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Mathematical study of toxin elimination by the liver, circulatory system and the kidneys
Estudio Matemático de la eliminación de toxinas por el hígado, el sistema circulatorio y los riñones

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Resumen En este estudio se presenta un modelo matemático mediante un sistema de ecuaciones diferenciales que simula el proceso de eliminación de toxinas a través del hígado, riñones y sistema circulatorio. Se realiza un estudio cualitativo para el caso crítico en el que aparecen un par de valores propios imaginarios puros y uno negativo, el sistema se reduce a la forma cuasi normal para facilitar su estudio y aportar conclusiones sobre el proceso de eliminación de toxinas en una persona sana. Adicionalmente, se realiza un estudio general sobre las características de sus principales funciones, enfermedades y cómo predecirlas.

Abstract In this study, a mathematical model is presented using a system of differential equations that simulates the toxin elimination process through the liver, kidneys and circulatory system. A qualitative study is carried out for the critical case in which a pair of pure imaginary eigenvalues and a negative one appear, the system is reduced to the quasi-normal form to facilitate its study and provide conclusions about the process of elimination of toxins in a person healthy. Additionally, a general study is carried out on the characteristics of its main functions, diseases and how to predict them.

Palabras Clave
Mathematical model, quasi-normal form, toxine elimination

Keywords
Modelo matemático, forma cuasi normal, eliminación de toxinas

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Introduction

A compartmental model essentially consists of a finite number of interconnected subsystems, called compartments, that exchange with each other and with the environment. Several behavioral models have been reported in the literature, among which it can be noted [1] where a model of elimination of a drug administered by ingestible route is presented, here sufficient conditions are provided for its elimination, the case in which it is administered nasal is presented in [3] and the case in which it is administered by injection is discussed in [2]. In all cases, a qualitative study of the system is carried out that allows predicting the future behavior of the process.

In [6] a mathematical study of the pollutant elimination process is carried out, where conclusions are provided on the situation they will present after being discharged into nature. In [4] the same process is modeled but by means of a non-autonomous periodic system, which is reduced to a system where the matrix of the linear part has constant coefficients. Additionally, in [5] the case of the elimination of contamination with periodic coefficients is addressed. In all cases, conditions are obtained for the prolonged non-contamination of the environment.

Our objective is to present a study of some characteristics of the circulatory system, the liver and the kidneys to carry out a simulation using a compartmental model using a system of differential equations for the elimination of toxins between these organs.

Liver

The liver is an attachment to the digestive system and is considered one of the largest organs in the human body. This organ is in the upper abdominal cavity, below the diaphragm and on the right side, has a reddish-brown color and weighs, on average, 1.5 kg. In addition, it has a smooth surface and four lobes: right, left, caudate, and square. Each lobe is made up of several cells known as hepatocytes.

The liver is related to important functions of our body, such as the regulation of the metabolism of various nutrients, proteins, carbohydrates and lipids, synthesis of proteins and other molecules, breakdown of hormones, storage of substances such as glycogen and excretion of toxic substances. In addition, it is related to the production of red blood cells in the embryo, it destroys these cells when they are old, in addition to synthesizing some coagulation factors. Despite the various functions of the liver, one of the main and best known is the formation and secretion of bile, a substance made up mainly of bile acids, phospholipids, cholesterol, inorganic salts and bilirubin. This, in turn, is responsible for giving color to the bile and is the result of the destruction of red blood cells.

Bile basically has two primary functions: excretion of some substances and the emulsion of fats, which helps in the digestion and absorption of lipids. In bile, toxins, substances in drugs and bilirubin are mainly eliminated. This process is known as liver detoxification. When the liver is suffering from an illness, some symptoms may arise. A person suffering from liver problems usually has jaundice, fatigue, nausea, vomiting, abdominal pain, bloating, among others. One of the most well-known and more specific clinical conditions of liver disease is jaundice, which is characterized by causing a yellow color in the skin and in the mucous membranes due to a high concentration of bilirubin in the blood.

Cirrhosis causes fibrosis of the liver and the appearance of nodules. One of the major problems that affect the liver is cirrhosis, a degeneration and inflammation of the organ causing from various factors. The most common cause of cirrhosis is alcoholism, but viral hepatitis and biliary diseases can trigger the problem. In addition It usually causes progressive fibrosis and the appearance of parenchymal nodules. Because it has vital functions, the liver is an extremely important organ for our survival. Therefore, when any symptoms appear, especially the yellowish coloration of the skin and eyes, seek medical attention immediately. Liver problems can be serious and even lead to the death of the patient [8].

