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The Interferon And Its Functions; Mathematical Modeling

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Abstract: In this article a general study is made about interferon, the production of interferon by the human body, thus the artificial incorporation into the human body, when necessary; its characteristics, its main function, detailing some aspects of the process of coping with the organism against viruses and diseases. A model is made by means of a system of differential equations that simulates the interaction process between the interferon and the contaminated cells, a qualitative study of that system is made, and conclusions are given regarding the functioning in a healthy person; in the critical case of a zero and a negative eigenvalue the system is reduced to the quasi-normal form to facilitate qualitative study.

Keywords: Interferon, immune system, mathematical modeling.

I. INTRODUCTION

Interferons belong to the class of cytokines and are glycoproteins secreted by cells of the immune system in order to combat elements foreign to the body, including parasites and viruses. There are several types of interferons, with alpha interferon being the most used as immunotherapy for cancer. Interferon is a molecule primarily produced by certain cells of the immune system, called mononuclear cells, and which exerts its modulating effects on the immune response by stimulating the proliferation and anti-cell toxicity of other cells of the immune system, including macrophages and cells NK (natural killer). In addition, interferon promotes cell differentiation of certain lymphocytes, called cytotoxic "T" lymphocytes, which act by destroying tumor cells or cells infected by viruses.

Finally, interferon induces the expression of substances on the surface of tumor cells, facilitating their recognition and destruction by other cells of the immune system. Alpha interferon has been used to treat some presentations of melanoma and kidney cancer, among other neoplasms. Recently, a new form of interferon-alpha, called pegylated interferon-alpha, has been researched, which apparently results in a lower incidence of side effects [10]. 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.

Interferons are glycoproteins that have several biological actions, including complex antiviral, immunomodulatory and antiproliferative effects. Its endogenous production and release occur in response to viruses and other inducers, with the exception of bacterial exotoxins, polyanions, some low molecular weight compounds and microorganisms with intracellular growth [10], [11], [12] and [18].

The first clinical trials conducted with Interferon date back to 1970 and used the type a produced in leukocytes from normal donors. A quantitative leap took place when using recombinant DNA techniques to produce the Human Recombinant Interferon a-2b. Recombinant interferon a-2b is a protein produced for use by injection. It is produced by a recombinant DNA technique expressed in Escherichia coli.

A wide range of RNA and DNA viruses are sensitive to Interferon, but the mechanism and degree of effect varies with the virus. Its antiviral activity is based on the fact that they combine with specific cellular surface receptors and inhibit the penetration, proliferation and release of viruses; the main effect being the inhibition of viral protein synthesis. The mechanism by which Interferon exerts its antitumor activity is not well understood. However, it is believed to exert an antiproliferative action on tumor cells and to modulate the host's immune response, which has an important role in antitumor activity. The biological activity of Interferon is restricted to a limited number of species besides man. "In vitro" studies have demonstrated antiproliferative and immunomodulatory activities. "In vivo" has been shown to inhibit tumor growth in mice.

The safety of using Interferon during pregnancy has not yet been established. It is recommended that it be used only if the potential benefits justify the potential risk to the fetus. Preliminary studies indicate dose-related menstrual irregularities and an increase in the rate of spontaneous abortions. It is not known whether the drug is excreted in human milk. Since many drugs are excreted in human milk and, due to the potential risks for serious adverse reactions in the infant, it is recommended that lactation or treatment be discontinued. Since experience with patients under the age of 18 is very limited, Interferon a-2b Recombinant Human should only be administered if the expected benefits outweigh the potential risks. When considering the use of Interferon as therapy, the physician must assess the need and usefulness of the drug against the risks of adverse reactions. Most adverse reactions are reversible and detectable in the beginning.

If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate measures taken, according to a physician's clinical assessment. The reinstatement of therapy should be carried out carefully, and the possibility of toxicity occurring again should be considered. It is recommended to carry out a control of patients who receive Interferon for a prolonged period and in high doses. The following laboratory tests should be carried out: complete blood count and white blood cell and platelet count; liver function test, enzyme measurement, electrolyte and calcium measurement [18].

Patients with previous cardiac abnormalities should be monitored with ECG during administration of Interferon, as in some cases arrhythmias may develop. As Interferon can affect the functions of the central nervous system, patients should be advised to pay attention or avoid driving vehicles or operating machinery, until treatment tolerance is confirmed. In some cases, patients who are depressed and / or have mental disorders, discontinuation of treatment should be considered. During the administration of Interferon, adequate hydration must be maintained, as the possibility of producing hypotension is related to fluid depletion. Water replacement may be necessary.

