GLOBAL STABILITY OF STEADY SOLUTIONS FOR A MODEL IN VIRUS DYNAMICS

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ABSTRACT. We consider a simple model for the immune system in which virus are able to undergo mutations and are in competition with leukocytes. It is related to several other concepts which have been proposed in the literature like the concepts of quasi-species, shapes and virulence. When mutations are not present, the system admits a globally attractive critical point. Mutations do not affect this picture for small perturbations and under strong structural assumptions. Releasing these assumptions leads to blow-up of the system.

1. A Model in Virus Dynamics

Modelling the immune system is a classical and widely treated question in mathematical biology. It covers several different aspects including for instance detailed description of the virus, antivirus and body dynamics, drug therapy, quasi-species and description of virus 'shape' ... A general account of these aspects can be found in the survey paper by Perelson and Weisbusch [8] and in the books by May and Novak [7] and Dieckmann and Heersterbeek [5]. The departing mathematical objects are differential systems for the density number of virus $v(t)$, of leukocytes $l(t)$ and possibly other quantities like available resources or various states of virus. A recent tendancy has been to introduce more structure in the description of the populations under investigation and for instance Bellomo *et al* [1], De Angelis and Jabin [3], Chaplain [2] consider that the densites depend on a virulence parameter leading to a system of transport equations on the densities $v(t,\mu)$ and $l(t,\mu)$ of virus and leukocytes with virulence μ.

The goal of this paper is to analyse the mathematical properties of a simple model, maybe the simplest one, which keeps the following features.
(i) When a single kind of virus is present, the immune response leads to a steady state where both virus and leukocytes are present and their interaction is at equilibrium. This corresponds to the recent tendency of immunology to postulate that the normal life follows from an equilibrium between various such interacting entities.
(ii) Mutations are present. To do that, we introduce a parameter μ which allows to represent various kinds of virus and leukocytes, and the mutation from one kind to another. The notion of physical shape has been used in order to describe these different kinds of virus, more genetic basis for explaining them are also advocated now. For our purpose this disctinction is not fundamental and we will think of μ as a real parameter which influences the dynamics. The possibility of an evolution of virus is the only issue on which we focus.
(iii)In the absence of virus, the leukocytes of all "shapes" are present.

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We insist that at this stage, this model is not supposed to be predictive, the above references contain many essential additional phenomena which are not present here. But it is intended to capture the previous features and see the effect of mutations on the global stability of the system, or by opposition, to the possible blow up. On the other hand it is not far from the behavior of experimental virus load curves that one can find in the literature. For instance numerical simulations show a pick after infection and afterwards, either a steady steady state is reached, or the total load increases slowly until a fast blow up occurs.

We denote by $\sigma = \sigma(\mu) > 0$ the reproduction rate of viruses, by $\eta = \eta(\mu) > 0$ a background nutriment for leukocytes. The parameters $\alpha = \alpha(\mu) > 0$, resp. $\beta = \beta(\mu) > 0$, denote the efficiency of leukocytes, resp. virus, against the opposite species. From a biological point of view it is natural to consider the case where these functions are not very smooth: small shape variation can induce large variations on these parameters.

We first consider the following system of ordinary differential equations modelling the virus and leukocyte dynamics without mutation.

$$\frac{dv}{dt} = \left(\sigma - \frac{\alpha l}{1+v}\right)v, \tag{1.1}$$

$$\frac{dl}{dt} = \left(\Sigma\big(\frac{\eta+v}{l}\big) - \beta\right)l, \tag{1.2}$$

and we will prove that it has indeed a single positive global attractor. It is a standard prey-predator system with the specificity that, without virus, leukocytes are present with a positive (a priori small) density while virus, without leukocytes, develop with a exponential law. This is due to our simplifying assumption of infinite resource. This system always reaches a steady state v_*, l_*, whatever is the initial state $v(0) > 0$, $l(0) > 0$ and under assumptions that are presented below. Here $\Sigma > 0$ represents a nonlinear reproduction rate of leukocytes that are feeded by the virus and resource.

The corresponding integro-differential system modelling the situation when mutations occur is written

$$\frac{dv}{dt} = \sigma((1-\theta)v + \theta K[v]) - \frac{\alpha l v}{1+v}, \tag{1.3}$$

$$\frac{dl}{dt} = \left(\Sigma\big(\frac{\eta+v}{l}\big) - \beta\right)l, \tag{1.4}$$

where $0 < \theta < 1$ is a real parameter, $K[v]$ is defined by

$$K[v](\mu) = \int K(\mu,\mu')v(\mu')\,d\mu',$$

where K is a nonnegative function, and we assume that

$$\int K(\mu,\mu')\,d\mu = 1 \quad \forall \mu' \in \mathbb{R}, \qquad \int K(\mu,\mu')\,d\mu' = 1 \quad \forall \mu \in \mathbb{R}. \tag{1.5}$$

As for the function $\Sigma(s)$ it satisfies, for $s \in [0,\infty)$

$$\Sigma(0) = 0,\ \Sigma'(s) > 0,\ \Sigma''(s) \le 0, \quad \text{and } \beta < \Sigma_\infty := \lim_{s\to\infty} \Sigma(s) < \infty. \tag{1.6}$$

Furthermore, we assume

$$\lim_{s\to\infty} s\Sigma'(s) = 0. \tag{1.7}$$

Our purpose here is to analyse several properties of this system with mutations. We show that it still has a single steady state, this performed in Section 2, and that it is stable under small perturbations (Section 4). Releasing some assumptions we show that the system can however blow up; bounded steady states do not exist and the dynamical blow-up is asserted by numerical simulations in Section 5.