Kidneys

The kidneys are two organs located on both sides of the spine, behind the last ribs, they measure approximately 12 centimeters and weigh about 150 grams each. The kidneys have three main functions: eliminate toxins or waste resulting from body metabolism, maintain a constant water balance in the body, eliminating excess water, salts and electrolytes, thus avoiding the appearance of edema and controlling the increase in blood pressure. These organs produce hormones such as erythropoietin, which is involved in the formation of red blood cells, vitamin D, which helps absorb calcium to strengthen bones, and renin, which is involved in regulating blood pressure.

Kidney diseases can be silent, but there are cases where the individual experiences some symptoms. The most well-known signs and symptoms are high blood pressure, bloody urine, foamy urine, presence of proteins in the urine, edema, elimination of very clear urine, anemia, pallor, tiredness, chest pain and drowsiness. When the disease is very advanced, there may be loss of appetite, nausea, vomiting, cramps, itching, loss of memory, lack of concentration, tremors, insomnia or drowsiness.

Approximately 70% of the weight of an adult individual is represented by water. Apparently the main purpose of the kidneys is to continually drain it from the body, as a mere harmless residue. But in fact, all that incoming water is necessary for organic functions. In addition to water ingested with solid and liquid food, man needs to supplement his needs with the intake of pure water, although the body itself produces water as a by-product of biochemical activities.

Almost all the water in the body is inside the cells. Blood contains only about 10% and the rest is distributed by other fluids. In addition to this function of conveying the essential substances to the body, water also functions as a temperature regulating element: perspiration moistens the skin, where evaporation steals heat and lowers the surrounding temperature. For these reasons, water levels in the body are essential for physiological balance, but the work of the kidneys does not have the sole or main purpose of eliminating excess water, in the urine, water enters again as a vehicle that allows the excretion of waste resulting from organic activity. A third function of the kidneys is to control the composition of the blood, with regard to the different inorganic salts, so important due to their osmotic function, this control of salt levels is done by eliminating excesses, through urine, every minute, about 1/5 of the blood passes through the kidneys, for filtration, the filtered product, however, is still much less concentrated than urine. The kidney itself will pass this filtrate through twisted tubules, so that water and other compounds are reabsorbed helping to keep water and other necessary substances in the body.

The kidneys control the amount of water and salt in the body, eliminate toxins, help control high blood pressure, produce hormones that prevent anemia and bone decalcification, eliminate some medications and other substances ingested. The main risk factors for kidney disease are hypertension, diabetes, family history of kidney disease, history of kidney disease in the past [8].

Circulatory system

The circulatory or cardiovascular system, formed by the heart and blood vessels, is responsible for transporting nutrients and oxygen to the different parts of the body. The blood circulation corresponds to the entire path of the circulatory system that blood carries out in the human body, so that in the complete path, blood passes through the heart twice, these circuits are called small circulation and large circulation.

The small circulation or pulmonary circulation consists of the path that the blood travels from the heart to the lungs and from the lungs to the heart. The heart, blood vessels, and blood make up the cardiovascular or circulatory system. Blood circulation allows the transport and distribution of nutrients, gaseous oxygen and hormones to the cells of the remaining organs, the blood also carries metabolic waste so that they can be eliminated from the body.

The great circulation or systemic circulation is the path of the blood, which leaves the heart to the other cells of the body and vice versa, in the heart, the arterial blood from the lungs is pumped from the left atrium to the left ventricle, from the ventricle it passes to the aortic artery, which is responsible for transporting this blood to the different tissues of the body.

The circulatory system consists of the following components: blood, which is responsible for transporting oxygen and nutrients through the bloodstream until it reaches the cells, the heart, which works as a double pump, so that the left side pumps arterial blood to different parts of the body, while the right side pumps venous blood to the lungs. The arteries are vessels of the circulatory system, which leave the heart and carry blood to other parts of the body. The veins are vessels of the circulatory system, which carry blood from body tissues to the heart and capillaries, this microscopic branches of arteries and veins in the circulatory system, have only one layer of cells, which allows the exchange of substances between blood and cells [8].

Several works, books and articles related to the processes of human life are known, Among these books dedicated to mathematical modeling, we indicate the following [11, 13, 12] in which real problems are simulated using differential equations and systems of equations, where in addition a certain treatment is made to give conclusions of the processes. In [12] the authors simulate the shape of the polymer formation process in blood using autonomous systems of third and fourth order differential equations, giving conclusions about the formation of polymers and domains.

