On the Dynamics of Certain Models Describing the HIV Infection

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Abstract This article concerns some global stability aspects of a class of models introduced by Nowak and Bangham that describe in a fairly successful way the initial phases of the HIV dynamics in the human body as well as some generalizations that take into account mutations. We survey recent results implying that the biologically meaningful positive solutions to such models are all bounded and do not display periodic orbits. For the mutationless cases the dynamics is characterized in terms of certain dimensionless quantities, the so-called basic reproductive rate and the basic defense rate. As a consequence, we infer that the finite dimensional models under consideration cannot account, without further modifications, for the third phase of the HIV infection. We conclude by suggesting a modification that according to our numerical simulations may describe the collapse of the infected patient.

1 Introduction

A better understanding of how entire populations of viruses, such as the HIV, interact with immune cells seems to be a key factor in the development of effective long-term therapies or possibly preventive vaccines for deadly diseases such as the acquired immunodeficiency syndrome [11]. Mathematical modeling of the underlying biological mechanisms and a good understanding of the theoretical implications of such models is crucial in this process. Indeed, it helps clarifying and testing assumptions, finding the smallest number of determining factors to explain the biological phenomena, and analyzing the experimental results [1]. Furthermore, modeling has already impacted on research at molecular level [11] and important results have

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been obtained in modeling the virus dynamics for several infections, such as the HIV [10, 15, 17], hepatitis B [7], hepatitis C [8], and influenza [2].

In this work we survey a class of models introduced by Nowak and Bangham in [10] as well as some extensions of these models that take into account mutations. Our main goal is to study the global dynamics of the models. It turns out that in this description two key dimensionless parameters play a crucial role. They are the *basic reproductive ratio* and the *basic defense ratio*.

For the first model under consideration, namely the one that takes into account the infected and uninfected concentrations of CD4+ T cells and the concentration of free HIV in the blood, for any biologically meaningful initial condition one of the following situations will happen: If the basic reproductive ratio is less than one, then eventually the virus is cleared and the disease dies out. If the basic reproductive ratio R_0 is greater than one, then the virus persists on the host approaching a chronic disease steady state. Finally, if $R_0 = 1$ then the two stationary states coincide and the biological solutions approach such state as time goes by. This first model does not consider the immune response provided by the cytotoxic T lymphocytes (CTL). The latter kill cells that are infected with viruses.

For the second model under consideration, namely the one that besides the aforementioned variables takes also into account the CTL response concentration, we also characterize the global dynamics according to the values of R_0 and the basic defense rate D_0. If $R_0 < 1$, then eventually the virus is cleared. If $1 < R_0 < 1 + (R_0/D_0)$, then generically the virus persists while the CTL response tends to zero.

We study a third model, also by [10] that besides the above variables takes into account mutations. In this case, if we start with biologically meaningfull initial data in the sense that all coordinates are non-negative, then they remain so for all future times and, furthermore, remain bounded. Recent results in [18] indicate that under mild hypothesis on the model parameters, the equilibria of such systems are globally asymptotically stable. Yet, the full characterization of the nongeneric cases remains open.

We remark in passing that although our focus is primarily HIV, the basic mutationless models we are considering may apply to many viral infections besides HIV [11].

The plan for this article goes as follows: In Section 2 we describe the models under consideration. Three of the models come from those proposed by Nowak and Bangham, while a fourth one involving possibly an arbitrary quantity of virus strains is also discussed. In Section 3 we present the mathematical statements, as well as some of their proofs, which characterize the long time behavior of the within-host infectious dynamics. In Section 4 we conclude with a discussion of the results and show some numerical simulations of an invading species illustrating the collapse of the infected individual.

2 Methods and Models

We start by recalling the path followed by the within-host HIV infection [11]. First, the HIV enters a T cell. Being a retrovirus, once the HIV is inside the T cell, it makes a DNA copy of its viral RNA. For this process it requires the reverse transcriptase (RT) enzyme. The DNA of the virus is then inserted in the T-cell's DNA. The latter in turn will produce viral particles that can bud off the T cell to infect other ones. Before one such viral particle leaves the infected cell, it must be equipped with *protease*, which is an enzyme used to cleave a long protein chain. Without protease the virus particle is incapable of infecting other T cells.

One of the key characteristics of HIV is its extensive genetic variability. In fact, the HIV seems to be changing continuously in the course of each infection and typically the virus strain that initiates the patient's infection differs from the one found a year ore more after the infection.

In what follows we present four models. Two of them do not take into account mutation, whereas the other ones consider mutation. The difference between the two latter ones is the possibility of mutation on an arbitrary set of strains. This could be a powerful tool in modeling the genetic variability of the HIV within-host variability.

2.1 Mutationless Models

Martin Nowak and Charles Bangham in [10] introduced a class of models for the time evolution of the HIV virus in the human organism. The simplest of such models considers the virus, the cells that it attacks, and the infected cells. It is given by

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay, \\ \dot{v} &= ky - uv. \end{aligned} \tag{1}$$

Here, the state variables of the system are:

x : Concentration of CD4+ T cells in the blood;
y : Concentration of infected CD4+ T cells by the HIV;
v : Concentration of free HIV in the blood.

The (positive) constants are:

λ : CD4+ T cell supply rate;
d : CD4+ T cell death rate;
β : Infection rate;
a : Death rate of the infected cells;
k : Free virus production rate;
u : Free virus death rate.

The first equation represents the CD4+ T cell rate of change in the blood. Free virus infect healthy cells at a rate proportional to the product of their concentrations,

xv. Thus, β is the constant that represents the efficacy of such process. On the other hand, positive cells are produced at a constant rate λ and die at a rate xd.

The second equation concerns the infected cells. They are produced at a rate βxv and perish at a rate ay.