In order to situate this model, we would like to give a formal derivation of virulence from mutations and show that they are in fact rather close. For the purpose of simplicity, we restrict our attention to the case of a single species (virus) and therefore we do not consider the loose part due to leukocytes in the equation for the virus. We also scale the mutation kernel in such a way that it represents very fast mutation but with little effect. Hence we introduce a small parameter ϵ and the scaled kernel K_ϵ is assumed to satisfy

$$K_\epsilon(\mu,\mu')\,(\mu'-\mu) \to A(\mu)\delta(\mu-\mu'), \quad A(\mu)>0.$$

Notice that such a kernel cannot satisfy (1.5), and therefore a rescalling σ large and θ close to 0 is also assumed here. Then, the dynamics is equivalently given by

$$\frac{dv}{dt} = \sigma_1 v + \int K_\epsilon(\mu,\mu')\Big(v(\mu')-v(\mu)\Big)d\mu',$$

Since K_ϵ concentrates on small mutations (μ close to μ') we may write the approximations

$$\begin{aligned}\frac{dv}{dt} &\approx \sigma_1 v + \int K_\epsilon(\mu,\mu')(\mu'-\mu)\frac{\partial v(\mu)}{\partial \mu}d\mu' \\ &\approx \sigma_1 v + A(\mu)\frac{\partial v(\mu)}{\partial\mu}. \qquad (1.8)\end{aligned}$$

Such a model is a simplified version of those derived and studied in [1], [3], [2] where μ is interpreted as a virulence parameter. We refer to these papers and the references therein for more complete models and biological interpretations. Notice also that this kind of asymptotics is classical in kinetic theory (grazing collisions), *cf* Degond and Lucquin [4], Villani [9].

We begin by analyzing the steady states of (1.1)–(1.2). As can be easily checked, there are exactly three such states, namely,

$$P_1=(0,0), \quad P_2=\big(0,\frac{\eta}{\Sigma^{-1}(\beta)}\big), \quad P_3=\big(\frac{\kappa-\eta}{1-\kappa},\frac{\sigma}{\alpha}\frac{1-\eta}{1-\kappa}\big), \quad \kappa(\mu)=\frac{\sigma}{\alpha}\Sigma^{-1}(\beta), \tag{1.9}$$

and we denote by $\bar{l}=\frac{\eta}{\Sigma^{-1}(\beta)}$. In order to have P_3 in the interior of the first quadrant

$$Q_+ = \{(v,l)\,:\, v>0,\, l>0\},$$

we impose the condition

$$\inf_{\mu\in\mathbb{R}}\Big(\kappa(\mu)-\eta(\mu)\Big)>0, \qquad \sup_{\mu\in\mathbb{R}}\kappa(\mu)<1, \tag{1.10}$$

and we discard the other alternative $1 < \kappa(\mu) < \eta$ for stability reasons that we explain now. We denote

$$f(v,l) = \left(\sigma v - \frac{\alpha l v}{1+v}, \left(\Sigma\left(\frac{\eta+v}{l}\right) - \beta\right) l\right).$$

The Jacobian matrix of f is then given by

$$Df(v,l) = \begin{bmatrix} \sigma - \left(\frac{\alpha l}{1+v} - \frac{\alpha l v}{(1+v)^2}\right) & \frac{-\alpha v}{1+v} \\ \Sigma'\left(\frac{\eta+v}{l}\right) & \Sigma\left(\frac{\eta+v}{l}\right) - \beta - \Sigma'\left(\frac{\eta+v}{l}\right)\frac{\eta+v}{l} \end{bmatrix}. \tag{1.11}$$

We then have

$$Df(P_1) = \begin{bmatrix} \sigma & 0 \\ 0 & \Sigma_\infty - \beta \end{bmatrix},$$

$$Df(P_2) = \begin{bmatrix} \sigma - \alpha \bar{l} & 0 \\ \Sigma^{-1}(\beta) & -\Sigma^{-1}(\beta) \end{bmatrix},$$

so that (1.6) and (1.10) imply that P_1 is a hyperbolic repeller and P_2 is a saddle point with stable manifold coinciding with the axis $v = 0$. The study of the character of the singularity P_3, as well as the knowledge of global structure of the phase portrait, depends on more detailed informations about the system (1.1)–(1.2) and so we postpone this study to Section 3 where we show that, for a prototypical function Σ, system (1.1) has P_3 as a global attractor for the whole region Q_+.

2. Stationary solutions for the model with mutation

In this section we prove that there is a unique steady solution of (1.3)-(1.4) with values in Q_+, and present a constructive algorithm to approach it. Our result is the following

Theorem 2.1. *Assuming (1.5)–(1.7) hold, for $\theta \in (0,1)$, there exists a steady solution to (1.3)–(1.4), $(v_{st}(\mu), l_{st}(\mu)) \in L^\infty(\mathbb{R})^2$, with values in Q_+. Moreover, this steady solution satisfies*

$$0 < \min_{\mathbb{R}} \frac{\kappa - \eta}{1-\kappa} \le v_{st}(\mu), \qquad \forall \mu \in \mathbb{R}.$$

For θ sufficiently small this solution is unique.

Proof. As a preparation, for each fixed $\mu \in \mathbb{R}$, we introduce the function

$$\psi_\mu(v) = \frac{v}{\kappa(\mu)} \frac{\eta+v}{1+v}.$$

A simple calculation leads to

$$\psi'_\mu(v) = \frac{1}{\kappa(\mu)} \frac{v^2+2v+\eta}{(1+v)^2} > 0, \quad \psi''_\mu(v) = \frac{1}{\kappa(\mu)} \frac{2-\eta}{(1+v)^3} > 0.$$

Further,

$$\psi'_\mu(0) = \frac{\eta}{\kappa} < 1, \quad \psi'_\mu(\infty) = \frac{1}{\kappa} > 1. \tag{2.1}$$

In particular, the point $P_3 = (v_*, l_*)$ defines the unique $v_*(\mu) > 0$ satisfying

$$\psi_\mu(v_*(\mu)) = v_*(\mu). \tag{2.2}$$

The steady solutions $(v(\mu), l(\mu))$ of (1.3)–(1.4) with values in Q_+ satisfy

$$\theta K[v](\mu) + (1-\theta)v(\mu) = \psi_\mu(v(\mu)), \qquad l(\mu) = \frac{1}{\Sigma^{-1}(\beta(\mu))}(\eta(\mu) + v(\mu)). \tag{2.3}$$

Consider a steady solution $(v(\mu), l(\mu))$ with values in Q_+, and a maximum point $v(\bar{\mu}) = \max v(\mu)$ (if it is not reached a maximizing sequence will do the job), then thanks to (1.5) we have

$$\psi_{\bar{\mu}}(v(\bar{\mu})) \leq v(\bar{\mu}), \text{ hence } v(\bar{\mu}) \leq v_*(\bar{\mu}). \tag{2.4}$$

This proves the a priori bound $v(\mu) \leq \max v_*(\mu')$. A similar argument on the minimum gives the a priori lower bound announced in the theorem.

