On the limits of the Volterra function in the Lyapunov method: the Anderson-May-Gupta model as a cautionary example

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ON THE LIMITS OF THE VOLTERRA FUNCTION IN THE LYAPUNOV METHOD: THE ANDERSON-MAY-GUPTA MODEL AS A CAUTIONARY EXAMPLE[†,‡]

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ABSTRACT. The Volterra-type Lyapunov functions are an ubiquitous tool for establishing global stability in systems appearing in mathematical biology. We show, however, that no function of this type can be a Lyapunov function for the endemic equilibria of a classical intra-host model of malaria — the AMG model. More precisely, we give a sharp condition on the model parameters for this to be the case. This condition leaves out a large and biologically meaningful parameter range that will have to be addressed by a different method. We also present a set of three alternative arguments that enlarge the range of parameters for which global stability can be obtained — including parameter ranges that are relevant to malaria.

1. INTRODUCTION

1.1. **Background.** The traditional mathematical analysis of epidemiological models usually starts with basic questions as well-posedness of the model, determination of the basic reproductive number, identification of equilibria, and local stability. Once this is settled, the next step is to establish global stability of the appropriate equilibria in the different parameter regimes. The importance of this analysis can been read from the introduction of [16] — see also [5]. Indeed, in many models the Sharp Threshold Property holds: (i) there exists an equilibrium without the disease — the so-called disease free equilibrium (DFE) — which exists for all valid parameter values; (ii) the DFE equilibrium is globally asymptotically stable when $\mathcal{R}_0 \leq 1$; (iii) when $\mathcal{R}_0 > 1$ there exists a unique equilibrium where the disease is present — the so-called endemic equilibrium (EE) — which is then globally asymptotically stable. The rationale behind this property is that although a system might have a complex transient dynamics, its long term behaviour is quite simple, with a dichotomy completely governed by $\mathcal{R}_0$. See [28] for the original reference and further discussion of this property.

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In order to verify the Sharp Threshold Property, one has to check that conditions (i)–(iii) above hold. Condition (i) is typically a straightforward computation. In order to check condition (ii), a linear Lyapunov function is usually sufficient. Condition (iii), however, is typically much harder to verify. In more complex models even existence and uniqueness can be a difficult issue. Indeed, in some cases existence can be ascertained by means of uniformly persistence and then verifying that an interior equilibrium is necessarily globally asymptotically stable yields also uniqueness and check that (iii) holds — eg. [9].

In any case, the use of Volterra type Lyapunov functions has proved to be quite an effective tool to establish that the endemic equilibrium is globally asymptotically stable. This function was first used by Volterra in [40], and later by Goh [6] (also [7])). It has been rediscovered later on and used for epidemic models by Lin and So [21] and Korobeinikov and Maini [17]. Since then, it has been successfully used in innumerous situations — eg. [8] , [5], [14], [10], [32], [30], [35], [31].

On one hand, while it is known that, when an equilibrium is globally asymptotically stable, then a Lyapunov function must exist ([22] and [23]) — the proofs of these results are non constructive and there is no guarantee that it will belong to a particular class of functions. On the other hand, the success of the Volterra Lyapunov function seems to have led to the belief that, at least for biological models, if the model is globally stable, then one should be able to tune the parameters of a Volterra Lyapunov function to show its global stability.

Finally, we would like to mention a few alternative approaches that have been used to show globally stability: (i) Beretta and Capasso [2] use of a skew-symmetry condition on the Jacobian of the matrix of the system to give a necessary condition for the global stability of the endemic equilibrium; (ii) Li and Muldowney [20] developed an approach that has ben widely used to deal with the global stability of the EE for many epidemic models; (iii) the use of techniques of monotone dynamical systems [13].

Here we will revisit the stability of a classical intra-host model of Malaria and show that (i) a Volterra-Lyapunov function for this model has to have a very specific form; (ii) this specific form cannot be a Lyapunov function for all biologically feasible parameter values; (iii) the use of three different techniques, namely monotone dynamical systems, asymptotically 2-D systems, and singular perturbations can be used to expand the range of parameters where global stability can be verified. In this particular case, these techniques will include parameter regimes that are relevant to Malaria. We also point out that, to the best of our knowledge, no rigorous proof that the Volterra-Lyapunov function can fail in situations where the model is globally stable has been provided so far.

1.2. **The Anderson-May-Gupta (AMG) model.** The original AMG [1] model is given by

$$\left\{\begin{array}{rcr} \dot{x} &=& \Lambda - \beta m x - \mu_x x, \\ \dot{y} &=& \beta m x - \mu_y y, \\ \dot{m} &=& r\mu_y y - \beta m x - \mu_m m, \end{array}\right. \tag{1}$$

where x is the concentration of uninfected erythrocytes (red blood cells) in the blood, y is the concentration of infected erythrocytes, and m the concentration of free merozoites. The parameters μ_x, μ_y and μ_m are respectively the death rates of the uninfected erythrocytes, infected parasites and free merozoites. The parameter β is the contact rate between erythrocytes and merozoites, it is the rate at which merozoites invade erythrocytes. Death of an infected erythrocyte results in the release of an average number of r merozoites. Λ is the rate at which new red cells are formed.

All the parameters are positive and the state variables x, y and m are nonnegative, i.e., $(x, y, m) \in \mathbb{R}^3_+$.

The term $-\beta m x$ in the third equation is important from a modelling point of view, for parasite and viral infections — in this case, differently form contact infections described by models like SIR or SEIR, the infective agent must enter the cell, and it is not able to infect other cells directly. However, its presence complicates the analysis considerably. Modified HIV models containing this term were studied by [4], but only partial results on the global stability were obtained. If this term is omitted, then System (1) becomes isomorphic to the standard SEIR epidemiological model or the May-Nowak in vivo HIV model [26]. For these models, the Sharp Threshold Property holds — cf. [19] and [17].

We will now briefly review the dynamical properties of the AMG system.

If we write $x^* = \frac{\Lambda}{\mu_x}$, then the basic reproduction number is given by

$$\mathcal{R}_0 = \frac{r\beta x^*}{\mu_m + \beta x^*}.$$

If $\mathcal{R}_0 \leq 1$ then the only non-negative equilibria is $(x^*, 0, 0)$ — known as the disease free equilibrium or DFE. In this case the DFE is both locally and globally asymptotically stable – cf. [14].

If $\mathcal{R}_0 > 1$ then the system is uniformly persistent [4] and there exists a unique positive equilibrium — known as the endemic equilibrium or EE– that is given by

$$\bar{x} = \frac{\mu_m}{\beta(r-1)},$$
$$\bar{y} = \frac{-\mu_m\mu_x + (r-1)\Lambda\beta}{\beta(r-1)\mu_y},$$
$$\bar{m} = \frac{-\mu_m\mu_x + (r-1)\Lambda\beta}{\beta\mu_m}.$$

Note that $\mathcal{R}_0 > 1$ implies $r > 1$.

The endemic equilibrium is always locally asymptotically stable when it exists — cf. [1, 14]. System (1) would satisfy the Sharp Threshold property [28] if one could show that the endemic equilibrium is globally asymptotically stable, when $\mathcal{R}_0 > 1$. While there are no contrary evidences to this fact, its proof has been elusive.

Indeed, in [14], partial results are obtained using a Lyapunov belonging to the class

$$V(x, y, m) = a(x - \bar{x}\log x) + b(y - \bar{y}\log y) + c(m - \bar{m}\log m), \tag{2}$$

where the coefficients in (2) are chosen such that the linear terms y and m and the bilinear terms in xm that appear in $\dot{V}$ cancel out. We will denote the function obtained with this particular choice of coefficients as V_{EE} — following the notation used in [14]:

$$V_{EE}(x, y, m) = (r-1)\bar{x}\left(\frac{x}{\bar{x}} - \log\frac{x}{\bar{x}}\right) + r\bar{y}\left(\frac{y}{\bar{y}} - \log\frac{y}{\bar{y}}\right) + \bar{m}\left(\frac{m}{\bar{m}} - \log\frac{m}{\bar{m}}\right). \tag{3}$$

There are also a number of incorrect or unusable claims in the literature: In [37], the authors claim to prove the global asymptotic stability of the endemic equilibrium using a result of [24] but their proof is not correct since in equation (20) they use the second additive compound matrix computed at the endemic equilibrium whereas (according to [24]) the second additive compound matrix must be computed at an arbitrary point. In [25] (theorem 4), globally asymptotic stability of the endemic equilibrium is addressed under the supplementary condition $(1-\frac{x}{\bar{x}})(1-\frac{m}{\bar{m}}) \geq 0$ which is not possible to verify.