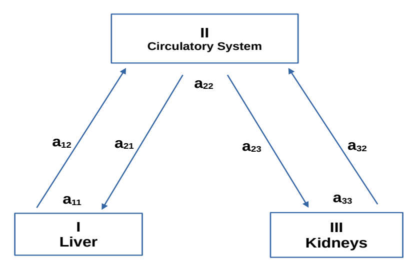
In [11] different real-life problems are treated using equations and systems of differential equations, all of them only in the autonomous case, where examples are developed and other problems and exercises are presented for them to be developed by the reader. The authors of [13] indicate a set of articles forming a collection of several problems that are modeled in different ways, but in general the qualitative and analytical theory of differential equations is used in both autonomous and non-autonomous cases.

Another of the works where medicine processes are modeled is the one corresponding to the insulin-glucose interaction. Insulin is a hormone produced by the pancreas, its function is to act in the reduction of blood glucose (blood glucose rate). It is responsible for the absorption of glucose by cells, when the insulin-glucose dynamics is not natural in the human body, diabetes can occur, this dynamic in both a normal person and a diabetic is modeled in [10, 9]. In [7] the case of tissue replacement is simulated, the case of the diabetic foot is seen. In [14] a mathematical study is carried out using differential equations of the lungs and the process of oxygenation of the blood.

1. Formulation of the mathematical model

For the elaboration of the model we will consider the basic principles that take place in the real phenomenon. It is known that the liver has the function of eliminating certain toxins received directly by food or ingested medicines, part of these can pass to the circulatory system and later to the kidneys where a large part of these can be eliminated through the circulatory system and the urine.

To carry out the simulation using a system of differential equations, the following compartments are considered: compartment one the liver, compartment two the circulatory system and compartment three the kidneys. The following notations will be used:
$\tilde{x}_1$ the total concentration of toxins in the compartment I.
$\tilde{x}_2$ the total concentration of toxins in the compartment II.
$\tilde{x}_3$ the total concentration of toxins in the compartment III.
In addition, $\bar{x}_1$, $\bar{x}_2$, and $\bar{x}_3$ the admissible values of toxins in compartments I, II and III respectively. Here the variables will be introduced x_1, x_2 and x_3 and defined as follows:
$x_1 = \tilde{x}_1 - \bar{x}_1$, $x_2 = \tilde{x}_2 - \bar{x}_2$ and $x_3 = \tilde{x}_3 - \bar{x}_3$ so if $x_1 \to 0$, $x_2 \to 0$ and $x_3 \to 0$ the following conditions are met $\tilde{x}_1 \to \bar{x}_1$, $\tilde{x}_2 \to \bar{x}_2$ and $\tilde{x}_3 \to \bar{x}_3$ which constitutes the main objective of this work.
$-a_{ij}x_i$ Represents the passage of the x_i element from the i compartment j and with positive sign the arrival at compartment j. Considering the previous principles, mathematical



modeling of the toxin elimination process takes the following form,

$$\begin{cases} x_1' = (a_{11} - a_{12})x_1 + a_{21}x_2 + X_1(x_1, x_2, x_3) \\ x_2' = a_{12}x_1 + (a_{22} - a_{21} - a_{23})x_2 + c_{32}x_3 + X_2(x_1, x_2, x_3) \\ x_3' = a_{23}x_2 + (a_{33} - a_{32})x_3 + X_3(x_1, x_2, x_3) \end{cases} \tag{1}$$

If the coefficient $a_{ii} \neq 0$ indicates that in compartment there were already toxins before the passage to another compartment and $X_i(x_1, x_2, x_3)$, for the $i = 1, 2, 3$ they are disturbances not inherent in the process, which could at a given moment produce certain changes and from a mathematical point of view they are infinitesimals of a higher order, those that admit the following development in series of potentials,

$$X_i(x_1, x_2, x_3) = \sum_{|p| \geq 2} X_i^p \, x_1^{p_1} \, x_2^{p_2} \, x_3^{p_3}, \quad |p| = p_1 + p_2 + p_3. \tag{2}$$

The system (1) can be written as follows,

$$\begin{cases} x_1' = a_1 x_1 + a_2 x_2 + X_1(x_1, x_2, x_3) \\ x_2' = b_1 x_1 + b_2 x_2 + b_3 x_3 + X_2(x_1, x_2, x_3) \\ x_3' = c_2 x_2 + c_3 x_3 + X_3(x_1, x_2, x_3) \end{cases} \tag{3}$$

where $a_1 = a_{11} - a_{12}$, $a_2 = a_{21}$, $b_1 = a_{12}$, $b_2 = a_{22} - a_{21} - a_{23}$, $b_3 = a_{32}$, $c_2 = a_{23}$ and $c_3 = a_{33} - a_{32}$. It is good to note that the parameters a_1, b_2 and c_3 indicated in the system (3) can have any sign.

