 1, 2020, Pag. 137-142
Recibido 06-2020, Aceptado 07-2020

Modelo matemático de la interacción virus-sistema inmune con activación de células NK
Mathematical model of the virus-immune system interaction with NK cell activation

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Resumen En el presente artículo se realiza un estudio de los diferentes tipos de patógenos, se investigan las características de los virus, sus manifestaciones y apariencia; se estudian las características del sistema inmune así como la inmunidad, ya sea innata o adquirida, que incluye la activación de las células NK; se investiga la relación entre los virus y el sistema inmunitario de una persona, además se analiza como el sistema inmunitario puede reaccionar ante la presencia de un virus. Esta dinámica se simula mediante un sistema de ecuaciones diferenciales ordinarias, se determinan los puntos de equilibrio y se determina el comportamiento de las trayectorias en una vecindad de las pocisiones de equilibrio.

Abstract In the present article a study of the different types of pathogens is carried out, the characteristics of the viruses, their manifestations and appearance are investigated; The characteristics of the immune system are studied, as well as immunity, whether innate or acquired, which includes the activation of NK cells; The relationship between viruses and a person's immune system is investigated, as well as how the immune system can react to the presence of a virus. This dynamics is simulated using a system of ordinary differential equations, the equilibrium points are determined and the behavior of the trajectories in a neighborhood of the equilibrium positions is determined.

Palabras Clave
Célula NK, Modelo Matemático, Sistema Inmune, Virus

Keywords
NK cells, Mathematical Model, immune system, virus

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Introduction

The immune system, is a set of elements that exist in the human body. These elements interact with each other and aim to defend the body against diseases, viruses, bacteria, microbes and others. The human immune system serves as a protection, a shield or a barrier that protects us from undesirable beings, antigens, that try to invade our body. Thus, it represents the defense of the human body.

When the immune system does not function properly, it decreases its ability to defend our body. Thus, we are more vulnerable to diseases such as tonsillitis or stomatitis, candidiasis, skin infections, ear infections, herpes, colds and flu. To strengthen the immune system and avoid problems with low immunity, special attention is needed with food. Some fruits help increase immunity, such as apples, oranges and kiwis, which are citrus fruits. The intake of omega 3 is also an ally for the immune system.

The immune system is made up of a complex of different cells that receive and emit different signals directed at white blood cells, thus regulating the body's defense mechanisms. The mediators of this interaction are proteins, peptides and other substances that for their activity are called immunomodulators. Biological immunomodulators are made up of a group of molecules with specific properties, many of them chemically and biologically very well characterized and others to be discovered. [15, 17, 21].

In the human organism there are own cells and improper cells, among the improper ones are pathogens; these improper cells can cause changes in the body, which can turn into diseases and even cause the person to die; pathogens can include viruses, bacteria, fungi and parasites; pathogens can be intracellular and extracellular.

Viruses are simple structures, they are considered mandatory intracellular parasites, because they depend on cells to multiply. Outside the intracellular environment, viruses are inert. However, once inside the cell, the replication capacity of viruses is surprising: a single virus is capable of multiplying, in a few hours, thousands of new viruses. Viruses are capable of infecting living beings from all domains. In this way, viruses represent the greatest biological diversity on the planet, being more diverse than bacteria, plants, fungi and animals combined [17].

When the human body is attacked by a virus, a reaction from the immune system to the person quickly occurs to prevent this aggression; there are occasions when this reaction is sufficient to free the organism from any infection, but in many cases this is not enough and it is necessary to supply medication and other artificial substances capable of adding immunity such as interferons, among others.

Immunity can be innate or acquired, acquired immunity is adaptive and is formed by lymphocytes; this is formed by cells and molecules with the great function of defending the organism from any aggressor, these cells and molecules have the capacity to kill, this is an instantaneous process, this being the first defense of the organism.

The NK cell, natural killer or killer cell is a lymphocyte and an important component of the innate immune system for the defense of the body. Its function is the destruction of infected cells and cancer cells, in addition to regulating immune responses. Morphologically, they are almost indistinguishable from large lymphocytes, except for the granules they contain. They are characterized by their granules and their structure. The lytic granules found in the cytoplasm of the NK cell are secretory lysosomes. This means that they have characteristics of both the lysosomal cell compartment and the specialized secretory mechanism of the NK cell. The result is a dual-function organelle, a function specialized in destructive activities due to its lysosomal properties and also an associated secretory function [1, 2, 16].