We now present an increasing approximation scheme in order to prove the existence of a steady solution of (1.3)–(1.4), assuming values in Q_+. For that we define an approximation scheme by

$$v^1(\mu) = \inf_{\mu' \in \mathbb{R}} v_*(\mu'),$$
$$\theta K[v^k](\mu) + (1-\theta)v^k(\mu) = \psi_\mu(v^{k+1}(\mu)),$$

with $v_*(\mu)$ as above. In order to prove that this is an increasing sequence, we argue again by monotonicity. Since $v^1(\mu) \leq v_*(\mu)$ and since ψ_μ is increasing and convex, then $\psi_\mu(v^1(\mu)) \leq v^1(\mu)$. On the other hand $\psi_\mu(v^2(\mu)) = v^1(\mu)$, therefore we have

$$v^2(\mu) \geq v^1(\mu).$$

We can then continue and iterate the argument, from which we deduce

$$\begin{aligned} \psi_\mu(v^3(\mu)) &= \theta K[v^2](\mu) + (1-\theta)v^2(\mu) \\ &\geq \theta K[v^1](\mu) + (1-\theta)v^1(\mu) \\ &= \psi_\mu(v^2(\mu)), \end{aligned} \tag{2.5}$$

and thus $v^3(\mu) \geq v^2(\mu)$. By iteration we deduce that v^k is an increasing sequence.

We can also provide an upper bound on the sequence v^k as follows. We notice that, thanks to the uniform monotonicity of ψ_μ, there is a convex function $\underline{\psi}$ such that

$$\underline{\psi}(v) \leq \psi_\mu(v) \ \forall v \geq 0, \qquad \underline{\psi}(0) = 0, \ 0 < \underline{\psi}'(0) < 1, \quad \text{and} \quad \underline{\psi}'(v) > 1 \quad \text{for } v \text{ large}.$$

This function admits a unique fixed point $\bar{v}$ and we know that $\bar{v} \geq v_*(\mu)$ for all μ. We claim that

$$v^k(\mu) \leq \bar{v}.$$

Indeed, this is true for $k = 1$, and by iteration, when the result holds for $k-1$ we have

$$\underline{\psi}(v^k(\mu)) \leq \psi_\mu(v^k(\mu)) = \theta K[v^{k-1}](\mu) + (1-\theta)v^{k-1}(\mu) \leq \bar{v}.$$

¿From this, we deduce that $v^k(\mu) \leq \bar{v}$ and the claim is proved. Hence, $\{v^k(\mu)\}_{k\in\mathbb{N}}$ is a monotone uniformly bounded sequence of functions, which implies the existence of the pointwise limit $v_{st}(\mu)$ which satisfies the equation and the announced a priori bounds.

We now prove uniqueness for θ small enough. We first notice that for θ sufficiently small, we have by uniform continuity of $\psi_\mu(\cdot)$ that $v - v_*$ is uniformly small and thus

$$\psi'_\mu(v) > 1, \text{ uniformly in } \mu \in \mathbb{R}. \tag{2.6}$$

We denote $\phi_{\mu,\theta}(v) = \psi_\mu - (1-\theta)v$, we have $\phi'_{\mu,\theta}(v) > \theta$, for $v_\theta(\mu) \le v \le \max v_*(\mu')$, uniformly in $\mu \in \mathbb{R}$. Hence, for any two steady solutions $(\bar v(\mu), l(\mu))$, $(\tilde v(\mu), \tilde l(\mu))$, with values in Q_+, we have

$$\left[\int_0^1 \phi'_{\mu,\theta}(s\bar v(\mu) + (1-s)\tilde v(\mu))\,ds\right](\bar v(\mu) - \tilde v(\mu)) - \theta K * (\bar v - \tilde v) = 0,$$

which, from (2.6), implies $\bar v(\mu) = \tilde v(\mu)$. In sum, there is at most one steady solution $(v_{st}(\mu), l_{st}(\mu))$ with values in Q_+. This concludes proof of the stated theorem.

3. Study of the dynamics in a simple case

In this section we proceed to the qualitative study of the dynamics of the system (1.1)-(1.2) and our main goal is to obtain sufficient conditions involving the coefficients $\sigma(\mu), \alpha(\mu), \beta(\mu), \eta(\mu)$ and the parameters in the definition of Σ, namely γ, s_* below, which ensure that the singularity $P_3(\mu)$, obtained in Section 1, is a global attractor for the whole region Q_+, with respect to the flow given by (1.1)-(1.2). Since in all this section we are only concerned with the system (1.1)-(1.2), throughout the remaining of the section we ommit completely the dependence on μ of the coefficients in this system.

For simplicity, we concentrate our analysis on the prototypical case where Σ is given by

$$\Sigma(s) = \begin{cases} \gamma s, & s \le s_*, \\ \gamma s_*, & s \ge s_* \end{cases}. \tag{3.1}$$

Once we obtain the referred conditions for the prototype model with Σ given by (3.1), conditions which give the same result for a more general Σ are easy to guess. For instance, we may assume only that Σ is increasing for $0 \le s \le s_*$, and $\Sigma(s) = \Sigma_\infty$ for $s \ge s_*$.

