

Immune response to a malaria infection: properties of a mathematical model

Journal:	<i>Journal of Biological Dynamics</i>
Manuscript ID:	TJBD-2007-0009.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	De Leenheer, Patrick; University of Florida Pilyugin, Sergei; University of Florida
Keywords:	immunology , epidemiology



IMMUNE RESPONSE TO A MALARIA INFECTION: PROPERTIES OF A MATHEMATICAL MODEL

Patrick De Leenheer¹ and Sergei S. Pilyugin²,

Department of Mathematics, University of Florida, Gainesville, FL 32611-8105, USA.

To our mentor and good friend Hal Smith, on the occasion of his 60th birthday.

ABSTRACT. We establish some properties of a within host mathematical model of malaria proposed by Recker et al [7, 8] which includes the role of the immune system during the infection. The model accounts for the antigenic variation exhibited by the malaria parasite (*P. falciparum*). We show that the model can exhibit a wide variety of dynamical behaviors. We provide criteria for global stability, competitive exclusion, and persistence. We also demonstrate that the disease equilibrium can be destabilized by non-symmetric cross-reactive responses.

1. INTRODUCTION

This paper addresses the within host dynamics of the malaria parasite *Plasmodium falciparum* whose infection mechanism we briefly review here. Infection starts when a human is bitten by an infected mosquito that releases sporozoites in the bloodstream. The sporozoites quickly enter the liver where they mature, replicate, and differentiate into merozoites. The merozoites are then released into the bloodstream, where they go on to infect erythrocytes (red blood cells). Merozoites reproduce within infected erythrocytes for a period of about two days. Finally the infected erythrocyte ruptures and releases new merozoites that repeat the infection cycle.

A discussion leading to a mathematical model that considers a single parasite variant can be found in [9, 4] and references therein. In practice however, there is a considerable diversity of the surface proteins (antigens) that are presented by the infected cells (erythrocytes). A mathematical model that includes an arbitrary number of parasite variants was studied in a very elegant paper by Iggidr et al [6] where a competitive exclusion principle was established. In the model of Iggidr et al, different variants compete for the same subset of host cells to infect, and as a result, only one variant survives while the others are driven to extinction. A more general mathematical model accounting for mutations between different parasite variants was analyzed in our recent work [3].

The mathematical models mentioned above do not include the effects of immune response mounted by the human host. Although many details of immune responses to *P. falciparum* are presently not well understood, there is evidence that the antigenic variation of the parasite during the course of infection prompts the immune system to mount both variant specific as well as cross reactive responses [1, 7, 8]. The primary distinction between specific and cross-reactive responses is that they target major (unique to each variant) or minor (shared among variants) epitopes, respectively, on the infected cell's surface.

The goal of this paper is to extend the analysis of the model proposed in [7, 8] which includes both variant-specific and cross-reactive immunity. We provide some results concerning the global behavior of this model by

- (1) Showing global asymptotic stability of the system in two extreme cases (no cross immunity and perfect cross immunity).
- (2) Showing the possibility of oscillatory destabilization in the case of partial cross immunity.
- (3) Establishing conditions for both competitive exclusion as well as for persistence.

Date: September 1, 2007.

¹email: deleenhe@math.ufl.edu. Supported in part by NSF grant DMS-0614651.

²email: pilyugin@math.ufl.edu. Supported in part by NSF grant DMS-0517954.

Our results indicate that depending on parameter values, this model can exhibit a wider variety of dynamical behaviors than reported previously [7, 8]. The full range of possible behaviors and biological implications is currently not fully understood and remains the objective of future research.

This paper is organized as follows. In Section 2 we formulate and slightly generalize the model from [7, 8] and in Section 3 we comment on the existence or non-existence of positive equilibria. In Section 4 we establish global asymptotic stability in several special cases: the case of a single variant, the case of no cross immunity, and the case of perfect cross immunity. In case of partial cross immunity, the dynamic picture is not as simple and this is illustrated in Section 5 by analyzing a particular example. In Section 6, we return to the general model and establish sufficient conditions for competitive exclusion as well as for persistence. These conditions are compared to similar ones for certain associated Lotka-Volterra systems of lower dimension. Section 7 summarizes our findings.

