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Numerical Simulation of HIV Model

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Abstract. *Since the decade of 1980, when HIV virus was discovered, many mathematical models have been developed. Some of them deal with the epidemiology of the disease, studying the interplay of the susceptible populations to HIV infection. Other models, approach the dynamics of the cells populations that are susceptible to infection, cells populations that become infected due to virus, viral load and the virus populations that suffer mutations from the antiviral therapy. Using the resources of the numerical simulations, our goal in this work, is to analyze the problem in distinct situations: with or without antiviral therapy in different stages of the process. We create a graphical interface on Microsoft Visual C++ language that implements several numerical methods. This interface lets, for the boarded model, change all of the parameters and initial conditions; and the numerical solution graphs are shown. In the model studied are included the immune response and the drug-therapy that act during the DNA transcription into the infected host-cell. It was possible, using the interface we made, to identify which parameters were more sensitive to applied variations.*

Keywords. *numerical simulation, variations of the parameters, HIV dynamics, immune response, drug-therapy.*

1. Introduction

In the last twenty years many mathematical models have been developed with the intention to understand phenomena associated to the HIV-1 infection, its impacts in the immune system and the decline of the counting of CD4+ T cells. Stochastic models can be used to describe initial stages of the disease, when a few virus and infected cells exist or in situations where the variability of individuals is relevant. On the other hand deterministic ones analyze the changes in the average of the cells number and are more applicable to the posterior stages of the HIV-1 infection process in which the populations of cells are great in number, Perelson et al (1999)

The numerical simulations associated to the mathematical modeling allow to evaluate distinct situations such as initial conditions in steady state, quasi-steady state or unsteady state, to modify parameters and constants of the model, even those that are badly defined a priori, to introduce drug-therapy at different moments of the HIV replication cycle and, moreover, to analyze parameters that induce alterations during the time of the infection dynamics through the process of the disease.

The biological phenomenon caused by the AIDS virus is extremely complex and still related questions exist that are not totally clarified. One of the basic characteristics is associated with the mechanisms of the immune system and with the fight against the infection by the host organism during the disease.

2. Modeling

Some aspects of the HIV infection can be considered at the moment we developed a mathematical model. They are: replication cycle, immune response and the drug-therapy effects.

2.1. Replication cycle

The Human Immunodeficiency Virus (HIV) is a retrovirus, a double strand RNA virus. Its main targets are the helper T cells, the macrophages and the dendritic cells. All these cells posses a receptor called CD4 that allow the virus fix on the host cell surface. After this, the viral RNA is released and then its transcription in DNA through the enzyme reverse transcriptase occurs. With the aid of another enzyme, called integrase, this DNA becomes then integrated to the host cell chromosome DNA.

Provirus, the viral DNA, can control the production of the new viruses that burst the host cell, characterizing the active infection. Alternatively, this integrated DNA cannot produce new particles of HIV virus but it can remain hidden in the host cell chromosome as provirus, characterizing this way the latent infection, and impeding its detection by the immune system.

Virus ability to remain as a provirus or latent virus is one of the reasons the antibodies anti-HIV developed by the infected individuals fail in inhibiting the progress of the infection. The virus also can move itself from an infected cell to another adjacent one not infected, through the fusing process, and then hiding itself from the immune system too.

In particular, the RNA viruses with the stage of the reverse transcription have a high rate of genetic mutation in relation to the DNA viruses. As a result, the HIV genome suffers changes many times per day in an infected person what makes the diagnostic vaccines development and tests difficulty.

But, how the immune system responds to the antigen presence, or any foreign substance?

2.2. Immune response

The immune response is basically characterized two ways: cellular immune response and the humoral immune response.

As soon as the antigen enters the body, it is found by the macrophages, cells that examine the foreign particles and present its results to CD4 positive T lymphocytes, the CD4+ T cells. The T letter reffers to the thymus, an organ responsible for the maturation of this cell after it have migrated from the bone marrow where it is produced and the term CD4 denoted an protein that exists on the cell surface. These cells usually are called T helper cells and work as the center of command of the immune system. Initially, the proliferation of CD4+ T cells occurs, in order to congregate efforts against the pathogen. If these cells consider that an immune response must be given, then a signal is sent. This signal can activate as much the cellular response as the humoral response.

Moreover, the activation of a second group of T cells, the CD8 positive T lymphocytes, CD8+ T cells, known as T killer cells, occurs. These cells are responsible for looking for and destroying the infected cells with that pathogeneses.

In the humoral immune response, mediated by antibodies, the CD4+ T cells put in action a third group of cells, the B lymphocytes (B cells). These are the blood cells that produce the antibodies. The main function of the antibodies is to destroy pathogeneses and, therefore to assist in the elimination of antigens.

Once the immune response is successful, some cells keep an antigen memory register. These cells are called memory cells. If the same pathogeneses, or a like one, is reintroduced in the host organism, a more aggressive and much faster response is executed, and the antigen is eradicated in more efficient and quicker way.

The classification of the progress of the HIV infection, according to the Centers for Disease Control and Prevention, an American Public Service of Health agency, responsible for epidemiological information, is based on the counting CD4+ T cells population. When the counting of these cells, that is normally around 1000 mm^{-3}, is lesser or 200 mm^{-3} equal in a HIV infected patient, then AIDS is diagnosed.