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

- $n_1 = -(a_1 + b_2 + c_3)$
- $n_2 = a_1b_2 + a_1c_3 + b_2c_3 - b_3c_1$
- $n_3 = a_2b_1c_2 + a_1b_3c_1 - a_1b_2c_3$.

Teorema 1 *The null solution (0,0,0) of the system* (3) *is asymptotically stable if and only if: $n_1 > 0$, $n_2 > 0$, $n_3 > 0$ and $n_1n_2 > n_3$, that is, this is the necessary and sufficient condition for the total toxin concentrations in the three compartments to converge to the admissible concentrations.*

Applying Hurwitz's theorem, to the system (3) all the eigenvalues of the characteristic equation have negative real part, therefore the trajectories of the system are asymptotically stable.

If in the characteristic equation $n_1 > 0$, $n_2 > 0$, $n_3 > 0$ and $n_1n_2 = n_3$, the matrix of the linear part of the system has a pair of pure imaginary eigenvalues $\lambda_1 = \sigma i$, $\lambda_2 = -\sigma i$ and a negative real eigenvalue $\lambda_3 = -n_1 < 0$, where $\sigma = \sqrt{n_2}$, that is, we are in the presence of a critical case, for which it is necessary to simplify the system and apply the qualitative theory of differential equations.

The non-degenerate linear transformation $X = SY$, reduces the system (3) to the form,

$$\begin{cases} y_1' = \sigma i y_1 + Y_1(y_1, y_2, y_3) \\ y_2' = -\sigma i y_2 + Y_2(y_1, y_2, y_3) \\ y_3' = \lambda_3 y_3 + Y_3(y_1, y_2, y_3) \end{cases} \tag{4}$$

Teorema 2 *There is the exchange of variables,*

$$\begin{cases} y_1 = z_1 + h_1(z_1, z_2) + h_1^0(z_1, z_2, z_3) \\ y_2 = z_2 + h_2(z_1, z_2) + h_2^0(z_1, z_2, z_3) \\ y_3 = z_3 + h_3(z_1, z_2) \end{cases} \tag{5}$$

that transforms the system (4) *in quasi-normal form,*

$$\begin{cases} z_1' = \sigma i z_1 + z_1P_1(z_1z_2) \\ z_2' = -\sigma i z_2 + z_2P_2(z_1z_2) \\ z_3' = \lambda_3 z_3 + Z_3(z_1, z_2, z_3), \end{cases} \tag{6}$$

where $h_1^0(z_1, z_2, z_3)$, $h_2^0(z_1, z_2, z_3)$, $Z_3(z_1, z_2, z_3)$, $h_1(z_1, z_2)$, $h_2(z_1, z_2)$, $h_3(z_1, z_2)$, $P_1(z_1z_2)$ and $P_2(z_1z_2)$ have similar development to X_i in (2)*, besides $z_2 = \bar{z}_1$. In addition, $h_1^0(z_1, z_2, z_3)$, $h_2^0(z_1, z_2, z_3)$ and $Z_3(z_1, z_2, z_3)$ annul for $z_3 = 0$.*

Demostración. Deriving the transformation (5) along the trajectories of systems (4) and (6) we obtain the system of equations,

$$\begin{cases} Y_1(z_1 + h_1 + h_1^0, z_2 + h_2 + h_2^0, z_3 + h_3) = z_1P_1(z_1z_2) + \\ \quad + \dfrac{\partial h_1}{\partial z_1}(\sigma i z_1 + z_1P_1(z_1z_2)) + \\ \quad + \dfrac{\partial h_1}{\partial z_2}(-\sigma i z_2 + z_2P_2(z_1z_2)) + \\ \quad + \dfrac{\partial h_1^0}{\partial z_1}(\sigma i z_1 + z_1P_1(z_1z_2)) + \\ \quad + \dfrac{\partial h_1^0}{\partial z_2}(-\sigma i z_2 + z_2P_2(z_1z_2)) + \\ \quad + \dfrac{\partial h_1^0}{\partial z_3}(\lambda_3 z_3 + Z_3(z_1, z_2, z_3)) - \sigma i(h_1 + h_1^0) \\ Y_2(z_1 + h_1 + h_1^0, z_2 + h_2 + h_2^0, z_3 + h_3) = z_2P_2(z_1z_2) + \\ \quad + \dfrac{\partial h_2}{\partial z_1}(\sigma i z_1 + z_1P_1(z_1z_2)) + \\ \quad + \dfrac{\partial h_2}{\partial z_2}(-\sigma i z_2 + z_2P_2(z_1z_2)) + \\ \quad + \dfrac{\partial h_2^0}{\partial z_1}(\sigma i z_1 + z_1P_1(z_1z_2)) + \\ \quad + \dfrac{\partial h_2^0}{\partial z_2}(-\sigma i z_2 + z_2P_2(z_1z_2)) + \\ \quad + \dfrac{\partial h_2^0}{\partial z_3}(\lambda_3 z_3 + Z_3(z_1, z_2, z_3)) + \sigma i(h_2 + h_2^0) \\ Y_3(z_1 + h_1 + h_1^0, z_2 + h_2 + h_2^0, z_3 + h_3) = Z_3(z_1, z_2, z_3) + \\ \quad + \dfrac{\partial h_3}{\partial z_1}(\sigma i z_1 + z_1P_1(z_1z_2)) + \\ \quad + \dfrac{\partial h_3}{\partial z_2}(-\sigma i z_2 + z_2P_2(z_1z_2)) - \lambda_3 h_3 \end{cases} \tag{7}$$