1.3. **Main result and outline.** In what follows, the expression Lyapunov function is to be understood as a Lyapunov function for the Endemic Equilibrium of System (1).

We will prove the following results

Theorem 1.1. *Let V be candidate Lyapunov function with the form given by Equation (2). Then V is a Lyapunov function for some non-empty subset of model parameters if, and only if, it is a multiple of V_{EE}.*

Theorem 1.2. *The function V_{EE} is a Lyapunov function if, and only if, we have*

$$\frac{\beta\Lambda}{\mu_x\mu_m} \leq \frac{4}{r-1}\left(r - \frac{1}{2}\right)^2 = 4r + \frac{1}{r-1}. \tag{4}$$

Remark 1.1. *Condition (4) is sharp, and it improves earlier results: In [14], the first sufficient condition is* $\frac{\beta\Lambda}{\mu_x\mu_m} \le \frac{r}{r-1} = 1 + \frac{1}{r-1}$*, and a weaker condition is* $\frac{\beta\Lambda}{\mu_x\mu_m} \le (\sqrt{r} + \sqrt{r-1})^2$*. In [4]:* $\beta\Lambda \le \min(\mu_x, \mu_y)\mu_y$*.*

This existence of the sharp condition (4) shows that the Volterra integral cannot be used to show global stability of the endemic equilibrium for the entire relevant range of parameters. Thus, alternative approaches are necessary and we present three such alternatives that yield partial answers: Firstly, we show that, when $\mu_x = \mu_y$, then the AMG system is asymptotically equivalent to a 2-D system, and then a global stability result can be obtained. Secondly, when $\mu_y < \mu_x$, we show that the AMG system is equivalent to a 3-D cooperative and irreducible system — and once again global stability follows. Finally, when $\dfrac{\mu_y}{\mu_x} \gg 1$ or $\dfrac{\mu_m}{\mu_x} \gg 1$, we present a separation of scales argument that reduces the problem to a 2-D one, where global stability can be shown.

The outline of the paper is as follows: Section 2 introduces a rescaled and rewritten equivalent system. Section 3 gives the proofs of Theorems 1.1 and 1.2. Section 4 presents a set of alternative approaches, as discussed above, that show global stability of the endemic equilibrium for a range of parameters which include values not covered by condition (4). A conjecture about the global stability of endemic equilibrium for all biologically feasible parameters is also given. A discussion is presented in Section 5.

2. Basic set-up

2.1. **A rescaled version of the AMG model.** In what follows, it will be convenient to work with a rescaled version of the AMG model. We rescale time with μ_x, and let

$$X_s = \frac{x^*}{\bar{x}} = (r-1)\frac{\beta\Lambda}{\mu_x\mu_m}, \quad \mu = \frac{\mu_y}{\mu_x}, \quad \nu = \frac{\mu_m}{\mu_x}.$$

In addition, let

$$x = \bar{x}X, \quad y = \bar{y}Y, \quad m = \bar{m}M.$$

Then the original AMG system can then be written as

$$(5)\qquad \begin{cases} \dot{X} &= X_s - X - (X_s - 1)MX, \\ \dot{Y} &= \mu\,(MX - Y), \\ \dot{M} &= \nu\left(\frac{rY}{r-1} - \frac{MX}{r-1} - M\right). \end{cases}$$

We also introduce a new parameter g:

$$(6)\qquad g = \frac{r(X_s - 1)}{X_s(r-1)} = \frac{r^2(\mathcal{R}_0 - 1)}{(r-1)^2\mathcal{R}_0} = \frac{r}{r-1} - \frac{r\,\mu_x\mu_m}{(r-1)^2\beta\Lambda}.$$

From the above, we can write

$$\mathcal{R}_0 = \frac{rX_s}{X_s + r - 1}.$$

The definitions given above are not completely independent — the relevant equivalences are given in the following result:

Lemma 2.1. *The above definitions imply the following equivalences:*

(1) $\mathcal{R}_0 > 1$ *is equivalent to* $g > 0$, $r > 1$ *and* $X_s > 1$.
(2) *The following conditions are equivalent:*
- $\dfrac{\beta\Lambda}{\mu_x\mu_m} \le \dfrac{4}{r-1}\left(r - \dfrac{1}{2}\right)^2 = 4r + \dfrac{1}{r-1}$ *(Condition (4)).*
-

$$(7)\qquad X_s \le 4\left(r - \frac{1}{2}\right)^2.$$

•

(8) $$g \leq \left(\frac{2r}{2r-1}\right)^2.$$

For System (5) the family of candidate Lyapunov functions given in (2) is given by

(9) $$V(X,Y,M) = A(X-\log X) + B(Y-\log Y) + C(M-\log M), \quad A,B,C>0.$$

In addition, the function V_{EE} is now given by

(10) $$V_{EE}(X,Y,M) = (r-1)\bar{x}(X-\log X) + r\bar{y}(Y-\log Y) + \bar{m}(M-\log M).$$

Finally, we will denote by $\mathcal{K}$ a compact attracting set for System (5).

2.2. **A convenient set of alternative variables.** As it will transpire in the proofs below, much of the stability results will depend on the ratio Y/M, and it turns out that it will be advantageous to set $Y = TM$ and work with

(11) $$\begin{cases} \dot{X} &=& -X + X_s - (X_s-1)\dfrac{XY}{T}, \\ \dot{Y} &=& \mu\left(\dfrac{X}{T}-1\right)Y, \\ \dot{T} &=& \mu(\lambda-1)T + \mu X - \dfrac{\lambda\mu r}{r-1}T^2 + \dfrac{\lambda\mu}{r-1}TX, \text{ with } \lambda = \dfrac{\nu}{\mu}. \end{cases}$$

3. Proof of Theorems 1.1 and 1.2

3.1. **Proof of Theorem 1.1.** Sufficiency follows from the results in [14] on the global stability of the Endemic Equilibrium when $\mathcal{R}_0 > 1$. Indeed, the authors proved that V_{EE} is a Lyapunov function provided that the parameters satisfy $\frac{\beta\Lambda}{\mu_x\mu_m} \leq (\sqrt{r}+\sqrt{r-1})^2$.

To prove necessity, we compute the derivative of V along the solutions of (5):

$$\begin{aligned}\dot{V} = \; & -\frac{A(X-1)\left((MX-1)X_s - MX + X\right)}{X} + \frac{B\mu(Y-1)(MX-Y)}{Y} \\ & -\frac{C\nu(M-1)(M(r+X-1)-rY)}{M(r-1)}.\end{aligned}$$

A straightforward computation shows that, irrespective of the value of the coefficients A, B and C, one always has that

$$\dot{V}(1,Y,Y) = 0.$$

In other words, $\dot{V}$ always vanishes in the line $X = 1$ and $Y = M$ — we will refer to this line as the *critical line.*

We now study the behaviour of $\dot{V}$ in the neighbourhood of this critical line:

$$\begin{aligned}\dot{V}(1+\delta,Y,Y) &= \partial_X\dot{V}(1,Y,Y)\delta + \frac{1}{2}\partial_X^2\dot{V}(1,Y,Y)\delta^2 + \mathcal{O}\left(\delta^3\right) \\ &= \frac{(Y-1)}{1-r}\Big((X_s-1)(r-1)A + (1-r)B\mu + C\nu\Big)\delta - AX_s\delta^2 + \mathcal{O}\left(\delta^3\right),\end{aligned}$$

and

$$\begin{aligned}\dot{V}(1,Y,Y+\delta) &= \partial_M\dot{V}(1,Y,Y)\delta + \frac{1}{2}\partial_M^2\dot{V}(1,Y,Y)\delta^2 + \mathcal{O}\left(\delta^3\right) \\ &= \frac{\delta(Y-1)(B\mu(r-1)-C\nu r)}{(r-1)Y} - \frac{C\delta^2\nu r}{(r-1)Y^2} + \mathcal{O}\left(\delta^3\right).\end{aligned}$$