As we saw, T cells, in particular CD4+ T, have a central role in the immunological system equilibrium. Therefore, its loss provokes disastrous effect in the functioning of the immune response and allows the immunodeficiency that characterizes AIDS. The reason for the fall of counting CD4+ T is unknown, as well as the processes that determine its rate of decline, Perelson et al (1999).

The incubation period of the disease that results from the primary infection among the patients is variable, from 3 to 6 weeks; and the duration of the symptoms from the HIV infection primary is also variable, Coffin et al (1997). Giving continuity to this phase, a long or short period of the infection for non-symptoms HIV can be followed, where the cells and body fluids shelter the virus. The reason for this period of time still remains unknown; even so this seems to be on the changes in the counting of CD4+ T cells.

2.3. Drug-therapy effects

The drug-therapy effects are related to the different moments of the replication cycle of the HIV.

Inhibitors that act during the process of viral transcription in the infected cell are called reverse transcriptase inhibitors. Inhibiting the effect of this enzyme the HIV can penetrate into the cell; however it will not infect it successfully: the copy of the genome of the viral DNA will not be made and, therefore the cell will not replicate itself. The transcriptase reverse inhibitors are classified in two groups: the nucleoside analog (as the AZT) and the nonnucleoside analog.

Now, the protease inhibitors make the infected cells produce viral noninfectious particles. Nevertheless, the particles that have already been produced remain infectious.

All of these inhibitors used separately posses the same problem: the virus quickly develops resistance, Nowak et al (2000) and Coffin et al (1997). Then, the adopted strategy most common for HIV-positive patients is a triple-therapy administration, e.g., using a combination of drugs, one protease inhibitor with two of reverse transcriptase, simultaneously. Still it is in debate when the treatment must be initiated.

Mathematically, to introduce an inhibitory effect, means to apply the parameters, which model pertinent biological characteristics, perturbations. It is possible to analyze the dynamics of the infection in a patient who is in steady state, or quasi-steady state or unsteady state, before the treatment being initiated and, furthermore, it still can be observed aspects of eradication of the viral population a long period with the different strategies of treatment.

3. Model

Kirschner et al (1996) developed the model that we will approach. In it has the inclusions of an immune response from the host organism, therefore, inside the T cell population is already inserted the CD8+ T cell population; and the monotherapy effects are modeled too.

During the immune response, the CD8+ T cells cannot become infected, once its function is to eliminate the resident viruses from the infected cells. Then,

$$\frac{dT}{dt} = s(t) - d_T T + p\frac{TV}{C+V} - z(t)k_V TV \quad (1)$$

$$\frac{dT^*}{dt} = z(t)k_V TV - \delta T^* - p\frac{T^*V}{C+V} \quad (2)$$

$$\frac{dV}{dt} = Np\frac{T^*V}{C+V} - k_T TV + g_V\frac{V}{b+V} \quad (3)$$

where

$$z(t) = \begin{cases} 1 & \text{, out of the treatment} \\ P(t) & \text{, during the period of treatment and } 0 < P(t) < 1. \end{cases} \quad (4)$$

with the initial conditions $T(0)$, $T^*(0)$ and $V(0)$.

The variables and parameters represent:

T	uninfected CD4+ T cell population
T^*	infected CD4+ T cell population
V	virus population
$s(t)$	source of new CD4+ T cells from the external sources as thymus
d_T	death rate of uninfected CD4+ T cell population
p	maximal proliferation of the uninfected CD4+ T cell population
k_V	rate CD4+ T cells became infected by free virus
δ	death rate of infected CD4+ T cell population
N	number of virus particles produced by bursting infected cells
k_T	rate CD8+ T cells *kill* virus
g_V	growth rate of external virus source other than T cells
C	half-saturation constant of the proliferation process
b	half-saturation constant of the external viral source

The initial conditions, constants and parameters values used are given in Kirschner et al (1996) and described in the Tab. (1).

Tabel 1. Initial conditions, constants and parameters of the model

Initial Conditions	
$T(0)$	1000 mm^{-3}
$T^*(0)$	0 mm^{-3}
$V(0)$	0.001 mm^{-3}
Parameters and Constants	
$s(t)$	$5 + \frac{5}{1+V}$
p	0.01 day^{-1}
d_T	0.02 day^{-1}
δ	0.24 day^{-1}
g_V	Varies
k_V	2.4 x 10^{-5} mm^3 day^{-1}
k_T	7.4 x 10^{-4} day^{-1}
C	100 mm^{-3}
b	10 mm^{-3}
N	1000

For the first term of the Equation (1),

$$s(t) = 5 + \frac{5}{1+V} \quad (5)$$

a function is chosen that decreases as the viral load increases and it is assumed that the uninfected T cells population is reduced by half. The term

$$p\frac{TV}{C+V} \quad (6)$$

denotes the proliferation of T cells where C is a constant of the saturation process. The used idea in this case it is that as much CD4+ T cells as CD8+ T cells will be stimulated by the HIV infection, however, knows that these cells in activity stimulate other CD4+ T and CD8+ T cells, which can or not be specific to HIV, Kirschner et al (1996).