Since the series $h_1(z_1, z_2)$, $h_2(z_1, z_2)$, $h_3(z_1, z_2)$, $h_1^0(z_1, z_2, z_3)$ and $h_2^0(z_1, z_2, z_3)$ have a development similar to the series X_i in equation (2), the expressions are obtained:
$\dfrac{\partial h_1}{\partial z_1}z_1 = p_1 z_1 \sum\limits_{|p| \geq 2} h_1^{(p)} z_1^{p_1 - 1} z_2^{p_2} z_3^{p_3} = p_1 \sum\limits_{|p| \geq 2} h_1^{(p)} z_1^{p_1} z_2^{p_2} z_3^{p_3} =$ $= p_1 h_1$. Similarly, the expressions:
$\dfrac{\partial h_1}{\partial z_2}z_2 = p_2 h_1$, $\dfrac{\partial h_2}{\partial z_1}z_1 = p_1 h_2$, $\dfrac{\partial h_2}{\partial z_2}z_2 = p_2 h_2$, $\dfrac{\partial h_1^0}{\partial z_1}z_1 = p_1 h_1^0$, $\dfrac{\partial h_1^0}{\partial z_2}z_2 = p_2 h_1^0$, $\dfrac{\partial h_1^0}{\partial z_3}z_3 = p_3 h_1^0$, $\dfrac{\partial h_2^0}{\partial z_1}z_1 = p_1 h_2^0$, $\dfrac{\partial h_2^0}{\partial z_2}z_2 = p_2 h_2^0$ and $\dfrac{\partial h_2^0}{\partial z_3}z_3 = p_3 h_2^0$.

Therefore, substituting these expressions in the equation

(7), we obtain

$$
\begin{cases}
Y_1(z_1+h_1+h_1^0, z_2+h_2+h_2^0, z_3+h_3) = z_1P_1(z_1z_2)+\\
\quad +(p_1-p_2-1)\sigma i h_1 + \dfrac{\partial h_1}{\partial z_1} z_1P_1(z_1z_2)+\\
\quad +\dfrac{\partial h_1}{\partial z_2} z_2P_2(z_1z_2) + \dfrac{\partial h_1^0}{\partial z_1} z_1P_1(z_1z_2)+\\
\quad +\dfrac{\partial h_1^0}{\partial z_2} z_2P_2(z_1z_2) + (p_1-p_2-1)\sigma i h_1^0+\\
\quad +\dfrac{\partial h_1^0}{\partial z_3}(\lambda_3z_3+Z_3(z_1,z_2,z_3))\\
Y_2(z_1+h_1+h_1^0, z_2+h_2+h_2^0, z_3+h_3) = z_2P_2(z_1z_2)+\\
\quad +(p_1-p_2+1)\sigma i h_2 + \dfrac{\partial h_2}{\partial z_1} z_1P_1(z_1z_2)+\\
\quad +\dfrac{\partial h_2}{\partial z_2} z_2P_2(z_1z_2) + \dfrac{\partial h_2^0}{\partial z_1} z_1P_1(z_1z_2)+\\
\quad +\dfrac{\partial h_2^0}{\partial z_2} z_2P_2(z_1z_2)(p_1-p_2+1)\sigma i h_2^0+\\
\quad +\dfrac{\partial h_2^0}{\partial z_3}(\lambda_3z_3+Z_3(z_1,z_2,z_3))\\
Y_3(z_1+h_1+h_1^0, z_2+h_2+h_2^0, z_3+h_3) = Z_3(z_1,z_2,z_3)+\\
\quad +(p_1-p_2-\lambda_3)h_3 + \dfrac{\partial h_3}{\partial z_1} z_1P_1(z_1z_2)+\\
\quad +\dfrac{\partial h_3}{\partial z_2} z_2P_2(z_1z_2)
\end{cases}
\tag{8}
$$