From these computations we observe that, unless the terms with order one vanish, there is always a neighbourhood of the critical line (by choosing the appropriate sign for δ) such that we have $\dot{V} > 0$. This observation leads to the following necessary conditions to ensure that $\dot{V} \le 0$:

$$\begin{array}{lcl} (X_s-1)\,(r-1)\,A + (1-r)\,B\mu + C\nu & = & 0, \\ B\mu(r-1) - C\nu r & = & 0. \end{array} \tag{12}$$

The solutions to the system above can be written in terms of B as

$$A = B\frac{\mu(r-1)}{r\,(X_s-1)},$$
$$C = B\frac{\mu(r-1)}{\nu r}.$$

With the particular choice

$$B = \frac{r\Lambda\,(X_s-1)}{\mu X_s},$$

we obtain, using the definition of X_s and the equilibrium relations, that $B = \mu_x r\bar{y}$, $A = (r-1)\dfrac{\Lambda}{X_s} = \dfrac{\bar{x}\Lambda}{x^*}(r-1) = \mu_x(r-1)\bar{x}$, and $C = \dfrac{\mu(r-1)}{\nu r}\mu_x r\bar{y} = \mu_x\bar{m}$. Hence,we arrive at $V = \mu_x V_{EE}$, which completes the proof.

3.2. **Proof of Theorem 1.2.** In this proof, it will be convenient to work with $V = \frac{V_{EE}}{\Lambda(r-1)}$ and write $\dot{V}$ using the parameter g. In this case, we obtain

$$\dot{V} = 2 - \frac{1}{X} - X + g\left(1 + X - \frac{Y}{M} - \frac{MX}{Y}\right). \tag{13}$$

On noticing that $\dot{V}$ depends only on X and on the ratio between Y and M, we opt to work in the projective line of the Y-M plane. Thus, we write $Y = TM$, and work in the alternative variable setting described in Section 2.2. In this setting, we have

$$\dot{V} = 2 - \frac{1}{X} - X + g\left(1 + X - T - \frac{X}{T}\right).$$

Remark 3.1. *In this new set of variables the critical line becomes $X = 1$ and $T = 1$.*

Thus $\dot{V} = 0$ is equivalent to the following cubic plane algebraic curve:

$$p(X,T) = X^2(T(g-1) - g) + TX(g + 2 - gT) - T = 0. \tag{14}$$

For $g \neq 1$, we can write the solution to $p(X,T) = 0$ for fixed T as

$$X_\pm(T) = \frac{g}{2(g-1)}\frac{T(T-T_+) \pm (T-1)\sqrt{T(T-T_c)}}{(T-T_*)},$$

where

$$T_* = \frac{g}{g-1}, \quad T_c = \frac{4}{g} \quad \text{and} \quad T_+ = \frac{g+2}{g}.$$

It is also convenient to write the product and sum of the roots:

$$\Pi(T) = \frac{-1}{g-1}\frac{T}{T-T_*} \quad \text{and} \quad \Sigma(T) = \frac{g}{g-1}\frac{T-T_+}{T-T_*}T.$$

Notice that we can use the expressions above when $g = 1$, if we replace $(g-1)(T-T_*)$ by 1.

The following list of facts is easily checked using the expressions above for p, $X_\pm$, Π and Σ:

(1) $p(1,1) = 0$ for any value of g and, in particular, $X_\pm(1) = 1$ — this will be termed the trivial solution;
(2) $X_\pm(T)$ is real if, and only if, $T \ge T_c$. In addition, $X_\pm(T_c) = \dfrac{2}{g-2}$ for $g \neq 2$;
(3) When $0 < g \le 1$ the only positive solution is the trivial one;

(4) When $g>1$, we have

$$X_+(T)= \frac{g\,(g-2)\,(-1+\mathrm{signum}(g-2))}{2\,(g-1)^3}\frac{1}{(T-T_*)} + \frac{\left(g^3-3g^2+2g+2\right)\mathrm{signum}(g-2)+g^3-3g^2+4g-4}{2\,(g-1)^2\,(g-2)} + \frac{\left(\left(g^5-6g^4+14g^3-18g^2+12g-2\right)\mathrm{signum}(g-2)+g^2\,(g-2)^3\right)}{(2g-2)\,(g-2)^3\,g}(T-T_*) + o(T-T_*)\,.$$

So in a neighborhood of T_*,

$$X_+(T)\sim\begin{cases}\dfrac{g\,(g-2)}{2\,(g-1)^3}\dfrac{1}{(T-T_*)} & \text{for } 1<g\le 2,\\ \dfrac{g-1}{g-2} & \text{for } g>2.\end{cases}$$

$$X_-(T)= -\frac{g\,(\mathrm{signum}(g-2)+1)\,(g-2)}{2\,(g-1)^3}\frac{1}{(T-T_*)} + \frac{\left(-g^3+3g^2-2g-2\right)\mathrm{signum}(g-2)+g^3-3g^2+4g-4}{2\,(g-1)^2\,(g-2)} + \frac{\left(\left(-g^5+6g^4-14g^3+18g^2-12g+2\right)\mathrm{signum}(g-2)+g^2\,(g-2)^3\right)}{2\,(g-1)\,(g-2)^3\,g}(T-T_*) + o(T-T_*)\,.$$

So in a neighborhood of T_*,

$$X_-(T)\sim\begin{cases}\dfrac{g-1}{g-2} & \text{for } 1<g\le 2,\\ \dfrac{-g(g-2)}{(g-1)^3}\dfrac{1}{(T-T_*)} & \text{for } g>2.\end{cases}$$

The following hold:

(a) we have $T_c\le T_*$ with equality only for $g=2$.

(b) for $T>T_*$, we have $X_+(T)>0$ and $X_-(T)<0$.

(c)

$$\lim_{T\to+\infty} X_+(T)=+\infty.$$

(d)

$$\lim_{T\to T_*^+} X_+(T)=\begin{cases}+\infty, & 1<g\le 2,\\ \dfrac{g-1}{g-2}, & g>2.\end{cases}$$

(5) When $g>2$, the following hold:

(a) $X_\pm(T)>0$ for $T\in(T_c,T_*)$.

(b)

$$\lim_{T\to T_*^-} X_-(T)=+\infty;$$

(c)

$$\lim_{T\to T_*^-} X_+(T)=\frac{g-1}{g-2}.$$

(6) When $2<g\le 4$, $X_-(T)\ge X_+(T)$ for $T\in(T_c,T_*)$ and with equality only at $T=T_c$.

(7) When $1<g\le 4$, the non-trivial solution with minimal X is given by (X_m,T_m), where $T_m=\dfrac{1}{\sqrt{g}-1}$ and $X_m=X_+(T_m)=T_m^2$.

(8) When $g > 4$, the non-trivial solution with minimal X, (X_m, T_m), satisfies $T_c < T_m < 1 < T_*$ and $X_m < \dfrac{2}{g-2}$.

In order to proceed with the proof of Theorem 1.2, we note that, in the (T, X) variables, the attracting compact set $\mathcal{K}$ is mapped into $T \geq 0$ and $0 \leq X \leq X_s$. Thus V will be a weak Lyapunov function if, and only if, the intersection of the zero set of $p(X,T)$ with $\mathcal{K}$ is only the trivial solution.

The proof of the Theorem is completed thanks to the three following facts:

(I) When $0 < g \leq 1$ there is no positive solution other than the trivial one.
(II) When $1 < g < 4$, there are no non-trivial solutions belonging to $\mathcal{K}$ if, and only if, $X_s \leq \dfrac{1}{(\sqrt{g}-1)^2}$.
(III) When $g \geq 4$, then there are always non-trivial solutions belonging to $\mathcal{K}$. Indeed, in this case $X_\pm$ always intersect transversally at $(1,1) \in \mathcal{K}$ and V_{EE} can never be a Lyapunov function, since $X_s > 1$.

These facts follow straightforwardly from the facts listed before; more precisely, (I) follows from (3), (II) follows from (7) and (III) folows from (8). See Figure 1 for a few examples of the curves $X_\pm$ for different values of g.