Theorem 3.1. *Let $\sigma, \alpha, \beta, \eta, \gamma, s_*$ satisfy the conditions*

(C1) $\eta\frac{\gamma}{\beta} < \frac{\sigma}{\alpha} < \frac{1}{s_*} < \frac{\gamma}{\beta}$;

(C2) $\Sigma_\infty > \beta + \sigma$.

There exists $\delta > 0$ such that, if

(C3) $\frac{\sigma - \beta}{\alpha} < \delta$,

then, the singularity P_3 in (1.9) *is a global attractor for the whole region Q_+, with respect to the flow given by* (1.1)-(1.2), *with* (3.1). *More precisely, given any solution of* (1.1)-(1.2) *and* (3.1), $(v(t), l(t))$, *with* $(v(0), l(0)) \in Q_+$, *then* $(v(t), l(t))$ *is defined for all* $t \in (-\infty, \infty)$, *and we have* $(v(t), l(t)) \to P_3$ *as* $t \to +\infty$.

Remark 3.1. Observe that, using (3.1) and the last inequality of (C1), $\Sigma^{-1}(\beta) = \frac{\beta}{\gamma}$, and thus the conditions C_1 imply (1.10).

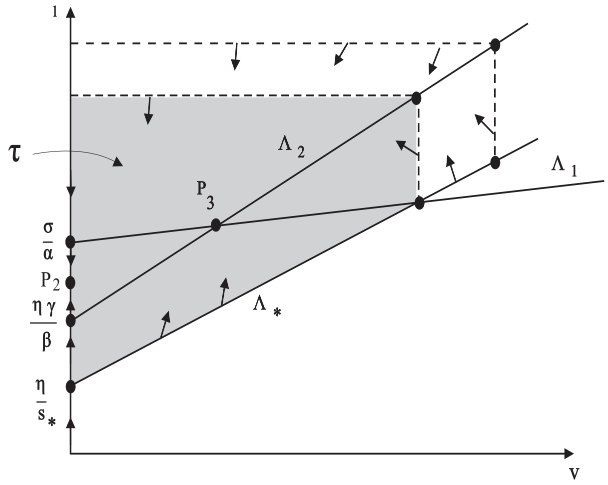

FIGURE 1. Vector field f and separation in regions from the lines Λ.

Proof. Let $f = (f_1, f_2)$ be the vector field defined in $\overline{Q_+}$ whose components are given by the right-hand sides of (1.1) and (1.2), respectively. Define the lines

$$\Lambda_1 : l = \frac{\sigma}{\alpha}(v+1), \qquad \Lambda_2 : l = \frac{\gamma}{\beta}(\eta + v), \qquad \Lambda_* : l = \frac{1}{s_*}(v+\eta).$$

The line Λ_1, over which $f_1 \equiv 0$, cuts the l-axis at $(0, \frac{\sigma}{\alpha})$ which, due to (C1), lies above $(0, \eta\frac{\gamma}{\beta})$, the point at which Λ_2, over which $f_2 \equiv 0$, cuts the same axis. Also, Λ_1 and Λ_2 intersect at P_3, which is coherent with the fact that the inclination of Λ_1, $\frac{\sigma}{\alpha}$ is smaller than that of Λ_2, $\frac{\gamma}{\beta}$, by (C1). We also notice that the transition line Λ_*, below which $f_2(v,l) = (\Sigma_\infty - \beta)l > 0$, intersects Λ_1 in Q_+ at a point (v_{*1}, l_{*1}), but does not meet Λ_2 in Q_+, again due to (C1). These elements are shown in figure 1. We have that $f_1 > 0$ below Λ_1, $f_1 < 0$ above Λ_1, $f_2 > 0$ below Λ_2 and $f_2 < 0$ above Λ_2. Taking the latter into account, we claim that condition (C2) implies that the field f, along the line Λ_*, is always pointing toward the upper region determined by Λ_* in Q_+. We only need to check that for

$$v < v_{*1} := \frac{\sigma s_* - \alpha\eta}{\alpha - \sigma s_*},$$

since for $v > v_{*1}$ we have $f_1 < 0$ and $f_2 > 0$, along Λ_*. Now, over Λ_*, for $v < v_{*1}$, we have

$$\begin{aligned}
\frac{f_2}{f_1} &= \frac{(\Sigma_\infty - \beta)(\eta + v)(1+v)}{(\sigma s_* - \alpha)v^2 + (\sigma s_* - \alpha\eta)v} \\
&> \frac{\Sigma_\infty - \beta}{\sigma s_* - \alpha\eta} \qquad \text{by (C1) and (C2)} \\
&> \frac{1}{s_*} \qquad\qquad \text{by (C2).}
\end{aligned}$$

We now consider the trapezium $\mathcal{T}$, bounded by the lines Λ_*,

$$\Lambda_4 : v = v_{*1}, \qquad \Lambda_5 : l = l_{42} := \frac{\gamma}{\beta}(\eta + v_{*1}),$$

and the l-axis, $v=0$. From the above discussion we deduce that such a trapezium is invariant, that is, along its boundary f is always pointing inwards, when it is not tangent. Moreover, since in $\mathcal{T}$ we have

$$\operatorname{div} f = \frac{\partial f_1}{\partial v} + \frac{\partial f_2}{\partial l} = \sigma - \frac{\alpha l}{(1+v)^2} - \beta - \gamma\frac{\eta+v}{l^2},$$

condition (C3) implies

$$\operatorname{div} f < 0, \qquad \text{in } \mathcal{T}, \tag{3.2}$$

for $\delta > 0$ sufficiently small. Now, (3.2) precludes the existence of periodic orbits in Q_+. Indeed, any such orbit would have to surround P_3, since P_3 is the only singularity in Q_+, as a consequence of the well known Poincaré-Bendixson lemma. But, since $\mathcal{T}$ is (positively) invariant, such orbit would have to lay entirely within $\mathcal{T}$, and this is impossible by (3.2), which tells that the flow generated by f strictly decreases volumes in $\mathcal{T}$. Hence, we conclude

(3.3) *There is no periodic orbit of* (1.1)-(1.2) *in* Q_+.

