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Mathematical modeling of antigenicity for HIV dynamics

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Abstract. – This contribution is devoted to a new model of HIV multiplication motivated by the patent of one of the authors. We take into account the antigenic diversity through what we define “antigenicity”, whether of the virus or of the adapted lymphocytes. We model the interaction of the immune system and the viral strains by two processes. On the one hand, the presence of a given viral quasi-species generates antigenically adapted lymphocytes. On the other hand, the lymphocytes kill only viruses for which they have been designed. We consider also the mutation and multiplication of the virus. An original infection term is derived. So as to compare our system of differential equations with well-known models, we study some of them and compare their predictions to ours in the reduced case of only one antigenicity. In this particular case, our model does not yield any major qualitative difference. We prove mathematically that, in this case, our model is biologically consistent (positive fields) and has a unique continuous solution for long time evolution. In conclusion, this model improves the ability to simulate more advanced phases of the disease.

Keywords: HIV modeling, antigenic variation, mutation, immune response

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AMS classification: 34-99, 65-05, 65Z05, 92B99, 92C50.

1) Introduction

Virus multiplication is at the basis of viral infection. Although the viral replication cycle involved makes heavy use of the infected cell's resources [18, 43], the enzyme(s) in charge of viral genome replication is(are) frequently encoded in the latter [7]. Compared to cellular polymerases, viral polymerases are usually more error-prone [24]. It follows that the viral mutation rate, defined as the average number of base changes at a given position of the genome per replication cycle, may be large compared to that observed in our own cells, which is about one in a billion [35]. For certain viruses, in particular retroviruses like HIV-1, it could be up to 1,000,000 times greater. By the end of 2007, the Los Alamos HIV data base listed over 230,000 different viral sequences (see www.hiv.lanl.gov). Given the small genome size of these viruses, chances are then that each member of a viral progeny carries mutations. A single point mutation may be enough to simultaneously affect two genes encoded in different, but overlapping reading frames, whilst silent mutations, which do not change amino acid coding, may nevertheless have important biological consequences [26].

A virus is mainly characterized by its ability to infect target cells (infectivity) and by its antigenic signature (antigenicity), defined as both the capacity to induce an immune response and also its strength and type. Immunogenicity is the ability of antigens to elicit a response from cells of the immune system. Mutations during virus replication may therefore release infective or non-infective viruses, of the same or of different antigenicity. For HIV-1, the ratio of infectious to non-infectious particles is estimated to range from 1:1 to 1:60,000, depending on the type of cell infected and the viral strain [40]. Whether the virus is infective or not, over 800 mutations affecting HIV-1 antigenicity were identified in its envelop gene (*env*) alone [25].

By encoding its own replication enzymes, the virus has control over its replication fidelity and thereby challenges heavily the immune system, due to the huge burden imposed by the number of infective virions produced and their antigenic diversity. This burden is even worse when the virus targets part of the immune system (CD4 displaying cells), as is the case for HIV-1. In addition, the immune cell proliferation induced by the viral attack will provide HIV-1 virions with new targets, engaging the cell-virus dynamics in an exponentially soaring extension regime.

Kinetic modeling is therefore of high interest for understanding the course of infection. It is a prerequisite for designing and optimizing treatment strategies based on antiviral drugs. A large number of deterministic and stochastic inter- and intra-cellular models of HIV dynamics have already been proposed ([16, 30, 31, 32, 33, 39, 41] among others), but none enable the prediction of the course of the disease in all its phases. For instance, even if, following antiviral treatment, the plasma load of the virus becomes undetectable, unscheduled bursts occur, probably fed by viral sanctuaries disseminated in various tissues and organs (lymph or neuronal tissues, gastro-intestinal or uro-genital tracts etc. See [36]). One may assume that, despite tissue-specific kinetic diversities, the course of infection in all sanctuaries (including plasma) obeys a common, complex host-predator relation,

differing only by sanctuary-specific parameters. The course of the global infection would then be the result of all local processes. This result would however not be a simple addition or superposition, as it is likely that each local process would provide viruses having locally-specified antigenicities and infectivities which may challenge the immune cells in the same or other sanctuaries.

What is the infection phenomenology ? As far as our study is concerned, the process involves four major participants or “fields”: uninfected T lymphocytes (denoted T), infected ones (U), infectious viruses (V) and non-infectious viruses (W). For each participant, a characteristic antigenicity is recognized by a lymphocyte, or displayed by a virus. In the following, we call *antigenicity* the variable associated to this biomolecular characteristic and denote it by the index j . Modeling this antigenicity can also be found in [1, 17, 29, 30, 31]. Such models are *microscopic* since they take into account a microscopic quantity that may not be easily measured biologically. Macroscopic models only use the sum of all the T_j and V_j . This modeling is necessary, since viruses devoid of antigenic diversity would be eliminated by the immune system. Actually, viral clearance is not observed and furthermore, it is the immune system that will ultimately collapse. So as to quantify this *biological reality*, we extend the classical biological definition by assuming we characterize the biomolecular viruses. Mainly our antigenicity is not linked to any virulence since we consider only infectious or non-infectious viruses and no intermediate state.

The evolution with time of T_j depends on three phenomena: regression of the T_j population due to the viral attack (whatever the antigenic pedigree of the infecting virus), which transforms T_j 's into U_j 's; the stimulation of the immune system by both infectious and noninfectious viruses of antigenicity j ; the natural fate of T_j independently of the viral presence, *i.e.* spontaneous generation and death of T_j species. The T_j population may include cross-reacting species, which are active also against a (limited) number of targets with different antigenicities. The lymphocytes U_j are derived only from the T_j population following viral attack. It is assumed also, that the switch from the T_j to the U_j state occurs only upon viral infection. Like the T_j , the U_j are subject to natural death. Viruses V_j and W_j are generated through infection of any susceptible T cell, whatever its antigenicity. The parent virus of V_j and W_j may be a V_j (no viral antigenicity modification) or a V_k of different antigenicity (viral antigenicity mutation). Viruses V_j and W_j will be the target of lymphocytes T_j exclusively. Both viral species have a natural death rate. Viruses V_j and W_j differ by mutations in genes involved in infectivity, but not affecting antigenicity j .

This modelling assumes that viral genome parts responsible for infectivity may differ from those responsible for antigenicity. Since the viral strategy is to escape the immune response whilst minimizing loss of infectivity, excess mutations in the antigenicity-specifying part of the viral genome would be more favorable. The immune system senses mainly the viral surface, hence mutations in the viral envelop genes would be most beneficial, but they should not, or marginally only, affect viral genome parts responsible for infectivity. HIV-1 handles in part this dilemma by introducing mutational hot-spots in its genome

([23] and the website <http://www.hiv.lanl.gov>), mainly in the envelop genes, where the mutation rate is much higher due to local sequence and structural particularities of the genome [4, 25].

What is the therapeutic motivation ?

Approved drugs for AIDS treatment are of three kinds mainly. Two of them inhibit reverse transcription (using nucleotide and non-nucleotide analogs) and the third inhibits a viral enzyme in charge of cleaving reverse transcriptase from a precursor protein. Because of its high mutation rate, HIV rapidly develops resistance to any one of these drugs taken individually. Resistance can be considerably delayed by using various combinations of these drugs (multitherapies). So far however, no combination has been found that could clear the virus. Therefore therapies are life-long and unfortunately have considerable side-effects.

Obviously, the high mutation rate of reverse transcriptase is central to the successful viral strategy. It allows the virus to escape the circulating immune cells (antigenic mutations) and to develop drug resistance, although over 90% of its progeny lacks infectivity and will therefore be rapidly cleared. The natural viral mutation rate is at the limit of the “error threshold” [5], as a slight increase would produce 100% non-infectious viruses. Conversely, reducing the mutation rate would reduce the antigenic diversity and allow the immune system to eliminate the stabilized viral strains, and drug resistance would vanish.

New AIDS therapy at stake?

A promising therapeutic approach would then be to take control of the viral mutation rate. This was shown to be feasible in [13] with a CNRS-filed patent based on this work USPTO 6,727,059, but also in [14, 20, 27], by supplying the reverse transcriptase with nucleotide analogs. Some of them relax while others reinforce the replication fidelity, without blocking reverse transcription. For a review see [2].

Both therapeutic strategies would give rise to specific viral dynamics. These need to be understood and assessed in detail. The medical decision to choose one particular strategy and setting up the adapted drug regimen for a patient, given his viral load and lymphocyte count (dose and extent of treatment, time expected to reach viral clearance etc) needs careful analysis. Simulation of viral dynamics with a drug regimen could help in reaching this decision. To this end, the present work is to build a realistic mathematical model of viral dynamics.

In the following we review some well-known models by giving an analysis of the stationary solutions (fixed points) and their stability in Section 2. In Section 3, we derive our new model precisely and Section 4 is devoted to a full study of its mathematical properties in a reduced case (only one antigenicity). We discuss this new model in Section 5 and conclude in Section 6.

2) Some popular models

Throughout this section, we review some well-known models. Some of them take specific biological reality into account. So as to come to a common description with our model presented later, we reduced them in a preliminary step when needed. When used, the fields T, U, V, W have the same meaning as above. When the model has a term identical to ours, we denote the parameter of the term as ours. When it is different, we denote it the same way as the authors and add a subscript depending on the authors. Also, we use the very same values of common parameters to have comparable results. We take most values from Snedecor [39] and check these values with other articles ([22, 28, 34], ...).

All the fields of the models are non-dimensionnalized by using the value of the non-infected lymphocytes at health (no virus and long time) as a characteristic value both for the lymphocytes (infected or not) and the virus.

For every model, we look for fixed points and study their stability. A fixed point of the model is supposed to represent a biological state lasting. In most articles, a fixed point is even considered as the state during the second phase where the viremia increases slowly but is not constant yet. The time scales are not made precise and so it is not so contradictory.

Throughout the article, we call health the state where there is no virus and only uninfected lymphocytes. In addition, we call seropositivity the state where viruses coexist with lymphocytes ($V \neq 0$). Notice that the link of our denomination with what is usually called “seropositivity” is not straightforward. We also define a seropositivity fixed point to be admissible if the fields are positive.

We gather here some mathematical study of well-known models. These results are already known throughout the literature. Indeed one may find in the article of de Leenheer and Smith [11], and an extension of Wang and Li [42], a very elegant way to study some of these models. In these articles, the authors use an abstract characterization of the 3D systems of ordinary differential equations that enable to have in a very elegant way the nature of the fixed points, limit cycles and stability thanks to general results on ordinary differential equations. They crucially use the decoupling in their 3D analysis that *a priori* cannot apply to any fully 4D system.

A thorough study of numerous models is also done in [8]. In this article, the authors point out that the fixed point viremia (V^*) is too dependent on the drug efficacy and that intermediate levels of virus are too low to be realistic (10^{-10} and so). They try numerous modifications, most of which do not improve the behavior. But they provide some compartment-like models that do not support those two critics.

2-1 Perelson’s model

In the review [32] (and numerous other papers with various coauthors), A. Perelson proposes a dynamical system to describe the interaction of HIV virus with CD4 lymphocytes. The model uses four fields that we will denote with our notations to ease comparisons: uninfected lymphocytes (T), infected lymphocytes (U), infectious *free* viruses

(V) and uninfected *free* viruses (W). After non-dimensionalizing with respect to the amount of lymphocytes in a safe body (and a given volume), the system reads:

$$(1) \quad \begin{cases} \frac{dT}{dt} = \beta(1 - T) - \delta_P VT \\ \frac{dU}{dt} = \delta_P VT - \alpha U \\ \frac{dV}{dt} = a\theta U - \sigma_P V \\ \frac{dW}{dt} = a(1 - \theta)U - \sigma_P W \end{cases}$$

In this system, when the parameters used by Perelson appear in terms that do not appear in our model, they are denoted with his notation with an index P . This model is already studied for instance in an article of Nowak and Bangham of 1996 [29].

2-1-1 Fixed points

One may state the following theorem concerning the fixed points of (1).

Theorem 1. *There exists only two fixed points to system (1). The first one is “health”: $(T^*, U^*, V^*, W^*) = (1, 0, 0, 0)$. The second one (seropositivity) reads:*

$$(2) \quad T^* = \frac{\alpha\sigma_P}{a\delta_P\theta}, \quad V^* = \frac{\beta}{\delta_P} \left(\frac{1}{T^*} - 1 \right), \quad W^* = \frac{1 - \theta}{\theta} V^*, \quad U^* = \frac{\sigma_P}{a\theta} V^*.$$

The seropositivity is admissible ($V \geq 0$) under the condition that

$$(3) \quad a\delta_P\theta - \alpha\sigma_P > 0.$$

The proof of this theorem is easy and left to the reader.

2-1-2 Stability of fixed points

So as to evaluate the local stability of fixed points, one must compute the Jacobian matrix dF of the right hand side:

$$(4) \quad dF(T^*, U^*, V^*, W^*) = \begin{pmatrix} -\beta - \delta_P V^* & 0 & -\delta_P T^* & 0 \\ \delta_P V^* & -\alpha & \delta_P T^* & 0 \\ 0 & a\theta & -\sigma_P & 0 \\ 0 & a(1 - \theta) & 0 & -\sigma_P \end{pmatrix}.$$

In the case of “health”, $(T^*, U^*, V^*, W^*) = (1, 0, 0, 0)$ it looks:

$$(5) \quad dF(1, 0, 0, 0) = \begin{pmatrix} -\beta & 0 & -\delta_P & 0 \\ 0 & -\alpha & \delta_P & 0 \\ 0 & a\theta & -\sigma_P & 0 \\ 0 & a(1 - \theta) & 0 & -\sigma_P \end{pmatrix}.$$

It enables to state a theorem of conditional stability for “health”.

Theorem 2. *Health as a fixed point is stable if and only if*

$$(6) \quad a\delta_P\theta - \alpha\sigma_P < 0.$$

The proof is very simple and left to the reader. The eigenvalues are real and take the values $-\beta, -\sigma_P, 1/2(-\alpha - \sigma_P \pm \sqrt{(\alpha - \sigma_P)^2 + 4a\delta_P\theta})$. The admissibility of the unstable direction can also be checked.

In the case seropositivity may occur, one may state the following theorem.

Theorem 3. *Under the admissibility assumption (3), the seropositivity fixed point (2) is stable.*

- Proof of Theorem 3.