The term, $k_V TV$, symbolizes the HIV infection that depends on the encounters between the T and V populations, represented by k_V. In order to introduce the effect of monotherapy using a reverse transcriptase inhibitor, the k_V parameter is multiplied by a $z(t)$ function, that acts only in the period of treatment. When the treatment is in proceeding, the given model is capable to imitate the effect of this inhibitor; therefore the viral infectivity is reduced.

In the equation (3), the term, $k_T TV$, represents a loss of viruses because of the action of pertaining T CD8+ cells to the immune system, where k_T is the rate under which these same cells eliminate virus. Finally, the last term symbolizes the growth of viral population, from other infected cells, such as macrophages. The growth rate is given by g_V, and the half-saturation constant of this process is b. This term also contains the viral natural death. During the course of infection before the decrease of the CD4+ T cells number, the quantity of virus is relatively small. Hence, this term is linearly approached for $g_V V$ and can easily enclose the virus clearance, says cV. As the disease proceeds the quantity of virus increases and, according to the Kirschner et al (1996), this cannot be modeled by a linear term.

During the course of the infection, the patient passes from an initial state to an infected steady state, usually referred as the period of latency and from this, due to mechanisms of the suitable infection, it reaches the AIDS. In the model, the term that produces this effect is g_V.

The Figure (1) shows numerical simulations with the next values: $g_V = 5$ (■), $g_V = 20$ (■) without the application of an inhibitor.

During the course of the infection, for $g_V = 5$ (■), we observe that T cells population soon suffer a fall in first days from the infection stabilizing itself after that. The infected cells and the viruses possess similar dynamic presenting changes not much relevant at the beginning and suffering increases well pronounces later. For $g_V = 20$ (■), we see the complete course of the HIV infection culminating in AIDS. The virus population increases without limits, the CD4+ T cells decay to a minimal value of the order of 10^{-1} mm^{-3}.

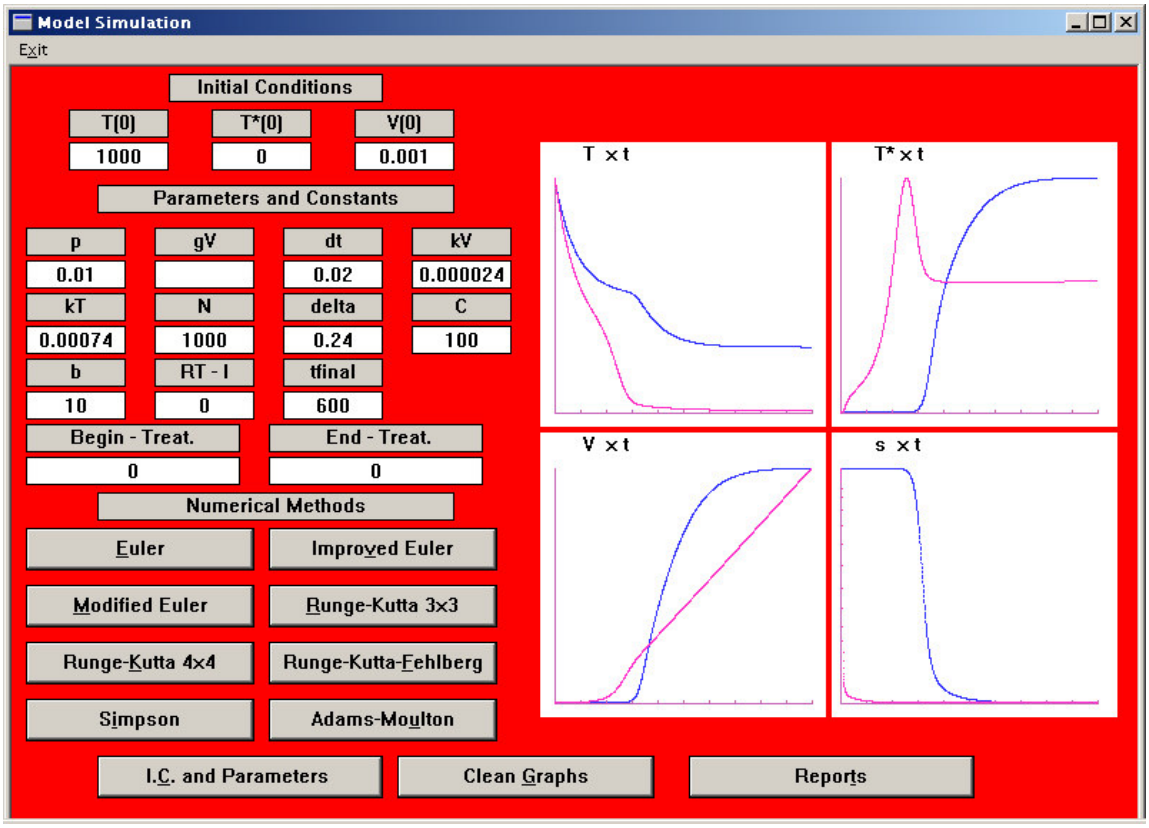

Figure 1. Numerical simulation to the model: $g_V = 5$ (■), $g_V = 20$ (■), $t_{final} = 600$ *days*.