2. GENERAL MODELING ASSUMPTIONS

The model that we study here was originally proposed by Recker et al [7] and later analyzed by Recker and Gupta [8]. The model has the following form

$$(2.1) \quad \dot{y}_i = y_i(\phi - \alpha_1 z_i - \alpha_2 w_i),$$

$$(2.2) \quad \dot{z}_i = \beta_1 y_i - \mu_1 z_i,$$

$$(2.3) \quad \dot{w}_i = \beta_2 \sum_{j=1}^n c_{ij} y_j - \mu_2 w_i,$$

where $i = 1, \dots, n$. The variables y_i , z_i , and w_i represent the abundance of the erythrocytes which are infected by the i -th variant, and the magnitudes of the specific and cross-reactive immune response respectively. We assume that the immune responses are induced proportionally to the parasitic load at the rates β_1 and β_2 . The coefficients μ_1 and μ_2 model the life-span of the corresponding immune responses. The efficiency of both responses are given by α_1 and α_2 . The coefficient ϕ represents the maximal growth rate of the parasite. We assume that all kinetic parameters are equal for all strains. Finally, we assume that each strain has a distinct major epitope, but two different strains may share common minor epitopes. In the model, we incorporate this assumption by introducing the non-negative cross-reactivity matrix C such that $c_{ij} > 0$ if the strains i and j share the same epitope and $c_{ij} = 0$ otherwise. In the sequel we will refer to some special cases for which we introduce the following terminology:

- (1) We say that there is no cross immunity when $C = I_n$, where I_n is the $n \times n$ identity matrix.
- (2) We say that there is perfect cross immunity when $C = \mathbf{1}\mathbf{1}'$. Here, $\mathbf{1} = (1, \dots, 1)' \in \mathbb{R}^n$.
- (3) In all other cases, we say that there is partial cross immunity.

For mathematical convenience, we perform a simple rescaling of the original variables and rewrite system (2.1) – (2.3) as

$$(2.4) \quad \dot{y}_i = y_i(1 - z_i - w_i),$$

$$(2.5) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(2.6) \quad \dot{w}_i = b \sum_{j=1}^n c_{ij} y_j - \mu_2 w_i,$$

and define

$$(2.7) \quad \gamma_1 := \frac{1}{\mu_1}, \quad \gamma_2 := \frac{b}{\mu_2}.$$

³Throughout the paper, we use the prime to denote the vector/matrix transpose. All vectors are denoted by bold face characters. We use the notation x_i for the i th coordinate of a vector \mathbf{x} .

The within-host replication of *P. falciparum* may be limited by the number of available erythrocytes which can be infected by the parasite. Hence, we modify equations (2.4) – (2.6) to include a (theoretically feasible) term for the carrying capacity,

$$(2.8) \quad \dot{y}_i = y_i \left(1 - \frac{y}{K} - z_i - w_i\right),$$

$$(2.9) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(2.10) \quad \dot{w}_i = b \sum_{j=1}^n c_{ij} y_j - \mu_2 w_i.$$