Apart from $\lambda = -\sigma_P$, the eigenvalues satisfy:

$$\begin{vmatrix} \lambda + \beta + \delta_P V^* & 0 & \delta_P T^* \\ -\delta_P V^* & \lambda + \alpha & -\delta_P T^* \\ 0 & -a\theta & \lambda + \sigma_P \end{vmatrix} = 0,$$

or $\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0$ with

$$(7) \quad b_1 = \frac{1}{\alpha\sigma_P}(\beta a\delta_P\theta + \alpha\sigma_P(\alpha + \sigma_P)), \quad b_2 = \frac{\beta a\delta_P\theta}{\alpha\sigma_P}(\alpha + \sigma_P), \quad b_3 = \beta(a\delta_P\theta - \alpha\sigma_P).$$

We need to use the Routh-Hurwitz Criterion ([21] p. 490) that gives necessary and sufficient conditions ensuring that the roots of the cubic polynomial have positive real parts. In our case, this criterion reads:

$$\Delta_1 = b_1 > 0, \quad \Delta_2 = \begin{vmatrix} b_1 & 1 \\ b_3 & b_2 \end{vmatrix} > 0, \quad \Delta_3 = \begin{vmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ 0 & 0 & b_3 \end{vmatrix} > 0.$$

The first condition is obviously satisfied. Thanks to condition (3), the third condition is equivalent to the second one. It happens that Δ_2 can be computed:

$$(8) \quad \Delta_2 = \frac{1}{\alpha^2\sigma_P^2}(\beta a\delta_P\theta + \alpha\sigma_P(\alpha + \sigma_P))(a\beta\delta_P\theta(\alpha + \sigma_P) + \alpha^2\sigma_P^2) - \beta(a\delta_P\theta - \alpha\sigma_P),$$

and this term is obviously positive because the only negative term is compensated by one of the expanded terms. \square

2-1-3 Some numerical simulations

So as to have simulations comparable with the other models studied in the present article, we use the same values of parameters as previously:

$$\beta = 0.01 \text{ day}^{-1}, \quad \alpha = 0.7 \text{ day}^{-1}, \quad a = 250 \text{ day}^{-1}.$$

Moreover, some other parameters were the same as in the Snedecor's model and we used the same values:

$$\delta_P = 0.0125 \text{ day}^{-1}, \quad \sigma_P = 2 \text{ day}^{-1}.$$

So as to be in the regime of health stable, we used $\theta = 0.1$. As can be checked on Figure 1, health is stable, although it needs numerous days to come back to health. The qualitative evolution of the lymphocytes and viruses is comparable to the one of Snedecor's Model

in Figure 4. The uninfected lymphocytes decrease to their minimum value (0.999625) in about six days. Then some hundreds of days are needed to get sufficiently close to 1.

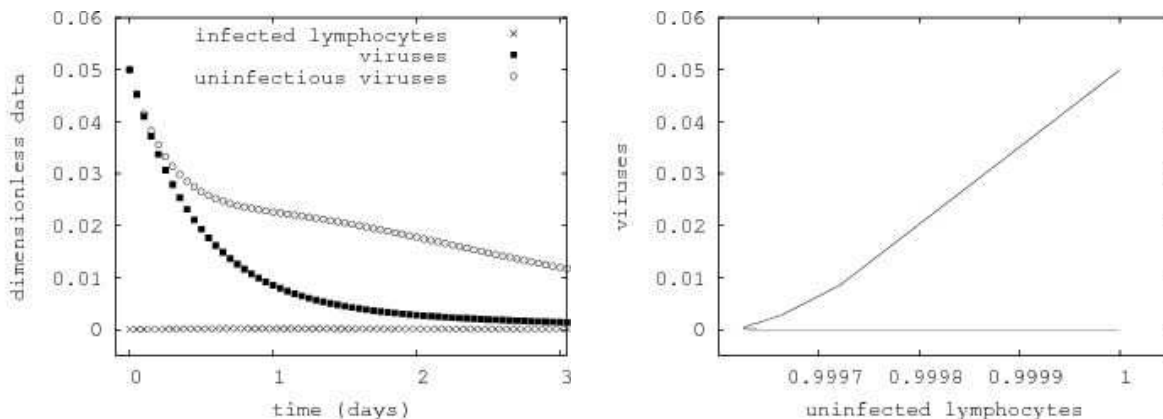


Figure 1. Numerical results for Perelson’s model with four equations. Case where the health is stable. Short time evolution on the left (3 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution.

So as to have a stable seropositive state, we only change θ for $\theta = 0.6$. Results can be seen on Figure 2. The global dynamics converges to the seropositivity with oscillations that could be a model of the ‘blips’. The maximum value of the free virus (about 2.2) is reached at day 39. Then the uninfected lymphocytes decrease until 0.599 at day 58. The minimum value of virus (0.019525) happens on the 116th day and the cycle goes on as shown in Figure 2 right. Such oscillation are sometimes interpreted as the “blips” (sudden bursts of viremia).

Notice that A.S. Perelson has discussed this model by proposing other terms for the infection (equation (10) in [10]), the immune system generation of T cells and of effectors, with and without saturation [10].

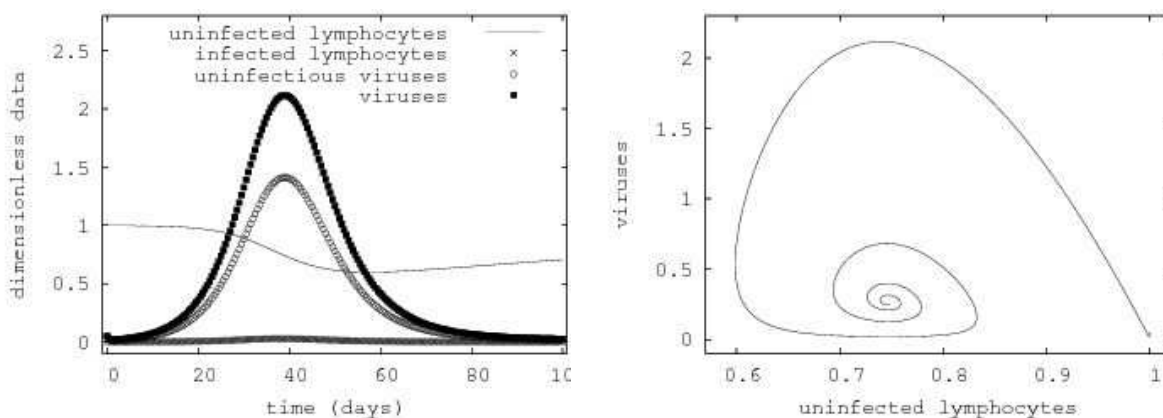


Figure 2. Numerical results for Perelson model with four equations. Case where the seropositive state is stable. Relatively short time evolution on the left (200 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution.

2-2 A reduced Snedecor's model

In [39], the author gives three models of the multiplication of virus HIV-1. Her goal is to model both drug resistance, the different behaviors in the lymphatic tissue and the peripheral blood, but also the immune system. Distinguishing the blood and lymphatic tissues drives the author to have numerous constants that model the fluxes between these body parts and enriches her model.

In order to have a common basis with other models, we need to reduce the above mentioned models to make their main features comparable with the features of other models. After non-dimensionalizing the three fields with respect to the health value of lymphocytes ($T^* = 2.5 \cdot 10^{11}$), we are lead to only one model in which the uninfected lymphocytes are denoted by T , the infected ones by U and the virus by V . We take the values of the parameters in the same body part (lymphatic tissue). The reduced Snedecor's model is written:

$$(9) \quad \begin{cases} \frac{dT}{dt} &= \beta(1 - T) + \frac{r_S}{\gamma_S + V}(T - 1) - (1 - \alpha_S)\beta_S VT \\ \frac{dU}{dt} &= +(1 - \alpha_S)\beta_S VT - \alpha U \\ \frac{dV}{dt} &= aU - \sigma_S V - \beta_S VT. \end{cases}$$

In this system, when the parameters used by S. Snedecor appear in terms that do not appear in other models, they are denoted with her notation with an index S . For instance, the division rate of T cells is $r_S = 0.004 \text{ day}^{-1}$, the treatment efficacy is $\alpha_S \in [0, 1]$, and the viral clearance is $\sigma_S = 2 \text{ day}^{-1}$. After non-dimensionalizing, the other parameters become

$$\beta_S = 0.0125 \text{ day}^{-1}, \gamma_S = 4 \times 10^{-5}, \beta = 0.01 \text{ day}^{-1}, \alpha = 0.7 \text{ day}^{-1}, \text{ and } a = 250 \text{ day}^{-1}.$$

2-2-1 Fixed points

In the present subsection, we prove the following proposition:

Proposition 4. *There exists a threshold*

$$(10) \quad \alpha_{S4} = 1 - \frac{\alpha(\beta_S + \sigma_S)}{a\beta_S}$$

such that if the efficacy parameter α_S is above α_{S4} then health is the only fixed point. If $\alpha_S < \alpha_{S4}$ there are two fixed points: health and a seropositivity.

- Proof of Proposition 4.

The search for fixed points gives two possibilities.

The first one is health: $T^* = 1, U^* = 0, V^* = 0$.

The existence of the second one depends on the therapy's efficacy parameter α_S . Different critical values of α_S will appear in the discussion. The solution for T is

$$T^* = \frac{\sigma_S/\beta_S}{\frac{a(1-\alpha_S)}{\alpha} - 1},$$

and is drawn in Figure 3 (left) with an infinite value for $\alpha_S = \alpha_{S3} = 1 - \alpha/a = 0.9972$. So, should a drug be very efficient ($\alpha_S > \alpha_{S3}$), then $T^* < 0$ and health would be the only solution. Then the solution V^* is a non-negative solution of the second order equation:

$$(11) \quad V^2(1 - \alpha_S)\beta_S T^* - V((r_S - \beta)(T^* - 1) - (1 - \alpha_S)\beta_S \gamma_S T^*) + \beta \gamma_S (T^* - 1) = 0.$$

Numerically, it seems that the discriminant is non-negative (see Figure 3 right) but indeed, it is negative between $\alpha_{S1} \simeq 0.54920378$ and $\alpha_{S2} \simeq 0.5492747378$ and the minimum is about -2×10^{-13} ! Notice that when perturbing the parameters this behavior remains. Except for α_S not too close to 1, the discriminant is small (see Figure 3 right). We have drawn in Figure 3 (center) the only admissible solution V^* as a function of α_S . It is then simple to have $U^* = (1 - \alpha_S)\beta_S V^* T^* / \alpha$.

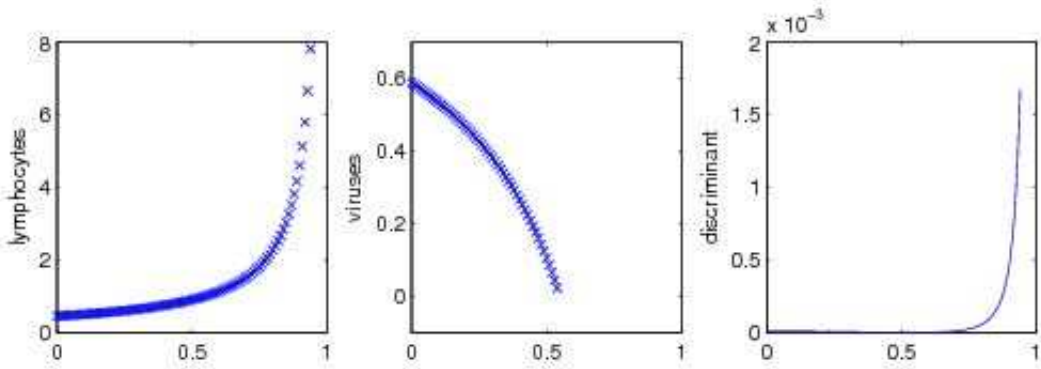


Figure 3. The fixed points T^* (lymphocytes), V^* (virus) and the discriminant of (11) as a function of the treatment efficacy α_S .

If we take care of retaining only admissible solutions ($(T^*, U^*, V^*) \geq 0$), we must force $T^* \geq 0$ or $\alpha_S \leq \alpha_{S3}$. Moreover, if T^* crosses 1 (for $\alpha_S = \alpha_{S4} = 0.5492$ exactly see (10)), the sign of the constant term in (11) changes and so does one solution V of (11). One may then summarize the discussion for T^* , and the two solutions V_1^* and V_2^* of (11) in Table . Indeed, there exists a non-health solution only for $\alpha_S \leq \alpha_{S4}$. Such a fixed point can be named seropositive solution. \square

α	0	α_{S4}	α_{S1}	α_{S2}	α_{S3}	1
T^*	+	+	+	+	+	-
$T^* - 1$	-	+	+	+	+	-
V_1^*	-	-	$V_1^* \in \mathbb{C}$	-	-	+
V_2^*	+	-	$V_2^* \in \mathbb{C}$	-	-	+
solution	(T^*, V_2^*)	\emptyset	\emptyset	\emptyset	\emptyset	\emptyset

Table 1. Second fixed point existence for reduced Snedecor's model.

2-2-2 Stability

Since the domain of admissible fixed points is not regular, the study of stability through the eigenvectors and eigenvalues at a corner (such as health) needs to be more precise. We define admissible directions to prohibit directions that do not enter the domain:

Definition 5. Let $X \mapsto f(X)$ a smooth function and the associated dynamical system $X'(t) = f(X)$. Let us denote \mathcal{B} the biologically admissible domain (all biological fields non-negative). Let X^* be a fixed point of a dynamical system ($f(X^*) = 0$) at the boundary $\partial\mathcal{B}$, and (λ, u) one of its eigenvalue/ eigenvector.

The eigenvector u is defined as admissible only if $\lambda > 0$ and either $X^* + \varepsilon u$ or $X^* - \varepsilon u$ for positive ε enters the domain.

The following proposition investigates the fixed points stability:

Proposition 6. Let α_{S4} as defined in (10). When health is the only fixed point ($\alpha_S > \alpha_{S4}$) it is stable. When there are two fixed points ($\alpha_S < \alpha_{S4}$), health is unstable in one admissible direction.

- Proof of Proposition 6.