To determine the series that intervene in the systems and the transformation, we will separate the coefficients of the power of degree $p=(p_1,p_2,p_3)$ in the following two cases:

Case I

Making $z_3=0$ in the system (8), is to say to the vector $p=(p_1,p_2,0)$ results the system,

$$
\begin{cases}
Y_1(z_1+h_1, z_2+h_2, h_3) = z_1P_1(z_1z_2) + (p_1-p_2-1)\sigma i h_1+\\
\quad +\dfrac{\partial h_1}{\partial z_1} z_1P_1(z_1z_2) + \dfrac{\partial h_1}{\partial z_2} z_2P_2(z_1z_2)\\
Y_2(z_1+h_1, z_2+h_2, h_3) = z_2P_2(z_1z_2) + (p_1-p_2+1)\sigma i h_2+\\
\quad +\dfrac{\partial h_2}{\partial z_1} z_1P_1(z_1z_2) + \dfrac{\partial h_2}{\partial z_2} z_2P_2(z_1z_2)\\
Y_3(z_1+h_1, z_2+h_2, h_3) = (p_1-p_2-\lambda_3)h_3+\\
\quad +\dfrac{\partial h_3}{\partial z_1} z_1P_1(z_1z_2) + \dfrac{\partial h_3}{\partial z_2} z_2P_2(z_1z_2).
\end{cases}
\tag{9}
$$

The system (9) allows to determine the coefficients of the series: $P_1(z_1z_2)$, $P_2(z_1z_2)$, $h_1(z_1,z_2)$, $h_2(z_1,z_2)$ and $h_3(z_1,z_2)$, where for being the resonant case, we deduce the form indicated for $P_1(z_1z_2)$ and $P_2(z_1z_2)$ and the remaining series are determined uniquely.

Case II)

When $z_3 \neq 0$ is obtained

$$
\begin{cases}
Y_1(z_1+h_1+h_1^0, z_2+h_2+h_2^0, z_3+h_3) = (p_1-p_2-1)h_1^0+\\
\quad +\dfrac{\partial h_1^0}{\partial z_1} z_1P_1(z_1z_2) + \dfrac{\partial h_1^0}{\partial z_2} z_2P_2(z_1z_2)+\\
\quad +\dfrac{\partial h_1^0}{\partial z_3}(\lambda_3z_3+Z_3(z_1,z_2,z_3))\\
Y_2(z_1+h_1+h_1^0, z_2+h_2+h_2^0, z_3+h_3) = (p_1-p_2+1)h_1^0+\\
\quad +\dfrac{\partial h_2^0}{\partial z_1} z_1P_1(z_1z_2) + \dfrac{\partial h_2^0}{\partial z_2} z_2P_2(z_1z_2)+\\
\quad +\dfrac{\partial h_2^0}{\partial z_3}(\lambda_3z_3+Z_3(z_1,z_2,z_3))\\
Y_3(z_1+h_1+h_1^0, z_2+h_2+h_2^0, z_3+h_3) = Z_3(z_1,z_2,z_3).
\end{cases}
\tag{10}
$$

Because the series of the system (6) are known expressions, the system (10) allows to calculate the series $h_1^0(z_1,z_2,z_3)$, $h_2^0(z_1,z_2,z_3)$ and $Z_3(z_1,z_2,z_3)$. This proves the existence of the exchange of variables. ■

In the system (6) the functions $P_1(z_1z_2)$ and $P_2(z_1z_2)$ admit the following development in series of powers

$$
P_1(z_1z_2) = \sum_{n=k}^{\infty} a_n(z_1z_2)^n + i\sum_{n=l}^{\infty} b_n(z_1z_2)^n \tag{11}
$$

Where $P_2(z_1z_2) = \bar{P}_1(z_1z_2)$, in addition a_k is the first non-zero coefficient and n is the corresponding power.