3. THE POSITIVE EQUILIBRIUM

Using the vector notation, we can express the equilibrium conditions of (2.4) – (2.6) as follows: $\mathbf{z}^* = \gamma_1 \mathbf{y}^*$, and $\mathbf{w}^* = \gamma_1 C \mathbf{y}^*$. The positive equilibrium must then satisfy the condition

$$(3.1) \quad \gamma_1 \mathbf{y}^* + \gamma_2 C \mathbf{y}^* = \mathbf{1}.$$

In case of perfect cross-reactivity, where $c_{ij} = 1$ for all i, j , there exists a positive solution of the form

$$y_i^* = \bar{y} = \frac{1}{\gamma_1 + n\gamma_2}, \quad i = 1, \dots, n,$$

which corresponds to a positive equilibrium. The positive equilibrium does not always exist. For instance, letting $n = 4$, $\gamma_1 = 1$, $\gamma_2 = \varepsilon > 0$, and

$$(3.2) \quad C = \begin{pmatrix} 1 & 1 & 1 & 0 \\ 1 & 1 & 1 & 0 \\ 1 & 1 & 1 & 1 \\ 0 & 1 & 1 & 1 \end{pmatrix},$$

the solution of (3.1) is given by

$$(y_1^*, y_2^*, y_3^*, y_4^*) = \frac{1}{1 + 3\varepsilon - \varepsilon^2} (1, 1, 1 - \varepsilon, 1),$$

which is positive if and only if $\varepsilon < \frac{-3 + \sqrt{13}}{2} \approx 0.3$.

4. SOME RESULTS ON GLOBAL STABILITY

4.1. The case $n = 1$. In the simplest case $n = 1$, the model

$$(4.1) \quad \dot{y} = y(1 - z - w),$$

$$(4.2) \quad \dot{z} = y - \mu_1 z,$$

$$(4.3) \quad \dot{w} = by - \mu_2 w,$$

admits a unique positive equilibrium

$$(y^*, z^*, w^*) = \left(\frac{1}{\gamma_1 + \gamma_2}, \frac{\gamma_1}{\gamma_1 + \gamma_2}, \frac{\gamma_2}{\gamma_1 + \gamma_2} \right)$$

which is globally stable. To see this, we rewrite (4.1–4.3) as

$$\dot{y} = y((z^* - z) + (w^* - w)),$$

$$\dot{z} = (y - y^*) - \mu_1(z - z^*),$$

$$\dot{w} = b(y - y^*) - \mu_2(w - w^*),$$

and define

$$V = \int_{y^*}^y \frac{s - y^*}{s} ds + \int_{z^*}^z (s - z^*) ds + \frac{1}{b} \int_{w^*}^w (s - w^*) ds.$$

The function V clearly has a unique global minimum at (y^*, z^*, w^*) . In addition,

$$\dot{V} = (y - y^*)((z^* - z) + (w^* - w)) + (z - z^*)((y - y^*) - \mu_1(z - z^*)) + \frac{1}{b}(w - w^*)(b(y - y^*) - \mu_2(w - w^*))$$

4 IMMUNE RESPONSE TO A MALARIA INFECTION: PROPERTIES OF A MATHEMATICAL MODEL

which simplifies to

$$\dot{V} = -\mu_1(z - z^*)^2 - \frac{\mu_2}{b}(w - w^*)^2.$$

Clearly, the equilibrium (y^*, z^*, w^*) is the only invariant set in $\{\dot{V} = 0\}$. LaSalle's invariance principle then implies global stability of (y^*, z^*, w^*) .

The same argument shows the global stability of the model (2.4) – (2.6) with $n > 1$ and no cross-reactivity because the system is uncoupled.

Assuming a carrying capacity for the infected cells we have a different model

$$(4.4) \quad \dot{y} = y\left(1 - \frac{y}{K} - z - w\right),$$

$$(4.5) \quad \dot{z} = y - \mu_1 z,$$

$$(4.6) \quad \dot{w} = by - \mu_2 w.$$

It is easy to see that the modified model (4.4–4.6) also admits a unique positive equilibrium (y^*, z^*, w^*) . Using the same function V as before, we observe that

$$\dot{V} = -\frac{1}{K}(y - y^*)^2 - \mu_1(z - z^*)^2 - \frac{\mu_2}{b}(w - w^*)^2.$$

We conclude again that the positive equilibrium is globally asymptotically stable.