The Jacobian matrix of the second member of (9) enables us to study the local behavior of the solutions. It is:

$$(12) \quad \begin{pmatrix} \frac{r_S V^*}{\gamma_S + V^*} - \beta - (1 - \alpha_S)\beta_S V^* & 0 & -(1 - \alpha_S)\beta_S T^* + \frac{r_S \gamma_S (T^* - 1)}{(\gamma_S + V^*)^2} \\ (1 - \alpha_S)\beta_S V^* & -\alpha & (1 - \alpha_S)\beta_S T^* \\ -\beta_S V^* & a & -\sigma_S - \beta_S T^* \end{pmatrix}.$$

In the case of the first fixed point (health $(T^*, U^*, V^*) = (1, 0, 0)$), the characteristic polynomial is $-(\beta + \lambda)(\lambda^2 + \lambda(\alpha + \sigma_S + \beta_S) + \alpha(\sigma_S + \beta_S) - (1 - \alpha_S)a\beta_S)$. The discriminant of the second order polynomial is $(\alpha - \sigma_S - \beta_S)^2 + 4(1 - \alpha_S)a\beta_S > 0$. So the roots are real and it is possible to discuss the sign of the roots. The already met threshold value $\alpha_{S4} = 0.5492$ (exactly see (10)) is still the key value for discussing on α_S . If $\alpha_S > \alpha_{S4}$, health is alone (*cf.* Theorem 4) and the roots are negative, so it is locally stable. If $\alpha_S < \alpha_{S4}$, there are two stable and one unstable eigenvector. We easily check that the unstable eigenvector at this fixed point (health), located at a corner of the domain, enters the domain in the sense that one direction along this eigenvector (among the two) lets all the fields be non-negative. So this direction of instability is admissible. \square

We checked numerically that the locally stable fixed point ($\alpha_S > \alpha_{S4}$: health alone) remains stable even under non-small perturbations. In Figure 4, we draw the dynamics of stable health. In this computation, we take the same parameters as Snedecor:

$$r_S = 4 \times 10^{-3} \text{ day}^{-1}, \sigma_S = 2 \text{ day}^{-1}, \beta_S = 1.25 \times 10^{-2} \text{ day}^{-1}, \gamma_S = 4 \times 10^{-5}, \\ \beta = 0.01 \text{ day}^{-1}, \alpha = 0.7 \text{ day}^{-1}, a = 250 \text{ day}^{-1},$$

and for the specific case of health stable, we take $\alpha_S = 0.6 > \alpha_{S4}$ for the treatment efficacy. The qualitative evolution of the pair lymphocytes-virus is comparable to the one

of Perelson's model presented on Figure 1. The number of virus loses a factor 5 in 3 days typically.

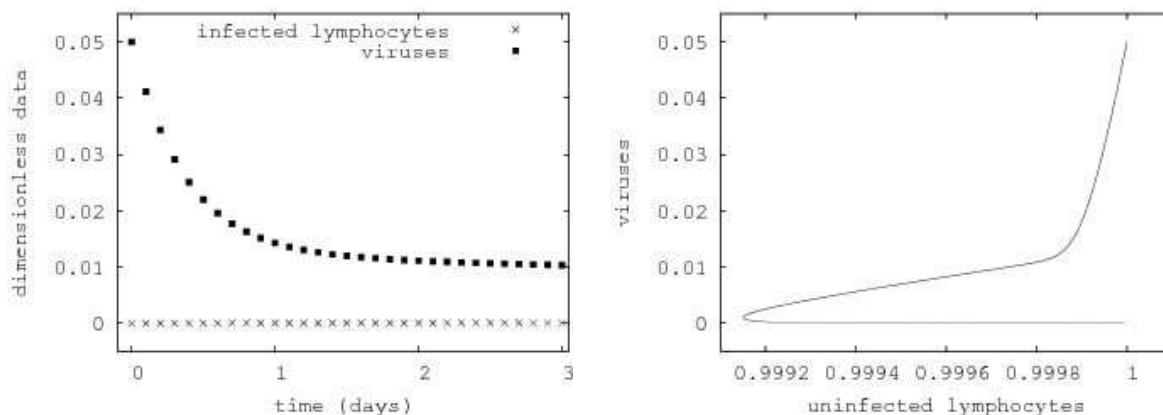


Figure 4. Numerical results for Snedecor model with three equations. Case where the health is stable. Short time evolution on the left (3 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution.

In the case where there exists also a second fixed point (seropositivity: $\alpha_S < \alpha_{S4}$), even odd initial conditions like $(T_0, U_0, V_0) = (1, 1, 1)$ lead to the second fixed point available. This second fixed point happens to be numerically locally stable as can be seen on Figure 5 where the parameters are the same as Snedecor's, as recalled above, except the therapy efficacy $\alpha_S = 0.3$. In this figure, one may check that health is locally unstable as the solution evades health to get closer to a seropositivity. Notice that this second fixed point can be interpreted as seropositivity. But as it is stable, the model predicts no death ... The oscillations around the fixed point could be seen as the observed 'blips' (sudden and brief bursts of viremia). But the time scale at which the system is sufficiently close to the fixed point is more than one year while in reality, the first phase of the infection takes some weeks.

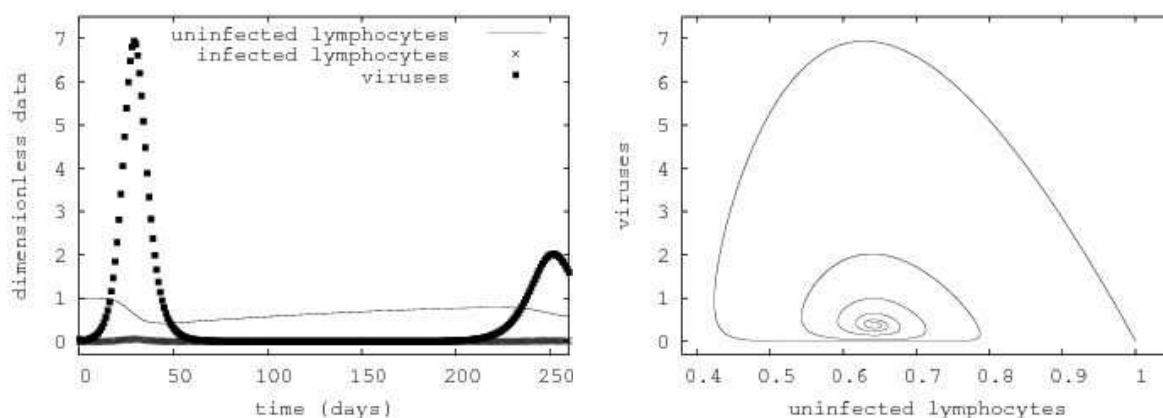


Figure 5. Numerical results for Snedecor model with three equations. Case where the seropositive state is stable. Relatively short time evolution on the left (260 days) and phase plane for lymphocytes and viruses on the right for a 900 days evolution.

2-2-3 Some comments

The disappearance of the second fixed point (seropositivity) when α_S increases could be meaningful. Yet in real life, even for very efficient drugs, the virus kills. Despite highly active multitherapies, over ten percent of AIDS patients face therapeutic escape due to viruses which were undetectable for years while developing resistance against all approved drugs. So, to what extent can *any* stable fixed point be meaningful? This criticism is valid for all the models analyzed in this article.

The original model makes a distinction between the drug-resistant and drug-sensitive viruses which is meaningful. But it makes no difference between infectious and non-infectious viruses.

In a sense, the Snedecor's model takes into account the immune system. But it was proved that "the growth fraction of CD4⁺ (...) was correlated (...) with viral load" [37]. No such correlation appears in her model. Indeed, the immune system is modeled only through its exhaustion when V is too large. The susceptibility to produce T in the presence of virus is not modeled as it is done in [17] with a term $\Sigma(V/T)T$.

If $\alpha_S = 0$ (no treatment), the coefficient before the terms of disappearance of T , of V and appearance of U is the same. The identity of the V and T terms indicates that in this model, each time a virus infects a T , it disappears. So viruses are assumed to be *free viruses*. Indeed, the author defines her field V as "free virus". Similarly, the term $-\beta_S VT$ in the evolution of V is by no means a model of the immune system response. Moreover, the author defines parameter β_S as "infection rate of ... T cells by ... virus". We emphasize here the coherence of Snedecor's model which takes into account "free virus": a free virus *disappears* each time it infects a lymphocyte. This property is not satisfied by most other models as it is stressed in [11] which emits the same critic (p. 1314) but argues that this neglect does not change the main features of the models.

In this model, viruses disappear only through natural death or infection of a T . So there is no immune system effect. Indeed, σ_S is called "viral clearance (death) rate", but it does not depend on T . This is frequent in HIV modelling, but not realistic unless the immune system is neglected! This is discussed in [32] (pp. 31-32) where the author acknowledges his trouble: "The fact that models with constant $[\sigma_S]$ can account for the kinetics of acute HIV infection is surprising".

2-3 A Nowak and May model

In [30], the authors also propose some models taking the antigenicity into account. In Chapter 12 of their book, they propose various models, suggesting that "antigenic variation generates the long-term dynamics that give rise to the overall pattern of disease progression in HIV infection" (p. 124). Their "general idea was that the rapid genetic variation of the virus generates over time viral populations (quasispecies) which are more and more adapted to grow well in the microenvironment of a given patient" (p. 124).

According to their best model, "The immune system and the virus population are in a defined steady-state only if the antigenic diversity of the virus population is below a

certain threshold value. If the antigenic diversity exceeds this threshold [then] the virus population can no longer be controlled by the immune system.” ([30] p. 125). Such a behavior seems meaningful. With our notations their model writes:

$$\begin{aligned}\frac{dV_j}{dt} &= V_j(r_{NM} - p_{NM}T_j - q_{NM}Z), \quad \forall i = 1, \dots, N \\ \frac{dT_j}{dt} &= c_{NM}V_j - b_{NM}T_j - UV T_j, \quad \forall i = 1, \dots, N \\ \frac{dZ}{dt} &= k_{NM}V - b_{NM}Z - u_{NM}V Z.\end{aligned}$$

where $V = \sum_j V_j$ and Z denotes the “cross-reactive immune response directed against all different virus strains” ([30] p. 130).

In the models they study, they set various parameters to values assumed to be constant. More precisely, they assume the parameters do not depend on N . Why is it impossible? Assume there were only linear and non-linear terms like:

$$\frac{dV_j}{dt} = r_{NM} V_j - p_{NM} T_j V_j \quad \forall j.$$

What is the integrated (in j) equation? If we assume all the populations T_j and V_j are independent on j , then $T_j = \sum_k T_k/N = T/N$ and $V_j = V/N$. Then the integrated (in j) equation is:

$$\frac{dV}{dt} = r_{NM} V - \frac{p_{NM}}{N} T V \quad \text{if } T_j = \frac{T}{N}, V_j = \frac{V}{N}.$$

Since it is the only equation biologically measurable, the measured parameter in an experiment will be p_{NM}/N and not p_{NM} . In other words $p_{NM} = O(N)$. This should modify the mathematical study.

The conclusion of their study is that *in their models* “the cross-reactive immune responses provide a selection pressure *against* antigenic variation, while strain-specific responses select *for* antigenic variation” [30].

3) A new model with antigenic variable

The biological diversity of antigenicities is already modeled in [1, 17, 30, 31]. Yet, in these references, the authors use a finite number of possibilities, most of the time in “flat” spaces of antigenicities. Since the antigenicity is a “microscopic” and unmeasurable quantity, these models (including ours) still need to prove they provide a significant insight.

So as to build up our model, we will follow the biological description of the various phenomena concerning the various fields: we denote $T_i(t)$ the uninfected lymphocytes of antigenicity $i \in \mathcal{A}$, $U_i(t)$ the infected lymphocytes of antigenicity i , $V_i(t)$ the infectious viruses of antigenicity i and $W_i(t)$ the non-infectious viruses of antigenicity i . The space \mathcal{A} is still undetermined. The best set is not known, but when trying to get a macroscopic model (by integration of antigenicity i), we will need to investigate the various possibilities

to get a limiting operator for $(t, i) \in \mathbb{R}^+ \times \mathcal{A}$. This is the issue of a forthcoming paper. We will also need the sum of each field:

$$T = \sum_j T_j, U = \sum_j U_j, V = \sum_j V_j \text{ and } W = \sum_j W_j.$$

3-1 Lymphocytes evolution

The variation in time of $T_j(t)$ (dT_j/dt) must take into account various phenomena:

- a natural death and generation modeled by a term like:

$$(13) \quad \left(\frac{dT_j}{dt} \right)_{\text{natural}} = -\beta_j T_j + \gamma_j$$

It has also been proposed a logistic term (for instance in [10]), but it prohibits high levels of T cells.

- when a virus (V_j or W_j) of antigenicity j is detected, the immune system generates lymphocytes of the same antigenicity to fight them. This can be modeled by an exponential multiplication whose time constant is roughly proportional to the inverse of the number of viruses $V_j + W_j$. This is a ‘‘Lotka-Volterra’’ type term that we met also in [29, 31, 10] for the cross-antigenic immune action (CTLs or effectors):

$$(14) \quad \left(\frac{dT_j}{dt} \right)_{\text{growth}} = +C_j(V_j + W_j) T_j$$

The generation of lymphocytes by the immune system is studied in [44]. The authors model it as a logistic growth $+CVT(1 - T/T_{max})$ (also discussed critically in [8]) to represent the ‘‘autocatalytic cell division’’. But surprisingly the effect of the immune system against virus or infected lymphocytes is neglected. They conclude that the ‘‘initial number of the HIV-specific CD4-T cells’’ is crucial. Yet, it depends on the definition of the initial time. At the very first time, it is necessarily small (for 5 liters of blood). Such a logistic term (whatever the infection term and wherever it models the natural growth or the immune system reactivity) would force the immune system not to have any overshoot of T cells ($T > T_{max}$). This is not realistic.

In their article [10], de Boer and Perelson investigate the immune system production of T and infection modeling. In this central article, but on macroscopic models, they propose a term like ours and even saturate it (their (13)). As they conclude ‘‘one may model disease progression by allowing the virus to evolve immune-escape variants increasing the diversity of the quasi-species [references proposed]. Since this requires high-dimensional models, this form of disease progression is not considered any further here’’ (p. 208). Such a study is the goal of the present article.