The third equation, represents the free virus dynamics. Infected cells release free virus at a rate proportional to their abundance, y, and free virus are removed from the system at rate uv.

A second model presented by Nowak and Bangham includes the presence of the defense cells in the organism but does not foresee mutation. It is given by:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay - pyz, \\ \dot{v} &= ky - uv, \\ \dot{z} &= cyz - bz. \end{aligned} \tag{2}$$

Here, the variables and constants are the same ones of System (1) and in addition we have:

z : CTL response concentration;
p : Infected cells elimination rate by the CTL response;
c : CTL reproduction rate;
b : CTL death rate.

The growth rate of the CTL response concentration in this model is take to be proportional to the product yz of infected cells and virus concentration.

2.2 Models with Mutation

The third model introduced by Nowak and Bangham, which now considers mutation, is given by:

$$\begin{aligned} \dot{x} &= \lambda - dx - x\Sigma_{i=1}^{n}\beta_i v_i \ , \\ \dot{y_i} &= \beta_i x v_i - a y_i - p y_i z_i \ , \\ \dot{v_i} &= k_i y_i - u v_i \ , \\ \dot{z_i} &= c y_i z_i - b z_i \ . \end{aligned}$$

Here, the index $i \in \{1,\ldots,n\}$ indicates the virus strain (or mutant) and n is the total number of strains. We remark that the only constants that depend on the virus strain are β_i (infection rate for the i-th virus) and k_i (production rate for the i-th virus).

We may assume, without loss of generality, that the virus production rate is a positive constant k independently of the virus strain. This is obtained after changing v_i into $k_i v_i/k$ and β_i into $k\beta_i/k_i$ in the previous system. Thus, we get

$$\begin{aligned}
\dot{x} &= \lambda - dx - x\Sigma_{i=1}^{n}\beta_i v_i \,, \\
\dot{y_i} &= \beta_i x v_i - a y_i - p y_i z_i \,, \\
\dot{v_i} &= k y_i - u v_i \,, \\
\dot{z_i} &= c y_i z_i - b z_i .
\end{aligned} \tag{3}$$

We shall now present a model that accounts for mutation both in terms of replication ability and escape from immune response. The equations of the model represent rate of change for uninfected cells, infected cells, free virus and CTL response, respectively. The model also simulates the mutation process of the virus.

The fundamental idea here lies in the fact that an integral operator could be used to model in a robust way the multitude of possible genetic variations. Indeed, the genome length of the HIV is of the order of $L = 10^4$ and this *in principle* could encode 4^L different strains [11, Sec. 8.1]. Although obviously most of these strains would not correspond to different viable antigenic responses, it stands to reason that such space could be very large indeed and endowed with a very complex landscape. The different virus strains will be indexed by a parameter $\mu \in \Omega$ where Ω is a set with as little structure as possible. The only structure we require is that it should be a σ-finite measure space. This is motivated by the idea that HIV mutations occur on a very large configuration space. This space, albeit finite, can be modeled by a infinite set in the same spirit of statistical or continuum mechanics.

The model takes the form:

$$\begin{aligned}
\dot{x} &= \lambda - dx - x\int \beta_\mu v_\mu d\mu \,, \\
\dot{y_\mu} &= \beta_\mu x v_\mu - a y_\mu - p y_\mu z_\mu \,, \\
\dot{v_\mu} &= k[(1-\theta)y_\mu + \theta \mathrm{K}[y](\mu)] - u v_\mu \,, \\
\dot{z_\mu} &= c y_\mu z_\mu - b z_\mu \,.
\end{aligned} \tag{4}$$

where $\theta \in [0,1]$ and the variables y, v and z are functions of the time $t \in [0,\infty)$ and of the virus mutation strain $\mu \in \Omega$. We summarize in Table 1 the biological meaning of the variables and parameters occurring in the model.

The mutation process is modeled as follows: Ω is a σ-finite measure space and the integral operator

$$\mathrm{K}[y](\mu) = \int_\Omega \mathrm{K}(\mu,\mu') y(\mu') d\mu'$$

gives the total of viruses that are transformed into strain μ virus.

We assume that K is positive and belongs to $L^1(\Omega \times \Omega)$. We will also assume that

$$\int_\Omega \mathrm{K}(\mu,\mu') d\mu' = \int_\Omega \mathrm{K}(\mu',\mu) d\mu' = \overline{\mathrm{K}} \in \mathbb{R}, \forall \mu \in \Omega. \tag{5}$$

It is natural to request that the total amount of virus, taking into account all strains, to be finite. Thus,

$$\int_\Omega v_\mu d\mu < \infty \,.$$

Table 1 Variables and parameters

Variable	Parameter
x	uninfected cells in the organism
y_μ	infected cells with the HIV of strain μ
v_μ	free HIV of strain μ
z_μ	CTL response that eliminates cells infected by strain μ HIV
λ	uninfected cells supply rate
d	uninfected cells death rate
β_μ	infection rate
a	infected cells death rate
k	free virus production rate
u	free virus death rate
p	infected cells elimination rate by CTL response
c	CTL reproduction rate
b	CTL death rate.

Likewise for y_μ and z_μ. It is also natural to require that all such quantities to be bounded almost everywhere in Ω. Thus, we consider the solutions of the system in the space

$$\mathfrak{M} := \mathbb{R} \oplus \left(L^\infty(\Omega, \mathbb{R}^3) \cap L^1(\Omega, \mathbb{R}^3)\right),$$

[14] carried out an analytic study of the integro-differential System (4). For such biologically meaningful initial conditions, existence and uniqueness of the solutions were established.

We observe that System (4) includes the model of Equation (3) as special case if we take Ω as a finite cardinality probability space.