4.2. **The case $n > 1$.** When there are two or more variants present, they can be antigenically distinct (no cross-reactivity), antigenically similar (perfect cross-reactivity, see above), or there may be partial cross-reactivity. In this section, we prove global convergence for the first two cases. We also show that adding a carrying capacity does not alter the conclusions.

4.3. **No cross-reactivity with carrying capacity.** The equations are

$$(4.7) \quad \dot{y}_i = y_i\left(1 - \frac{1}{K} \sum_{j=1}^n y_j - z_i - w_i\right),$$

$$(4.8) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(4.9) \quad \dot{w}_i = by_i - \mu_2 w_i,$$

for $i = 1, \dots, n$, and they admit a unique positive equilibrium. The Lyapunov function is

$$V = \sum_{i=1}^n \left(\int_{y_i^*}^{y_i} \frac{s - y_i^*}{s} ds + \int_{z_i^*}^{z_i} (s - z_i^*) ds + \frac{1}{b} \int_{w_i^*}^{w_i} (s - w_i^*) ds \right).$$

Indeed, equation (4.7) can be equivalently written as

$$y_i = y_i \left(\frac{1}{K} \sum_{j=1}^n (y_j^* - y_j) + (z_i^* - z_i) + (w_i^* - w_i) \right),$$

and after simplifications we find that

$$\dot{V} = -\frac{1}{K} \left(\sum_{j=1}^n (y_j^* - y_j) \right)^2 - \mu_1 \sum_{i=1}^n (z_i - z_i^*)^2 - \frac{\mu_2}{b} \sum_{i=1}^n (w_i - w_i^*)^2.$$

Thus the positive equilibrium is globally asymptotically stable.

4.4. **Perfect cross-reactivity without carrying capacity.** The equations are

$$(4.10) \quad \dot{y}_i = y_i(1 - z_i - w_i),$$

$$(4.11) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(4.12) \quad \dot{w}_i = b \sum_{j=1}^n y_j - \mu_2 w_i,$$

for $i = 1, \dots, n$ and they admit a unique positive equilibrium. We observe that for all i, j

$$\dot{w}_i - \dot{w}_j = -\mu_2(w_i - w_j),$$

hence all pairwise differences $w_i - w_j$ decay exponentially to zero. To make this argument formal, using $w = w_1$ and $w_j = w + u_j$ for $j \neq 1$ we rewrite equations (4.10–4.12) as

$$(4.13) \quad \dot{y}_1 = y_1(1 - z_1 - w), \quad \dot{y}_j = y_j(1 - z_j - (w + u_j)), \quad j \neq 1,$$

$$(4.14) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(4.15) \quad \dot{w} = b \sum_{j=1}^n y_j - \mu_2 w,$$

$$(4.16) \quad \dot{u}_j = -\mu_2 u_j, \quad j \neq 1.$$

Clearly, the system (4.13–4.16) is asymptotic to the limiting system

$$(4.17) \quad \dot{y}_i = y_i(1 - z_i - w),$$

$$(4.18) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(4.19) \quad \dot{w} = b \sum_{j=1}^n y_j - \mu_2 w.$$

The Lyapunov function for (4.17–4.19) has the form

$$V = \sum_{i=1}^n \left(\int_{y_i^*}^{y_i} \frac{s - y_i^*}{s} ds + \int_{z_i^*}^{z_i} (s - z_i^*) ds \right) + \frac{1}{b} \int_{w^*}^w (s - w^*) ds.$$

Indeed, after simplifications, we find that

$$\dot{V} = -\mu_1 \sum_{i=1}^n (z_i - z_i^*)^2 - \frac{\mu_2}{b} (w - w^*)^2,$$

and then global asymptotic stability of the limiting system (4.17–4.19) follows from Lasalle's invariance principle. Finally, Theorem F.1 in [10] implies convergence to the positive equilibrium for system (4.10–4.12).