We take the function $z(t) = (1- \eta_{RT})P$, with $0 < P(t) = P < 1$, during the period of treatment. The term η_{RT} represents the efficiency of the inhibitor that is being applied. In the interface this term is denoted by RT-I and can be taken as any value between 0 and 1. For simplification, in the monotherapy simulations we are considering that $P(t) = P = constant$, for several beginnings of treatment. One of the treatment starting at 100 *days* and the other one in 200 *days*, both with a period of treatment of 250 *days*. The Figure (2) presents the attained results.

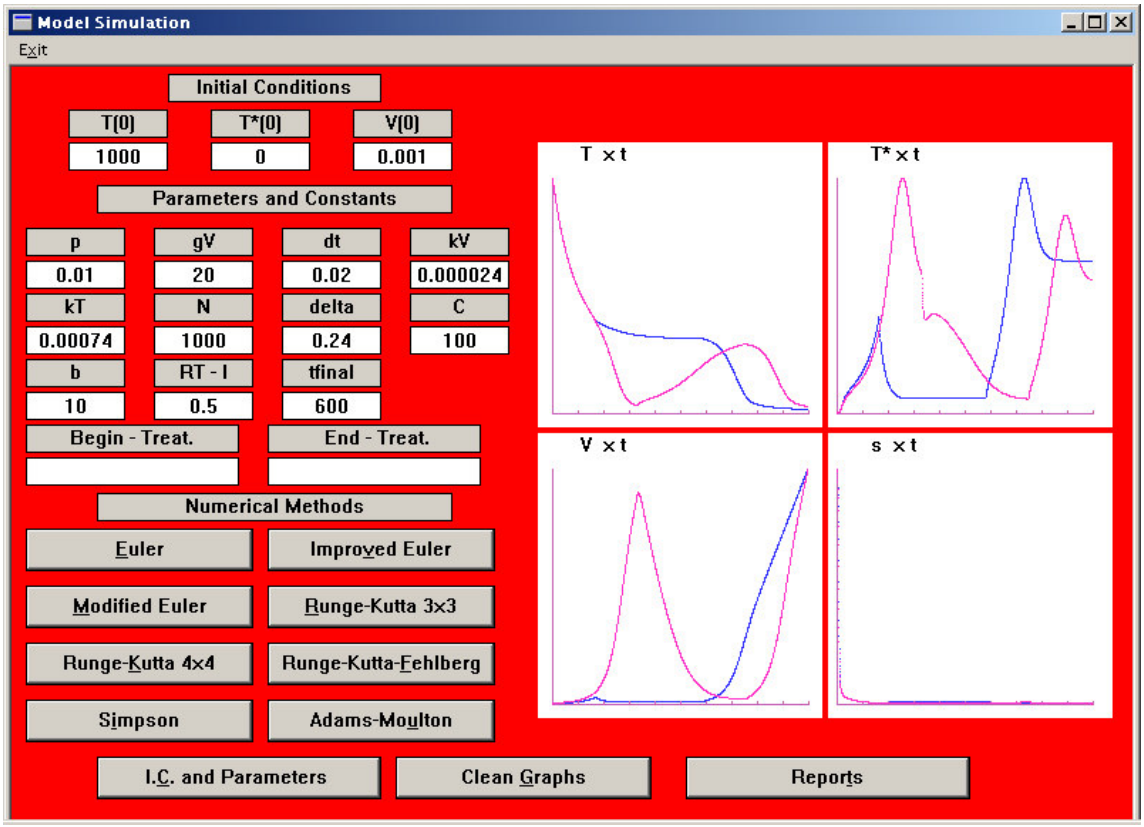

Figure 2. Model simulation: periodic treatments with beginnings at 100 *days* (■) and at 200 *days* (■)

In the Figure (2), we see initially, a rough decay in the T cells population, an increase as much viral load, V, as the infected cells, T^*, occurs, followed by a recovery of the T cells, and a decrease for V and T^* populations, if the treatment is initiated later (■).

For both cases, the viral load tends to increase unlimitedly as the time increases, reaching in $t_{final} = 600$ *days*, values of the order of 10^5 mm^{-3}.

The treatment that would be initiated later it was capable to lead a recovery in the counting of the T cells population and also it was capable to lead a decrease the virus population even though for a short period of time (See Fig. 2 (■)). The same behavior is not kept if the treatment is initiated early (See Fig. 2 (■)).

4. Simulations and results

We are interested in studying the behavior of the numerical solutions when we apply effect of perturbation in the parameters of the model. For in such a way, it is necessary to analyze the convergence and the stability of the numerical results.

A graphical interface was developed for us in Guedes et al (2001), using *Microsoft Visual C++*, which solves the system given by Eq. (1), Eq. (2) and Eq. (3), with different numerical methods.

The convergence and the stability of each numerical method are assured, because the integration step is computed for each set of parameters from initial approximation attained through the local discretization error of the Euler's method. With our interface it is possible, in one same graph, to show off the tests proceeding from different variations applied in the parameters and the interpretation of them is direct.

For the most parameters that we analyze, we use the following conditions for the variations: of ±10%, ±20% and ±50%. We fix different periods of treatment, and we admitted for the $z(t)$, only the variations of -10%, -20% e -50%, because the others there are not sense.

The tests have been made assuming that one parameter varies, while the others remain unchanged in relation to the original data given from Kirschner's et al (1996) paper.