3 Results

We will start by describing the stationary solutions of System (1) following [14]. We remark that some of the results for the three state-variable systems therein overlap with the comprehensive analysis developed by [4] that used different techniques. They are presented here for the sake of completeness.

It is easily verified that the stationary solutions are

$$X_1^\star = (x_1^\star, y_1^\star, v_1^\star) = \left(\frac{\lambda}{d}, 0, 0\right)$$

and

$$X_2^\star = (x_2^\star, y_2^\star, v_2^\star) = \left(\frac{ua}{\beta k}, \frac{k\beta\lambda - uda}{\beta ak}, \frac{k\beta\lambda - uda}{\beta au}\right).$$

The stationary solution $X_1^\star$ corresponds to the absence of the HIV in the organism. On the other hand, the stationary solution $X_2^\star$ corresponds to an equilibrium of infected cells and T cells.

In order to perform the analysis of the infinitesimal behavior of the stationary solutions it is convenient to write the System (1) in the form $\dot{X} = F(X)$ where $X = (x, y, v)$ and $F : \mathbb{R}^3 \to \mathbb{R}^3$ is defined by

$$F(X) = \begin{bmatrix} \lambda - dx - \beta xv \\ \beta xv - ay \\ ky - uv \end{bmatrix}.$$

The Jacobian of F takes the form

$$DF(X) = \begin{bmatrix} -d - \beta v & 0 & -\beta x \\ \beta v & -a & \beta x \\ 0 & k & -u \end{bmatrix}.$$

For generic parameters the matrices $DF(X_1^\star)$ and $DF(X_2^\star)$ have nonzero determinant and are hyperbolic points. From the Hartman-Grobman Theorem [6] it follows that the local (infinitesimal) behavior of the system in a neighborhood of the point $X_1^\star$, respectively $X_2^\star$, is determined by the sign of the real part of the eigenvalue of $DF(X_1^\star)$, respectively $DF(X_2^\star)$.

It turns out to be useful to consider what we will call in the sequel *basic reproductive ratio*

$$R_0 := \frac{k\lambda\beta}{dau}.$$

It consists of a dimensionless parameter that considers the ratio of the parameters that contribute to the increase of the variables divided by the parameters that contribute to their depletion. The next result states if R_0 is small, i.e. less than 1, then the equilibrium of infected cells and T cells is unstable while the absence of HIV in the organism is an attractor. The picture is reversed if $R_0 > 1$. More precisely, we have that

Lemma 1. *If $R_0 = 1$, then $X_1^\star = X_2^\star$ and $DF(X_1^\star) = DF(X_2^\star)$ possesses two negative eigenvalues and a null one. If $R_0 \neq 1$ the local behavior of the stationary solutions is described according to the following:*

	$R_0 < 1$	$R_0 > 1$
$DF(X_1^\star)$	*3 eigenvalues with negative real part* **(attractor)**	*2 eigenvalues with negative real part and 1 with positive real part* **(source)**
$DF(X_2^\star)$	*2 eigenvalues with negative real part and 1 with positive real part* **(source)**	*3 eigenvalues with negative real part* **(attractor)**

Remark 1. We remark that if $R_0 < 1$ then $X_2^\star$ is not in the biologically relevant domain because two of its components become negative.

We now describe the stationary solutions for System (2). Here, we have three stationary points. They are

$$X_1^\star = \left(\frac{\lambda}{d}, 0, 0, 0\right),$$
$$X_2^\star = \left(\frac{ua}{\beta k}, \frac{k\beta\lambda - uda}{\beta ak}, \frac{k\beta\lambda - uda}{\beta au}, 0\right), \text{ and}$$
$$X_3^\star = \left(\frac{\lambda cu}{dcu + \beta kb}, \frac{b}{c}, \frac{kb}{cu}, \frac{\beta\lambda kc - adcu - a\beta kb}{(dcu + \beta kb)p}\right).$$

The stationary solution $X_1^\star$, once again, corresponds to the absence of the HIV in the organism. The stationary solution $X_2^\star$ corresponds, as previously, to a balance of infected and normal cells. The absence of defense cells in the organism ($z = 0$) means that we are back to the previous model. The stationary solution $X_3^\star$ corresponds to a balance between positive, infected, and defense cells. Biologically this point corresponds to the *HIV latency period*, or either, the second phase of the HIV infection.

As in the analysis of the model of Equation (1), it will be convenient to write the system in the form $\dot{X} = F(X)$ where now $X = (x, y, v, z)$ and the function $F : \mathbb{R}^4 \to \mathbb{R}^4$ is given by

$$F(X) = \begin{bmatrix} \lambda - dx - x\beta v \\ x\beta v - ay - pyz \\ ky - uv \\ cyz - bz \end{bmatrix}.$$

In the next lemma we collect some information on the infinitesimal behavior of the system in a neighborhood of the stationary points $X_1^\star, X_2^\star$ and $X_3^\star$.