Granular NK lymphocytes are identified by their ability to recognize and kill tumor cells or cells infected by viruses and bacteria, without the need for a sensitizing antigen. NK killer cells could differentiate cells infected by a virus or tumor cells that have undergone malignant transformations. They are able to identify which cells are the host's own and which are foreign.

In addition to this system, they release interferon and other cytokines to trigger their nonspecific response and destroy the cell that expelled this substance when it is attacked by a viral action. NK cells are activated by interferons, which are produced by virus-infected cells (it is a feedback process) After the specific immune system is activated, antibodies have an activating role in NK cells. When a cell is infected with viruses, its antigens are presented on the surface of the infected cell and antibodies linked to NK, in turn, bind to the infected cell.

Natural killer cells are a third population of lymphocytes, different from B lymphocytes and T lymphocytes, and belong to the innate immune system. They come from the bone marrow and are found in the blood and lymphatic tissues, especially in the spleen; They are morphologically characterized by being mainly large lymphocytes with cytoplasmic granules. They are a highly heterogeneous subpopulation; whose main functions are cytotoxicity and cytokine secretion. NK cells are activated through contact with sensitive cells or target cells or by the action of soluble mediators, mainly cytokines.

The participation of NK cells is relevant in the first events of the defensive response. Among the best-known examples that respond according to this pattern, in animal models, are infections caused by mononuclear blood cells, which significantly increase this production by bacterial stimulation. The success, therefore, of the immune response will depend on the result of the balance between the production of pro-inflammatory and anti-inflammatory cytokines [1, 2, 16, 22].

Interferons are glycoproteins that have several biological actions, including complex antiviral, immunomodulatory and antiproliferative effects. Its production and endogenous release occurs in response to viruses and other inducers, with the exception of bacterial exotoxins, polyanions, some low molecular weight compounds and microorganisms with intracellular growth [20].

There are many diseases that are transmitted from person to person directly, and different forms of contagion are used for this purpose, often through speech or breathing or in some other way; but in many other cases this transmission can be carried out by means of a vector being the mosquito the most common. It is said that the cases of maximum risk are adults of the third age and especially those who suffer from some chronic disease; but practice has shown that in the face of this disease, there is no one safe, and it can have a slow evolution that acts in a fulminating way.

Today the most worrying situation is given by coronavirus, a respiratory disease that so many lives have claimed, there are many ideas on how to fight this disease; but the method that most researchers agree on, is given by the method of isolating the infected to prevent possible transmission to other people [18, 19]. In [19] this process of coronavirus contagion is simulated using a generalization of the logistical method to characterize the process when it grows and when it decreases; indicating the moment of the curve's concavity change.

One of the treatments that has already given results is interferon alfa b_2, in addition to others already tested in the treatment of other diseases such as AIDS, hepatitis, among others. Alpha b_2 interferon, was developed by the Cuban Genetic Engineering and Biotechnology Center and has already been used in different parts of the world with highly reliable results [5, 13].

In [3] different real-life problems are treated using equations and systems of differential equations, all of them only in the autonomous case; where examples are developed and other problems and exercises are presented for them to be developed by the reader. The authors of [4] indicate a set of articles forming a collection of several problems that are modeled in different processes, but in general the qualitative and analytical theory of differential equations is used in both autonomous and non-autonomous cases, in both books the authors address the problem of epidemic development.

In the work [19], the logistic model is used to simulate population growth, which are applied to the development of epidemics, but different forms of the logistic model are presented. There are multiple works devoted to the study of the causes and the conditions under which an epidemic may develop, among which we can indicate [12].

The problem of epidemic modeling has always been of great interest to researchers, such as [6, 7, 8, 9, 10, 11, 13] and [14]. In this work we will apply the generalized logistic model, where the case of the growth and decrease of the infected are applied in the same equation; to model the development of epidemics, a model that allows forecasts of future behavior.

1. MODEL FORMULATION

The human body works like a prefect machine, producing enzymes, hormones and substances that will be used according to needs; but there are occasions that this is not enough due to the causes of those needs, for example in the case of the appearance of a virus situation in which in general artificial supplies are necessary to achieve an effective coping with the situation.

In order to formulate the model using a system of differential equations, the following variables will be introduced:
x_1 is the total concentration of healthy immune cells at the moment t.
x_2 is the total virus concentration at the time t.
x_3 is the concentration of currently activated NK cells t.