In [17], the authors model ‘‘antigenicity’’ through a real variable. At first glance, one may believe that their term $\Sigma((\eta + V)/T)T$ (with our notations), where η is the resource, is like our’s for infection. Although the Σ function has the same properties as our J (see later), our term models infection, while their’s models the reactivity of the

immune system. So they even have opposite sign. Their term should be compared to our $C_j(V_j + W_j)T_j$ except that they bound the importance of V for production of T , so modeling a kind of exhaustion of the immune system very interesting.

the viruses attack lymphocytes independently of the antigenicity. More precisely, there are two regimes:

+ If $V/T \leq 1$ as a virus may attack only one lymphocyte T_k [12], the ratio of attacked lymphocytes is V/T . If we introduce a time constant, it gives a term like:

$$\left(\frac{dT_j}{dt}\right)_{\text{infection}} \simeq -\frac{1}{\tau_j} \left(\frac{V}{T}\right) T_j, \quad \text{if } \frac{V}{T} \leq 1.$$

+ If $V/T \geq 1$, as a virus may infect only one lymphocyte [12] only part of the viruses may infect the lymphocytes. More precisely, no more than T viruses may infect. In other words, the ratio of attacked lymphocytes may not be superior to 1. There is a kind of saturation of the efficacy of predators V_j while the number of lymphocytes decreases with time. Up to a time constant, we saturate the infection ratio:

$$\left(\frac{dT_j}{dt}\right)_{\text{infection}} \simeq -\frac{1}{\tilde{\tau}_j} T_j, \quad \text{if } \frac{V}{T} \geq 1.$$

+ If $V/T \sim 1$, the two terms must match by continuity, and so $\tau_j = \tilde{\tau}_j$. This complex behavior may be compiled due to a non-linear function J of the “min-mod” type:

$$(15) \quad J(\xi) = \begin{cases} \xi & \text{if } \xi \ll 1 \\ 1 & \text{if } \xi \gg 1 \end{cases}.$$

The effect discussed here can be modeled by

$$(16) \quad \left(\frac{dT_j}{dt}\right)_{\text{infection}} = -\frac{1}{\tau_j} J\left(\frac{V}{T}\right) T_j.$$

In order to justify our essentially linear term in (16) in an other way, we make hereafter various assumptions and wonder how our term should behave upon these assumptions, seen how reality behaves.

Firstly we assume that we double V_j (and only it) without changing V or to a noticeable extent, while V/T remains small. Then the effect does not change and so the term must not change. This prohibits a simple term like $-V_j/\tau_j$.

Secondly we assume that all the V_i are doubled (including V_j) and so V is doubled too for a still small V/T . Obviously the effect is doubled. So the modeling term should depend on V_i (whatever i) only through V .

Thirdly we assume that we double T_j , and only it (not the more general T_i), without changing T (or to a noticeable extent) nor V (and still $V/T \ll 1$). Then the effect doubles. It proves that the term should depend linearly on T_j .

At this stage, we have a linear dependance both in V and T_j . If we do not take care, we might deduce a $-VT_j/\tau_j$ term that leads to $-VT/\tau$ when integrated over j . We still need to explain why our term *may not* depend linearly on T although it depends on T_j .

To that end, we make the assumption that we double *all* the T_i (including T_j). Since a virus may infect only one lymphocyte at a time, the effect should not be modified

as the limiting parameter is not the amount of lymphocytes but the amount of viruses. Indeed, assume a patient has caught any disease that makes his immune system produce lymphocytes, it should not make the HIV infection more virulent, in the first stage where $V/T \ll 1$. This is satisfied by our term and not by $-VT_j/\tau_j$.

Notice that by summing over j and assuming τ_j constant, we find $dT/dt = -V/\tau$ in the first regime ($V \leq T$) and $dT/dt = -T/\tau$ in the second regime ($V \geq T$). Moreover, if $V \gg T$ the effect does not depend on V as the limiting factor is the presence of lymphocytes. These are expected as they seem natural. Most authors have considered that the infection term should be quadratic like $-VT/\tau$ (mass-action). This conclusion may not be drawn from our considerations. It is even denied as the regimes exclude one another. It must be recalled that all the models are designed to be tested with the only biologically meaningful fields $T+U$ and $V+W$. Yet the phenomenon we model is modeled by two terms of opposite signs that simplify in the evolution equation of $T+U$. So it should never be measured in macroscopic fields. Yet, it translates into the model a crucial biological reality. So this term would deserve to be tested and such a test is postponed to a forthcoming research.

A term very similar to ours can be found in the article of de Boer [9] who uses a Michaelis-Menten kinetic: $-\beta TV/(h+T+V)$ for the infection (and parameters h and β). Such a term saturates the infection when there are numerous $T+V$. But for moderate or low $T+V$, the term is essentially quadratic (mass-action). The authors critic models “for acute HIV infection [that] tend to ignore saturations effects and have simple “mass-action” terms”. They also give a toy model

$$\frac{dV}{dt} = (r - kT)V,$$

for which the infection would get cleared as soon as $T > r/k$ “which is *independent* of the size of the pathogen population ... which is entirely unrealistic”. Their model is extended in [1] to take into account “specific parts of the viral proteins, i.e., epitopes” that are the same as our antigenicities. But no real mutation is modeled. Their equations do not model the immune system effect against the virus.

An explicit discussion of such a term is also done in [8] (p. 37) where the authors discuss the classical mass-action term for infection. As they say, this notion “is valid when the system is well mixed [...] and there are significant quantities of each reactant.”. They propose various terms which have the same behavior as ours. When they try a Michaelis-Menten like term (such as $kVT/(\alpha + V + T)$ or our term), it does not prohibit their two main critics for admissibility of models: it reaches too low viremia that should mean extinction and still has a strong dependence of the fixed point V^* on the drug efficacy. So they reject such an infection term. Why this critic does not apply to our model? First their definition of V is for *free* virus. So vanishing viremia does not prove there is no more virus in the body. Second the immune system is indeed sufficiently strong to eradicate any *given* antigenicity. Only the endless mutation and sanctuaries kill the patient. So “macroscopic” models, such as the ones they consider, should not

be able to model the race between the immune system and the virus whose *differences* of velocities may explain the slow eradication of lymphocytes. This is more likely to be contained in “microscopic” models taking antigenicity and mutation into account. Notice that the authors exhibit some models that do not have the two main drawbacks. They are compartment-like models where the drug is not efficient in a compartment. So, in a sense they are rather similar to full our model with $N > 1$.

In [17], the authors model “antigenicity” through a real variable. Their infection term is of the shape $VT/(1+V)$ which does not depend on antigenicity, models a saturation effect on V but not on T .

The consolidated evolution equation for the lymphocytes is the sum

$$(17) \quad \begin{aligned} \frac{dT_j}{dt} &= \left(\frac{dT_j}{dt}\right)_{\text{natural}} + \left(\frac{dT_j}{dt}\right)_{\text{growth}} + \left(\frac{dT_j}{dt}\right)_{\text{infection}} \\ \frac{dT_j}{dt} &= -\beta_j T_j + \gamma_j + C_j(V_j + W_j) T_j - \frac{1}{\tau_j} J \left(\frac{V}{T}\right) T_j. \end{aligned}$$

3-2 Infected lymphocytes evolution

The evolution of infected lymphocytes depends on various effects:

- the infection of a lymphocyte by a virus (same term as for T_j (16) with a plus sign) generates an infected lymphocyte U_j :

$$\left(\frac{dU_j}{dt}\right)_{\text{generation}} = +\frac{1}{\tau_j} J \left(\frac{V}{T}\right) T_j;$$

- and a natural death:

$$\left(\frac{dU_j}{dt}\right)_{\text{natural}} = -\alpha_j U_j.$$

Notice, that the death rate of infected lymphocytes is about 70 times greater than that of uninfected lymphocytes. Indeed, in [39], the author proposes various articles among which [16] for the death rate of infected lymphocytes and [37] for the death rate of uninfected lymphocytes. The ratio of these rates is about 70.

To summarize, we have:

$$(18) \quad \frac{dU_j}{dt} = \left(\frac{dU_j}{dt}\right)_{\text{generation}} + \left(\frac{dU_j}{dt}\right)_{\text{natural}} = +\frac{1}{\tau_j} J \left(\frac{V}{T}\right) T_j - \alpha_j U_j.$$

3-3 Infectious and non-infectious virus evolution

The multiplication of viruses is the main phenomenon and occurs in the infected lymphocytes. So the sum in j growth term of $V + W$ must be

$$(19) \quad \sum_j \left(\frac{d(V_j + W_j)}{dt}\right)_{\text{growth}} = \left(\frac{d(V + W)}{dt}\right)_{\text{growth}} = aU,$$

as taken into account by [30], [39] and [32] (whether they distinguish infectious and non-infectious virus or not).

We do not distinguish infecting and free viruses as the other authors do. This would have led us to three identical terms (up to the sign). Two terms for the infection of T lymphocytes in the evolution equations of T (sign -) and of U (sign +). One more term for the disappearance of a virus in the evolution equation of V (sign -). The latter is almost always omitted. One potential justification for this omission is offered by the authors of [33] (p. 10) who argue that the term $k_i T_i V$ is small in comparison with cV . In [29], the authors say (note 20) that “if a large number of virus particles is produced, only a few of which will end up in host cells, then a constant death term is a reasonable approximation”.

The evolution of virus depends also on mutations. Some of them modify the ability to infect and others the antigenicity. Here, those two properties are considered as independent, as mentioned in the introduction where references are given.

Only one parameter θ measures the probability to mutate to an infectious offspring (necessarily from an infectious virus). So $1 - \theta$ is the probability to mutate to a non-infectious offspring. Since we assume antigenicity and ability to infect are independent, we may assume θ does not depend on j (nor k).

Let us denote S_{kj} the probability to mutate from an antigenicity k (only V_k as W_k does not even infect and so does not mutate) to an antigenicity j (either V_j or W_j) per unit of time. So we have:

$$(20) \quad S_{kj} \geq 0, \quad \sum_j S_{kj} = 1,$$

and S_{kj} depends *a priori* on the number of antigenicities. The offspring of a virus V_k will mutate to V_j with the probability θS_{kj} (the case $k = j$ where there is no mutation is included). So it will mutate to W_j with the probability $(1 - \theta)S_{kj}$.

As a consequence of the assumption that antigenicity and ability to infect are independent, equation (19) can be split into two parts :

$$(21) \quad \left(\frac{dV}{dt} \right)_{\text{growth}} = a\theta U, \quad \left(\frac{dW}{dt} \right)_{\text{growth}} = a(1 - \theta)U.$$

Notice that the value of θ suggested by [40] ranges from 1 to 1/60,000. But [25] found in one experiment a ratio θ close to 1/8. To fix the ideas, we suggest in the following to set $\theta = 1/10$.

The value of S_{kk} is considered as relatively low by the biological community but we have not found any precise and trust-worthy proposition in the literature.

The distribution $k \mapsto S_{kj}$ for $j \neq k$ needs to be non-uniform for a biological reason. As is well known ([4], [23]), there exist mutationnal hot spots in the HIV virus. We may guess these hot spots will elicit non-uniform distribution of the antigenicity during multiplication/mutation. The precise value of the probability $k \mapsto S_{kj}$ is of course an open problem.

3-3-1 Infectious virus

The infectious virus variation (dV_j/dt) depends on various effects.

- The first and most complex is multiplication and mutation. By wondering what takes place in the biology, we are going to determine the fields present in the modeling term.

As multiplication takes place in the infected lymphocytes, if there were no such lymphocytes ($U = 0$), whatever might be the number of (free) viruses, there would be no multiplication and the term would be zero. This would almost occur in the end of the disease. More precisely, as once a virus has infected a lymphocyte, no more viruses may infect it [12], U is a good measure of the total number of infectious viruses. Note that in our model V is the number of free and infecting viruses. So there must be a dependance on U (or U_j at this stage).

As the antigenicity of an infected lymphocyte has no link with the antigenicity of the multiplying virus, the involved field must be U (and not U_j).

As there are mutations from any antigenicity k , the V_k mutate and their offspring is made of either V_j or W_j with probability θS_{kj} or $(1 - \theta)S_{kj}$ respectively. So there must be $\sum_k S_{kj}\theta V_k$ in the modeling term.

What can be the modeling term ? Up to now, we have $U(\sum_k S_{kj}\theta V_k)$ times an unknown term $A(t)$. Once summing over the antigenicity, we must find $a\theta U$. So because of (21), $A(t)$ is such that:

$$\sum_j \left(\frac{dV_j}{dt} \right)_{\text{growth}} = \sum_j A(t)U \left(\sum_k S_{kj}\theta V_k \right) = a\theta U \Rightarrow A(t) = \frac{a}{V},$$

because $\sum_j S_{kj} = 1$. So our modeling term for multiplication with mutation to V_j ($V_k \rightarrow V_j$) is:

$$(22) \quad \left(\frac{dV_j}{dt} \right)_{\text{growth}} = a \frac{U}{V} \sum_k S_{kj}\theta V_k.$$

- attack of the viruses by the lymphocytes of the same antigenicity produced by the immune system:

$$(23) \quad \left(\frac{dV_j}{dt} \right)_{\text{lymphocyte}} = -\xi_j V_j T_j.$$

Once compiled, the evolution equation is:

$$(24) \quad \frac{dV_j}{dt} = \left(\frac{dV_j}{dt} \right)_{\text{growth}} + \left(\frac{dV_j}{dt} \right)_{\text{lymphocyte}} = \frac{aU}{V} \sum_k S_{kj}\theta V_k - \xi_j V_j T_j.$$

3-3-2 Non-infectious viruses

The variation of non-infectious viruses (dW_j/dt) may be modeled by various effects and translated into various terms similar to infectious ones:

- mutation from an antigenicity k (V_k with V_j included) to W_j :

$$\left(\frac{dW_j}{dt} \right)_{\text{growth}} = \frac{aU}{V} \sum_k S_{kj}(1 - \theta)V_k;$$

- attack of the virus by the lymphocytes of the very same antigenicity. Notice that as the immune system may not detect whether a virus is infectious or not the ξ_j must be the same as for V_j :

$$\left(\frac{dW_j}{dt}\right)_{\text{lymphocyte}} = -\xi_j W_j T_j.$$

Once compiled the evolution equation reads:

$$(25) \quad \frac{dW_j}{dt} = \left(\frac{dW_j}{dt}\right)_{\text{growth}} + \left(\frac{dW_j}{dt}\right)_{\text{lymphocyte}} = \frac{aU}{V} \sum_k S_{kj}(1-\theta)V_k - \xi_j W_j T_j.$$

As for V_j , the lymphocytes do attack only the virus of the same antigenicity. Moreover, they cannot make a distinction between infectious or non-infectious viruses.