The initial conditions have been taken as $T(0) = 1000$ mm^{-3}, $T^*(0) = 0$ mm^{-3} and $V(0) = 0.001$ mm^{-3}. This means that we are studying a recently infected individual that is not in steady state, nor close it. The final time has been taken as 3650 *days*. As the value of g_V can be modified depending on the situation that desire to analyze, we choose $g_V = 20$. The justification for this choice is the fact of that as bigger the value of g_V is, more quickly will occur progression to AIDS (See Fig. (1)).

5. Variations in the parameters

The data for each parameter under variation are described in the Tab. (2). Value 0% denotes the correspondent to the original value of each parameter for the model.

As we said before, the numerical simulations have been made assuming that one parameter varies, while the others remain unchanged in relation to the original data given from Tab. (1).

We decide to comment groups of different parameters, because they got similar behaviors, except for the scale of values.

Table 2. Variations in the parameters given in the model, with $g_V = 20$.

	Parameters						
	-50%	**-20%**	**-10%**	**0%**	**10%**	**20%**	**50%**
p	0.005	0.008	0.009	0.01	0.011	0.012	0.015
d_T	0.01	0.016	0.018	0.02	0.022	0.024	0.03
δ	0.12	0.192	0.216	0.24	0.264	0.288	0.36
g_v	10	16	18	20	22	24	30
k_V	1.20E-05	1.92E-05	2.16E-05	2.40E-05	2.64E-05	2.88E-05	3.60E-05
k_T	3.70E-04	5.92E-04	6.66E-04	7.40E-04	8.14E-04	8.88E-04	1.11E-03
C	50	80	90	100	110	120	150
b	5	8	9	10	11	12	15
N	500	800	900	1000	1100	1200	1500
$z(t)$	0.5	0.8	0.2	1	-	-	-

5.1. Variations in the parameters p, k_V and N

The Figure (3), presents the results of the numerical simulations when variations as the described ones for the Tab. (2) are applied to parameters p, k_V and N.

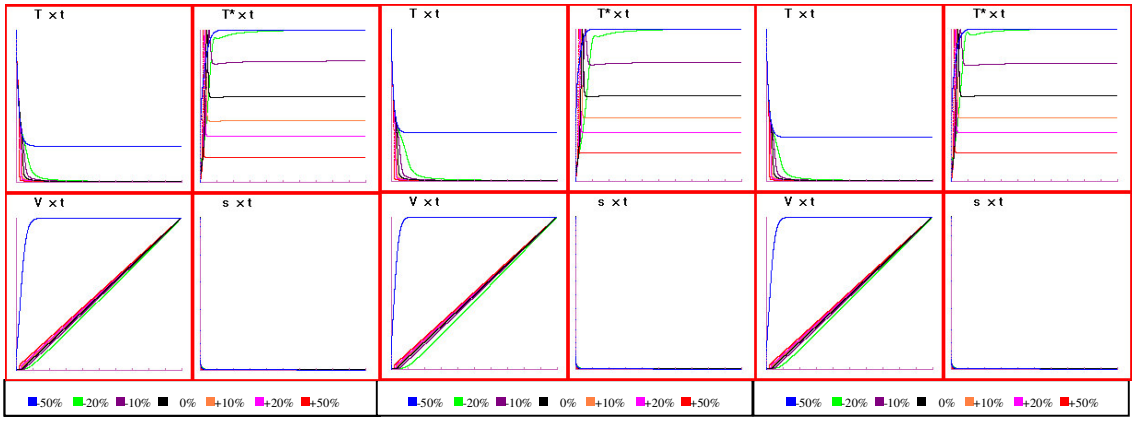

Figure 3. Variations in the parameters p, k_V and N, respectively.

We observe that the behavior of the solution will be modified as lesser the value of any one of these parameters is.

The T cells population, T, tends to diminish quickly, however stabilizing in a 200 mm^{-3} superior value, in the early years. The viral load and the infected cells, V and T^* respectively, increase considerably soon in the initial years, but after they reach a stability in a value above of 10^2 mm^{-3} for V and of the order of 10^0 for T^*.

On the other hand, as bigger the variation is applied in any one of the parameters, p, k_V and N, more quickly the decline in the counting of T cells will occur reaching a value of the order of 10^{-1} and, therefore, 200 mm^{-3} inferior. The virus population, V, will increase reaching in t_{final} = 3650 *days* a value of the order of 10^5. The infected cells, T^*, increase quickly arriving at a value of order 10^2 (t ≈ 70 *days*) and diminishing until reaching a stability.

5.2. Variations in the parameters δ and k_T

Applying to the parameters δ and k_T variations as the described ones for the Tab. (2), we got the results shown in the Fig. (4).