In addition, it will be denoted by
$V_\alpha = \{(\bar{x}_1,\bar{x}_2,\bar{x}_3) \in \mathbb{R}^3 / a-\alpha < \bar{x}_1 < a+\alpha,$
$b-\alpha < \bar{x}_2 < b+\alpha,\ c-\alpha < \bar{x}_3 < c+\alpha\}$. The set of values for the permissible concentrations of the healthy cells and the virus, respectively.

Remark 1 *If you are considering that the initial encounter is favorable to viruses, otherwise there would be no viral process. Here the signs of the coefficients of the previous development correspond to the characteristics of the problem addressed.*

In this way the model will be given by the following system of differential equations.

$$\begin{cases} x_1' = a_1x_1 - a_2x_1x_2 - a_3x_1^2 + X_1(x_1,x_2,x_3) \\ x_2' = -b_1x_2 + b_2x_1x_2 - b_3x_2x_3 + X_2(x_1,x_2,x_3) \\ x_3' = -c_1x_3 + c_2x_2x_3 + X_3(x_1,x_2,x_3). \end{cases} \tag{1}$$

Where the coefficients have the following meanings:
a_1 represents the increase of healthy immune cells with respect to your concentration.
a_2 represents the reduction of healthy immune cells by meeting with virus.
a_3 represents the decrease of immune cells in the absence of viruses
b_1 represents the reduction of virus with respect to your concentration.
b_2 represents the increase of virus by meeting with healthy immune cells.
b_3 represents the reduction of virus by meeting NK cells.
c_1 represents the reduction of NK cells with respect to your concentration.
c_2 represents the increase of NK cells by meeting with healthy immune cells.

And functions $X_i(x_1,x_2,x_3)$, $(i=1,2,3)$ they are disturbances not inherent in the process that can cause changes at any given time; from a mathematical point of view, they are infinitesimals of a higher order in a neighborhood of origin, these functions admit the following development in series of powers,
$X_i(x_1,x_2,x_3) = \sum_{|p|\geq 2} X_i^{(p)} x_1^{(p_1)} x_2^{(p_2)} x_3^{(p_3)},\ |p| = p_1+p_2+p_3,$
$(i=1,2,3)$.

The main objective of this work is to determine the equilibrium positions and to study the trajectories of the system in the vicinity of the equilibrium positions. If the functions $X_i(x_1,x_2,x_3)$, $(i=1,2,3)$ are identically null, then the system (1) takes the form,

$$\begin{cases} x_1' = a_1x_1 - a_2x_1x_2 - a_3x_1^2 \\ x_2' = -b_1x_2 + b_2x_1x_2 - b_3x_2x_3 \\ x_3' = -c_1x_3 + c_2x_2x_3. \end{cases} \tag{2}$$

The equilibrium positions of the system (2) are the points,
$P_1(0,\ 0,\ 0)$, $P_2\big(\frac{a_1}{a_3},\ 0,\ 0\big)$, $P_3\big(\frac{b_1}{b_2},\ \frac{a_1b_2-a_3b_1}{a_2b_2},\ 0\big)$,
$P_4\big(0,\ \frac{c_1}{c_2},\ -\frac{b_1}{b_3}\big)$ and
$P_5\big(\frac{a_1c_2-a_2c_1}{a_3c_2},\ \frac{c_1}{c_2},\ \frac{a_1b_2c_2-a_2b_2c_1-a_3b_1c_2}{a_3b_3c_2}\big)$.

The study of the point P_4, lack biological sense.

The point $P_1(0,0,0)$, has a positive eigenvalue, therefore, the equilibrium position is unstable.

1.1 Analysis at point P_2

To the point $P_2\left(\frac{a_1}{a_3},\ 0,\ 0\right)$, is to say when the NK cells are not yet activated, it is necessary to make a change of variables to analyze the behavior of the trajectories in a neighborhood of that point. The transformation of coordinates, $x_1 = y_1 + \frac{a_1}{a_3}$, $x_2 = y_2$, $x_3 = y_3$ reduces the system (2) in the next system,

$$\begin{cases} y_1' = -a_1 y_1 - \dfrac{a_1 a_2}{a_3} y_2 - a_3 y_1^2 - a_2 y_1 y_2 \\ y_2' = \dfrac{a_1 b_2 - a_3 b_1}{a_3} y_2 + b_2 y_1 y_2 - b_3 y_2 y_3 \\ y_3' = -c_1 y_3 + c_2 y_2 y_3. \end{cases} \tag{3}$$

The characteristic equation of the matrix of the linear part of the system (3) has the form,

$$\mathrm{Det}\begin{pmatrix} -a_1 - \lambda & -\dfrac{a_1 a_2}{a_3} & 0 \\ 0 & \dfrac{a_1 b_2 - a_3 b_1}{a_3} - \lambda & 0 \\ 0 & 0 & -c_1 - \lambda \end{pmatrix} = 0.$$

So, it has, $(a_1 + \lambda)(c_1 + \lambda)(a_1 b_2 - a_3(b_1 + \lambda)) = 0$.