3-4 The dynamical system

When we collect equations (17), (18), (24) and (25), our model reads finally as said in [15]:

$$(26) \quad \frac{dT_j}{dt} = -\beta_j T_j + \gamma_j + C_j(V_j + W_j) T_j - \frac{1}{\tau_j} J \left(\frac{V}{T}\right) T_j,$$

$$(27) \quad \frac{dU_j}{dt} = +\frac{1}{\tau_j} J \left(\frac{V}{T}\right) T_j - \alpha_j U_j,$$

$$(28) \quad \frac{dV_j}{dt} = \frac{a\theta U}{V} \sum_k S_{kj} V_k - \xi_j V_j T_j,$$

$$(29) \quad \frac{dW_j}{dt} = \frac{a(1-\theta)U}{V} \sum_k S_{kj} V_k - \xi_j W_j T_j.$$

Very simple manipulation enable macroscopic laws to be proven:

$$\begin{aligned} \frac{d(V+W)}{dt} &= aU - \sum_j \xi_j (V_j + W_j) T_j; \\ (30) \quad \frac{d\left[T + U + \sum_j \left(\frac{C_j}{\xi_j} (V_j + W_j)\right)\right]}{dt} &= -\sum_j \beta_j T_j + \sum_j \gamma_j - \sum_j \alpha_j U_j + aU \sum_j \frac{C_j}{\xi_j}. \end{aligned}$$

Since we see no reason why ξ_j or C_j should depend on j , the equation (30) could be considered as a simple linear combination of the integrated versions of (26-29). Such a law could be experimentally checked.

There remains the problem of initial conditions and the way they enter into the evolution model with mutations. Indeed, in most ordinary differential systems, as soon as a function is identically zero in a subdomain, it remains so (Cauchy-Picard Theorem). Moreover, 10^{-20} or 10^{-40} are numerically very different while they both mean “zero”. In simulations of mutation, we will need a quantic jump. All this is postponed to a forthcoming article.

The dynamical system (26-29) depends on several parameters (α_j, β_j, \dots). The meaning of some of them is clear and can be easily found either in the literature or from simple

biological data. In the latter case, parameter identification based on a good methodology enables the numerical resolution of an inverse problem. Such studies can be found in [6, 19, 38].

4) Mathematical properties

Starting from (26-29), we make the various fields dimensionless by using the value of $T_{\text{equil}} = \gamma_j/\beta_j$ at equilibrium as a characteristic value. Then we let $N = 1$:

$$T = \frac{T_j}{T_{\text{equil}}}, \quad U = \frac{U_j}{T_{\text{equil}}}, \quad V = \frac{V_j}{T_{\text{equil}}}, \quad W = \frac{W_j}{T_{\text{equil}}}.$$

We also define dimensionless parameters:

$$\omega = C_j T_{\text{equil}}, \quad \zeta = \xi_j T_{\text{equil}}.$$

With these notations, the system reads:

$$(31) \quad \frac{dT}{dt} = \beta(1 - T(t)) - \frac{T(t)}{\tau} J\left(\frac{V(t)}{T(t)}\right) + \omega(V(t) + W(t))T(t),$$

$$(32) \quad \frac{dU}{dt} = \frac{T(t)}{\tau} J\left(\frac{V(t)}{T(t)}\right) - \alpha U(t),$$

$$(33) \quad \frac{dV}{dt} = a\theta U(t) - \zeta V(t)T(t),$$

$$(34) \quad \frac{dW}{dt} = a(1 - \theta)U(t) - \zeta W(t)T(t).$$

The unknown fields for (31-34) are dimensionless whereas the time variable remains dimensioned (by days). Since we assume there is only one antigenicity ($N = 1$), mutation disappears. Hereafter, we prove the solution remains admissible and exists globally. Then we look for the fixed points and study their stability.

The very elegant method of [11] cannot apply to our system since it is 4D fully coupled even in its simplified form (31-34). Moreover their results (even for their system (8)) do not apply to our system since our infection term is not the mass-action. In addition, they do not study models where the immune system produces T because of infection (our $C(V + W)T$) and their system (8) is not really coupled for W like ours.

4-1 The solution remains admissible

We intend to prove that the system (31-34) is mathematically well posed and biologically meaningful: it does not exhibit negative values of the fields for admissible initial conditions. To that purpose, we make various assumptions on the parameters:

$$(35) \quad \begin{cases} \beta, \tau, \omega, \alpha, \zeta \text{ are real positive and } 0 < \theta < 1, \\ J(\bullet) \text{ is a real function concave over } [0, \infty[, J(0) = 0, J'(0) = 1, \\ J(x) \rightarrow 1 \text{ when } x \rightarrow +\infty \text{ and } J \text{ is bounded on } \mathbb{R}^-. \end{cases}$$

From the biological meaning of the system, we define the set of admissible fields:

$$(36) \quad \mathcal{B} = \{(T, U, V, W), T > 0, U \geq 0, V \geq 0, W \geq 0\},$$

and its interior:

$$(37) \quad \mathring{\mathcal{B}} = \{(T, U, V, W), T > 0, U > 0, V > 0, W > 0\}.$$

Due to the Cauchy-Picard theorem, we know that there exists a local in time solution. The question is then whether this local solution is admissible. Our main result is the following Theorem.

Theorem 7 (Biological consistence). *The solution $(T(t), U(t), V(t), W(t))$ of system (31-34) with an initial condition in \mathcal{B} remains in \mathcal{B} .*

To prove Theorem 7, we will need various lemmas. The first one states that the number of lymphocytes does not vanish in finite time.

Lemma 8. *If the initial condition (T_0, U_0, V_0, W_0) is in \mathcal{B} , then $T(t) > 0$ for all time for which the fields T, U, V, W are defined.*

- Proof of Lemma 8.

Thanks to the Cauchy-Picard theorem [3], we know that for t sufficiently small, $T(t)$ is positive. So if there exists at least one time \tilde{t} such that $T(\tilde{t}) = 0$, then we define t^* to be the smallest and we have $t^* > 0$. Since $J(\bullet)$ is bounded (whatever V and T), (31) writes at that time

$$\frac{dT}{dt}(t^*) = \beta > 0.$$

As a consequence, for t below and sufficiently close to t^* , $T(t) < 0$. But as $T_0 > 0$, from the intermediate value theorem, there exists a t' smaller than t^* for which $T(t') = 0$. This contradicts the assumption that t^* is the smallest and completes the proof. \square

We need now to study the various cases where the initial conditions are either in $\mathring{\mathcal{B}}$ or on the boundary of \mathcal{B} . This will be discussed through some lemmas where the initial condition has either zero, three, two or one initial vanishing fields. In the case of initial condition in the interior of \mathcal{B} , one may state the following Lemma.

Lemma 9 (Zero vanishing initial condition). *If the initial condition of system (31-34) is in $\mathring{\mathcal{B}}$, then the solution remains in $\mathring{\mathcal{B}}$ for any $t \geq 0$ provided it exists.*

- Proof of Lemma 9.

We will discuss the cases where one, two or three fields vanish simultaneously.

- Let us assume W vanishes first and alone (before the other fields) and then let us denote t^* the smallest time for which W vanishes. On $[0, t^*]$, one has:

$$(38) \quad V(t) > 0, U(t) > 0, W(t) \geq 0, W(t^*) = 0,$$

in addition to the fact that $T(t) > 0$ (see Lemma 8). The equation (34) writes $\frac{dW}{dt} = a(1 - \theta)U(t^*) > 0$ because $0 < \theta < 1$ (see the assumption (35)). So, there exists a time \tilde{t} smaller than t^* at which $W(\tilde{t}) < 0$. From the intermediate value theorem, one may conclude that there exists a time smaller than t^* (and than \tilde{t}) at which W vanishes. This contradicts the definition of t^* and so W may not vanish first.

Identical arguments enable to prove that V may not vanish first. To prove that U may not vanish first neither, we assume that t^* is the first vanishing time of U . So, on $[0, t^*]$:

$$(39) \quad U(t) \geq 0, \quad U(t^*) = 0, \quad V(t) > 0, \quad W(t) > 0.$$

Thanks to Lemma 8, one has $T(t^*) > 0$ and so $\frac{dU}{dt}(t^*) = J\left(\frac{V}{T}\right) \frac{T(t^*)}{\tau} > 0$. In a similar way to the two previous cases, one gets a time \tilde{t} smaller than t^* for which $U(\tilde{t}) < 0$. Thanks to the intermediate value theorem, one gets also a time smaller than t^* where U vanishes. This contradicts the definition of t^* . So U may not vanish first neither.

- Let us discuss now the case where two fields vanish simultaneously. The case where V and W vanish simultaneously and alone is impossible for the same arguments as the case where W vanishes first. The case where U and W vanish simultaneously and alone may be treated in the same way as the case of U vanishing first. The only remaining case is if U and V vanish simultaneously (and not W). Let us then define t^* the smallest such vanishing time. The Cauchy-Picard theorem, applied to the system (31-34) with reversed time, enables us to claim that the (unique) solution is also such that

$$\frac{dT}{dt} = \beta(1 - T(t)) + \omega W(t)T(t), \quad \frac{dW}{dt} = -\zeta W(t)T(t), \quad U(t) = V(t) = 0,$$

for all time t in $[t^* - \epsilon, t^*]$ for some $\epsilon > 0$. This contradicts the definition of t^* as the smallest vanishing time.

- In the case where U, V and W vanish at the same time, the proof is the same as for Lemma 10. □

The following Lemma solves the case of three vanishing initial fields.

Lemma 10 (Three vanishing initial conditions). *If the initial condition is $T_0 > 0, U_0 = V_0 = W_0 = 0$, then the solution is unique and is health.*

- Proof of Lemma 10.

The proof relies only on the Cauchy-Picard theorem which states that

$$T(t) = 1 - (1 - T_0) \exp(-\beta t),$$

and the other fields identically zero. □

The next Lemma deals with the case where two initial fields vanish.

Lemma 11 (Two vanishing initial conditions). *If the initial condition is among*

$$(40) \quad T_0 > 0, \quad U_0 = V_0 = 0, \quad W_0 > 0,$$

$$(41) \quad T_0 > 0, \quad U_0 > 0, \quad V_0 = W_0 = 0,$$

$$(42) \quad T_0 > 0, \quad U_0 = 0, \quad V_0 > 0, \quad W_0 = 0,$$

the solution of system (31-34) remains in \mathcal{B} .

- Proof of Lemma 11.

The proof distinguishes various cases.

- In the case (40), the Cauchy-Picard theorem enables us to claim that there exists a solution of (31-34) for which $U(t) = V(t) = 0$, and the fields $T(t), W(t)$ satisfy

$$(43) \quad \frac{dT}{dt} = \beta(1 - T(t)) + \omega W(t) T(t)$$

$$(44) \quad \frac{dW}{dt} = -\zeta W(t) T(t).$$

Let us assume W vanishes at some times. Among these times, we chose t^* to be the smallest. On the compact set $[0, t^*]$, T is continue and so bounded by $\gamma > 0$. So (44) enables to claim

$$\frac{dW}{dt} \geq -\gamma\zeta W \quad \text{then} \quad W(t) \geq W_0 \exp(-\zeta\gamma t) \quad \text{for } t \geq 0$$

which contradicts the assumption that $W(t^*) = 0$. So W may not vanish in finite time and so in the case (40), $W(t) > 0$ for any positive time and $U = V = 0$.

- In the case (41), $\frac{dV}{dt} > 0$ and so $V(t) > 0$ for t small enough. Similarly, for t small enough, $W(t) > 0$. So for t small enough, the solution enters the interior of \mathcal{B} . Such a new initial condition has been adressed in Lemma 9. So the solution remains in \mathcal{B} .
- In the case (42), $\frac{dU}{dt} > 0$ thanks to (32), and so $U(t) > 0$ for t sufficiently small. Indeed, $\frac{dW}{dt} = 0$ but $\frac{d^2W}{dt^2} = a(1 - \theta) \frac{dU}{dt} > 0$. This is enough to assess that $W(t) > 0$ for t sufficiently small. Using the new “initial” condition at this time, we are driven back to the case treated by Lemma 9. This completes the proof. \square

Lemma 12 (One vanishing initial condition). *If one and only one initial field vanishes, the solution remains in \mathcal{B} .*

- Proof of Lemma 12.

If $U_0 = 0$ (and $V_0 W_0 > 0$), then $\frac{dU}{dt}(0) = \frac{1}{\tau} T J(\frac{V}{T}) > 0$. One may conclude in a similar way to the case (42) treated in Lemma 11. If $V_0 = 0$ (and $U_0 W_0 > 0$), then $\frac{dV}{dt}(0) = a\theta U_0 > 0$. So in finite time, one is driven back to the case treated in Lemma 9 (zero vanishing initial condition). If $W_0 = 0$ (and $U_0 V_0 > 0$), the argument is very similar. \square

- Proof of Theorem 7.

Up to now, we have proved that if the initial condition does not vanish (Lemma 9), vanishes three times (Lemma 10), two times (Lemma 11), or once (Lemma 12), the solution remains in \mathcal{B} . This completes the proof of Theorem 7. \square

4-2 Global existence

The following Theorem states that the solution remains finite and so is global in t .

Theorem 13. *Let*

$$(45) \quad \eta = a\omega - \alpha\zeta,$$

and

$$(46) \quad \gamma = \left| \frac{\eta}{\zeta} \right|.$$

If the initial condition (T_0, U_0, V_0, W_0) is in \mathcal{B} , then the solution of (31-34) satisfies:

$$(47) \quad T(t) + U(t) + \frac{\omega}{\zeta}(V(t) + W(t)) \leq T_0 + U_0 + \frac{\omega}{\zeta}(V_0 + W_0) + \beta t \quad \text{if } \eta \leq 0,$$

and

$$(48) \quad T(t) + U(t) + \frac{\omega}{\zeta}(V(t) + W(t)) \leq (T_0 + U_0 + \frac{\omega}{\zeta}(V_0 + W_0)) e^{\gamma t} + \frac{\beta}{\gamma} (e^{\gamma t} - 1) \quad \text{if } \eta > 0.$$

As a consequence, the solution is finite for all time $t \in [0, +\infty[$ and so is global.