We shall call the constant $D_0 := \frac{c\lambda}{ab}$ *the basic defense rate*. Together with the basic reproductive ratio it is another important dimensionless parameter. It is the ratio of the growth parameters of the immune system and their corresponding death rates. The importance of this constant in our analysis starts with the following:

Lemma 2. *If $R_0 = 1$ then $X_1^\star = X_2^\star$ and $DF(X_1^\star)$ has a vanishing eigenvalue. If $R_0 = 1 + \frac{R_0}{D_0}$ then $X_2^\star = X_3^\star$ and $DF(X_2^\star)$ has a vanishing eigenvalue. If $R_0 \neq 1$ and $R_0 \neq 1 + \frac{R_0}{D_0}$, then the infinitesimal behavior of the stationary solutions is described by the following:*

	$R_0 < 1$	$1 < R_0 < 1 + \frac{R_0}{D_0}$	$R_0 > 1 + \frac{R_0}{D_0}$
$DF(X_1^\star)$	*4 eigenvalues with negative real part* **(attractor)**	*3 eigenvalues with negative real part and 1 with positive real part* **(saddle)**	*3 eigenvalues with negative real part and 1 with positive real part* **(saddle)**
$DF(X_2^\star)$	*3 eigenvalues with negative real part and 1 with positive real part* **(saddle)**	*4 eigenvalues with negative real part* **(attractor)**	*3 eigenvalues with negative real part and 1 with positive real part* **(saddle)**
$DF(X_3^\star)$	*at least 1 eigenvalue with negative real part*	*at least 1 eigenvalue with negative real part*	*at least 2 eigenvalues with negative real part*

Remark 2. As in Model 1, the case $R_0 < 1$ leads to $X_2^\star$ and $X_3^\star$ out of the biologically relevant region. Furthermore, if $R_0 < 1 + (R_0/D_0)$ the stationary point $X_3^\star$ is out of the biological range as well. We will show that this range is positively invariant and thus the biologically relevant solutions cannot approach such steady states.

Since the cases where $R_0 = 1$ or $R_0^{-1} + D_0^{-1} = 1$ are nongeneric, we now focus on interpreting the consequences of Lemma 2 away from such situations. If $R_0 < 1$, then arbitrary initial conditions (at least close to the equilibrium point) will lead to the clearing of the virus and the disappearence of the infection. It will follow, as a consequence of the results in the next two sections, that this is in fact the case for *arbitrary* positive initial conditions. If $1 < R_0 < 1 + (R_0/D_0)$ then, at least in a neighborhood of the equilibrium point $X_2^\star$, the disease will approach a uniformly persistent state where the CTL response concentration will vanish. In fact, as will be explained in the next two sections, generically the biological solutions will converge to this steady state. See Theorem 1.

3.1 Boundedness and Positivity

In this paragraph we will answer the following basic question: Will the solutions of Models (1) and (2) that start from biologically meaningful initial values preserve such property for future times? Here, by biologically meaningful we mean that all coordinates are non-negative and bounded for all times. We split the discussion into two parts, namely, positivity and boundedness.

3.1.1 Positivity

Let $\mathbb{R}_+$ denote the set of non-negative real numbers. Obviously, a solution (x, y, v, z) to System (1) only admits a biological interpretation if $(x, y, v, z) \in \mathbb{R}_+^4$. As remarked before, the System (2) reduces to System (1) if $z = 0$. Hence, we will state all the results for System (2).

Proposition 1. *Let $\varphi : [t_0, +\infty) \to \mathbb{R}^4$ be a solution of System (2). If $\varphi(t_0) \in \mathbb{R}^4_+$ then $\varphi(t) \in \mathbb{R}^4_+$ for all $t \in [t_0, \infty)$.*

The proof of this result is a straightforward case by case analysis of the behavior of solutions to System (2) whenever one of its components vanishes.

The above result also holds for the case that includes mutation given in Equation (3).

Proposition 2. *Let $\varphi : [t_0, \infty) \to \mathbb{R}^{3n+1}$ be a solution of System (3). If $\varphi(t_0) \in \mathbb{R}^{3n+1}_+$ then $\varphi(t) \in \mathbb{R}^{3n+1}_+$ for all $t \in [t_0, \infty)$.*

3.1.2 Boundedness

We already have a lower bound given by Propositions 1 and 2 for the solutions of Models (1) and (2) with positive initial values. We now show that the solutions are bounded from above.

We denote by $C_{\mathrm{b}}(I)$ the set of continuous and bounded functions defined on the interval I and taking values in $\mathbb{R}^n$.

Proposition 3. *Let $\varphi : [t_0, \infty) \to \mathbb{R}^4$ be a solution of System (2). If $\varphi(t_0) \in \mathbb{R}^4_+$ then $\varphi \in C_{\mathrm{b}}[t_0, \infty)$.*

Proof. Because of Proposition 1, it only remains to prove the existence of an upper bound to the nonnegative solutions of System (2).

We start with $x(t)$. Since $\beta, x(t), v(t) \geq 0$ we have from

$$\dot{x} = \lambda - dx - \beta xv \leq \lambda - dx.$$

$$x(t) \leq x(t_0) + \frac{\lambda}{d} \quad \text{for all} \quad t \geq t_0. \tag{6}$$

We now go on to prove that $y(t) \in C_{\mathrm{b}}[t_0, \infty)$. From

$$\dot{y} = \beta xv - ay - pzy,$$

since $z(t) \geq 0$ and $y(t) \geq 0$, we have that

$$\dot{y} + ay \leq \beta xv = \lambda - (\dot{x} + xd) \, .$$

Thus,

$$\frac{d}{dt}(ye^{ta}) \leq (\lambda - \frac{d}{dt}(xe^{td})e^{-td})e^{ta}$$

and so

$$\int_{t_0}^{t} \frac{d}{ds}(y(s)e^{sa})ds \leq \int_{t_0}^{t} (\lambda e^{-sd} - \frac{d}{ds}(x(s)e^{sd})e^{s(a-d)})ds.$$

Integrating by parts

$$\int_{t_0}^{t} \frac{d}{dt}(xe^{sd})e^{s(a-d)}ds = x(s)e^{sa}|_{t_0}^{t} - (a-d)\int_{t_0}^{t} x(s)e^{sa}ds.$$

Thus,

$$\begin{aligned} y(t) \leq\ & y(t_0)e^{a(t_0-t)} + \frac{\lambda}{a}(1-e^{a(t_0-t)}) \\ & - \left(x(t) - x(t_0)e^{a(t_0-t)} - (a-d)\int_{t_0}^{t} x(s)e^{a(s-t)}ds\right). \end{aligned} \tag{7}$$