Several works, books and articles related to processes in human life are known; among these books dedicated to mathematical modeling we indicate the following [6], [7] and [8] in which real problems are simulated by means of differential equations and systems of equations, where in addition a certain treatment is done to give conclusions of the processes. In [8] the authors simulate the shape of the process of polymer formation in the blood using autonomous systems of differential equations of third and fourth order, giving conclusions on the formation of polymers and domains.

In [7] different problems of real life are treated by means of differential equations and systems of equations, all of them only in the autonomous case; where examples are developed and other problems and exercises are placed for them to be developed by the reader. The authors of [6] 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.

A compartment system essentially consists of a finite number of interconnected subsystems, called compartments, which exchange between and with the environment, amount of concentration of materials or substances, each compartment is defined by its physical properties; in particular, the dynamics of a drug in the human body were treated, not all drugs have the same path, but in the ingestible case in [1], sufficient conditions are given for their elimination; the case of an inhalable drug is treated in [3] and injectable in [2], in all cases after the qualitative study of the system used in the modeling the future situation of the process is predicted.

Insulin is a hormone produced by the pancreas; its function is to act in reducing glycemia (blood glucose rate). It is responsible for the absorption of glucose by cells; when insulin-glucose dynamics are not natural in the human body, diabetes can be produced, this dynamics in both a normal and diabetic person is modeled in [14] and [15]. The case of tissue replacement is simulated in [5], in particular the case of diabetic foot is seen.

Studies carried out by [24] have allowed the development of a mathematical model for the transmission of infectious diseases; this dynamic of contagion is modeled by means of sexual activity and, here, the concept of individuals susceptible to contagion with the disease is used.

The authors in [13], developed a mathematical model on the transmission of blennorrhagia, where they study exhaustively the behavior of the trajectories of the system that simulates the process in a neighborhood of the equilibrium points, offering conclusions regarding the future of the disease; giving in addition a method for the identification of the coefficients, where it has a series of data corresponding to a certain population.

In addition, works [19] and [20] referring to the transmission of sexually transmitted diseases are indicated. The case in which homosexuals appear in the transmission of sexually transmitted diseases is dealt with in [21], where conclusions are reached regarding the state of the disease at a given time.

II. MODEL FORMULATION

In order to simulate the process of the interaction between interferon in the development of the organism's defenses in the presence of viruses and contaminated cells, it is necessary to take into account some basic principles regarding this process, firstly that the contaminated cells are added proportionally its concentration and decreases with the addition of interferon; that the variation of the interferon is added with the addition of the contaminated cells and decreases with its own concentration, because it increases according to what the organism needs.

In order to formulate the model using a system of differentiable equations, the following variables will be introduced:

-$\tilde{x}_1$ is the total density of cells contaminated at the time t.

-$\tilde{x}_2$ is the total density of interferon at the moment t.

In addition, $\bar{x}_1$ and $\bar{x}_2$ the values of the contaminated cells and the interferon respectively.

Here the variables will be introduced x_1 and x_2 defined as follows: $x_1 = \tilde{x}_1 - \bar{x}_1$ and $x_2 = \tilde{x}_2 - \bar{x}_2$ so if $\bar{x}_1 \to 0$ and $\bar{x}_2 \to 0$ the following conditions would be met $\tilde{x}_1 \to \bar{x}_1$ and $\tilde{x}_2 \to \bar{x}_2$, which would constitute the main objective of this work. In this way the model will be given by the following system of equations,

$$\begin{cases} x_1' = a_1 x_1 - a_2 x_2 + X_1(x_1, x_2) \\ x_2' = a_3 x_1 - a_4 x_2 + X_2(x_1, x_2) \end{cases} \qquad (1)$$

Where $X_i(x_1, x_2)$, $(i = 1,2)$ 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,

$$X_i(x_1, x_2) = \sum_{|p| \geq 2} X_i^p x_1^{p_1} x_2^{p_2} \; (i = 1,2), |p| = p_1 + p_2$$

The coefficients indicated in the system have the following meaning.

a_1 represents the growth of contaminated cells in the absence of interferon.
a_2 represents the decrease of cells contaminated by the action of interferon.
a_3 represents the growth of interferon by the presence of contaminated cells.
a_4 represents the natural degrowth of interferon in the absence of contaminated cells.