- Proof of Theorem 13.

By adding (31-32) and $\frac{\omega}{\zeta}$ times the sum of (33) and (34), all the non-linear terms disappear and one has:

$$(49) \quad \frac{dT}{dt} + \beta T + \frac{dU}{dt} - \frac{\eta}{\zeta} U + \frac{\omega}{\zeta} \frac{d}{dt}(V + W) = \beta.$$

Thanks to Theorem 7, the solution remains in \mathcal{B} and so $U \geq 0$. Moreover if $\eta \leq 0$, we can minorate the fourth term of (49) by 0 because $\zeta > 0$. As a consequence,

$$\frac{d}{dt} \left(T + U + \frac{\omega}{\zeta}(V + W) \right) \leq \beta,$$

and the relation (47) is a simple consequence of the integration in time of the previous inequality.

If $\eta > 0$, we integrate between 0 and t the equation (49), and owing to the positivity of T , one has

$$(50) \quad T + U + \frac{\omega}{\zeta}(V + W) \leq T_0 + U_0 + \frac{\omega}{\zeta}(V_0 + W_0) + \beta t + \gamma \int_0^t U(t') dt'.$$

Let us denote

$$\delta_0 \equiv T_0 + U_0 + \frac{\omega}{\zeta}(V_0 + W_0) \quad \text{and} \quad \phi(t) \equiv \int_0^t U(t') dt'.$$

Due to Theorem 7 we know that the solution remains in \mathcal{B} ($T > 0, V \geq 0, W \geq 0$), the equation (50) enables to write:

$$(51) \quad \begin{aligned} \frac{d\phi}{dt} &\leq \delta_0 + \beta t + \gamma\phi(t), \\ \frac{d}{dt}(\exp(-\gamma t)\phi) &\leq \exp(-\gamma t)(\delta_0 + \beta t). \end{aligned}$$

The inequality (51) can be integrated ($\phi(0) = 0$):

$$\exp(-\gamma t)\phi(t) \leq \left[-\frac{\beta}{\gamma}t - \frac{1}{\gamma} \left(\delta_0 + \frac{\beta}{\gamma} \right) \right] \exp(-\gamma t) + \frac{1}{\gamma} \left(\delta_0 + \frac{\beta}{\gamma} \right),$$

or

$$\gamma\phi(t) \leq - \left(\beta t + \delta_0 + \frac{\beta}{\gamma} \right) + \left(\delta_0 + \frac{\beta}{\gamma} \right) \exp(+\gamma t).$$

With such a bound for ϕ , one may take back the right hand side of (50):

$$T + U + \frac{\omega}{\zeta}(V + W) \leq \delta_0 + \beta t + \gamma\phi \leq \delta_0 \exp(\gamma t) + \frac{\beta}{\gamma}(\exp(\gamma t) - 1),$$

which is the inequality (48). This completes the proof. \square

4-3 Fixed points

Looking for fixed points of (31-34), we must find solutions of the associated stationary system:

$$(52) \quad \begin{aligned} 0 &= \beta(1 - T) - \frac{T}{\tau} J\left(\frac{V}{T}\right) + \omega(V + W)T, \\ \frac{T}{\tau} J\left(\frac{V}{T}\right) &= \alpha U, \\ a\theta U &= \zeta VT, \\ a(1 - \theta)U &= \zeta WT. \end{aligned}$$

We will prove the following property:

Proposition 14. *Let η defined in (45) and*

$$(53) \quad \begin{aligned} \rho &= \frac{\alpha\zeta\tau}{a\theta}, \\ \bar{V} &= \frac{\beta a\theta}{a\omega - \alpha\zeta}. \end{aligned}$$

The fixed points of (31-34) depend on the sign of η . Three cases must be distinguished.

- *If $\eta > 0$, the fixed points are either health and seropositivity (if $\rho < 1$), or only health (if $\rho \geq 1$).*
- *If $\eta = 0$, there is no fixed point else than health.*
- *If $\eta < 0$, health is always a solution. Moreover, there appears a non-explicit threshold value L and three sub-cases depending on L :*
 - + *When $\rho < 1$ there is one seropositivity fixed point.*
 - + *When $1 < \rho < L$, there are two seropositivity fixed points.*
 - + *When $\rho > L$ there is no seropositivity solution.*

- *Proof of Proposition 14.*

One finds easily that

$$(54) \quad \begin{aligned} (1 - \theta)V &= \theta W, \\ U &= \frac{\zeta}{a}(V + W)T = \frac{\zeta}{a\theta}VT. \end{aligned}$$

Then, the system (52) reduces to

$$(55) \quad 0 = \beta(1 - T) - \frac{\alpha\zeta}{a\theta}VT + \frac{\omega}{\theta}VT,$$

$$(56) \quad \frac{T}{\tau}J\left(\frac{V}{T}\right) = \frac{\alpha\zeta}{a\theta}VT.$$

Since $T = 0$ is not a solution, one may simplify T in (56). Equation (55) gives T :

$$(57) \quad T = \frac{\beta}{\beta - \frac{(\omega a - \alpha\zeta)}{a\theta}V} = \frac{1}{1 - V/\bar{V}}.$$

Thanks to the value of T given by (57), we are driven to solve (56) in the form:

$$(58) \quad J\left(V\frac{(\bar{V} - V)}{\bar{V}}\right) = \frac{\alpha\zeta\tau}{a\theta}V = \rho V.$$

Three cases appear to solve this equation.

- If $\eta > 0$, we must find the solution V of (58) where $\bar{V} > 0$. To guarantee $T \geq 0$, we must have $V < \bar{V}$. Since the function $V \mapsto J(V(\bar{V} - V)/\bar{V})$ is symmetric with respect to $\bar{V}/2$ and the right hand side ρV is a linear function of V , only two subcases must be distinguished according to the Figure 6.

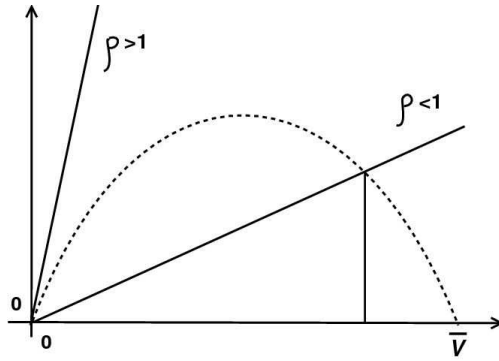


Figure 6. Two characteristic shapes of the curves $V \mapsto \rho V$ and $V \mapsto J(V(\bar{V} - V)/\bar{V})$ (dotted) for $\eta > 0$.

This discussion is summarized in the following:

1. If $\rho < 1$ there are two solutions:
 - (i) $V_1 = 0 \Rightarrow T_1 = 1, U_1 = 0 = W_1$;
 - (ii) $V_2 > 0 \Rightarrow T_2 > 1$.

The first one will be denoted health and the second one seropositivity. We notice that $V_2 < \bar{V}$ and in the end, the condition on V to ensure $T > 0$ is satisfied.

2. If $\rho \geq 1$, the only solution is health.

- If $\eta = 0$, then $\bar{V} = \infty$. There is no solution.
- If $\eta < 0$, then $\bar{V} < 0$ and there is no constraint on V to ensure that $T \geq 0$. Unlike the case $\eta > 0$, the parabola inside the function J is of the type $y = +x^2$ instead of $y = -x^2$.

So as to circumvent this, we will invert the function $V \mapsto V(1 - V/\bar{V})$ on \mathbb{R}^+ where it is one-to-one. For any $V \in \mathbb{R}^+$ (we look for non-negative V), there is a unique $X \in \mathbb{R}^+$ such that

$$(59) \quad X = V(1 - V/\bar{V}) \Leftrightarrow V = \psi(X) = \frac{\bar{V} + \sqrt{\bar{V}^2 - 4\bar{V}X}}{2}.$$

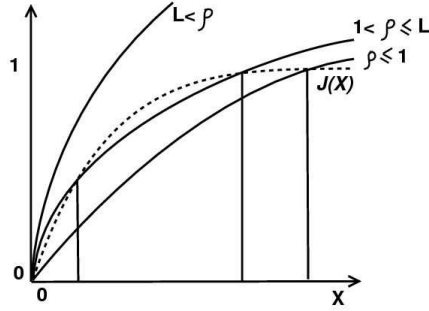


Figure 7. Three characteristic shapes of the curves $X \mapsto \rho\psi(X)$ and J (dotted) with $J \equiv \tanh$ and $\eta < 0$.

Then equation (58) amounts to

$$(60) \quad J(X) = \rho\psi(X).$$

1. If $\rho \leq 1$, there are two solutions denoted X_i^1 :
 - (i) $X_1^1 = 0$ corresponding to health ;
 - (ii) $X_2^1 > 0$ corresponding to seropositivity.
2. If $1 < \rho \leq L$ there are three solutions denoted by X_i^2 :
 - (i) $X_1^2 = 0$ corresponding to health ;
 - (ii) $X_2^2 > 0$ corresponding to seropositivity ;
 - (iii) $0 < X_3^2 < X_2^2$ corresponding to seropositivity.

Notice that there is no explicit value of L . Yet for $J \equiv \tanh$ and $\bar{V} \simeq -0.054$, we could numerically find $L \simeq 3.7$.

3. If $\rho > L$, there is only one solution $X_1^3 = 0$ (health). □

4-4 Stability

The Jacobian matrix is, at every fixed point:

$$\begin{pmatrix} \frac{V}{T\tau} J' \left(\frac{V}{T} \right) - \frac{\beta}{T} & 0 & \omega T - J' \left(\frac{V}{T} \right) / \tau & \omega T \\ J \left(\frac{V}{T} \right) / \tau - \frac{V}{T\tau} J' \left(\frac{V}{T} \right) & -\alpha & J' \left(\frac{V}{T} \right) / \tau & 0 \\ -\zeta V & a\theta & -\zeta T & 0 \\ -\zeta W & a(1 - \theta) & 0 & -\zeta T \end{pmatrix}.$$

If we compute the characteristic polynomial through the last right column, we find:

$$(61) \quad \left\{ \begin{array}{l} P(\lambda) = -(\zeta T + \lambda) \left| \begin{array}{ccc} \frac{V}{T\tau} J' \left(\frac{V}{T} \right) - \frac{\beta}{T} - \lambda & 0 & \omega T - J' \left(\frac{V}{T} \right) / \tau \\ J \left(\frac{V}{T} \right) / \tau - \frac{V}{T\tau} J' \left(\frac{V}{T} \right) & -\alpha - \lambda & J' \left(\frac{V}{T} \right) / \tau \\ -\zeta V & a\theta & -\zeta T - \lambda \end{array} \right| \\ -\omega T \left| \begin{array}{ccc} J \left(\frac{V}{T} \right) / \tau - \frac{V}{T\tau} J' \left(\frac{V}{T} \right) & -\alpha - \lambda & J' \left(\frac{V}{T} \right) / \tau \\ -\zeta V & a\theta & -\zeta T - \lambda \\ -\zeta W & a(1 - \theta) & 0 \end{array} \right|. \end{array} \right.$$

Thanks to (54), we can easily simplify the second line of the second determinant of (61).

As a consequence one may write:

$$P(\lambda) = -(\zeta T + \lambda) \left| \begin{array}{ccc} \frac{V}{T\tau} J' \left(\frac{V}{T} \right) - \frac{\beta}{T} - \lambda & 0 & \omega T - J' \left(\frac{V}{T} \right) / \tau \\ J \left(\frac{V}{T} \right) / \tau - \frac{V}{T\tau} J' \left(\frac{V}{T} \right) & -\alpha - \lambda & J' \left(\frac{V}{T} \right) / \tau \\ -\zeta V & a\theta & -\zeta T - \lambda \end{array} \right| \\ -\omega T (\zeta T + \lambda) \left| \begin{array}{ccc} J \left(\frac{V}{T} \right) / \tau - \frac{V}{T\tau} J' \left(\frac{V}{T} \right) & -\alpha - \lambda & \\ -\zeta W & a(1 - \theta) & \end{array} \right|.$$

In the general case, no more factorization could be found and the polynomial is

$$(62) \quad \left\{ \begin{array}{l} P(\lambda) = -(\zeta T + \lambda) \left[\left(\frac{V}{T\tau} J' \left(\frac{V}{T} \right) - \frac{\beta}{T} - \lambda \right) \left(-\frac{a\theta}{\tau} J' \left(\frac{V}{T} \right) + (\alpha + \lambda)(\zeta T + \lambda) \right) \right. \\ \left. + \left(\frac{\omega T}{\theta} - \frac{1}{\tau} J' \left(\frac{V}{T} \right) \right) \left(\frac{a\theta}{\tau} \left(J \left(\frac{V}{T} \right) - \frac{V}{T\tau} J' \left(\frac{V}{T} \right) \right) - (\alpha + \lambda)\zeta V \right) \right]. \end{array} \right.$$

4-4-1 Stability of the health state

In the case of health ($T = 1, U = 0 = V = W$), the eigenvalues are zeros of (62) which can be rewritten thanks to (53):

$$(63) \quad P(\lambda) = (\zeta T + \lambda)(\beta + \lambda) \left(\frac{a\theta}{\tau}(-1 + \rho) + \lambda(\alpha + \zeta) + \lambda^2 \right) = 0.$$

We will prove the following theorem.

Theorem 15. *If $\rho > 1$, health is (locally) stable.*

If $\rho < 1$, there exists one positive eigenvalue associated to an admissible eigenvector in the sense of Definition 5.

- Proof of Theorem 15.