Theorem 2 *The necessary and sufficient condition for the trivial solution of the system (3) to be asymptotically stable is that $a_1 b_2 > a_3 b_1$.*

The previous conditions are consequences of Hurwitz's theorem, guaranteeing asymptotic stability from the first approximation system.

Remark 3 *Whenever the condition is met $a_1 b_2 > a_3 b_1$ with the presence of a virus, it will not be necessary to reactivate NK cells to control the virus; and consequently there will be no consequence for the patient whenever the considered point is in the set of admissible values, that is, $P_2(\frac{a_1}{a_3},\ 0,\ 0) \in V_\alpha$.*

Example 4 *Be the system*

$$\begin{cases} y_1' = -0.10 y_1 - 0.06 y_2 - 0.30 y_1^3 - 0.20 y_1 y_2 \\ y_2' = -0.26 y_2 + 0.10 y_1 y_2 - 0.60 y_2 y_3 \\ y_3' = -0.10 y_3 + 0.30 y_2 y_3. \end{cases} \tag{4}$$

The Eigenvalues of fundamental matrix of system (4) are $\lambda_1 = -0.266667$, $\lambda_2 = -0.1$ and $\lambda_3 = -0.1$

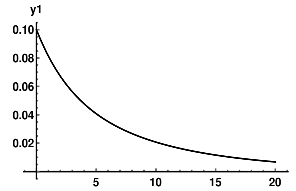

Figure 1. Trajectories of $y_1(t)$ in the **Example 4**

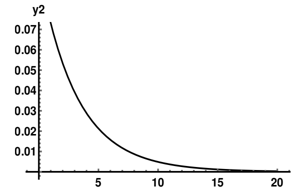

Figure 2. Trajectories of $y_2(t)$ in the **Example 4**

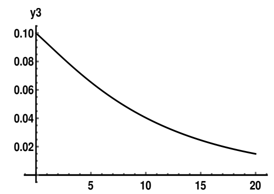

Figure 3. Trajectories of $y_3(t)$ in the **Example 4**

1.2 Analysis at point P_3

To the point $P_3\left(\frac{b_1}{b_2},\ \frac{a_1 b_2 - a_3 b_1}{a_2 b_2},\ 0\right)$, that is to say in the case where NK cells have not yet been activated, and there is a virus present, for this to make biological sense the condition must be met $a_1 b_2 > a_3 b_1$, which coincides with the stability condition of the system 2; it is necessary to change variables, $x_1 = z_1 + \frac{b_1}{b_2}$, $x_2 = z_2 + \frac{a_1 b_2 - a_3 b_1}{a_2 b_2}$ and $x_3 = z_3$ that reduces the system (2) to the system,

$$\begin{cases} z_1' = -\dfrac{a_3 b_1}{b_2} z_1 - \dfrac{a_2 b_1}{b_2} z_2 - a_3 z_1^2 - a_2 z_1 z_2 \\ z_2' = \dfrac{a_1 b_2 - a_3 b_1}{a_2} z_1 + \dfrac{a_3 b_1 b_3 - a_1 b_2 b_3}{a_2 b_2} z_3 + b_2 z_1 z_2 - b_3 z_2 z_3 \\ z_3' = \dfrac{a_1 b_2 c_2 - a_3 b_1 c_2 - a_2 b_2 c_1}{a_2 b_2} z_3 + c_2 z_2 z_3. \end{cases} \tag{5}$$