To complete the analysis we still need to prove the following two assertions:

(3.4) *Any solution* $(v(t), l(t))$ *is defined for all* $t \in (-\infty, +\infty)$.

and

(3.5) *All orbits enter the trapezium* $\mathcal{T}$.

To prove (3.4), we denote $\tau = -t$, and observe that, by (1.2), we have

$$\frac{dl}{dt} \le (\Sigma_\infty - \beta) l(t), \qquad \frac{dl}{d\tau} \le \beta\, l(\tau),$$

which by Gronwall's lemma gives

$$l(t) \le l(0) e^{(\Sigma_\infty - \beta)t}, \qquad l(\tau) \le l(0) e^{\beta\tau}.$$

On the other hand, we have

$$\frac{dv}{dt} \le \sigma v(t), \qquad \frac{dv}{d\tau} \le \alpha l(0) e^{\beta\tau} v(\tau),$$

and again by Gronwall's lemma we obtain

$$v(t) \le e^{\sigma t}, \qquad v(\tau) \le v(0) e^{\frac{\alpha l(0)}{\beta}(e^{\beta\tau}-1)},$$

which concludes the proof of (3.4).

We are now going to prove (3.5) in order to conclude our analysis. To achieve this goal we make use of a direct analysis of trajectories; more systematic, but also longer to explain in our context, methods using compactifications are possible (see, e.g., [6]). We compute first

$$\frac{d}{dt}\Big(\frac{l}{v}\Big) = \frac{l}{v}\Big(\Sigma(\frac{\eta+v}{l}) - \beta - \sigma + \frac{l}{1+v}\Big). \tag{3.6}$$

When the initial state belongs to the lower region determined by Λ_*, and as long as the trajectories belong to that region, we have

$$\frac{d}{dt}\Big(\frac{l}{v}\Big) \ge \frac{l}{v}\Big(\Sigma_\infty - \beta - \sigma\Big).$$

By (C2), this implies that in finite time the trajectory has to cross Λ_*. Then, it has also entered the region above Λ_1 which means that $\frac{dv}{dt} < 0$ and this leads the trajectories to enter the region above Λ_2 from which obviously it has to enter the trapezium $\mathcal{T}$ and we reach our conclusion. When the initial state belongs to the upper region determined by Λ_*, then the end of the above argument concludes. In all cases we obtain (3.5) and the proof of Theorem 3.1 is complete.

□

4. Dynamics for the model with mutations

Now we consider the dynamics for the general model (1.3)-(1.4) accounting for mutations. The idea is to use all the informations obtained in the last section concerning the model without mutations, (1.1)-(1.2), in order to get qualitative information about the dynamics governed by the system (1.3)-(1.4). First, to emphasize the dependence on θ we denote the steady solution of (1.3)-(1.4) by $(v_{st}^\theta(\mu), l_{st}^\theta(\mu))$ and set $P_3(\mu) = (v_*(\mu), l_*(\mu))$, where $v_*(\mu)$ coincides with that given by (2.2). We need regularity for this section and in order to make the analysis simpler, we assume now smoothness of all the datas; for compactness we also assume that they are periodic with period 1 in μ, and finally we assume that K is a (periodic) convolution kernel i.e. $K := K(\mu - \mu')$.

The purpose of this section is the proof of the following theorem.

Theorem 4.1. *Given initial data* $(v(0,\mu), l(0,\mu)) = (v_0(\mu), l_0(\mu))$ *smooth periodic with period 1 and assuming values in* Q_+, *there exists* $\theta_0 \in (0,1)$, *such that if* $0 < \theta < \theta_0$, *then the corresponding solutions of* (1.3)-(1.4), (3.1), $(v^\theta(t,\mu), l^\theta(t,\mu))$, *satisfy*

$$(v^\theta(t,\mu), l^\theta(t,\mu)) \to (v_{st}^\theta(\mu), l_{st}^\theta(\mu)), \qquad \text{as } t \to \infty. \tag{4.1}$$

Proof. From the discussion in section 2 we have that $\min_* v(\mu') \le v_{st}^\theta(\mu) \le \max v_*(\mu')$, if θ is small. Also, from (2.3), we see that $\{(v_{st}^\theta, l_{st}^\theta) : \theta \in [0,1]\}$ is compact in $C_{per}(\mathbb{R})$, the Banach space of the continuous periodic functions (with period 1). Moreover, from (2.3) we also see that any converging subsequence of $(v_{st}^\theta, l_{st}^\theta)$, as $\theta \to 0$, must converge to $(v_*(\mu), l_*(\mu))$, hence we get

$$(v_{st}^\theta, l_{st}^\theta) \to (v_*(\mu), l_*(\mu)), \quad \text{as } \theta \to 0, \text{ uniformly for } \mu \in \mathbb{R}. \tag{4.2}$$

Now, we may choose $r > 0$ sufficiently small such that the ball $B \subset Q_+$ with radius r centered at $(v_*(\mu), l_*(\mu))$ verifies that the field f^μ is nontangent and entering into B everywhere along $S = \partial B$, uniformly for $\mu \in \mathbb{R}$, where $f^\mu = (f_1^\mu, f_2^\mu)$ is the vector field whose components are given by the right-hand members of (1.1) and (1.2), respectively. This is true since it is true for the linear part of f^μ at $(v_*(\mu), l_*(\mu))$. Also, because of (4.2), we may take θ_0 such that

$$(v_{st}^\theta(\mu), l_{st}^\theta(\mu)) \in B, \quad \forall \mu \in \mathbb{R}, \text{ if } 0 \le \theta < \theta_0. \tag{4.3}$$