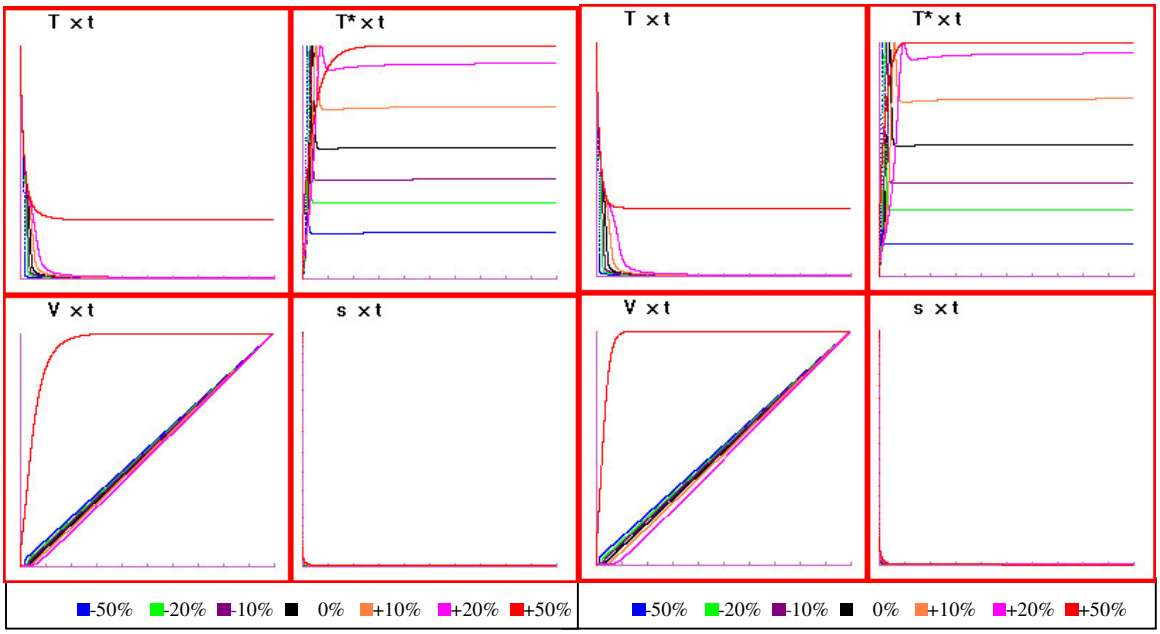

Figure 4. Variations in the parameters δ and k_T, respectively.

We notice that the resultant behaviors in this case are inverse to the gotten ones in the previous case. Or either, as bigger the value of any one of these parameters is, the T cells, T, tend to diminish quickly and soon reaching stability in a superior 200 mm^{-3} value. The populations of virus and infected cells, V and T^* respectively, increase considerably in early years, reaching after that a stability in a value above the 10^2 mm^{-3} for V and of 10^0 mm^{-3} for T^*.

On the other hand, how lesser the variation applied in any one of the parameters, δ and k_T, more quickly the viral load, V, will increase reaching in $t_{final} = 3650$ *days* a value of the order of 10^5 and will still occur the decline in the T cells population reaching a value of the 10^{-1} order. The infected cells, T^*, will increase quickly and soon they will decay ($t \approx 48$ *days*) reaching a stability lesser than 10^2 mm^{-3}.

5.3. Variations in the parameters d_T and g_V

In the Figure (5), we present the results of the variations applied to the parameters d_T and g_V, respectively.

For the parameter d_T, we observe that the behavior of the solution will be modified as lesser the value of the variation is applied in it.

The T cells population will suffer two declines: first of them the slowest one in the first years in relation to the second one. The virus population, V, will not suffer relevant modifications in the early years, following an unlimited increase from this point up. For the infected cells population, T^*, we see an enormous increase before the first year, decaying quickly and reaching a stability around the 10^0 mm^{-3}.

Variations that increase the original value of the parameter d_T, provoke only alterations in the infected cells population, T^*. The bigger the variation the fast increase of this population, followed by a stability ($t \approx 128$ *days*) of the order of 10^1.

The dynamics of the solution will be modified as lesser the value of the variation is applied in the parameter g_V. The T cells population will suffer two declines: the first of them in the early years is the faster one in relation to the second one.

The infected cells population, T^*, show a slower increase in the beginning, then decaying and reaching a stability around the 10^1 mm^{-3}. The virus population, V, will not suffer relevant modifications in the first year, followed by an unlimited increase from this point on.