The characteristic equation of the matrix of the linear part of the system (5) has the form,

$$\lambda^3 + \frac{a_2 a_3 b_1 + a_2 b_2 c_1 + a_3 b_1 c_2 - a_1 b_2 c_2}{a_2 b_2} \lambda^2 + \mathscr{A}\lambda - \mathscr{B},$$

where $\mathscr{B} = \dfrac{b_1(a_3 b_1 - a_1 b_2)(a_2 b_2 c_1 + a_3 b_1 c_2 - a_1 b_2 c_2)}{a_2 b_2^2}$,

$$\mathscr{A} = \frac{b_1(a_2 b_2(a_1 b_2 + a_3(c_1 - b_1)) + a_3 c_2(a_3 b_1 - a_1 b_2))}{a_2 b_2^2}.$$

Theorem 5 *The trivial solution of the system (5) is asymptotically stable if and only if conditions are met:*

$\mathscr{C}_1$**:** $a_2 b_2 c_1 + a_3 b_1 c_2 > a_1 b_2 c_2$

$\mathscr{C}_2$**:** $a_2 c_2(a_3 b_1 - a_1 b_2)(a_3 b_1 + 2 b_2 c_1) + (a_3 b_1 - a_1 b_2)^2 c_2^2 + + a_2^2 b_2(a_3 b_1(c_1 - b_1) + b_2(a_1 b_1 + c_1^2)) > 0$.

Remark 6 *Whenever the conditions are met $\mathscr{C}_1$ and $\mathscr{C}_2$, it will not take much reactivation of NK cells to control the virus; and consequently there will be no consequence for the patient whenever the considered point is in the set of admissible values, that is, $P_3\left(\frac{b_1}{b_2},\ \frac{a_1 b_2 - a_3 b_1}{a_2 b_2},\ 0\right) \in V_\alpha$.*

Example 7 *Be the system*

$$\begin{cases} z_1' = -0.033 z_1 - 0.033 z_2 - 0.10 z_1^2 - 0.10 z_1 z_2 \\ z_2' = 0.50 z_1 - 0.50 z_3 + 0.30 z_1 z_2 - -0.30 z_2 z_3 \\ z_3' = -0.16 z_3 + 0.20 z_2 z_3. \end{cases} \tag{6}$$

The Eigenvalues of fundamental matrix of system (6) are $\lambda_1 = -0.166667$, $\lambda_2 = -0.0166667 + 0.128019i$ *and* $\lambda_3 = -0.0166667 - 0.128019i$

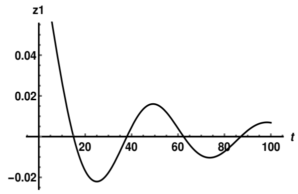

Figure 4. Trajectories of $z_1(t)$ in the **Example 6**

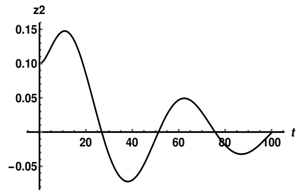

Figure 5. Trajectories of $z_2(t)$ in the **Example 6**

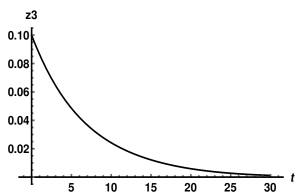

Figure 6. Trajectories of $z_3(t)$ in the **Example 6**

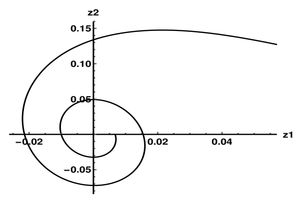

Figure 7. Trajectories of z_1 vs z_2 in the **Example 6**

Remark 8 *If the condition* $\mathscr{C}_1$ *is not met, then the system (5) is unstable, therefore it makes biological sense to activate the NK cells and therefore the point* P_5 *take action.*

1.3 Analysis at point P_5

To $P_5(\dfrac{a_1c_2 - a_2c_1}{a_3c_2}, \dfrac{c_1}{c_2}, \dfrac{a_1b_2c_2 - a_2b_2c_1 - a_3b_1c_2}{a_3b_3c_2})$, it is necessary to make a change of variables to analyze the behavior of trajectories in a neighborhood at that point.

The transformation of coordinates, $x_1 = w_1 + h$, $x_2 = w_2 + k$ and $x_3 = w_3 + l$ reduces the system (2) in the next system,

$$\begin{cases} w_1' = a_1 - a_2k - a_3h)w_1 - a_2hw_2 - a_2w_1w_2 - a_3w_1^2 \\ w_2' = b_2kw_1 + (b_2h - b_1 - b_3l)w_2 - b_3kw_3 + b_2w_1w_2 - \\ \quad -b_3w_2w_3 \\ w_3' = c_2lw_2 + (c_2k - c_3)w_3 + c_2w_2w_3. \end{cases} \tag{7}$$

where $h = \dfrac{a_1c_2 - a_2c_1}{a_3c_2}$, $k = \dfrac{c_1}{c_2}$ and

$l = \dfrac{a_1b_2c_2 - a_2b_2c_1 - a_3b_1c_2}{a_3b_3c_2}$.