Define

$$S_{\mu,t} = \Phi_{-t}^\mu(S), \ t > 0,$$

where Φ_{-t}^μ is the flow generated by f^μ backward to the time $-t$. Denote by $B_{\mu,t}$ the open set bounded by $S_{\mu,t}$. Let t_μ be such that

$$(v_0(\mu), l_0(\mu)) \in S_{\mu,t_\mu}. \tag{4.4}$$

We assume, without loss of generality, that $t_\mu > \delta > 0$. Clearly, there exists a compact $\mathcal{K} \subset Q_+$ such that

$$B_{\mu,t_\mu} \subset \mathcal{K}, \quad \forall \mu \in \mathbb{R}. \tag{4.5}$$

For each fixed μ, we consider the orbit of (1.1)-(1.2) starting from $(v_0(\mu), l_0(\mu))$ at $t = 0$. Let $\mathcal{O}_\mu$ denote the piece of this orbit corresponding to the interval $(0, t_* + 2)$, where

$$t_* = \sup_{\mu\in\mathbb{R}} t_\mu.$$

Also, let $\mathcal{O}^\theta_\mu$ be the trajectory described in the (v, l)-plane by $(v^\theta(t, \mu), l^\theta(t, \mu))$, for $t \in (0, t_* + 2)$. We will prove (4.1) by showing first that

$$\begin{aligned}&\exists\theta_0, \textit{ s.t., for } \theta \in [0, \theta_0),\ \mathcal{O}^\theta_\mu \textit{ is transversal to all } S_{\mu,t},\\ &\textit{for } 0 \le t \le t_\mu - \delta, \textit{ uniformly for } \mu \in \mathbb{R}.\end{aligned} \tag{4.6}$$

First of all, we need to show the existence of a smooth periodic (in μ) solution $(v^\theta(t, \mu), l^\theta(t, \mu))$ of (1.3)-(1.4), (3.1), with initial data $(v_0(\mu), l_0(\mu))$, defined for all $t \in [0, \infty)$, if θ is sufficiently small. For the local existence we may use the standard approximation method based on Banach's fixed point theorem. Namely, we define

$$\tilde v(t) = v_0 + \int_0^t \{\sigma((1-\theta)v + \theta K * v) - \frac{\alpha l v}{1+v}\}\, ds, \tag{4.7}$$

$$\tilde l(t) = l_0 + \int_0^t (\Sigma(\frac{\eta + v}{l}) - \beta) l\, ds, \tag{4.8}$$

and prove that the operator $(v, l) \mapsto (\tilde v, \tilde l)$ is a contraction in the Banach space $C_{per}(\mathbb{R} \times [0, \rho))$, of the continuous functions in $\mathbb{R} \times [0, \rho)$ periodic in μ, for $\rho > 0$ sufficiently small. This is a routine verification. Now, we claim that, for θ sufficiently small,

$$(v^\theta(t, \mu), l^\theta(t, \mu)) \in \bar B_{\mu,t_\mu} \quad \forall\mu \in \mathbb{R},\ t \in [0, \rho). \tag{4.9}$$

Indeed, if (4.9) is not true, there exists $t_0 \in [0, \rho)$ such that

$$t_0 = \inf\{t \in [0, \rho) : \exists\mu \in \mathbb{R},\ (v^\theta(t, \mu), l^\theta(t, \mu)) \notin \bar B_{\mu,t_\mu}\}.$$

Hence, for all $\mu \in \mathbb{R}$ we have $(v^\theta(t_0, \mu), l^\theta(t_0, \mu)) \in \bar B_{\mu,t_\mu}$, and there exists $\mu_0 \in [0, 1]$ such that

$$(v^\theta(t_0, \mu_0), l^\theta(t_0, \mu_0)) \in S_{\mu_0,t_{\mu_0}} \text{ and } f^{\mu_0,\theta}(t_0) \text{ is pointing outwards } \bar B_{\mu_0,t_{\mu_0}},$$

where $f^{\mu_0,\theta}(t_0)$ denotes the vector whose components are given by the right-hand sides of (1.3) and (1.4), respectively, evaluated for $(v, l) = (v^\theta(t, \cdot), l^\theta(t, \cdot))$, $\mu = \mu_0$, $t = t_0$. But, because of (4.5), for $\theta < \theta_0$, with θ_0 independent of μ_0, we must have that $f^{\mu_0,\theta}(t_0)$ is pointing inwards $\bar B_{\mu_0,t_{\mu_0}}$, as long as $(v^\theta(t_0, \mu), l^\theta(t_0, \mu)) \in \bar B_{\mu,t_\mu}$, for all $\mu \in \mathbb{R}$, which gives a contradiction and proves (4.9).

In view of (4.9), we see that $(v^\theta(t, \mu), l^\theta(t, \mu))$ may be extended to be defined for all $t \in [0, \infty)$. We now resume the proof of (4.6). An easy application of Gronwall's lemma, departing from (4.7), (4.8), for a general θ and $\theta = 0$, implies

$$\|v^\theta(t) - v^0(t)\|_\infty + \|l^\theta(t) - l^0(t)\|_\infty \le C\theta e^{Ct}, \quad 0 \le t \le t_* + 2, \tag{4.10}$$

for a certain constant $C > 0$. We then deduce from (1.1)-(1.2) and (1.3)-(1.4) that

$$\sup_{\mu\in\mathbb{R}} |f^\mu(t) - f^{\mu,\theta}(t)| \le C\theta e^{Ct}, \quad 0 \le t \le t_* + 2, \tag{4.11}$$

for another constant $C > 0$. Inequalities (4.10) and (4.11) imply that $\mathcal{O}_\mu$ and $\mathcal{O}^\theta_\mu$ are arbitrarily close in C^1, uniformly for $\mu \in \mathbb{R}$, if θ is small enough. Hence, we can find $\theta_0 \in (0, 1]$ such that (4.6) holds.