The discriminant of the non-reduced second order polynomial in (63) is $(\alpha - \zeta)^2 + 4a\theta/\tau > 0$. This enables us to claim that:

- if $\rho > 1$, the four roots are negative and so the evolution is (locally) stable;
- if $\rho < 1$, there exists one (and only one) positive root and so the evolution is locally unstable in one direction. We still have to prove that the eigenvector \vec{v} associated to a

positive eigenvalue of (63) is admissible. In other words, we need to prove that \vec{v} is such that for $\varepsilon > 0$ or $\varepsilon < 0$ small enough, $(1, 0, 0, 0) + \varepsilon\vec{v}$ has its four components non-negative. To prove this, we write the system satisfied by the eigenvector:

$$(64) \quad \begin{pmatrix} -(\beta + \lambda) & 0 & \omega - 1/\tau & \omega \\ 0 & -(\alpha + \lambda) & 1/\tau & 0 \\ 0 & a\theta & -(\zeta + \lambda) & 0 \\ 0 & a(1 - \theta) & 0 & -(\zeta + \lambda) \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

where $\rho < 1$ and λ is the (unique) positive root of (63). More precisely, λ is the unique root of the third term: $a\theta(-1 + \rho)/\tau + \lambda(\alpha + \zeta) + \lambda^2$. As this second order polynomial is the determinant of the 2×2 submatrix in the center of the matrix in (64), and because of the very particular shape of the lines 2 and 3, we can claim these lines are bound. It suffices then to take out the third line to be driven to the system equivalent to (64):

$$\begin{cases} (\beta + \lambda)x_1 & = & (\omega - 1/\tau)x_3 + \omega x_4 \\ (\alpha + \lambda)x_2 & = & x_3/\tau \\ a(1 - \theta)x_2 & = & (\zeta + \lambda)x_4. \end{cases}$$

As $\lambda > 0$, we can see that there exists solutions such that x_2, x_3, x_4 be non-negative. So, at least locally the solution in the direction of this eigenvector is admissible and the proof is complete. \square

4-4-2 Stability of seropositivity

We have no rigorous study of the stability/unstability of seropositivity. So we use numerical simulations. In this subsection, we take

$$\beta = 0.01 \text{ day}^{-1}, \alpha = 0.7 \text{ day}^{-1}, \omega = 0.01 \text{ day}^{-1}, a = 250 \text{ day}^{-1}, \theta = 0.1,$$

and initial values

$$T(0) = 1, \quad U(0) = 0, \quad V(0) = W(0) = 0.05.$$

The other parameters (τ, ζ) are taken so as to illustrate the fixed points depicted in Proposition 14. We provide the evolution on a short time and a phase portrait for each case. Let us remind the fixed points:

1. $\eta > 0$.

(i) If $\rho < 1$: health (partially unstable) and one seropositivity numerically stable as can be seen on Figure 8 In this simulation, $\eta = 1.8, \rho = 0.28$. The effect of the infection is to *emphasize* the activity of the immune system ;

(ii) If $\rho \geq 1$: only health (stable), as in Figure 9 ($\eta = 0.4, \rho = 1.68$). Minimum value for lymphocytes is obtained for $t \simeq 0.8$ day and maximal one for $t \simeq 16.4$ days.

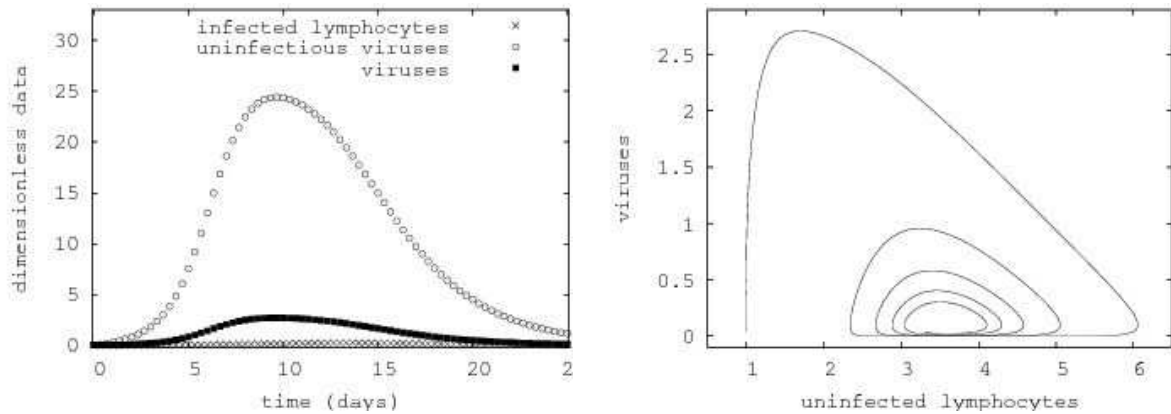


Figure 8. Numerical results for our model. Case where a seropositive state is stable ($\tau = 10, \zeta = 1$). Relatively short time evolution on the left (25 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution.

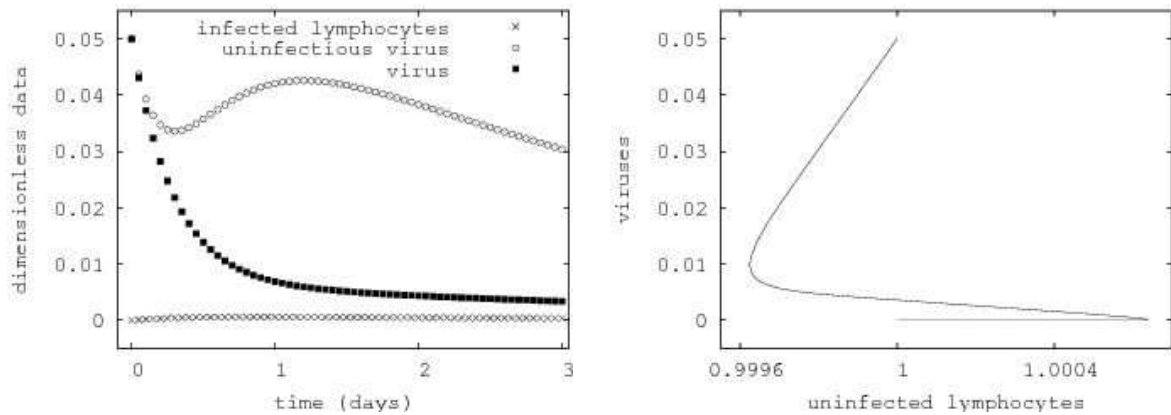


Figure 9. Numerical results for our model. Case where the health is stable ($\tau = 20, \zeta = 3$). Short time evolution on the left (3 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution.

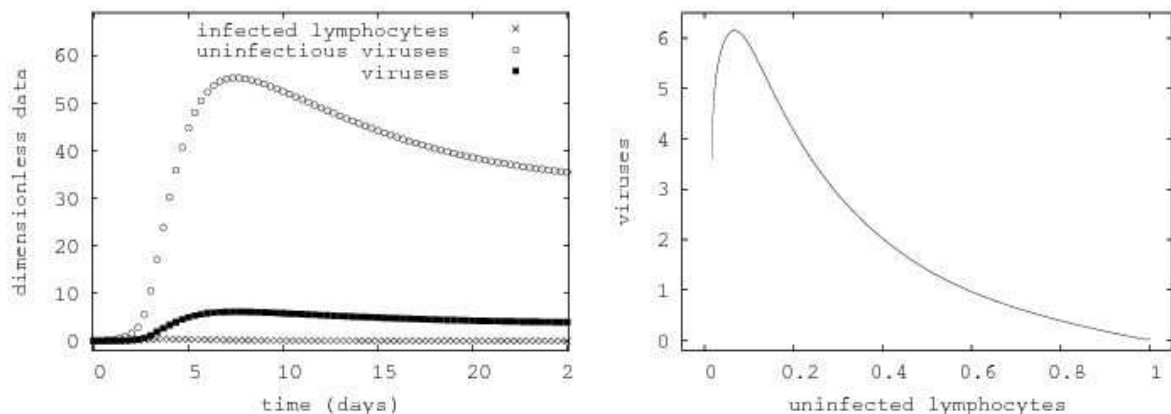


Figure 10. Numerical results for our model. Case where a seropositive state is stable ($\tau = 1, \zeta = 10$). Relatively short time evolution on the left (25 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution. The effect of the infection is to reduce drastically the efficacy of the immune system.

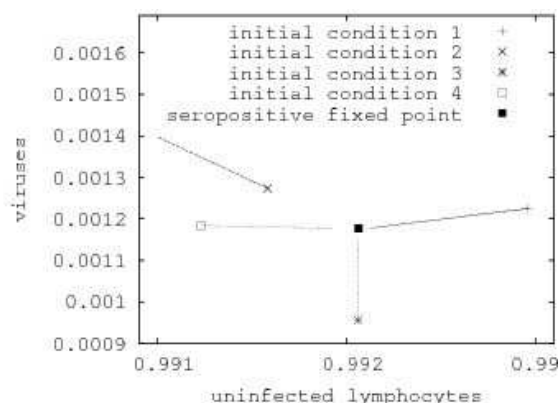


Figure 11. Numerical results for our model with 4 equations ($\tau = 6$, $\zeta = 6$). Simulations are initialized with states very close to the fixed point in directions that correspond to eigenvectors. The seropositive state is unstable in one direction among four.

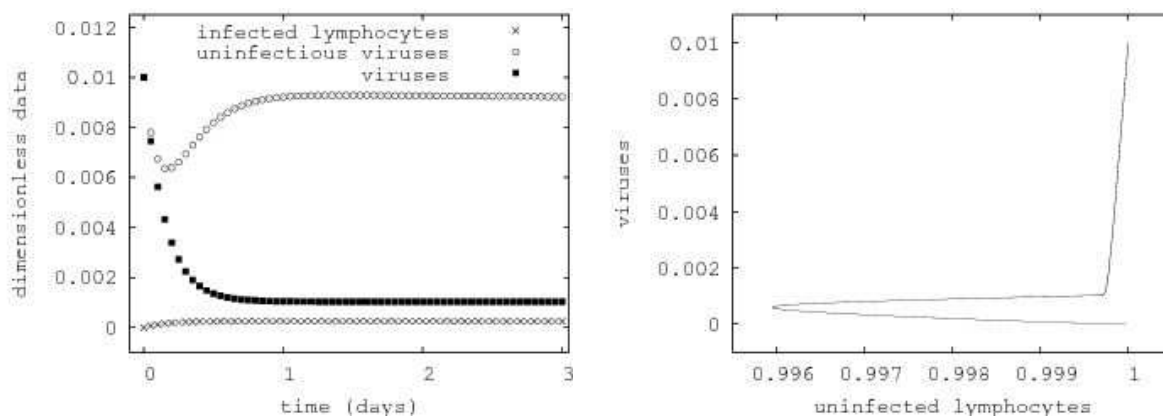


Figure 12. Numerical results for our model with 4 equations. Case where health is stable ($\tau = 6$, $\zeta = 6$) only for small perturbations. Relatively short time evolution on the left (3 days) and phase plane for lymphocytes and viruses on the right for a 1500 days evolution.

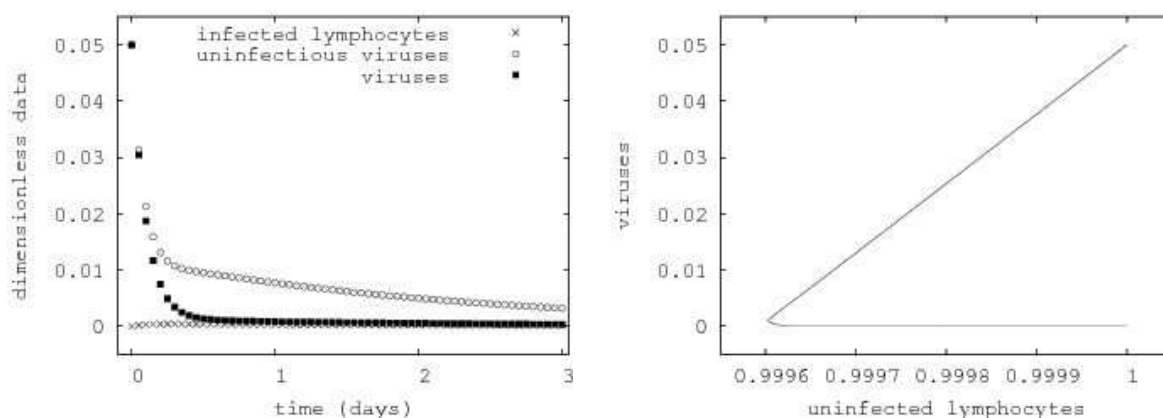


Figure 13. Numerical results for our model. Case where the health is stable ($\tau = 10$, $\zeta = 10$). Short time evolution on the left (3 days) and phase plane for lymphocytes and viruses on the right for a 600 days evolution.

2. $\eta < 0$.

(i) If $\rho < 1$: health (partially unstable) and one seropositivity numerically stable as can be seen on Figure 10 ($\eta = -4.5, \rho = 0.28$). The effect of the infection is to *reduce* the activity of the immune system at a very low level ($\simeq 0.015$ times the level of health);

(ii) If $1 < \rho < L$: health (stable) and two seropositivities. We choosed the parameters $\zeta = 6, \tau = 6$ ($\eta = -1.7, \rho = 1.008$) for simulation. A first seropositive state ($T^* \simeq 0.129, U^* \simeq 0.03073, V^* \simeq 0.992, W^* \simeq 8.9$) was numerically found to be locally stable (not shown). A second seropositive state ($T^* \simeq 0.992, U^* \simeq 0.00028, V^* \simeq 0.00117, W^* \simeq 0.01058$) is very close to health and is locally unstable since it has three negative and one positive eigenvalues. So as to illustrate this, we have taken initial data

$$X_j = X^* + \varepsilon V_j, \quad 1 \leq j \leq 4,$$

where X^* is the fixed point, V_j is one of its eigenvector and ε is sufficiently small. This experiment is depicted in Figure 11. Note that although health is locally stable, initial conditions with a viral load of 5% drove the state to a seropositivity state. This proves that the basin of attraction is small. So we provide a simulation with an initial viral load of only 1% in Figure 12 ;

(iii) If $L < \rho$: health is stable as one may see on Figure 13 ($\eta = -4.5, \rho = 2.8$). Minimum value for lymphocytes is obtained for $t \simeq 2.6$ days.

5) Discussion of the present model

Various effects are supposed to be more or less incorporated in any model and specifically ours. They are discussed hereafter.