The characteristic equation of the matrix of the linear part of the system (7) has the form $\lambda^3 + n_1\lambda^2 + n_2\lambda + n_3 = 0$ where n_1, n_2 and n_3 have the form,

$n_1 = b_3l + a_2k + 2a_3h - a_1 - b_2h + b_1$,

$n_2 = b_2c_2hk + b_3c_3kl - b_2c_1h + a_1b_2h - a_1b_3l - a_2b_2hk + {} + a_2b_1k + a_2b_3kl - 2a_3b_2h^2 + 2a_3b_1h + 2a_3b_3l - {} - 2a_3c_2hk + 2a_3c_1h + a_2b_2hk - a_1b_1$,

$n_3 = a_1b_2c_1h - a_1b_2c_3hk - a_1b_3c_3kl + a_2b_2c_2hk^2 + {} + a_2b_3c_1kl - 2a_3b_1c_2hk + 2a_3b_1c_1h + 2a_3b_3c_3hkl$.

Theorem 9 *The equilibrium position* P_5 *asymptotically stable if and only if the conditions are met* $n_i > 0$, *(i=1,2,3) and* $n_1n_2 > n_3$.

The proof of this theorem is obtained from the previous and from the conditions of Hurwitz's theorem.

Remark 10 *If the conditions* $n_i > 0$, $(i = 1, 2, 3)$ *and* $n_1n_2 > n_3$ *of the theorem (9) are met, the values of the virus concentrations, the concentrations of immune cells healthy and the NK cell concentrations are kept close to* P_5 *and if the coordinates of that point are close to the optimal concentration values, i.e.* $P_5 \in V_\alpha$, *there will be no adverse consequences for the patient, it will be in a basal state.*

Example 11 *Be the system*

$$\begin{cases} w_1' = -0.4875w_1 - 0.1w_1^2 - 2.4375w_2 - 0.5w_1w_2 \\ w_2' = 0.0075w_1 + 0.3w_1w_2 - 0.005w_3 - 0.2w_2w_3 \\ w_3' = 2.685w_2 + 0.4w_2w_3. \end{cases} \tag{8}$$

The Eigenvalues of fundamental matrix of system (8) are $\lambda_1 = -0.449122$, $\lambda_2 = -0.0191892 + 0.113584i$ *and* $\lambda_3 = -0.0191892 - 0.113584i$

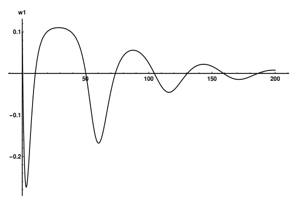

Figure 8. Trajectories of $w_1(t)$ in the **Example 8**

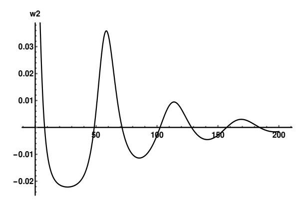

Figure 9. Trajectories of $w_2(t)$ in the **Example 8**

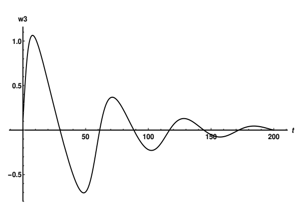

Figure 10. Trajectories of $w_3(t)$ in the **Example 8**

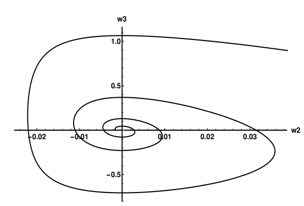

Figure 11. Trajectories of w_2 vs w_3 in the **Example 8**

Acknowledgments

The authors appreciate the technical support and invaluable feedback provided by Digna de la Caridad Bandera Jiménez, Adriana Rodríguez Valdés, Manuel de Jesús Salvador Álvarez, Hilda Morandeira Padrón, Itciar Arias Portales and Sergio Miranda Reyes. We also thank to Universidad de Oriente, Dirección de DATYS-Santiago de Cuba, Dirección Provincial de Salud Pública and managers of the provincial government of Santiago de Cuba.

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