4.5. Perfect cross-reactivity with carrying capacity. The equations are

$$(4.20) \quad \dot{y}_i = y_i \left(1 - \frac{1}{K} \sum_{j=1}^n y_j - z_i - w_i \right),$$

$$(4.21) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(4.22) \quad \dot{w}_i = b \sum_{j=1}^n y_j - \mu_2 w_i,$$

for $i = 1, \dots, n$ and they admit a unique positive equilibrium. Arguing as before, we consider the limiting system

$$(4.23) \quad \dot{y}_i = y_i \left(1 - \frac{1}{K} \sum_{j=1}^n y_j - z_i - w \right),$$

$$(4.24) \quad \dot{z}_i = y_i - \mu_1 z_i,$$

$$(4.25) \quad \dot{w} = b \sum_{j=1}^n y_j - \mu_2 w,$$

for which the Lyapunov function is

$$V = \sum_{i=1}^n \left(\int_{y_i^*}^{y_i} \frac{s - y_i^*}{s} ds + \int_{z_i^*}^{z_i} (s - z_i^*) ds \right) + \frac{1}{b} \int_{w^*}^w (s - w^*) ds.$$

Indeed, after simplifications,

$$\dot{V} = -\frac{1}{K} \left(\sum_{j=1}^n (y_j^* - y_j) \right)^2 - \mu_1 \sum_{i=1}^n (z_i - z_i^*)^2 - \frac{\mu_2}{b} (w - w^*)^2,$$

implying global asymptotic stability of the positive equilibrium.

5. ANALYSIS OF A SPECIFIC CASE WITH PARTIAL CROSS IMMUNITY

In this section, we illustrate some dynamic possibilities exhibited by the model (2.4) – (2.6). In particular, we argue that a positive equilibrium can be unstable for some parameter values. We consider a specific case of (2.4) – (2.6) with $n = 3$,

$$\begin{aligned} \dot{y}_1 &= y_1(1 - z_1 - w_1), & \dot{z}_1 &= y_1 - \mu_1 z_1, & \dot{w}_1 &= b(y_1 + y_2) - \mu_2 w_1, \\ \dot{y}_2 &= y_2(1 - z_2 - w_2), & \dot{z}_2 &= y_2 - \mu_1 z_2, & \dot{w}_2 &= b(y_1 + y_2 + y_3) - \mu_2 w_2, \\ \dot{y}_3 &= y_3(1 - z_3 - w_3), & \dot{z}_3 &= y_3 - \mu_1 z_3, & \dot{w}_3 &= b(y_2 + y_3) - \mu_2 w_3. \end{aligned}$$

This system has a 6 dimensional invariant set $\{y_1 = y_3, z_1 = z_3, w_1 = w_3\}$. The dynamics on this invariant set is described by the equations

$$(5.1) \quad \begin{aligned} \dot{y}_1 &= y_1(1 - z_1 - w_1), & \dot{z}_1 &= y_1 - \mu_1 z_1, & \dot{w}_1 &= b(y_1 + y_2) - \mu_2 w_1, \\ \dot{y}_2 &= y_2(1 - z_2 - w_2), & \dot{z}_2 &= y_2 - \mu_1 z_2, & \dot{w}_2 &= b(2y_1 + y_2) - \mu_2 w_2. \end{aligned}$$

For convenience, we arrange the state variables as $(y_1, z_1, w_1, y_2, z_2, w_2)$. The Jacobian of (5.1) is given by

$$J = \begin{pmatrix} 1 - z_1 - w_1 & -y_1 & -y_1 & 0 & 0 & 0 \\ 1 & -\mu_1 & 0 & 0 & 0 & 0 \\ b & 0 & -\mu_2 & b & 0 & 0 \\ 0 & 0 & 0 & 1 - z_2 - w_2 & -y_2 & -y_2 \\ 0 & 0 & 0 & 1 & -\mu_1 & 0 \\ 2b & 0 & 0 & b & 0 & -\mu_2 \end{pmatrix}.$$