3.3. **An alternative proof to Theorem 1.2.** We will have to distinguish the cases $g \leq 1$ and $g > 1$. When $\mathcal{R}_0 > 1$, we have $X_s > 1$ and it is easy to see that the set $\{(X, Y, T) : 0 \leq X \leq X_s\}$ is a positively invariant set for System (11).

Recall that we have $\dot{V}(X,T) = 2 - \dfrac{1}{X} - X + g\left(1 + X - T - \dfrac{X}{T}\right)$.

$1 + X - T - \dfrac{X}{T} = 1 + X - 2\sqrt{X} - (T + \dfrac{X}{T} - 2\sqrt{X}) = (1-\sqrt{X})^2 - \dfrac{(T-\sqrt{X})^2}{T} \leq (1-\sqrt{X})^2$

Hence, $\dot{V} \leq -\dfrac{(X-1)^2}{X} + g(1-\sqrt{X})^2 = f(X)$. If $g \leq 1$ then it is clear that Condition (8) is satisfied and that $f(X) \leq 0$. Now, for $g > 1$ it is possible to write $f(X) = \dfrac{1}{X}(g-1)\left(\sqrt{X}-1\right)^2\left(\sqrt{X} - \dfrac{1}{\sqrt{g}-1}\right)\left(\dfrac{1}{\sqrt{g}+1} + \sqrt{X}\right)$. Since $g > 1$, the sign of $f(X)$ for $X > 0$ is given by the sign of $\sqrt{X} - \dfrac{1}{\sqrt{g}-1}$. Hence, for $X > 0$, $f(X) \leq 0 \iff X \leq \left(\dfrac{1}{\sqrt{g}-1}\right)^2$. Therefore, $f \leq 0$ on $(0,\ X_s]$ if, and only if, $X_s \leq \left(\dfrac{1}{\sqrt{g}-1}\right)^2$. We then deduce that $X_s \leq \left(\dfrac{1}{\sqrt{g}-1}\right)^2 \implies \dot{V} \leq 0$.

On the other hand

$$\begin{aligned}\dot{V}(X, \sqrt{X}) &= -\frac{(X-1)^2}{X} + g(1-\sqrt{X})^2 \\ &= (1-\sqrt{X})^2\left(g - \frac{(1+\sqrt{X})^2}{X}\right) = (1-\sqrt{X})^2\left(g - \left(1 + \frac{1}{\sqrt{X}}\right)^2\right).\end{aligned}$$

Thus $\dot{V} \leq 0 \implies \sqrt{g} \leq 1 + \dfrac{1}{\sqrt{X}}$, and in particular $\sqrt{g} \leq 1 + \dfrac{1}{\sqrt{X_S}}$ which implies $X_s \leq \left(\dfrac{1}{\sqrt{g}-1}\right)^2$.

Hence

$$\dot{V} \leq 0 \iff X_s \leq \left(\frac{1}{\sqrt{g}-1}\right)^2.$$

We have $X_S = \dfrac{r}{r+g(1-r)}$, so $X_s \le \left(\dfrac{1}{\sqrt{g}-1}\right)^2 \iff g \le \left(\dfrac{2r}{2r-1}\right)^2$. Using the expression of $g = \dfrac{r(X_S-1)}{X_S(r-1)}$ and the fact that $r > 1$, the later inequality is equivalent to $\left(r - \dfrac{4r^2}{(2r-1)^2}(r-1)\right) X_S \le r$, which is equivalent to $X_s \le (2r-1)^2$.

To conclude,

$$\dot V \le 0 \iff g \le \left(\frac{2r}{2r-1}\right)^2 \iff X_s \le (2r-1)^2.$$

4. Beyond the negative-definite approach

We will now present alternative arguments that allow to show that System (1) is globally asymptotically stable when $\mu \le 1$ and when $\mu \gg 1$ — this will include parameter regimes for which condition (8) is not satisfied. When $\mu = 1$ we show that system is asymptotically a 2-D one and for $\mu < 1$ we show that it is equivalent to a cooperative system in an appropriate new set of state variables. , we employ a separation of scales argument (justified by Tikhonov's theorem) for $\mu \gg 1$ which, once again, reduces the problem to a two dimensional one. Finally, we give an example that is not covered by any of these or previous results.

4.1. The case $\mu = 1$. Let $N = \alpha X + Y$ and $S = \alpha X + 2Y + \alpha' M$, where $\alpha = \dfrac{\mu}{X_s - 1}$ and $\alpha' = \mu \dfrac{r-1}{\nu}$.

Then system (5) is given by

$$(15)\qquad \begin{cases} \dot N &= \alpha X_s - N - (\mu-1)Y, \\ \dot S &= \alpha X_s - \nu S + (\nu-1)N + (\nu + \mu(r-2)+1)Y, \\ \dot Y &= \mu\left(\dfrac{1}{\alpha\alpha'}(S-N-Y)(N-Y) - Y\right). \end{cases}$$

The endemic equilibrium is now written as $\bar N = \alpha + 1$, $\bar S = \alpha + \alpha' + 2$, $\bar Y = 1$. Notice that we always have $N > Y$, $S > N$ and $S > 2Y$.

If $\mu = 1$, we have

$$(16)\qquad \begin{cases} \dot N &= \alpha X_s - N, \\ \dot S &= \alpha X_s - \nu S + (\nu-1)N + (\nu+r-1)Y, \\ \dot Y &= \dfrac{1}{\alpha\alpha'}(S-N-Y)(N-Y) - Y. \end{cases}$$

System (16) is a triangular system (the first equation depends only on the variable N), and we have that $\lim_{t\to\infty} N(t) = \alpha X_s$. Since $\mu = 1$, we have $\alpha X_s = \alpha(\frac{1}{\alpha}+1) = \alpha + 1 = \bar N$. All the solutions are bounded. Therefore, the stability properties of system (16) are the same as those of the following planar system (thanks to [39], [34], [3]):

$$(17)\qquad \begin{cases} \dot S = \alpha X_s - \nu S + (\nu-1)\bar N + (\nu+r-1)Y = \nu(\bar N - S) + (\nu+r-1)Y, \\ \dot Y = \dfrac{1}{\alpha\alpha'}(S - \bar N - Y)(\bar N - Y) - Y. \end{cases}$$

Applying Bendixson's Criterion to (17) we obtain

$$-\nu - \frac{S-2Y}{\alpha\alpha'} - 1 < 0,$$

since $S > 2Y$. Therefore, the endemic equilibrium is a globally asymptotically stable equilibrium for System (16).

4.2. **The case $\mu < 1$.** Instead of use S, let $Z = Y + \alpha' M$ — so that $S = N + Z$. In the N,Z,Y variables we have

$$\left\{\begin{array}{rcl} \dot{N} & = & \alpha X_s - N - (\mu - 1)Y, \\ \dot{Z} & = & -\nu Z + (\mu(r-1) + \nu)Y, \\ \dot{Y} & = & \mu\left(\dfrac{1}{\alpha\alpha'}(Z-Y)(N-Y) - Y\right). \end{array}\right. \tag{18}$$

The Jacobian of (18) is

$$J = \begin{pmatrix} -1 & 0 & 1-\mu \\ 0 & -\nu & \mu(r-1)+\nu \\ \dfrac{\mu(Z-Y)}{\alpha\alpha'} & \dfrac{\mu(N-Y)}{\alpha\alpha'} & -\mu\left(\dfrac{N+Z-2Y}{\alpha\alpha'} + 1\right) \end{pmatrix}.$$

Since we have $Z > Y$ and $N > Y$, then J is Metzler provided $\mu \leq 1$, and it is also irreducible provided $\mu < 1$. Since there is only one interior equilibrium all orbits in the interior will converge to this equilibrium — cf. [12, Theorem 10.3].

Therefore, the endemic equilibrium is a globally asymptotically stable equilibrium for System (18) even if condition (4) is not satisfied and hence the Lotka-Volterra function type (2) cannot be a Lyapunov function.