Thus, remarking that, for all $t \geq t_0$, $x(t) \geq 0$, $e^{a(t_0-t)} \in [0,1]$, and $x(t)$ is bounded, we get the boundedness of y. To get more precise bounds we break the analysis into two cases, depending on the sign of $a-d$. If $a-d \leq 0$, then (7) implies that

$$y(t) \leq y(t_0) + \frac{\lambda}{a} + x(t_0) \quad \text{for all} \quad t \geq t_0.$$

If $a-d \geq 0$, then it follows from (6) and (7) that

$$y(t) \leq y(t_0) + \frac{\lambda}{a} + x(t_0) + \frac{(a-d)}{a}\left(\frac{\lambda}{d} + x(t_0)\right)(1-e^{a(t_0-t)})$$

Thus,

$$y(t) \leq y(t_0) + \frac{\lambda}{d} + \left(2 - \frac{d}{a}\right)x(t_0) \quad \text{for all} \quad t \geq t_0$$

Let us now analyze $v(t)$. The equation $\dot{v} = ky - uv$, implies that

$$\frac{d}{dt}(ve^{ut}) = kye^{ut}.$$

Integrating the differential equation, it follows that

$$v(t) = v(t_0)e^{u(t_0-t)} + k\int_{t_0}^{t} y(s)e^{u(s-t)}ds. \tag{8}$$

Since we have already shown that $y \in C_{\mathrm{b}}[t_0,\infty)$ we have

$$v(t) \in C_{\mathrm{b}}[t_0,\infty).$$

Finally, it remains to show that $z(t) \in C_{\mathrm{b}}[t_0,\infty)$. Combining the equations for $\dot{y}$ and $\dot{z}$ in System (2) we get

$$\dot{z} + bz = cyz = \frac{c}{p}(\beta vx - \dot{y} - ay).$$

Using the equation $\dot{x} = \lambda - dx - \beta xv$, we have that

$$\dot{z} + bz = \frac{c}{p}(\lambda - dx - \dot{x} - \dot{y} - ay).$$

Hence,

$$z(t) = \left(z(t_0) - \frac{c}{p}\left(\lambda b^{-1} + y(t_0) + x(t_0)\right)\right) e^{b(t_0-t)} + \frac{c}{p}\left(\lambda b^{-1} - y(t) - x(t)\right) + \frac{c}{p}\left((b-d)\int_{t_0}^{t} x(s)e^{b(s-t)}ds + (b-a)\int_{t_0}^{t} y(s)e^{b(s-t)}ds\right). \quad (9)$$

Since x and $y \in C_{\mathrm{b}}[t_0,\infty)$ we have that $z(t) \in C_{\mathrm{b}}[t_0,\infty)$. $\square$

Proposition 4. *Let $\varphi : [t_0,\infty) \to \mathbb{R}^{3n+1}$ be a solution of System (3). If $\varphi(t_0) \in \mathbb{R}^{3n+1}_{+}$ then $\varphi \in C_{\mathrm{b}}[t_0,\infty)$.*

Proof. We proved in Proposition 2 that the components of the solutions to System (3) are bounded from below by 0. It remains to show that they have an upper bound.

We shall start by analyzing $x(t)$. Since $x(t) \geq 0$, $v_i(t) \geq 0$ and $\beta_i \geq 0$ for all $t \geq t_0$,

$$\dot{x} = \lambda - dx - x\sum_{i}^{n} \beta_i v_i$$

implies that $\dot{x} + dx \leq \lambda$. Thus, as in the proof of the Proposition 3, we have that

$$x(t) \leq x(t_0) + \frac{\lambda}{d} \quad \text{for all} \quad t \geq t_0.$$

For the boundedness of $y(t)$, we look at the equation $\dot{y}_i = \beta_i x v_i - a y_i - p y_i z_i$. From Proposition 3 we have that

$$\sum_{i}^{n} \dot{y}_i + a\sum_{i}^{n} y_i \leq x\sum_{i}^{n} \beta_i v_i.$$

Let us set $Y(t) := \sum_i^n y_i(t)$, $V(t) = \sum_i^n v_i(t)$ and $Z(t) := \sum_i^n z_i(t)$. Since $x\sum_i^n \beta_i v_i = \lambda - \dot{x} - dx$, we have that

$$\dot{Y}(t) + aY(t) \leq \lambda - \dot{x}(t) - dx(t).$$

As in Proposition 3,

$$Y(t) \leq Y(t_0) + \max\left\{\frac{\lambda}{d}, \frac{\lambda}{a}\right\} + \max\left\{1, 2 - \frac{d}{a}\right\} x(t_0) = \overline{Y},$$

that is, $Y(t) \in C_{\mathrm{b}}[t_0,\infty)$. Since $y_i \geq 0$ for all $i = 1,\ldots,n$, we have that $y_i(t) \leq Y(t) \leq \overline{Y}$. Thus, $y_i \in C_{\mathrm{b}}[t_0,\infty)$ for all $i = 1,\ldots,n$.

In the case of v, we have that

$$\dot{V}(t) + uV(t) = k(\theta Y(t) + (1-\theta)\overline{K}Y(t)) = k(\theta + (1-\theta)\overline{K})Y(t),$$

because $\displaystyle\sum_{j=1}^{n} K_{i,j} = \overline{K}$. As we saw in the proof of Proposition 3,

$$V(t) \leq V(t_0) + \frac{k}{u}(\theta + (1-\theta)\overline{K})\overline{Y} = \overline{V},$$

that is, $V(t) \in C_{\mathrm{b}}[t_0, \infty)$. We conclude that $v_i(t) \in C_{\mathrm{b}}[t_0, \infty)$ for all $i \in \{1, \ldots, n\}$.