Equations (5.1) admit at most four equilibria:

- (1) The zero equilibrium E_{00} exists for all parameter values and is always unstable since the Jacobian $J(E_{00})$ (not shown) has eigenvalues $\lambda_{1,2} = 1$, $\lambda_{3,4} = -\mu_1$, $\lambda_{5,6} = -\mu_2$.
- (2) The nonnegative (semitrivial) equilibrium

$$E_{10} = \left(\frac{1}{\gamma_1 + \gamma_2}, \frac{\gamma_1}{\gamma_1 + \gamma_2}, \frac{\gamma_2}{\gamma_1 + \gamma_2}, 0, 0, \frac{2\gamma_2}{\gamma_1 + \gamma_2} \right)$$

exists for all parameter values. The Jacobian $J(E_{10})$ (not shown) has eigenvalues $\lambda_4 = \frac{\gamma_1 - \gamma_2}{\gamma_1 + \gamma_2}$, $\lambda_5 = -\mu_1$, $\lambda_6 = -\mu_2$, and $\lambda_{1,2,3}$ are eigenvalues of the matrix

$$\begin{pmatrix} 0 & -y_1 & -y_1 \\ 1 & -\mu_1 & 0 \\ b & 0 & -\mu_2 \end{pmatrix}.$$

From the preceding stability analysis in Section 3, we already know that $\text{Re}(\lambda_{1,2,3}) \leq 0$. Using the Routh-Hurwitz criterion, it is not difficult to show that in fact $\text{Re}(\lambda_{1,2,3}) < 0$. Hence, the stability of E_{10} is determined by the sign of λ_4 . Specifically, E_{10} is (locally) stable if $\gamma_1 < \gamma_2$, and unstable if $\gamma_1 > \gamma_2$.

- (3) The nonnegative (semitrivial) equilibrium

$$E_{01} = \left(0, 0, \frac{\gamma_2}{\gamma_1 + \gamma_2}, \frac{1}{\gamma_1 + \gamma_2}, \frac{\gamma_1}{\gamma_1 + \gamma_2}, \frac{\gamma_2}{\gamma_1 + \gamma_2} \right)$$

exists for all parameter values. The Jacobian $J(E_{01})$ (not shown) has eigenvalues $\lambda_1 = \frac{\gamma_1}{\gamma_1 + \gamma_2}$, $\lambda_2 = -\mu_1$, $\lambda_3 = -\mu_2$, and $\lambda_{4,5,6}$ are eigenvalues of the submatrix

$$\begin{pmatrix} 0 & -y_2 & -y_2 \\ 1 & -\mu_1 & 0 \\ b & 0 & -\mu_2 \end{pmatrix}.$$

As we argued previously, $\text{Re}(\lambda_{4,5,6}) < 0$. Since $\lambda_1 > 0$, E_{01} is always unstable.

- (4) The positive (nontrivial) equilibrium E_{11} exists if and only if $\gamma_1 > \gamma_2$, i.e. precisely when E_{10} is unstable. The (y_1, y_2) coordinates of E_{11} are given by

$$y_1 = \frac{\gamma_1}{(\gamma_1 + \gamma_2)^2 - 2\gamma_2^2}, \quad y_2 = \frac{\gamma_1 - \gamma_2}{(\gamma_1 + \gamma_2)^2 - 2\gamma_2^2}.$$

The common denominator is positive if and only if $\gamma_1 > (\sqrt{2} - 1)\gamma_2$, and the numerator of y_2 is positive if and only if $\gamma_1 > \gamma_2$. Hence both y_1 and y_2 are positive if and only if $\gamma_1 > \gamma_2$. The remaining coordinates of E_{11} are expressed in terms of y_1 and y_2 as follows,

$$z_i = \gamma_1 y_i \quad (i = 1, 2), \quad w_1 = \gamma_2(y_1 + y_2), \quad w_2 = \gamma_2(2y_1 + y_2).$$