The characteristic equation of the matrix of the linear part of the system (1) has the following form,

$$\begin{vmatrix} a_1 - \lambda & -a_2 \\ a_3 & -a_4 - \lambda \end{vmatrix} = 0$$

This expression is equivalent to,

$$\lambda^2 + (a_4 - a_1)\lambda + (a_2 a_3 - a_1 a_4) = \mathbf{0} \qquad \mathbf{(2)}$$

In this case, applying the first approximation method, the following result is arrived at.

Theorem1: The null solution of the system (1) is asymptotically stable if and only if the following conditions are met: $a_4 > a_1$ and $a_2 a_3 > a_1 a_4$, otherwise, it is unstable. The proof is a direct consequence of the conditions of Hurwitz's theorem.

Note1: If the conditions $a_4 > a_1$ and $a_2 a_3 > a_1 a_4$ are satisfied, then the total concentrations of contaminated cells and interferon will converge to allowable values and therefore the patient will not have any laughs due to the disease he is suffering from.

In this model it is absolutely possible the case where $a_4 > a_1$ and $bc = ad$ this causes the matrix of the linear part of the system (2) to have a zero eigenvalue and a negative one; this constitutes a critical case, it is to say a case that cannot be solved by applying the method of first approximation. In that case, by means of a non-degenerate transformation $X = SY$, the system (2) can be transformed into the system,

$$\begin{cases} y_1' = Y_1(y_1, y_2) \\ y_2' = \lambda_2 y_2 + Y_2(y_1, y_2) \end{cases} \qquad \mathbf{(3)}$$

Where $\lambda_2 < 0$ as the system (3) constitutes a critical case, for which the first approximation method cannot be applied, in this case the second Liapunov method will be applied once this system is reduced to the quasi-normal form.

Theorem2: The exchange of variables,

$$\begin{cases} y_1 = z_1 + h_1(z_1) + h^0(z_1, z_2) \\ y_2 = z_2 + h_1(z_1) \end{cases} \quad \textbf{(4)}$$

transforms the system (3) into a quasi-normal form,

$$\begin{cases} z_1' = Z_1(z_1) \\ z_2' = \lambda z_2 + Z_2(z_1, z_2) \end{cases} \quad \textbf{(5)}$$

Where h^0 and Z_2 cancel each other out $z_2 = 0$.

Demonstration: Deriving the transformation (4) along the trajectories of the systems (3) and (5) the system of equations is obtained,

$$\begin{cases} p_2\lambda h^0 + Z_1(z_1) = Y_1 - \frac{dh_1}{dz_1}Z_1 - \frac{\partial h^0}{\partial z_1}Z_1 - \frac{\partial h^0}{\partial z_2}Z_2 \\ \lambda h_2 + Z_2 = Y_2 - \frac{dh_2}{dz_1}Z_1 \end{cases} \quad \textbf{(6)}$$

To determine the series that intervene in the systems and the transformation, we will separate the coefficients of the powers of degree $p = (p_1, p_2)$ in the following two cases: CaseI) Making in the system (6) $z_2 = 0$, is to say for the vector $p = (p_1, 0)$ the system results,

$$\begin{cases} Z_1(z_1) = Y_1(z_1 + h_1, h_2) - \frac{dh_1}{dz_1}Z_1 \\ \lambda h_2 = Y_2(z_1 + h_1, h_2) - \frac{dh_2}{dz_1}Z_1 \end{cases} \quad \textbf{(7)}$$

The system (7) allows determining the series coefficients, Z_1, h_1 and h_2, where for being the resonant case $h_1 = 0$, and the remaining series are determined in a unique way. CaseII) For the case when $z_2 \neq 0$ of the system (6) it follows that,

$$\begin{cases} p_2\lambda h^0 = Y_1(z_1 + h_1, h_2 + z_2) - \frac{\partial h^0}{\partial z_1}Z_1 - \frac{\partial h^0}{\partial z_2}Z_2 \\ Z_2 = Y_2(z_1 + h_1, h_2 + z_2) \end{cases} \quad \textbf{(8)}$$

Because the system series (5) are known expressions, the system (8) allows you to calculate the series h^0 and Z_2. This proves the existence of variable exchange.