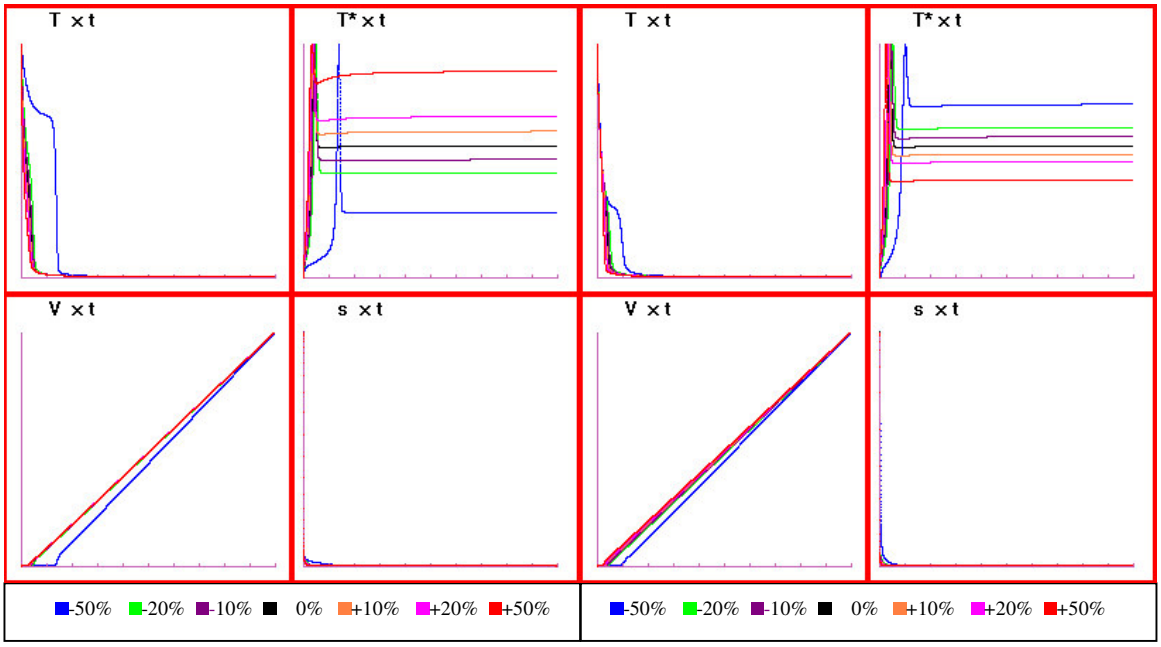

Figure 5. Variations in the parameters d_T and g_V, respectively

5.4. Variations in the parameters *C* and *b*

The results of the applications of variations in parameters *C* and *b* are represented in the Fig. (6).

For parameter *b* no relevant alteration in the dynamics of populations *T*, T^* and *V* was observed. For parameter *C*, we notice that populations *T* and *V* do not show modifications in its original behaviors.

The population of infected cells, T^*, on the other hand presents some alterations in relation to the reached stability. However, all they are of the order of 10^1.

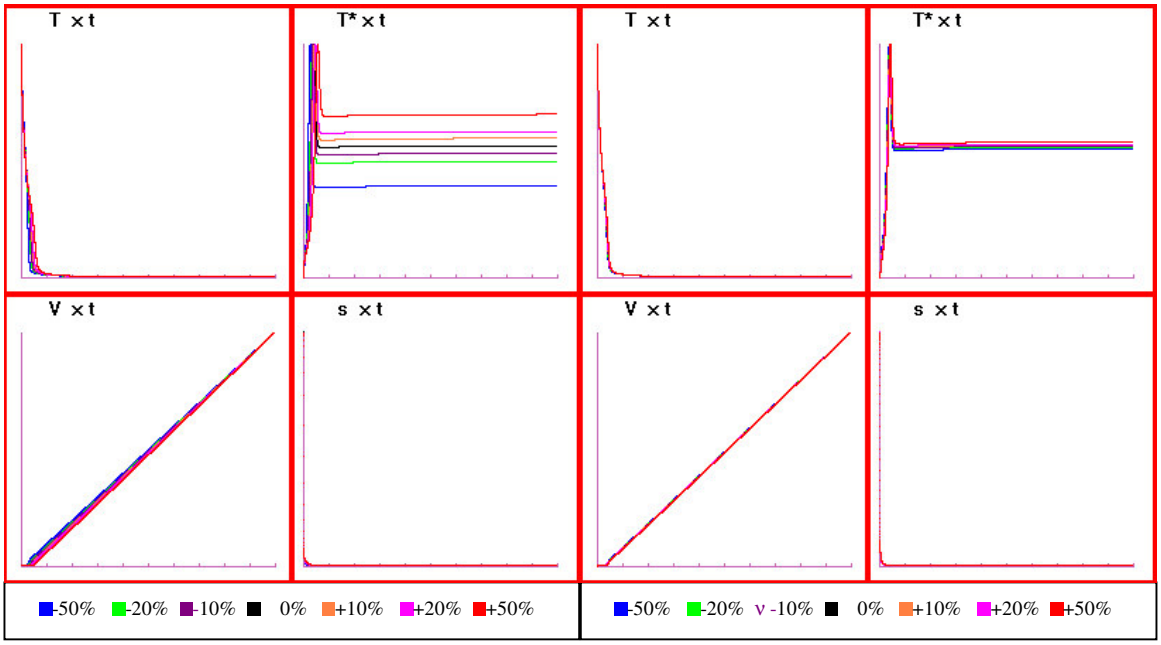

Figure 6. Variations in the parameters *C* and *b*, respectively

5.4. Variations in the parameter *z(t)*

In the Figure (7), we can see the variations applied in the parameter *z*(*t*) at two different periods of treatment: one of them from 100 to 350 *days* and the other one from 200 to 450 *days*, respectively.