Clearly, these four quantities are positive whenever y_1 and y_2 are positive. The Jacobian of (5.1) at E_{11} is given by

$$(5.2) \quad J(E_{11}) = \begin{pmatrix} 0 & -y_1 & -y_1 & 0 & 0 & 0 \\ 1 & -\mu_1 & 0 & 0 & 0 & 0 \\ b & 0 & -\mu_2 & b & 0 & 0 \\ 0 & 0 & 0 & 0 & -y_2 & -y_2 \\ 0 & 0 & 0 & 1 & -\mu_1 & 0 \\ 2b & 0 & 0 & b & 0 & -\mu_2 \end{pmatrix}.$$

As we showed previously,

$$\det J(E_{11}) = y_1 y_2 \mu_1^2 \mu_2^2 ((\gamma_1 + \gamma_2)^2 - 2\gamma_2^2) > 0,$$

thus $J(E_{11})$ cannot have zero eigenvalues.

Lemma 5.1. *If $\mu_1 = \mu_2 = \mu$, all six eigenvalues of $J(E_{11})$ have negative real parts.*

Proof. If $\mu_1 = \mu_2 = \mu$, the characteristic polynomial of $J(E_{11})$ has the following form:

$$p(\lambda) = (\mu + \lambda)^2 \left(\xi^2 + \xi(1+b)(y_1 + y_2) + y_1 y_2(1 + 2b - b^2) \right),$$

where $\xi = \lambda(\mu + \lambda)$. Clearly, two roots are given by $\lambda_{1,2} = -\mu$. The remaining four roots can be obtained by solving the quadratic equation in ξ . We have

$$y_1 = \frac{\mu}{1 + 2b - b^2}, \quad y_2 = \frac{\mu(1-b)}{1 + 2b - b^2},$$

hence $b \in [0, 1)$. Substituting the values of y_1 and y_2 , we have

$$\xi^2 + \xi \frac{\mu(1+b)(2-b)}{1 + 2b - b^2} + \frac{\mu^2(1-b)}{1 + 2b - b^2} = 0.$$

The discriminant of this equation is

$$\mathcal{D} = \mu^2 \frac{(1+b)^2(2-b)^2 - 4(1-b)(1+2b-b^2)}{(1+2b-b^2)^2}.$$

Simplifying the numerator, we find that

$$\mathcal{D} = \mu^2 \frac{b^2(3-b)^2}{(1+2b-b^2)^2} \geq 0.$$

Hence the roots are

$$\xi_1 = -\mu, \quad \xi_2 = -\mu \frac{1-b}{1+2b-b^2}.$$

The corresponding lambdas are solutions of

$$\lambda_{3,4}^2 + \mu\lambda_{3,4} + \mu = 0, \quad \lambda_{5,6}^2 + \mu\lambda_{5,6} + \mu \frac{1-b}{1+2b-b^2} = 0.$$

The positivity of coefficients in the above quadratics implies that $\text{Re}(\lambda_{3,4,5,6}) < 0$. \diamond

5.1. Destabilizing the positive equilibrium. In this section, we show that there exist a nonempty set of parameter combinations such that E_{11} is unstable. We prove the following Theorem.

Theorem 5.2. *Consider the system (5.1) with $b = 1$, $\mu_1 = \varepsilon$, and $\mu_2 = c\varepsilon$. There exist $\varepsilon^* > 0$ and $c^* > 1$ such that for all $0 < \varepsilon < \varepsilon^*$ and $c > c^*$, the Jacobian at the positive equilibrium E_{11} has two real negative eigenvalues, and two pairs of complex eigenvalues with positive and negative real parts respectively. In particular, the positive equilibrium E_{11} is locally unstable with two-dimensional unstable manifold.*

Proof. At the positive equilibrium E_{11} , we have

$$y_1 = \frac{c^2\varepsilon}{c^2 + 2c - 1}, \quad y_2 = \frac{c(c-1)\varepsilon}{c^2 + 2c - 1}.$$