4.3. $\mu \gg 1$**.** Let us write $\mu = \epsilon^{-1}$, with $0 < \epsilon \ll 1$. Then the AMG system can be written as:

$$\left\{\begin{array}{rcl} \dot{X} & = & X_s - X - (X_s - 1)MX, \\ \dot{M} & = & \nu\left(\dfrac{rY}{r-1} - \dfrac{MX}{r-1} - M\right), \\ \epsilon\dot{Y} & = & MX - Y. \end{array}\right. \tag{19}$$

Since $Y = MX$ is a globally stable equilibria of the last equation, we can use Tikhonov's Theorem [36,38] to conclude that solutions of System (19) are close to solutions of the following reduced system:

$$\begin{array}{rcl} \dot{X} & = & X_s - X - (X_s - 1)MX, \\ \dot{M} & = & \nu M\left(X - 1\right). \end{array} \tag{20}$$

In view of the fact that $(1, 1)$ is a globally asymptotically stable equilibrium for System (20), one expects that the endemic equilibrium is also globally asymptotically stable in this regime. This is the contents of the next result.

Proposition 4.1. *For sufficiently small and positive values of ϵ the interior equilibrium $(1, 1, 1) = \mathbf{1}^*$ of System (19) is globally asymptotically stable.*

Proof. It is easy to check that there exits a compact absorbing K for System (19). In addition, since this system is also uniformly persistent, we can choose K with a positive distance to the boundary of the positive orthant. Let D and G be the orthogonal projections of K onto $(X, M) \geq 0$ and $Y \geq 0$, respectively. Moreover, this set K can also be chosen such that D is a compact absorbing set for System (20).

The reduced System (20) has $(1, 1)$ as its unique interior equilibrium — which is always locally stable — provided $X_s > 1$. Its global stability follows by noticing that $\varphi(X, M) = \dfrac{1}{M}$ is a Dulac function for System (20) in the positive quadrant. Notice also that as a differential equation in the fast time τ, $Y_\tau = MX - Y$ is globally attractive on $\mathbb{R}^+$, provided $MX > 0$ — a condition that is always satisfied over D.

Therefore, we have that all hypothesis of Tikhonov's theorem are verified — cf. [38, Theorem 1.1]. Furthermore, the equation $Y_\tau = MX - Y$ trivially satisfy the additional stability assumptions needed for the improved asymptotic results by O'Malley and Vasil'eva — cf. [38, Theorem 2.1].

Finally, we also observe that since the solutions of System (19) never leave D or G, the approximations provided by Tikhonov's theorem are valid globally in time — see the remark in [38, pg. 750]. More precisely, let $(X^\epsilon, M^\epsilon, Y^\epsilon)$ be the solution to (19) with an interior initial condition (X_0, M_0, Y_0) and let (X^0, M^0) be the solution to (20) with initial condition (X_0, M_0) — set $Y^0 = M^0 X^0$. Then, if we write $\|\cdot\|_{\infty,\tau}$ to denote the uniform norm on $[\tau, \infty)$ we have, for sufficiently small ϵ, that

$$\|Z^\epsilon - Z^0\|_{\infty,0} \leq C_1\epsilon, \text{ with } Z = X, M \text{ and } \|Y^\epsilon - Y^0\|_{\infty,\bar{\tau}} \leq C_2\epsilon,$$

for some $C_1, C_2, \bar{\tau} > 0$ that can be taken independently of ϵ.

The remainder of the proof is split in two subcases that depend on the value of the parameter g. For $0 < g < 4$, there is a neighbourhood U of $\mathbf{1}^*$ such that $\dot{V}_{EE} \leq 0$, vanishing only on the intersection of the critical line with U — recall the discussion in Section 3, from which follows that the size of U depends only on the quantity $4-g$ and hence that it can be taken independently of ϵ.

In particular, let $\delta = \operatorname{dist}(\mathbf{1}^*, \partial U) > 0$ and notice that for $\tau > \bar{\tau}$, $Z = X, Y, M$ and $\epsilon < \frac{\delta}{2}$, we have that

$$\begin{aligned}\|Z^\epsilon - \mathbf{1}^*\|_{\infty,\bar{\tau}} &\leq \|Z^\epsilon - Z^0\|_{\infty,\bar{\tau}} + \|Z^0 - \mathbf{1}^*\|_{\infty,\bar{\tau}} \\ &\leq C\epsilon + \underbrace{\|Z^0 - \mathbf{1}^*\|_{\infty,\bar{\tau}}}_{<\frac{\delta}{2} \text{ for large } \bar{\tau}} \\ &< \delta.\end{aligned}$$

Thus, global stability of $\mathbf{1}^*$ follows from an application of LaSalle's principle.

For $g \geq 4$, further work is needed. In this case, the standard estimate for the size of the local basin of attraction of an equilibrium that is locally asymptotically stable scales with ϵ — cf. [33, Theorem 3.26].

In order to ensure that the solution of System (19) is trapped in this basin of attraction, we need to proceed to the next order in the expansion — see for instance [27, pages 46–51]. More precisely, let us write

$$(X^\epsilon, Y^\epsilon, M^\epsilon) = (X^0, Y^0, M^0) + \epsilon(X^1, Y^1, M^1) + o(\epsilon).$$

In this case, inserting the above expansion into System (19) and collecting the terms that are first order in ϵ we get, from the third equation of System (19), an equation for Y^1 that read as follows:

$$Y^1 = -\dot{Y}^0 + X^0 M^1 + X^1 M^0,$$

and, from the first and second equations, we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} X^1 \\ M^1 \end{pmatrix} = A(t)\begin{pmatrix} X^1 \\ M^1 \end{pmatrix} + b(t), \quad \begin{pmatrix} X^1(0) \\ M^1(0) \end{pmatrix} = 0,$$

with

$$A(t) = \begin{pmatrix} M^0(1-X_s) - 1 & X^0(1-X_s) \\ \nu M^0 & \nu(1-X^0) \end{pmatrix} \quad \text{and} \quad b(t) = \begin{pmatrix} 0 \\ -\frac{r\nu}{r-1}\dot{Y}^0 \end{pmatrix}.$$

The error estimate then becomes

$$\|Z^\epsilon - Z^0 - \epsilon Z^1\|_{\infty,0} \leq C_3\epsilon^2, \text{ with } Z = X, M \text{ and } \|Y^\epsilon - Y^0 - \epsilon Y^1\|_{\infty,\tilde{\tau}} \leq C_4\epsilon^2,$$

for some $C_3, C_4, \tilde{\tau} > 0$ that can be taken independent of ϵ—cf. the analysis on [27, pages 56–58].

Let

$$\begin{aligned} A_\infty &= \lim_{t\to\infty} A(t) \\ &= \begin{pmatrix} -X_s & 1-X_s \\ \nu & 0 \end{pmatrix}, \end{aligned}$$

and notice also that $\lim_{t\to\infty} b(t) = 0$.

Thus, for $\bar{t}$ sufficiently large we have that $A(t) = A_\infty + b(t)$ with $\|b(t)\|$ small.

$$\begin{aligned}\|\Pi_{A(t)}(t,0)\| &= \|\Pi_{A(t)}(\bar{t},0)\Pi_{A_\infty+b(t)}(t,\bar{t})\| \\ &\le C\|\Pi_{A_\infty+b(t)}(t,\bar{t})\| \\ &\le C\mathrm{e}^{-\alpha(t-\bar{t})},\end{aligned}$$

for $t > \bar{t}$ and for some $\alpha, C > 0$.

Therefore, let U now denote the basin of attraction of $\mathbf{1}^*$ and let $\delta = \mathrm{dist}(\mathbf{1}^*, \partial U) > 0$, with $\delta < \bar{C}\epsilon$, and notice that for $\tau > \bar{\tau}$, $Z = X, Y, M$ we have

$$\begin{aligned}\|Z^\epsilon - \mathbf{1}^*\|_{\infty,\bar{\tau}} &\le \|Z^\epsilon - Z^0 - \epsilon Z^1\|_{\infty,\bar{\tau}} + \|Z^0 - \mathbf{1}^*\|_{\infty,\bar{\tau}} + \epsilon\|Z^1\|_{\infty,\bar{\tau}} \\ &\le C\epsilon^2 + \underbrace{\|Z^0 - \mathbf{1}^*\|_{\infty,\bar{\tau}} + \epsilon\|Z^1\|_{\infty,\bar{\tau}}}_{<\epsilon^2 \text{ for large } \bar{\tau}} \\ &< \bar{C}\epsilon.\end{aligned}$$

Thus, for $t > \bar{t}$, the solution is trapped inside U and, hence, converge to $\mathbf{1}^*$.