As far as $z_i(t)$ is concerned, using the equation $\dot{z}_i = cy_iz_i - bz_i$, we get

$$\sum_i^n \dot{z}_i + b\sum_i^n z_i = \frac{c}{p}\left(x\sum_i^n \beta_i v_i - \sum_i^n \dot{y}_i - a\sum_i^n y_i\right).$$

Thus, as before,

$$\dot{Z}(t) + bZ(t) = \frac{c}{p}(\lambda - dx(t) - \dot{x}(t) - \dot{Y}(t) - aY(t)).$$

The inequality (9) is now written as

$$\begin{aligned} Z(t) = &\left(Z(t_0) - \frac{c\lambda}{pb} + \frac{c}{p}Y(t_0) + \frac{c}{p}x(t_0)\right)e^{b(t_0-t)} + \frac{c\lambda}{pb} - \frac{c}{p}Y(t) \\ &-\frac{c}{p}x(t) + \frac{c}{p}(b-d)\int_{t_0}^t x(s)e^{sb}ds + \frac{c}{p}(b-a)\int_{t_0}^t Y(s)e^{sb}ds. \end{aligned}$$

So, $Z(t) \leq \overline{Z}$, where $\overline{Z}$ is a constant that depends only on $x(t_0)$ and $Y(t_0)$. It follows that $Z(t) \in C_{\mathrm{b}}[t_0, \infty)$. Consequently, $z_i(t) \in C_{\mathrm{b}}[t_0, \infty)$ for all $i \in \{1, \ldots, n\}$.

3.2 Stability of the Equilibrium Points

The global stability of the equilibrium points of Systems (1) and (2) in the biologically interesting region defined by the positive orthant has attracted several authors. Proofs of these global stability characteristics of the mutationless models (1) and (2) were given in [5], using Hirsch's theory of competitive differential systems, and more recently by [3] (for system1) and [4] using Lyapunov functions. More recently, the second author in collaboration with M. Souza in [18] established global stability of the equilibrium points for systems that include those of the form (3) under some hypothesis on the corresponding coefficients. This was done by exhibiting suitable Lyapunov functions. As a consequence of such results one can state the following:

Theorem 1. *Let $\varphi : [t_0, \infty) \to \mathbb{R}^4$, $\varphi(t) = (x(t), y(t), v(t), z(t))$, be a solution of System (2) such that $\varphi(t_0) \in \mathbb{R}^4_+$.*

- *If $R_0 \leq 1$, then $\lim_{t\to\infty} \varphi(t) = X_1^\star$.*
- *If $R_0 > 1$ and $(y(t_0), v(t_0)) = (0,0)$, then $\lim_{t\to\infty} \varphi(t) = X_1^\star$.*
- *If $1 < R_0 \leq 1 + (R_0/D_0)$ and $y(t_0) + v(t_0) \neq 0$ then $\lim_{t\to\infty} \varphi(t) = X_2^\star$.*
- *If $R_0 > 1 + (R_0/D_0)$, $z(t_0) = 0$, and $y(t_0) + v(t_0) \neq 0$ then $\lim_{t\to\infty} \varphi(t) = X_2^\star$.*
- *If $R_0 > 1 + (R_0/D_0)$, $z(t_0) > 0$ and $y(t_0) + v(t_0) \neq 0$ then $\lim_{t\to\infty} \varphi(t) = X_3^\star$.*

The asymptotic behaviour of the solutions of the System (1) can be promptly inferred from the result above. One has just to notice that System (2) reduces to System (1) when restricted to the invariant hypersurface $z = 0$.

Thus, the generic biologically relevant solutions of the models without mutation belong to the basin of attraction of some stationary point of system. This extends a result of [10] who observed this for initial conditions close to the stationary solutions. This also shows that these models do not simulate the last phase of the HIV since the solutions always converge to the absence of virus or the period of latency. In Section 4 we take up this issue by considering mutation and the invasion of an opportunistic virus numerically.

4 Discussion

A number of models for the within-host viral infection by HIV have been proposed and studied by different authors. In particular, a class of three state-variable models was introduced by [16] that modifies the first equation of System (1) to a logistic type form. Namely, the first equation takes the form

$$\dot{x} = \lambda - dx + px(1 - x/x_m) - \beta xv, \tag{10}$$

A global analysis of both three-dimensional models was performed by [4]. It overlaps consistently with Theorem 1. Since they also consider models for which the first equation takes the form (10), their models in some situations may give rise to periodic orbits or oscillations. This however, is not the case for our models.

In fact, for the three dimensional models under consideration the solutions of the system eventually enter in the basin of attraction of some stationary point of system. [10] observed this for initial conditions close to the stationary solutions in the mutationless models. Thus the models under consideration do not simulate the last phase of the HIV since the solutions always converge to the absence of virus or to a latency state.

It is well recognized that the HIV does not kill any vital organ [11]. Nevertheless, it destabilizes the immune system leaving the body defenseless to opportunistic virus attacks.

Several mathematical models have been devised to describe the slow decline in the numbers of CD4 cells in the HIV infection and the interaction between HIV and other opportunistic infections [9, 11, 13, 16]. Furthermore, a number of alternative approaches have been proposed to model the third phase of the HIV infection and the onset of AIDS. See for example [11, 20, 12] and references therein. We close this article by considering a model that takes into account the action of an opportunistic virus after the HIV infection. The main point being that of illustrating the potential of the models that include mutation in a general context such as Equation (11) and the need for further mathematical inquire into this direction.