Teorema 3 *If $a_k<0$, the trajectories of the system* (6) *are asymptotically stable, otherwise they are unstable.*

Demostración. Let the Lyapunov function

$$
V(z_1,z_2,z_3) = z_1z_2 + z_3^2. \tag{12}
$$

Its derivative along the trajectories of the system (6) has the following expression,

$$
\frac{dV}{dt} = 2a_k(z_1z_2)^{n+1} + 2\lambda_3z_3^2 + \mathscr{R}(z_1,z_2,z_3),
$$

which is negative, since in $\mathscr{R}(z_1,z_2,z_3)$ the powers of degrees higher than those indicated in the initial part of the expression are grouped therefore, by the principle of the first approximation we can conclude that the equilibrium position is asymptotically stable. ■

In this case, it can be seen that the variation in the amount of drug in the body it decreases over time and the patient will remain in the baseline state.

Ejemplo 4 *Let be the following system of equations that simulates the process of elimination of toxins by means of the liver, the circulatory system and the kidneys*

$$
\begin{cases}
x_1' = -2x_1 + x_2 - x_1x_2^2x_3^2\\
x_2' = x_1 + 2x_2 - 9x_3 - 2x_1^2x_2x_3^4\\
x_3' = x_2 - 2x_3 - 3x_1^4x_2^2x_3.
\end{cases}
$$

In this case, the conditions indicated above are satisfied, the eigenvalues of fundamental matrix are $2i$, $-2i$ *and -2. The transformation* $X = SY$, *reduces the system to the form,*

$$\begin{cases} y_1' = y_1 + y_2 + 9y_3 - \mathscr{C}[2(y_1+y_2+9y_3)(y_1+y_2+y_3)^3 + \\ \quad +(y_1+iy_2)(y_1+y_2+y_3) - \\ \quad -27(y_1+iy_2)(y_1+y_2+9y_3)^3]\mathscr{A} \\ y_2' = (2-2i)y_1 + (2+2i)y_2 + \\ \quad +\mathscr{C}[2(y_1+y_2+9y_3)(y_1+y_2+y_3)^3 + \\ \quad +(y_2-iy_1)(y_1+y_2+y_3) + \\ \quad +27i(y_1+iy_2)(y_1+y_2+9y_3)^3]\mathscr{A} \\ y_3' = y_1+y_2+y_3 + \\ \quad +i(y_1+iy_2)^2(y_1+y_2+y_3)(y_1+y_2+9y_3)\mathscr{B} \end{cases}$$

where:

$\mathscr{A} = (y_1+iy_2)(y_1+y_2+y_3)(y_1+y_2+9y_3)$

$\mathscr{B} = -3(y_1+y_2+9y_3)^3 + y_1+y_2+y_3,$

$\mathscr{C} = \frac{1}{2} + \frac{i}{2}.$

Doing the exchange of variables (5) *the system is transformed in the quasi-normal form*

$$\begin{cases} z_1' = 2iz_1 - \frac{415}{2}z_1^4 z_2^3 + \frac{605i}{2}z_1^4 z_2^3 + 2z_1^3 z_2^2 - 4iz_1^3 z_2^2 + \dots \\ z_2' = -2iz_2 - \frac{415}{2}z_1^3 z_2^4 - \frac{605i}{2}z_1^3 z_2^4 + 2z_1^2 z_2^3 + 4iz_1^2 z_2^3 + \dots \\ z_3' = -2z_3 - 111iz_1^6 z_3 + 111iz_2^6 z_3 + \dots \end{cases}$$

here the series $h_1(z_1,z_2)$, $h_2(z_1,z_2)$, $h_3(z_1,z_2)$, $z_1P_1(z_1z_2)$, $z_2P_2(z_1z_2)$, $h_1^0(z_1,z_2,z_3)$, $h_2^0(z_1,z_2,z_3)$ *and* $Z_3(z_1,z_2,z_3)$ *are:*

$$\begin{aligned} h_1(z_1,z_2) = &\left(\tfrac{25}{2}+\tfrac{25i}{2}\right)z_1^7 + \left(\tfrac{71}{2}+\tfrac{175i}{2}\right)z_1^6 z_2 + \\ &+\left(\tfrac{955}{2}+\tfrac{955i}{2}\right)z_1^6 z_3 - \left(\tfrac{25}{2}+\tfrac{29i}{2}\right)z_2^7 - \\ &-\left(\tfrac{955}{2}+\tfrac{1043i}{2}\right)z_2^6 z_3 + \dots \end{aligned}$$

$$\begin{aligned} h_2(z_1,z_2) = &\left(-\tfrac{25}{2}+\tfrac{29i}{2}\right)z_1^7 - \left(\tfrac{179}{2}-\tfrac{95i}{2}\right)z_1^6 z_2 - \\ &-\left(\tfrac{955}{2}-\tfrac{1043i}{2}\right)z_1^6 z_3 + \left(\tfrac{25}{2}-\tfrac{25i}{2}\right)z_2^7 + \\ &+\left(\tfrac{955}{2}-\tfrac{955i}{2}\right)z_2^6 z_3 + \dots \end{aligned}$$