□

Remark 4.1. *It is also worthwhile to point out that the regime $\mu \gg 1$ is indeed relevant to malaria. The lifespan of a healthy blood cell is typically 40 days , while for an infected one is about one day —cf. [11]. Since $\mu = \dfrac{\mu_y}{\mu_x}$, values of 40 or more are typical.*

4.4. $\nu \gg 1$. A similar argument works in this case as well. The reduced system is now given by

$$\begin{aligned}\dot{X} &= X_s - X - (X_s - 1)\frac{rYX}{X + r - 1}, \\ \dot{Y} &= \mu Y\left(\frac{rX}{X + r - 1} - 1\right),\end{aligned} \tag{21}$$

where

$$M = \frac{rY}{X + r - 1}.$$

Notice also that $\varphi(Y) = \dfrac{1}{Y}$ is a Dulac function for system (21). See Figure 4 for a an example of the dynamics in this regime.

Remark 4.2. *This also a relevant regime for Malaria. Indeed, according to [11], for malaria in men we have $\nu \approxeq 1920$*

4.5. **An example with $\mu > 1$ but with $\mu = \mathcal{O}(1)$.** Consider System (5) with the following parameters:

$$\mu = \nu = \frac{6}{5}, \quad r = \frac{3}{2} \quad \text{and} \quad X_s = 5.$$

Using a geometrical approach, we can show that the equilibrium is also globally asymptotically stable with these parameters.This can be done by carefully following a typical orbit and then showing that it either must converges to the endemic equilibrium or ending up in a faith set $\mathcal{F}$. The choice of such a set carries some freedom, which can be explored to provide a 'good geometry', from which convergence to the endemic equilibrium follows. Further details will be provided elsewhere [15].

4.6. **A conjecture on global stability.** In view of the global stability of the endemic equilibrium, $\mathbf{1}^*$, for both $0 < \mu \le 1$ and $\mu \gg 1$, together with the non dependence of $\mathcal{R}_0$ on μ suggests that μ should be the relevant parameter for stability and, hence, that a bifurcation analysis with respect to μ might complete the global stability picture.

We begin by gathering some previous results in a convenient way:

Lemma 4.1. *Assume that $X_s > 1$ (which implies $r > 1$ and $\mathcal{R}_0 > 1$). Then the following holds: (i) the AMG system is uniformly persistent; (ii)$\mathbf{1}^*$ is locally asymptotically stable; (iii) the DFE equilibrium is a saddle with an unstable manifold of dimension one. (iv) the AMG system is competitive. In particular, no homoclinic orbit may exist.*

The following result is a recast of a result in [19] and we provide a sketch of the proof for the convenience of the reader:

Lemma 4.2. *Assume $X_s > 1$. If $\mathbf{1}^*$ is not globally asymptotically stable, then there exists an unstable periodic orbit and this orbit lies on the boundary of basin of attraction of $\mathbf{1}^*$.*

Proof. Let U be the basin of attraction At μ^*, we must have that $\Sigma = \partial U \cap \operatorname{int}(K)$ is nonempty – recall that K is a compact absorbing set associated to the AMG system. Hence $\bar{\Sigma}$ is invariant and must contain a periodic orbit γ (since it does not contain any equilibrium point). Notice also that this orbit is also in the alpha limit set of $\mathbf{1}^*$ and, hence, cannot be stable. □

Lemma 4.3. *Assume that $X_s > 1$ and the endemic equilibrium is globally asymptotically stable. Then the AMG system is a Kupka-Smale system— and indeed a Morse-Smale system, since it is competitive.*

Proof. (i) the equilibria is always hyperbolic; (ii) since the endemic equilibrium is globally asymptotically stable there are no periodic orbits; (iii) the unstable manifold of the DFE intersects the stable manifold of the endemic equilibrium transversally. □

In what follows, we recall that K is an absorbing set for the AMG System and we will write U to denote the basin of attraction of $\mathbf{1}^*$.

Proposition 4.2. *Let μ^* be the largest value such that $\mathbf{1}^*$ is globally asymptotically stable on $(0, \mu^*)$. Then, generically, a saddle-node bifurcation of periodic orbits occurs at μ^*.*

Proof. From Lemma 4.2, there exists a periodic unstable orbit $\gamma \in \partial U$.

Let $\zeta_{1,2}$ be the Floquet multipliers of γ, with $|\zeta_1| \le |\zeta_2|$. Since the AMG System is competitive, then $0 < \zeta_1 < 1$ with $|\zeta_2| > \zeta_1$ — cf. [29].

Since γ is a non structurally stable orbit (it does not exist for $\mu < \mu^*$) it is non-hyperbolic. Thus $|\zeta_2| = 1$, and hence $\zeta_2 = 1$ — cf. [18]. Therefore at $\mu = \mu^*$ a saddle-node bifurcation of periodic orbits must occur generically [18]. Notice that this argument precludes, at least generically, period doubling and torus bifurcations. □

Remark 4.3. *For $\mu > \mu^*$, but with $\mu - \mu^*$ small, then γ is hyperbolic, and hence a saddle orbit, and another periodic orbit, stable, will also exists in this regime. Moreover, since the AMG system is analytic and relative prime, only a finite number of bifurcations might happen at $\mu = \mu^*$ — cf. Wintner's principle of natural termination. Notice also that there exists μ^{**} with $1 < \mu^* < \mu^{**}$ such that the families of bifurcations born at $\mu = \mu^*$ will terminate at $\mu \le \mu^{**}$*

As a matter of fact, numerical simulations with $\mu, \nu > 1$ suggest that, as $t \to \infty$, the solution approaches either the surface $Y = MX$ or the surface $M = \dfrac{rY}{X + r - 1}$ — and, as we saw above, on these surfaces the system is globally asymptotically stable.

Conjecture 4.1. *For $\mu > 1$, every interior solution approaches either the surface $Y = MX$ or the surface $M = \dfrac{rY}{X + r - 1}$, depending on which is the largest one. This implies that the AMG system satisfies the Sharp Threshold property for all $\mu > 0$.*

5. Discussion

Since their most recently rediscovery by [17, 21], the Volterra-type Lyapunov functions have been a workhorse in establishing global stability results in a variety of models in mathematical biology. This successful track record brought them a distinguished status as tools to prove global stability – cf. [5] and [28].

In this work, we revisited the study of the global dynamics of the AMG system – a well-known in-vivo model to Malaria that is also equivalent to a within-host HIV model. We then showed the following results: (i) there exists a unique Volterra function (up to scaling and an additive constant) that can be a candidate Lyapunov function; (ii) this function cannot be a Lyapunov function for the range of parameters that is biologically relevant. As a matter of fact, we present a necessary and sufficient condition for this Volterra candidate function be a Lyapunov function for the AMG system.

It is worthwhile to notice that, despite its apparent simplicity, a complete characterisation of the global dynamics of the AMG system has not been rigorously established yet. Indeed, it is believed that AMG system has the Sharp Threshold Property [28], but so far a proof of this fact has been elusive — the proof that the endemic equilibrium is globally asymptotically stable has only been provided in certain cases. There are, nevertheless, a number of claims of complete proofs which are either incorrect or which are equivalent to conditions that cannot be verified.

In addition, we have enlarged the range of parameters where global stability of the endemic equilibrium holds by using a set of different approaches: (i) a change of state variables that turn the system in either (i-a) a strongly monotone system or (i-b) a triangular system that is asymptotically 2-D; (ii) exploit the existence of a large parameter and Tikhonov's theorem (together with some extensions) to obtain a reduced 2-D system that is globally stable — and that this global stability implies the global stability of the full system. This extended parameter range include regimes that are relevant to Malaria. Furthermore, we have also provided an example of a set of parameter values for which we can also show global stability of the endemic equilibrium — this uses an alternative geometrical technique that will be discussed elsewhere [15].

Finally, we hope that these results will raise caution among mathematical modellers that, while the Lotka-Volterra function is a formidable tool, it also has its limitations. While this might sound obvious, we are not aware of any example where is rigorously shown that the Lotka-Volterra is not a Lyapunov function for all the relevant parameters. This failure shows that further tools for studying global stability are already needed to fully characterise biologically relevant systems as the AMG model.