If in system (5) the function Z_1 admits the following development in power series:

$$Z_1(z_1) = \alpha z_1^s + \ldots$$

Where α is the first non-zero coefficient and s is the corresponding power.

Theorem3: If $\alpha < 0$ and s is odd, so the trajectories of the system (5) are asymptotically stable, otherwise they are unstable.

Demonstration: Consider the Lyapunov function defined positive,

$$V(z_1, z_2) = \frac{1}{2}(z_1^2 + z_2^2)$$

The function V is such that its derivative along the trajectories of the system (5) has the following expression,

$$V'(z_1, z_2) = \alpha z_1^{s+1} + \lambda z_2^2 + R(z_1, z_2)$$

The derivative $V'(z_1, z_2)$ function V, is defined as negative, because in function $R(z_1, z_2)$ there are only terms with a degree greater than $s + 1$ with respect to z_1 and with a degree greater than the second with respect to z_2, so the null solution of the system (5) has to be asymptotically stable, thus showing the teorama3.

Note2: If the conditions $\alpha < 0$ and s is odd are satisfied, then the total concentrations of contaminated cells and interferon will converge to acceptable values and therefore the patient will be in a baseline state, not running any type of risk.

Example: Whether the System of equations,

$$\begin{cases} x_1' = -x_1^3 - x_1^4 \\ x_2' = \sqrt{2}x_2 - x_1^2 x_2^3 \end{cases} \quad \textbf{(7)}$$

The system (7) satisfies the conditions indicated above. A theoretical study could be done using Liapunov's second method to draw conclusions, but here the graph of the trajectories is made to prove this theory.

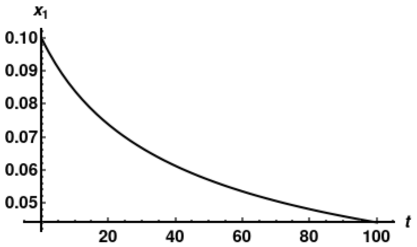

Fig. 1: Graph of x_1 against t.

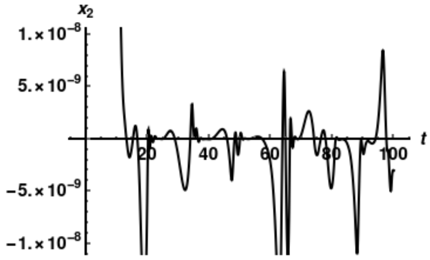

Fig. 1: Graph of x_2 against t.

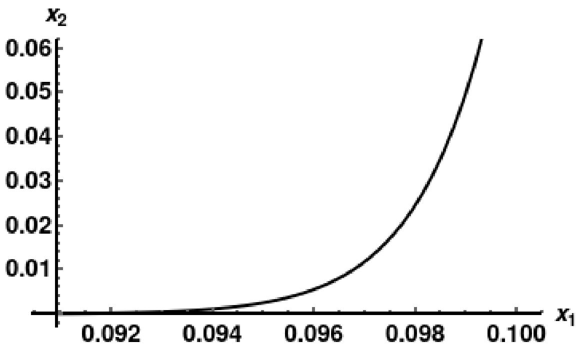

Fig. 1: Graph of x_2 against x_1.

In the graph of x_2 against x_1 if the convergence of trajectories to the origin of coordinates is perceived, this is in line with what was seen before. This makes the total concentrations of interferon and contaminated cells converge to allowable values, this corroborates what has been demonstrated in theory. In these conditions the patient will remain in a basal state, however these conditions are satisfied.

III. CONCLUSION

1. If $a_4 > a_1$ e $a_2 a_3 > a_1 a_4$ then the concentrations of contaminated cells and interferon converge to allowable values.

2. The critical case considered when $a_4 > a_1$ and $a_2 a_3 = a_1 a_4$ it is absolutely possible, in this case you have a zero and a negative eigenvalue.

3. Theorem2 gives the methodology to reduce the system to the quasi-normal form for the critical case when a zero and a negative eigenvalue appear, this allows to make a qualitative study without great difficulties.

4. If $\alpha < 0$ and s is unique then, for the critical case considered, the concentrations of contaminated cells and interferon converge to allowable values; otherwise, the patient would have to be in crisis at any time, in which case measures would have to be taken to avoid worse consequences.

5. The graph corresponding to the example shown shows that when the conditions of theorem3 are met, the total concentrations of the contaminated cells and interferon converge to allowable values.

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