The model is given by the following system of equations:

$$\begin{aligned}
\dot{x} &= \lambda - dx - x\int \beta_\mu v_\mu d\mu - \alpha x v_o \\
\dot{y_\mu} &= \beta_\mu x v_\mu - a y_\mu - p y_\mu z_\mu \\
\dot{v_\mu} &= k[(1-\theta)y_\mu + \theta K[y](\mu)] - u v_\mu \\
\dot{z_\mu} &= c y_\mu z_\mu - b z_\mu \\
\dot{v_o} &= m v_o - \alpha x v_o - \omega v_o
\end{aligned} \tag{11}$$

where v_0, the new variable of the system, stands for opportunistic virus. The additional (positive) constants are

α : meeting rate of opportunistic virus with the uninfected cells;
m : reproduction rate of the opportunistic virus;
ω : death rate of the opportunistic virus.

The term that represents the encounter between T cells and the opportunistic virus is $\alpha x v_o$. It appears in the first and in the last equation of the model. The equation for the opportunistic virus has the term $m v_o$ that represents the reproduction of the opportunistic virus. The opportunistic virus infected cells are not considered in this model. The term ωv_o corresponds to the decline of the opportunistic virus. We do not take into account the type of opportunistic virus attacking the organism. The parameter values, the constants and the initial conditions for the opportunistic virus can be found in Table 2.

Table 2 Numerical experiment list

Number of Strains	m	o	α	$v_o(100)$	Figure
20	3.1	0.01	0.01	10^{-3}	1
100	3.1	0.01	0.01	10^{-3}	2 and 4
100	1.2	1.2	0.1	10^{-3}	3

Table 3 Parameters, constants, and initial conditions

λ	10 day$^{-1}\times$ mm^{-3}	β	2.4×10^{-5} day$^{-1}\times$ mm^{-3}
a	1 day$^{-1}\times$ mm^{-3}	p	0.8 day$^{-1}\times$ mm^{-3}
c	0.2 day$^{-1}\times$ mm^{-3}	d	0.02 day^{-1}
k	360 day^{-1}	u	2.4 day^{-1}
b	1.2 day^{-1}	θ	0.5
N	20	$x(0)$	10^3 mm^{-3}
$y(\mu,0)$	0 mm^{-3}	$z(\mu,0)$	10^{-6} mm^{-3}
$v_0(0)$	10^{-3} mm^{-3}	$v(\mu,0)$	0 mm^{-3}

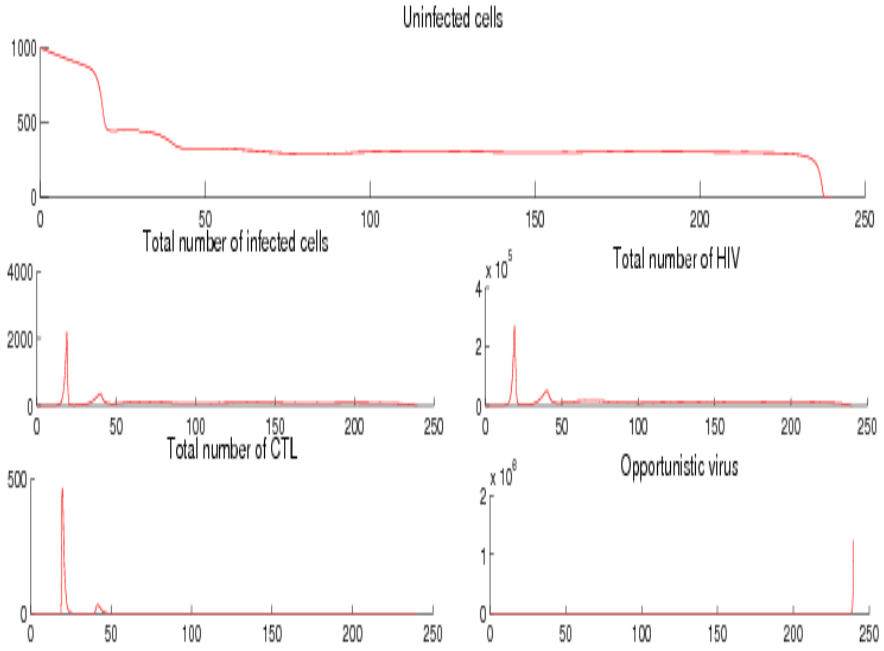

Fig. 1 The number of opportunistic virus in the system presents a considerable growth and the number of uninfected cells converged to zero.

The functions $\beta(\mu)$ and $K(\mu,\mu')$ are taken as Gaussians. The parameters, constants and initial conditions appearing in System (4) can be found in Table 3.

We have started by simulating the infection using the Model (4) for a certain time interval $[t_0,t]$. From the corresponding solution at hand we used $x(t)$, $y_\mu(t)$, $v_\mu(t)$ and $z_\mu(t)$ as initial conditions for the Model (11). The graph of the corresponding solutions are shown as indicated in Table 2. The numerical solutions were found using MatLab's function *ode*23*s*. More information concerning the implementation and validation of the numerical methods to obtain the reported results can be found in [14].

In Figures 1 and 2 we show simulations where the number of opportunistic virus in the system presents a considerable growth and the number of uninfected cells converged to zero. On the other hand, in Figure 3 the presence of the opportunistic virus has not caused any change on the equilibrium of the system. In Figure 4 the equilibrium of the system was preserved but nevertheless the number of opportunistic virus presented a considerable growth.