We now conclude the proof of (4.1). From (4.6) we deduce that

$$(v^\theta(t,\mu), l^\theta(t,\mu)) \in B, \quad \forall \mu \in \mathbb{R}, \quad \text{for any } t_* + 1 < t < t_* + 2.$$

Now, arguing as above, we obtain similarly that $(v^\theta(t_*+1,\mu), l^\theta(t_*+1,\mu)) \in \bar{B}$, for all $\mu \in \mathbb{R}$, implies that

$$(v^\theta(t,\mu), l^\theta(t,\mu)) \in \bar{B}, \quad \text{for all } t > t_* + 1,\ \mu \in \mathbb{R}, \tag{4.12}$$

where we use the fact that, for θ sufficiently small, $f^{\mu_0,\theta}(t)$ is pointing inwards B if $(v^\theta(t,\mu_0), l^\theta(t,\mu_0)) \in S$ and $(v^\theta(t,\mu), l^\theta(t,\mu)) \in \bar{B}$, for all $\mu \in \mathbb{R}$.

Let $T_t, T_t^\theta, U_t, U_t^\theta$ denote the semigroups generated, respectively, by the linear part (in the Taylor expansion) of the right-hand side of (1.1)-(1.2) at (v_*, l_*), by the linear part of the right-hand side of (1.3)-(1.4) at $(v_{st}^\theta, l_{st}^\theta)$, by the right-hand side of (1.1)-(1.2) and by the right-hand side of (1.3)-(1.4). The open set $\mathcal{B} = C_{per}(\mathbb{R}; B)$ remains invariant under these semigroups for $t \in [0,\infty)$. Set $z = (v,l)$, $z_{st}^\theta = (v_{st}^\theta, l_{st}^\theta)$. The proof of (4.1) will be concluded as soon as we show that

$$\begin{gathered} \exists c \in (0,1),\ s.t.\ \forall \tau \in [1/2,1], \\ \|U_\tau^\theta[z] - z_{st}\|_\infty < c\|U_{1/2}^\theta[z] - z_{st}\|_\infty,\ \forall z \in \mathcal{B}. \end{gathered} \tag{4.13}$$

Indeed, (4.13) implies

$$\|U_{\tau+(k-1)/2}^\theta[z] - z_{st}\|_\infty < c^k \|U_{1/2}^\theta[z] - z_{st}\|_\infty, \qquad \forall k \in \mathbb{N},\ \tau \in [1/2,1],$$

and this, together with (4.12), clearly implies (4.1). Now, let $A(z)$ and $A^\theta(z)$ be the linear parts of the right-hand sides of (1.1)-(1.2) and (1.3)-(1.4) at z, respectively. We have

$$A^\theta(z_{st}^\theta) = A(z_{st}^\theta) + \theta I_1 + \theta K * \cdot,$$

where I_1 is the projection $I_1(v,l) = v$. Thus,

$$\|A^\theta(z_{st}^\theta) - A(z_*)\| \le O(\theta),$$

as linear operators in $C_{per}(\mathbb{R})$, where $O(\theta) \to 0$ as $\theta \to 0$, which then implies

$$\|T_\tau^\theta - T_\tau\| \le O(\theta), \tag{4.14}$$

uniformly for $\tau \in [1/2,1]$, also as linear operators in $C_{per}(\mathbb{R})$, where again $O(\theta) \to 0$ as $\theta \to 0$. But, we know that z_* is an attractor of U_τ and, hence, there exists $c \in (0,1)$ such that

$$\|T_\tau\| < c, \quad \text{as linear operator in } C_{per}(\mathbb{R}), \text{ uniformly for } \tau \in [1/2,1].$$

¿From (4.14), we then obtain that, for certain $\theta_0 \in (0,1)$, there exists $c \in (0,1)$ such that, if $\theta < \theta_0$,

$$\|T_\tau^\theta\| < c, \quad \textit{as linear operator in } C_{per}(\mathbb{R}),\ \textit{uniformly for } \tau \in [1/2,1]. \tag{4.15}$$

It is also clear that, for some constant $C > 0$, independent of θ, we have

$$\sup_{t\in[0,1]} \|T_t^\theta\| \le C.$$

Now, setting $w(t) = U_t^\theta[z] - z_{st}^\theta$, we have

$$\frac{dw}{dt} = A^\theta(z_{st}^\theta)w + R(z, z_{st}^\theta),$$

where $\|R(z, z_{st}^\theta)\|_\infty \le C\|z - z_{st}^\theta\|_\infty^2$, for some $C > 0$, independent of θ. From Duhamel's principle, it then follows

$$w(t) = T_t^\theta[w(1/2)] + \int_{1/2}^t T_{t-s}^\theta[R(U_s^\theta[z], z_{st}^\theta)]\, ds, \qquad \text{for } t \in [1/2, 1],$$

and so

$$\max_{t\in[1/2,1]} \|w(t)\|_\infty \le c\|w(1/2)\|_\infty + Cr \max_{t\in[1/2,1]} \|w(t)\|_\infty,$$

which, if r is small enough, gives

$$\max_{t\in[1/2,1]} \|w(t)\|_\infty \le c\|w(1/2)\|_\infty,$$

for some $c \in (0, 1)$, as asserted. This concludes the proof. □

5. The route to catastrophe

In this section we discuss the possible reasons that could lead the system (1.3)–(1.4) to blow-up as observed in some cases of HIV for instance. The result in Theorem 3.1 shows that this can only happen because of mutations since the single virus system has a globally attractive critical point P_3. On the other hand, Theorem 4.1 seems to indicate that mutations by themselves are not enough to destabilize the system which converges to the steady state built in Theorem 2.1, but a complete answer to this question is of interest and is left open here. We give two possible scenarios for unstability. The first one is the blow up of steady states for some values of μ which are attained by mutations. The second one is a change of regime in the dynamics due to the lack of smoothness of the coefficients.