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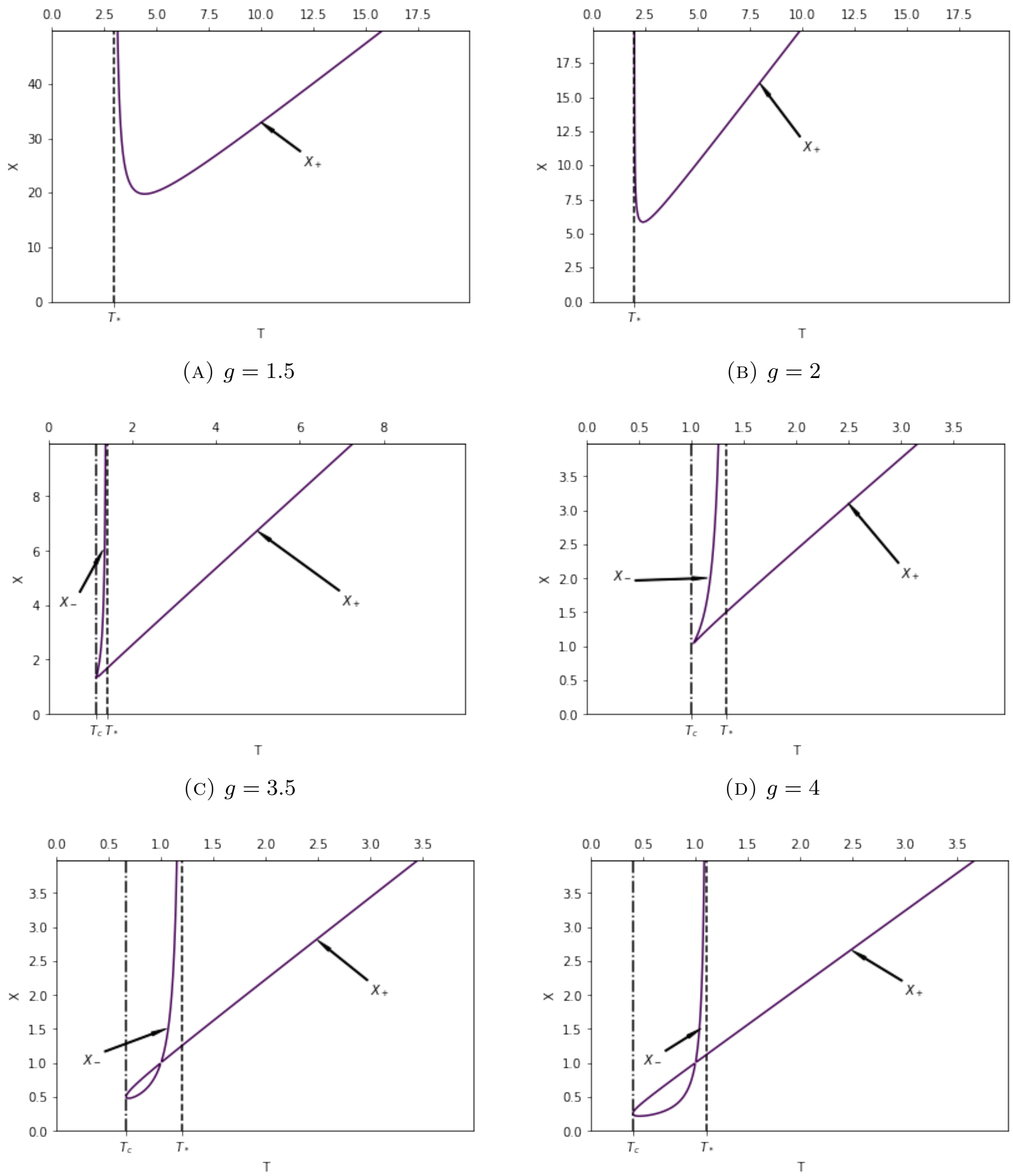


(A) $g = 1.5$

(B) $g = 2$

(C) $g = 3.5$

(D) $g = 4$

(E) $g = 6$

(F) $g = 10$

FIGURE 1. Examples of $p(X, T) = 0$ curves.

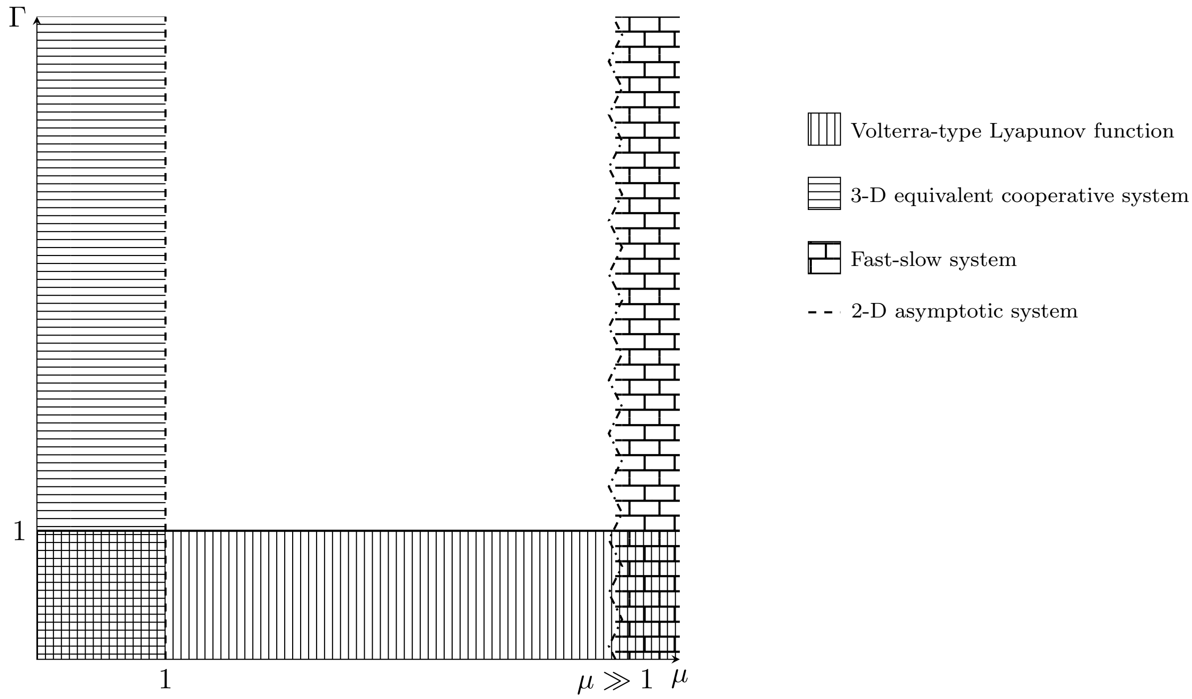
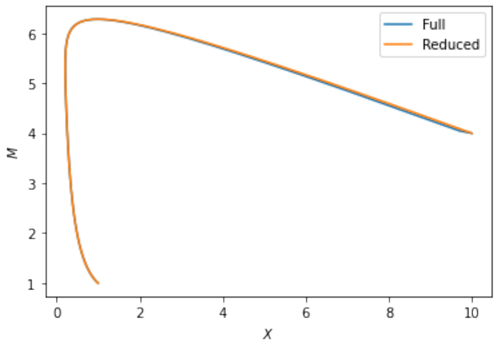
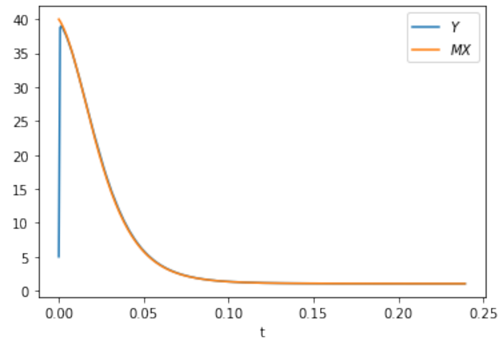