From the numerical results presented herein we conclude that the presence of the opportunistic virus may or may not lead the system to an equilibrium state different from the ones of the previous system. Since the human organism is constantly in

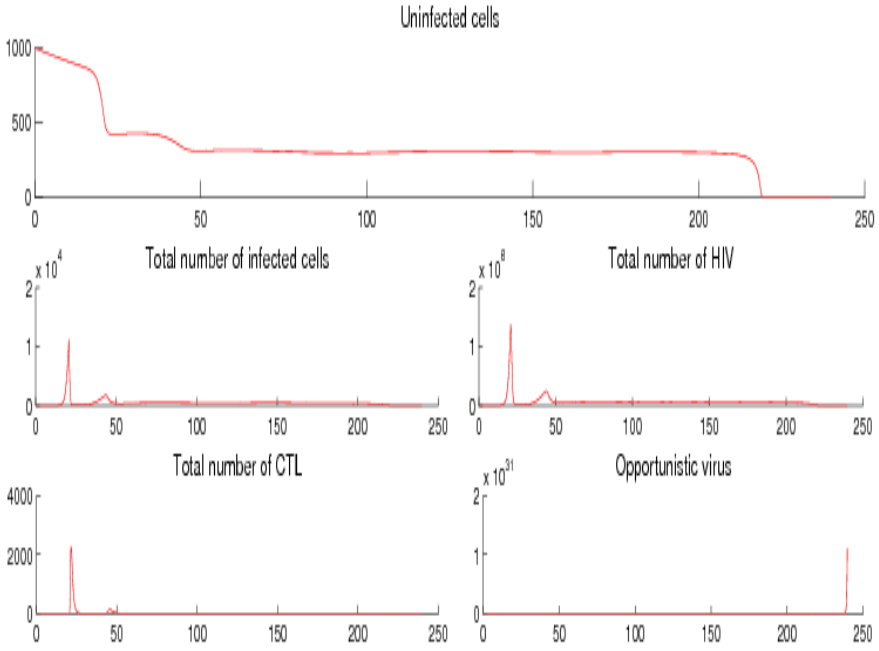

Fig. 2 The number of opportunistic virus in the system presents a considerable growth and the number of uninfected cells converged to zero.

contact with different kinds of virus this suggests a way to model the post-latency period and the possible collapse of the infected individual.

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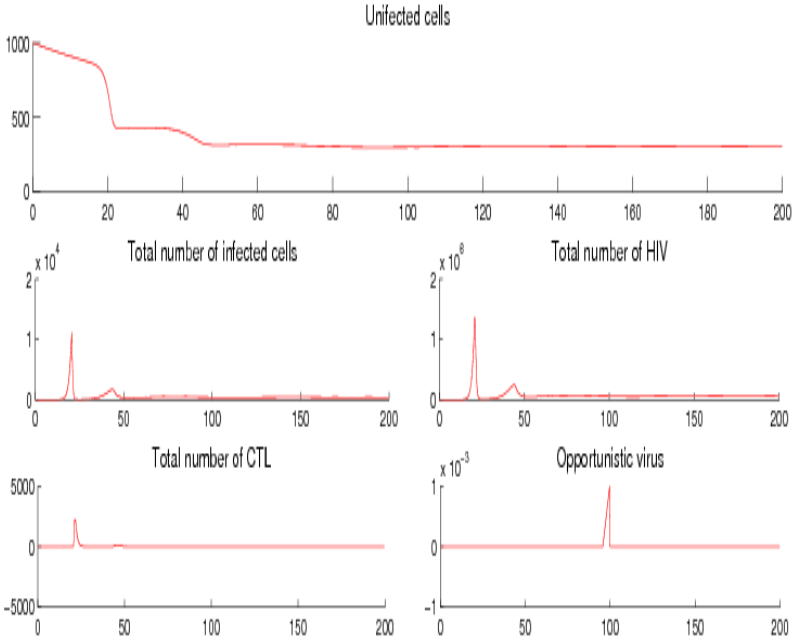

Fig. 3 In this simulation, the presence of the opportunistic virus has not caused any change on the equilibrium of the system.

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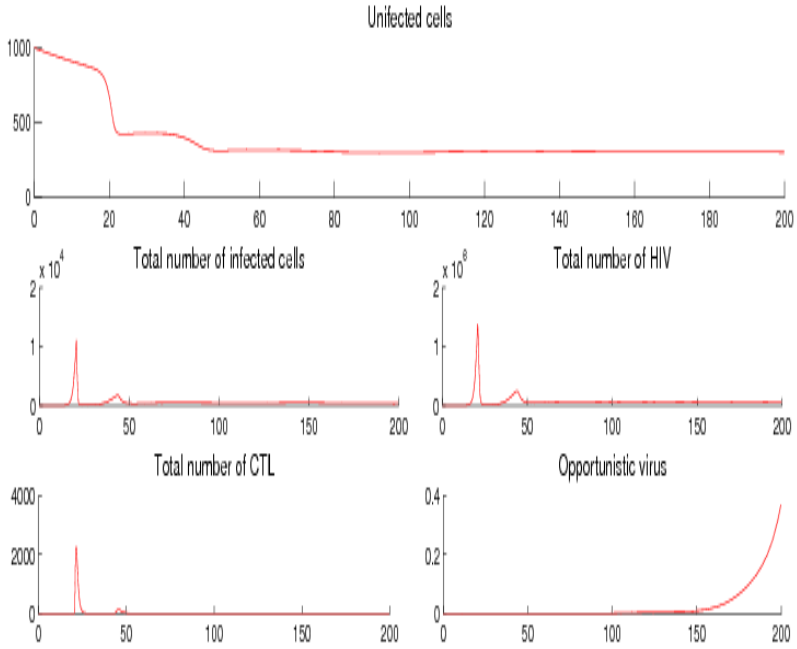

Fig. 4 In this simulation the equilibrium between uninfected cells and virus was preserved in the sense that the population of uninfected cells did not go to zero but the number of opportunistic virus grew.