Therefore we first release the assumption (1.10) in such a way that the attractive point $P_3(\mu)$ is not uniformly bounded. Namely, we rather assume

$$\kappa(\mu) < 1 \quad \forall \mu \in \mathbb{R}, \qquad \kappa(\mu) \to 1 \text{ as } \mu \to \infty. \tag{5.1}$$

This condition is too weak to ensure blow-up by itself, and we also assume two additional structures in the datas (see the construction in Section 2)

$$\frac{\partial}{\partial \mu}\psi_\mu(v) \le 0, \quad \frac{\partial}{\partial v}\psi_\mu(v) \ge 1 - \theta, \tag{5.2}$$

$$K(\mu, \mu') = 0 \quad \text{for } \mu \le \mu', \quad \frac{\partial K}{\partial \mu}(\mu, \mu') \ge 0. \tag{5.3}$$

We also recall from Section 2 that the steady state is given by

$$\psi_\mu(v_{st}) = (1 - \theta)v_{st} + \theta K[v_{st}], \tag{5.4}$$

and that (5.1) is equivalent to

$$v_*(\mu) < \infty \quad \forall \mu \in \mathbb{R}, \qquad v_*(\mu) \to \infty \ \text{ as } \ \mu \to \infty. \tag{5.5}$$

We are going to show that, with this conditions, the steady state which exists by a simple variant of the argument in Section 3, is unbounded.

As a first property, we notice that condition (5.2) implies

$$\frac{\partial v_{st}(\mu)}{\partial \mu} \ge 0. \tag{5.6}$$

Indeed, after differentiating (5.4), we deduce

$$\frac{d}{d\mu}\big(\psi_\mu(v_{st}(\mu))\big) = \frac{\partial \psi_\mu(v_{st})}{\partial v}\,\frac{\partial v_{st}(\mu)}{\partial \mu} + \frac{\partial \psi_\mu}{\partial \mu}(v_{st}) = (1-\theta)\,\frac{\partial v_{st}(\mu)}{\partial \mu} + \partial\partial\mu K[v_{st}].$$

Hence

$$\left(\frac{\partial \psi_\mu(v_{st})}{\partial v} - 1 + \theta\right)\,\frac{\partial v_{st}(\mu)}{\partial \mu} = -\frac{\partial \psi_\mu}{\partial \mu}(v_{st}) + \partial\partial\mu K[v_{st}] \geq 0,$$

because of (5.2) and (5.3). Since $\frac{\partial \psi_\mu(v)}{\partial v} \geq 1-\theta$, we conclude (5.6). Then, we use assumption (5.3) and (5.6) to deduce that

$$\psi_\mu(v_{st}) = (1-\theta)v_{st} + \theta K[v_{st}] \geq v_{st}.$$

A condition which implies that

$$v_{st}(\mu) \geq v_*(\mu) \to \infty \quad \text{as } \mu \to \infty. \tag{5.7}$$

This statement proves blow-up of steady states under the effect of mutations. We have investigated the dynamical behavior based on numerical simulations. From various tests, we have obtained blow-up under more general conditions which are compatible with uniformly bounded steady states. In other word, the smallness condition in Theorem 4.1 seems necessary. We illustrate the transition from a regime where mutations occur smoothly and keep virus at a low load, to a regime where mutations induce an oscillatory regime by increasing the corresponding $\kappa(\mu)$. We have chosen the following values of the various adimensionalized parameters, with 40 discrete values of μ, we have initially $v^0(\mu) = 0$ except the first four for which $v^0(\mu) = .5$, the leukocytes load is initially chosen at the corresponding steady state ignoring the mutations (P_2). Next, the parameters of the leukocytes dynamics are $\beta = .8$, $\eta = .2$, $\Sigma(u) = \frac{4u}{4+u}$, so that $\Sigma(1) = \beta$. The virus dynamics parameters are $\sigma = 2.$ and $\kappa(\mu) = .25(1+(\mu-.5)_+^2)$. The mutation rate is taken to 10^{-4} and we have chosen a kernel K which is rather in the form derived in (1.8) since we choose, at the discrete level $K[v](\mu) = v(\mu-1)$ in order to create new virus load gradually. The total loads are presented in figure 5. A possible interpretation is that, after the initial infection where only few mutants are present, the system reaches an equilibrium state where the total loads increase slowly due to appearance of new mutants. After some time, a significant amount of virus with a higher value of the parameter κ creates an important virus load. This last stage is however partially irrealistic since it does not correspond to a leukocytes load break down which is usually observed.

6. Conclusion

We have presented a simple model for immune response which takes into account virus mutations. This system admits a steady state which is unique for small mutation rates. Existence of a solution has been proved, for large times they converge toward the steady state for small perturbations. Several possible scenarios are possible for explaining departure form equilibrium, either by the parameters of the problem which can induce the blow-up of the steady state or by the dynamics itself.

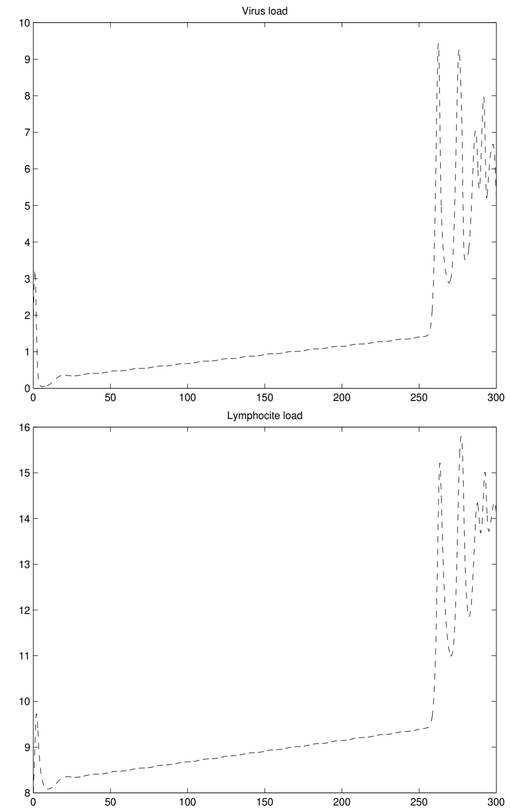

FIGURE 2. Total virus (up) and leukocytes (down) loads for a model with mutations.

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