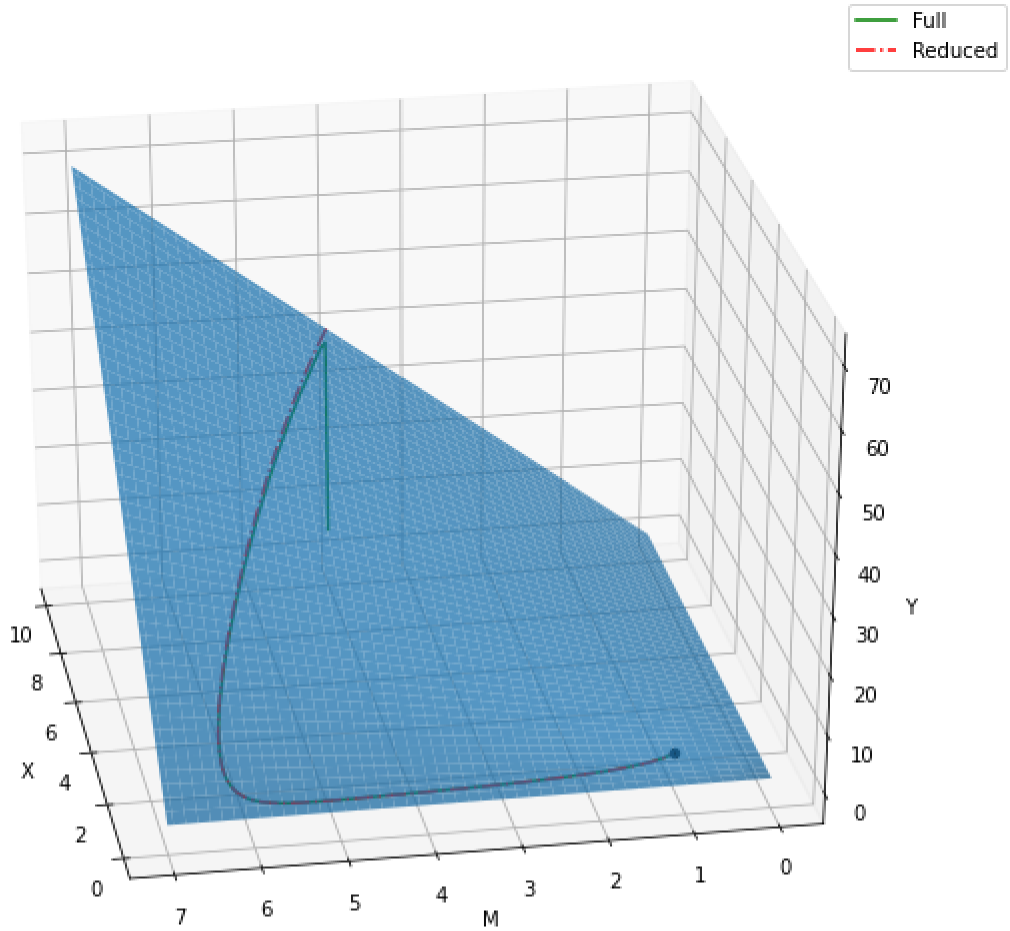
FIGURE 2. Parameter range where global stability of endemic equilibrium is known and approach used — $\Gamma = \dfrac{X_s}{4(r-1/2)^2}$. The parameter ν does not seem to play a fundamental role in the stability features, except by allowing a two-dimensional reduction when it is large.



(A) X-M projection

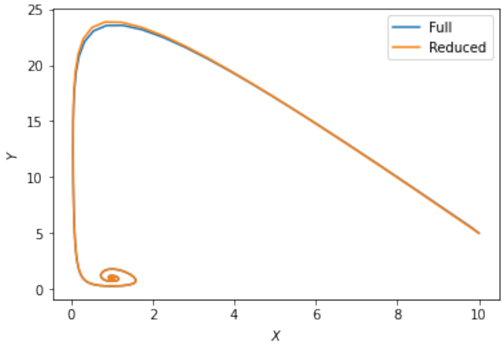


(B) Y and MX

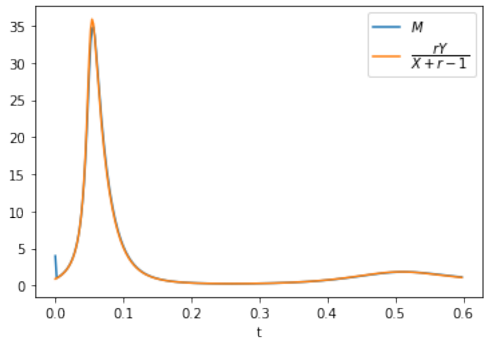


(C) full picture

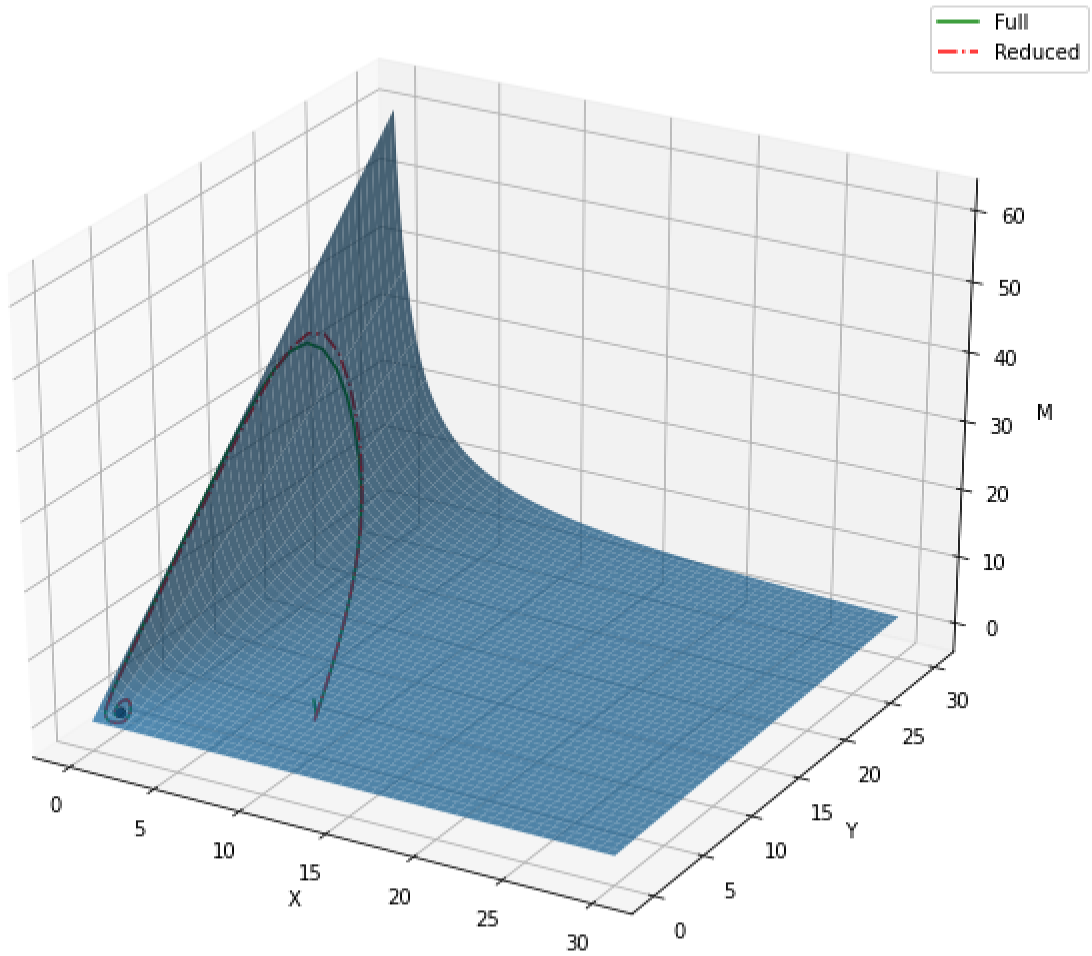
FIGURE 3. Full and reduced solutions. Parameters: $X_s = 10$, $r = 2$, $\nu = 3$ and $\mu = 5000$.



(A) X-Y projection



(B) Y and $\dfrac{rY}{X+r-1}$



(C) full picture

FIGURE 4. Full and reduced solutions. Parameters: $X_s = 10$, $r = 2$, $\nu = 1500$ and $\mu = 50$.