$$\begin{aligned} h_3(z_1,z_2) = &-3iz_1^7 + (6-15i)z_1^6 z_2 - 111iz_1^6 z_3 + 3iz_2^7 + \\ &+111iz_2^6 z_3 + \dots \end{aligned}$$

$$z_1P_1(z_1z_2) = -\left(\tfrac{415}{2}-\tfrac{605i}{2}\right)z_1^4 z_2^3 + \dots$$

$$z_2P_2(z_1z_2) = -\left(\tfrac{415}{2}+\tfrac{605i}{2}\right)z_1^3 z_2^4 + \dots$$

$$h_1^0(z_1,z_2,z_3) = \left(\tfrac{955}{2}+\tfrac{955i}{2}\right)z_1^6 z_3 - \left(\tfrac{955}{2}+\tfrac{1043i}{2}\right)z_2^6 z_3 + \dots$$

$$h_2^0(z_1,z_2,z_3) = -\left(\tfrac{955}{2}-\tfrac{1043i}{2}\right)z_1^6 z_3 + \left(\tfrac{955}{2}-\tfrac{955i}{2}\right)z_2^6 z_3 + \dots$$

$$Z_3(z_1,z_2,z_3) = -111iz_1^6 z_3 + 111iz_2^6 z_3 + \dots$$

Taking the Lyapunov function (12), *its derivative with respect to t is* $-415(z_1z_2)^4 - 4z_3^2 + \dots < 0$ *then, the equilibrium position is asymptotically stable.*

As the graphs show, the convergence of the total toxin concentrations in each of the compartments to the admissible concentrations is deduced, this indicates that the patient in a future time will remain in a basal state.

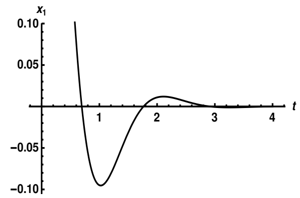


Figure 1. Graph of $x_1(t)$ in the **Example 4**

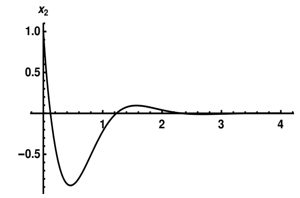


Figure 2. Graph of $x_2(t)$ in the **Example 4**

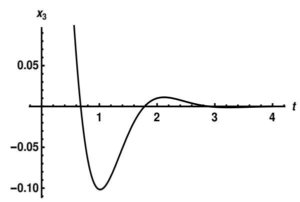


Figure 3. Graph of $x_3(t)$ in the **Example 4**

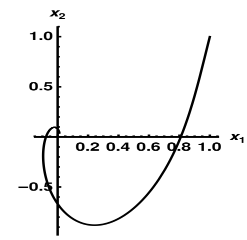


Figure 4. Graph of $x_1(t)$ vs $x_2(t)$ in the **Example 4**

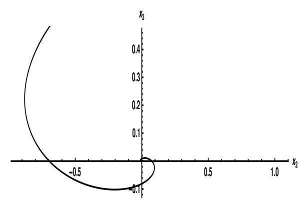


Figure 5. Graph of $x_2(t)$ vs $x_3(t)$ in the **Example 4**

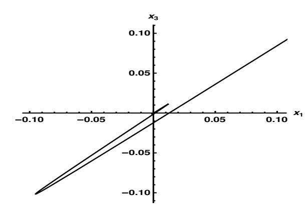


Figure 6. Graph of $x_1(t)$ vs $x_3(t)$ in the **Example 4**

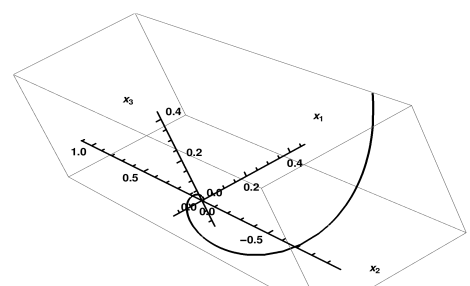


Figure 7. Graph of $x_1(t)$, $x_2(t)$ and $x_3(t)$ in the **Example 4**

2. Conclusions

We have carried out a qualitative study for the critical case in which a pair of pure imaginary eigenvalues and a negative one appear, for which the system was reduced to the quasi-normal form, thus facilitating its study and understanding of the process of elimination of toxins in a healthy person.

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