- If a model considers the field of *free* viruses, then infection makes an uninfected lymphocyte and a *free* virus disappear and an infected lymphocyte appear at the same time. Three identical terms (up to a \pm sign) should be present in such a model. It is not often the case. Since V_j includes not only free viruses but also *infecting* viruses, we are not forced to have the same three terms.

- We characterize each virus by its antigenicity and by the information that it is infectious or not. We characterize the lymphocytes by the virus antigenicity against which they have been designed. Mutation is then only a probabilistic phenomenon and the main modeling question is the space in which it takes place and its probabilistic law. Such a study is postponed to a forthcoming article.

- By explicitly deriving our model, we justify our “piecewise linear” term to model infection, although most authors use a mass-action quadratic term (for a discussion, see [8, 9]).

Very likely, the reason why the modeling of infection has not been much studied is that the only biologically measured field is $T + U$. So the term modeling this phenomenon disappears in any evolution equation on $T + U$. Yet it models a crucial reality and deserves more attention.

- We model the production of T_j by the immune system once it has detected the V_j . The production depends on the V_j population, and so our term is quadratic. It has no counterpart in any model we read. This term could be balanced by the quadratic term modeling the immune system effect against each strain of virus which is present in some models ([17, 31]) including ours.
- The multiplication/mutation of the virus is the most challenging phenomenon. Since only one virus may infect a lymphocyte [12], we may assume U is a good measure of the total number of *infecting* viruses. This assumption is very likely but would deserve to be further tested. Then, since the antigenicity of a U_j has no link with the antigenicity of the virus infecting it, we need to take into account the pure multiplication of V_j phenomenon. A simple modeling of mutation generates our term.
- We model the effect of the immune system against the viruses by a term depending quadratically on V_j and T_j since these quantities are effective in the same regime. Such a term can be found in the models depending on antigenic variation in [30] (chapter 12 and 13) and [31] but in these models the lymphocyte's generation is modeled only through a linear term in V_j .
- With further assumptions, one may find a linear combination of the $T + U$ and $V + W$ evolution such that this new combination is simply linear in T, U, V, W because the non-linearities may simplify. This could be experimentally tested.
- The overall behavior of all the systems studied above (including ours if $N = 1$) allows the fields to remain non-negative and be attracted by some fixed points. So all these models predict convergence to some fixed point which is never immuno-suppressed ($T = 0$). We consider this to be a major drawback for the long term modeling of HIV infection. This opinion is shared by the authors of [31] and they propose modifications to the Nowak-Bangham models enabling the longer term evolution modeling.
- Notice that the only physical field is $T = \sum_j T_j$ and not T_1 (with $N = 1$) as used in our mathematical study. As a consequence, the widening of antigenicity support is a phenomenon not included in the case $N = 1$ nor in any other well-known “macroscopic” model reviewed above. Since the “microscopic” models use a finite domain of antigenicity, they no more include the widening of antigenicity support. As de Boer and Perelson conclude their study of numerous macroscopic models in [10]: “one may model disease progression by allowing the virus to evolve immune-escape variants increasing the diversity of the quasi-species [...]. Since this requires high-dimensional models, this form of disease progression is not considered any further here”. It would of course be of interest to get an experimental illustration of the viral dynamics as exposed in the present study. As described in [13], nucleotide analogs can be selected to take control over the mutational drift of the virus, in particular abolishing ($N = 1$), or reducing (one may even reach precisely $N = 2$) the drift. Starting with a $N = 1$ experiment (no drift), T, U can be counted by flow cytometry, for instance using a dye adsorbed by life cells (T_1), not by dead ones (U_1). The virus populations V_1 and W_1 can be counted by the capacity to infect (V_1)

or not infect (W_1) T_1 cells. The latter will be labeled (for instance fluorescence-tagged antibody grown against T_1). The same counting would be repeated in a $N = 2$ experiment, in which the fluorescent label of T_1 will allow to count T_2 , etc... An entirely different strategy would be to look for a macroscopic version of our model. Such a model would depend on T, U, V, W instead of $(T_i, U_i, V_i, W_i)_{i=1, \dots, N}$, but remains to be determined.

6) Conclusion

We have thoroughly studied previous models of HIV multiplication by systems of differential equations. Some of them were reduced to be single-antigenic. With such a reduction, all of these models have fixed points that prohibit modeling of the last phase of the disease where the T count vanishes. This is also criticized in recent research [31].

Moreover, we propose a model taking into account new phenomena among which lymphocytes generation by the immune system according to the presence of specific viruses, and immune effect against each virus strain. We also model infection and mutation/generation through new algebraic terms. This model is derived due to explicit arguments. It will be tested further in forthcoming research.

Although the *reduced* version of our model has the same drawback of not enabling the immunity exhaustion, its general version takes into account the strains' diversity (here denoted as antigenicity) and the specificity of the immune response. So our full model should enable to account for the last phase of the HIV infection where the lymphocytes' count vanishes. This will be studied in a forthcoming article.

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References

- [1] Christian L. Althaus and Rob J. De Boer. Dynamics of immune escape during HIV/SIV infection. *PLoS Comput. Biol.*, 4(7):e1000103, 07 2008.
- [2] JP. Anderson, R. Daifuku, and LA. Loeb. Viral error catastrophe by mutagenic nucleosides. *Annu. Rev. Microbiol.*, 58:183–205, 2004.
- [3] VI. Arnold. *Ordinary Differential Equations*. The MIT Press., Massachusetts, 1978.
- [4] K. Bebenek, J. Abbotts, SH. Wilson, and TA. Kunkel. Error-prone polymerization by HIV-1 reverse transcriptase. Contribution of template-primer misalignment, miscoding, and termination probability to mutational hot spots. *J. Biol. Chem.*, 268(14):10324–34, 1993.
- [5] CK. Biebricher and M. Eigen. The error threshold. *Virus Res.*, 107(2):117–127, 1993.
- [6] D.M. Bortz and P. W. Nelson. Model selection and mixed-effects modeling of HIV infection dynamics. *Bull. Math. Biol.*, 68(8):2005–2025, 2006.

- [7] AL. Brass, DM. Dykxhoorn, Y. Benita, N. Yan, A. Engelman, R.J. Xavier, J. Lieberman, and Elledge SJ. Identification of host proteins required for HIV infection through a functional genomic screen. *Science*, 319(5865):921–6, 2008.
- [8] DS. Callaway and AS. Perelson. HIV-1 infection and low steady state viral loads. *Bull. Math. Biol.*, 64:29–64, 2002.
- [9] R.J. De Boer. Understanding the failure of CD8+ t-cell vaccination against simian/human immunodeficiency virus. *J. Virol.*, 81(6):2838–2848, 2007.
- [10] R.J. De Boer and AS. Perelson. Target cell limited and immune control models of HIV infection: A comparison. *J. Theor. Biol.*, 190:201–214, 1998.
- [11] P. De Leenheer and HL. Smith. Virus dynamics: a global analysis. *SIAM J. Appl. Math.*, 63(4):1313–1327, 2003.
- [12] K. Dern, H. Rübsamen-Waigmann, and RE. Unger. Inhibition of HIV type 1 replication by simultaneous infection of peripheral blood lymphocytes with human immunodeficiency virus types 1 and 2. *AIDS Res. Hum. Retroviruses*, 17(4):295–309, 2001.
- [13] V. Derrien. *Fidelity and termination of polymerization by reverse transcriptases in vitro*. PhD thesis, Paris-Sud University, 1998.
- [14] WC. Drosopoulos, LF. Rezende, MA. Wainberg, and VR. Prasad. Virtues of being faithful: can we limit the genetic variation in human immunodeficiency virus? *J. Mol. Med.*, 76(9):604–12, 1998.
- [15] F. Dubois, HVJ. Le Meur, and C. Reiss. Modélisation de la multiplication du virus HIV. In Congrès d’Analyse NUMérique, editor, *SMAI*, Praz-sur-Arly, 2007.
- [16] D. Finzi and RF. Silliciano. Viral dynamics in HIV-1 infection. *Cell*, 93(5):665–71, 1998.
- [17] H. Frid, P-E. Jabin, and B. Perthame. Global stability of steady solutions for a model in virus dynamics. *Math. Model. Numer. Anal.*, 37(4):709–723, 2003.
- [18] K. Fujii, JH. Hurley, and EO. Freed. Beyond Tsg101: the role of Alix in ‘ESCRTing’ HIV-1. *Nat. Rev. Microbiol.*, 5(12):912–6, 2007.
- [19] J. Guedj, R. Thiebaut, and D. Commenges. Practical identifiability of HIV dynamics models. *Bull. Math. Biol.*, 69(8):2493–513, 2007.
- [20] KS. Harris, W. Brabant, S. Styrchak, A. Gall, and R. Daifuku. KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. *Antivir. Res*, 67:1–9, 2005.

- [21] P. Henrici. *Applied and Computational Complex Analysis*. John Wiley, New-York, 1974.
- [22] AV. Herz, S. Bonhoeffer, RM. Anderson, RM. May, and MA. Nowak. Viral dynamics *in vivo*: limitations on estimates of intracellular delay and virus decay. *Proc. Natl. Acad. Sci. USA*, 93:7247–7251, 1996.
- [23] J. Ji and LA. Loeb. Fidelity of HIV-1 reverse transcriptase copying a hypervariable region of the HIV-1 env gene. *Virology*, 199(2):323–30, 1994.
- [24] E. Kashkina, M. Anikin, F. Brueckner, RT. Pomerantz, WT. McAllister, P. Cramer, and D. Temiakov. Template misalignment in multisubunit RNA polymerases and transcription fidelity. *Mol. Cell.*, 24(2):257–66, 2006.
- [25] DL. Kothe, Y. Li, JM. Decker, F. Bibollet-Ruche, KP. Zammit, MG. Salazar, Y. Chen, Z. Weng, EA. Weaver, F. Gao, BF. Haynes, GM. Shaw, BT. Korber, and BH. Hahn. Ancestral and consensus envelope immunogens for HIV-1 subtype C. *Virology*, 352(2):438–49, 2006.
- [26] S. Mueller, D. Papamichail, JR. Coleman, S. Skiena, and E. Wimmer. Reduction of the rate of poliovirus protein synthesis through large-scale codon deoptimization causes attenuation of viral virulence by lowering specific infectivity. *J. Virol.*, 80(19):9687–96, 2006.
- [27] E. Murakami, A. Basavapathruni, WD. Bradley, and KS. Anderson. Mechanism of action of a novel viral mutagenic covert nucleotide: molecular interaction with HIV-1 reverse transcriptase and host cell DNA polymerases. *Antivir. Res.*, 67:10–17, 2005.
- [28] PW. Nelson, JE. Mittler, and AS. Perelson. Effect of drug efficacy and the eclipse phase of the viral life cycle on estimates of HIV viral dynamic parameters. *J. Acquir. Immune Defic. Syndr.*, 26(5):405–412, 2001.
- [29] MA Nowak and Bangham. CRM. Population dynamics of immune responses to persistent viruses. *Science*, 272:74–79, 1996.
- [30] MA. Nowak and RM. May. *Virus dynamics. Mathematical Principles of Immunology and Virology*. Oxford University Press, 2000.
- [31] DH. Pastore and JP. Zubelli. On the dynamics of certain models describing the HIV infection. In Mauricio Peixoto Alberto Adrego Pinto and David Rand, editors, *Dynamics and Games in Science, in honour of Mauricio Peixoto and David Rand*. Springer-Verlag, 2010.
- [32] AS. Perelson. Modelling viral and immune system dynamics. *Nature Rev. Immunol.*, 2:28–36, 2002.

- [33] AS. Perelson and P. Nelson. Mathematical analysis of HIV-1 dynamics *in vivo*. *SIAM Review*, 41(1):3–44, 1999.
- [34] AS. Perelson, AU. Neumann, M. Markowitz, JM. Leonard, and DD. Ho. HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science*, 271(5255):1582–6, 1996.
- [35] J. Petravic, L. Loh, SJ. Kent, and MP. Davenport. CD4+ target cell availability determines the dynamics of immune escape and reversion *in vivo*. *J. Virol.*, 82(8):4091–101, 2008.
- [36] M. Recher, KS. Lang, A. Navarini, L. Hunziker, PA. Lang, K. Fink, S. Freigang, P. Georgiev, L. Hangartner, R. Zellweger, A. Bergthaler, AN. Hegazy, B. Eschli, A. Theodorides, LT. Jeker, D. Merkler, B. Odermatt, M. Hersberger, H. Hangartner, and RM. Zinkernagel. Extralymphatic virus sanctuaries as a consequence of potent T-cell activation. *Nat. Med.*, 13(11):1316–23, 2007.
- [37] N. Sachsenberg, AS. Perelson, S. Yerly, GA. Schockmel, D. Leduc, B. Hirschel, and L. Perrin. Turnover of CD4+ and CD8+ lymphocytes in HIV-1 infection as measured by Ki-67 antigen. *J. Exp. Medecine*, 187(8):1295–1303, 1998.
- [38] A. Samson, M. Lavielle, and F. Mentré. The SAEM algorithm for group comparison tests in longitudinal data analysis based on non-linear mixed-effects model. *Stat Med.*, 26(27):4860–75, 2007.
- [39] SJ. Snedecor. Comparison of three kinetic models of HIV-1 implications for optimization of treatment. *J. Theor. Biol.*, 221:519–541, 2003.
- [40] JA. Thomas, DE. Ott, and RJ. Gorelick. Efficiency of human immunodeficiency virus type 1 postentry infection processes: evidence against disproportionate numbers of defective virions. *J. Virol.*, 81(8):4367–70, 2007.
- [41] HC. Tuckwell and E. Le Corfec. A stochastic model for early HIV-1 population dynamics. *J. Theor. Biol.*, 195(4):451–63, 1998.
- [42] L. Wang and M.Y. Li. Mathematical analysis of the global dynamics of a model for HIV infection of CD4+ T cells. *Math. Biosci.*, 200(1):44–57, 2006.
- [43] D. Warrilow, L. Meredith, A. Davis, C. Burrell, P. Li, and D. Harrich. Cell factors stimulate human immunodeficiency virus type 1 reverse transcription *in vitro*. *J. Virol.*, 82(3):1425–37, 2008.
- [44] D. Wodarz and D.H. Hamer. Infection dynamics in HIV-specific CD4 T cells: does a CD4 T cell boost benefit the host or the virus? *Math. Biosci.*, 209(1):14–29, 2007.