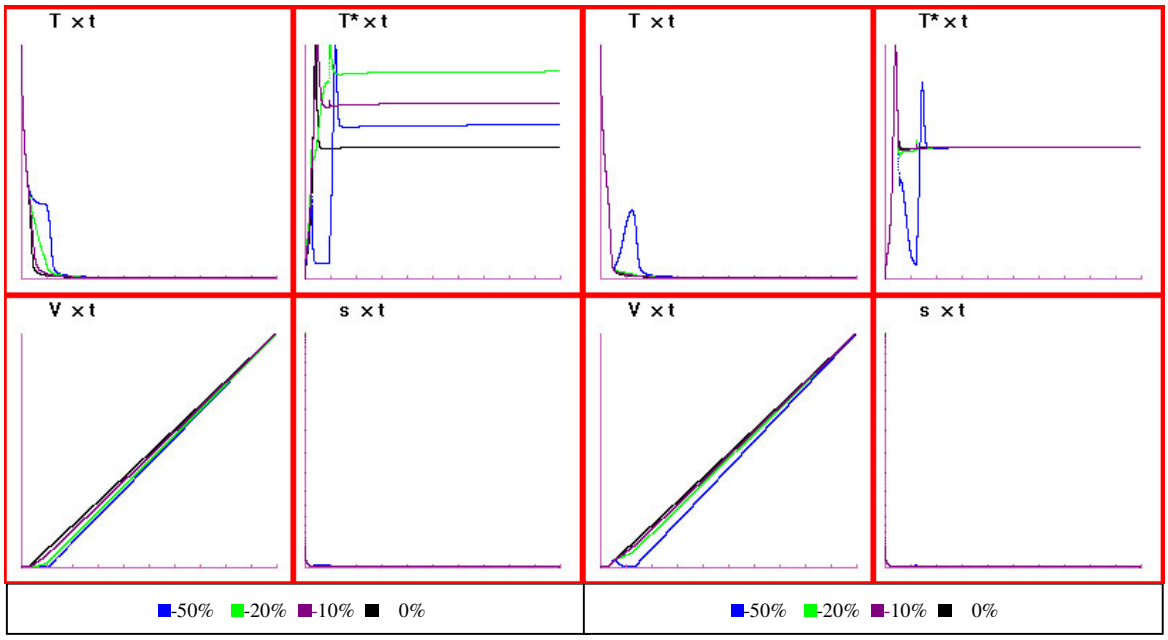

Figure 7. Variation in the parameter $z(t)$ for treatments with beginnings and ends from 100 to 350 *days*; and from 200 to 450 *days*, respectively.

We observed in the Figure (7) that the bigger value of $z(t)$, the faster the population of virus, V, will grown. For treatments begun later (Fig. (7), right (■)), the population of T cells, T, will decay at the beginning followed by an increase diminishing again. With the infected cells population, T^*, we observed a decaying when inhibitor is applied that is followed by an increase and a later decay until reaching stability. When treatment is begun later it provokes a recuperation of the T cells population but, on the other hand for both the cases, the population of virus, V, tends to grown unlimitedly.

We simulated the same variations applied to the parameter $z(t)$ with the period of treatment begin in 100 *days* and finished in 3650 *days*, which corresponds to final time of all the simulations. For this case, we obtained the Fig. (8).

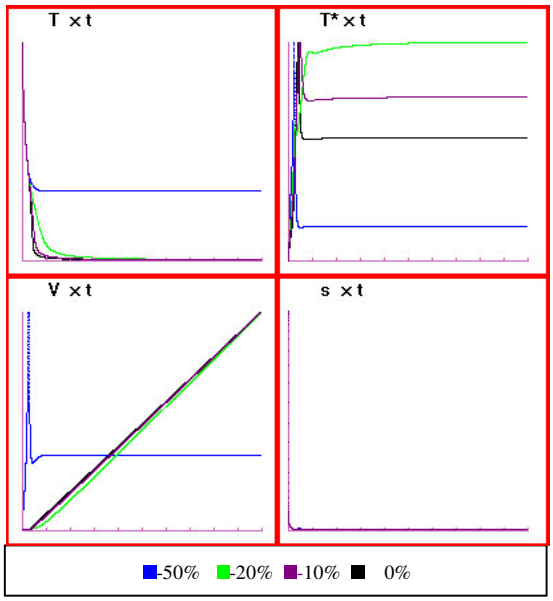

Figure 8. Variation in the parameter $z(t)$ for treatment with beginning and end in 100 and 3650 *days*.

Observing the Figure (8), we noted that the more significant variation in the behavior of the solution for T and V, is associated to –50%(■). The population of cells T, T, suffers an initial decay until reaching a stability of 10^2 mm^{-3} order. The population of virus, V, and the population of infected cells, T^*, will show the same behavior: will grown in the first months, then decaying and stabilizing.

6. Conclusions

All the results, we reached after studying the parameters sensibility and relation to the variations applied to them resulted of the interface we created. In it the interpretation of the numerical values is immediate and as we have said before the convergence and stability of the numerical methods are guaranteed.

Using the numerical simulations it was possible to study the problem with unsteady state initial conditions and identify which parameters were more sensitive to the applied variations in their original values.

Analyzing the final results we have:

- the great part of the parameters shows sensibility to the applications variations sometimes in those that augmented and sometimes in those that diminished their original values;
- we got similar behaviors for different parameters like p, k_V and N; δ and k_T; d_T and g_V; C and b;
- alterations in the groups of parameters p, k_V and N, and δ and k_T modified in an inverse way their behaviors;
- none of the variations applied in the parameters was capable to present the virus population erradicated;
- long periods of treatments did not imply a totally reduction virus population (See Fig. (8)).

So, we can model functions that vary in time for the analyzed parameters in a way to refine the given model. The results of combination of drugs may be introduced using the parameters, for example, N and p. Treatment strategies may also be suggested in respect to the treatment beginning, and the way which the treatment will be applied, continuously or periodically.

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