Hence, E_{11} exists as long as $c > 1$. The Jacobian of interest $J(\varepsilon) = J(E_{11})$ has the form (5.2) with y_1, y_2, μ_1, μ_2 given above. The characteristic polynomial of $J(\varepsilon)$ has the form

$$p(z, \varepsilon) = \varepsilon^4 a_0(c) + \varepsilon^3 a_1(c)(1 + O(\varepsilon))z + \varepsilon^2 a_2(c)(1 + O(\varepsilon))z^2 + \varepsilon^2 a_3(c)(1 + O(\varepsilon))z^3 + \varepsilon a_4(c)(1 + O(\varepsilon))z^4 + \varepsilon a_5(c)z^5 + z^6,$$

where

$$a_0(c) = \frac{c^3(c-1)}{c^2+2c-1}, \quad a_1(c) = \frac{4c^4(c-1)}{(c^2+2c-1)^2}, \quad a_2(c) = \frac{2c^3(c-1)}{(c^2+2c-1)^2}, \\ a_3(c) = \frac{3c(2c-1)(c^3+3c^2+c-1)}{(c^2+2c-1)^2}, \quad a_4(c) = \frac{2c(2c-1)}{c^2+2c-1}, \quad a_5(c) = 2(c+1).$$

Since $p(z, 0) = z^6$, $J(0)$ has a zero eigenvalue of multiplicity 6. Now we expand the roots of p in powers of ε . First, we evaluate $p(k\varepsilon^\alpha, \varepsilon)$ and find that the leading terms are

$$p(k\varepsilon^\alpha, \varepsilon) = \varepsilon^4 a_0(c) + k\varepsilon^{3+\alpha} a_1(c)(1 + O(\varepsilon)) + k^2 \varepsilon^{2+2\alpha} a_2(c)(1 + O(\varepsilon)) \\ + k^3 \varepsilon^{2+3\alpha} a_3(c)(1 + O(\varepsilon)) + k^4 \varepsilon^{1+4\alpha} a_4(c)(1 + O(\varepsilon)) + k^5 \varepsilon^{1+5\alpha} a_5(c) + k^6 \varepsilon^{6\alpha},$$

Now we construct the Newton diagram [2], that is,

$$n(\alpha) = \min(4, 3 + \alpha, 2 + 2\alpha, 2 + 3\alpha, 1 + 4\alpha, 1 + 5\alpha, 6\alpha),$$

which has two positive vertices at $(1/2, 3)$ and $(1, 4)$. Hence, the leading power of z is either $\alpha = 1/2$ or $\alpha = 1$.

- Case $\alpha = 1$ corresponds to $z = k\varepsilon + o(\varepsilon)$. To determine the value of k , we set the leading terms of $p(k\varepsilon, \varepsilon)$ equal to zero and obtain the equation $a_0(c) + ka_1(c) + k^2 a_2(c) = 0$. Simplifying this equation, we find that it is equivalent to

$$\frac{c^3(c-1)}{(c^2+2c-1)^2} (2k^2 + 4ck + (c^2 + 2c - 1)) = 0.$$

Since $c > 1$, the roots are

$$k_{1,2} = -c \pm \frac{c-1}{\sqrt{2}}$$

which are both strictly negative.

- Case $\alpha = 1/2$ corresponds to $z = r\varepsilon^{1/2} + l\varepsilon + o(\varepsilon)$. Expanding $p(r\varepsilon^{1/2} + l\varepsilon, \varepsilon)$, we find up to the two lowest orders of ε that

$$p(r\varepsilon^{1/2} + l\varepsilon, \varepsilon) = \varepsilon^3 r^2 (a_2(c) + a_4(c)r^2 + r^4) \\ + r\varepsilon^{7/2} (a_1(c) + 2la_2(c) + r^2 a_3(c) + 4r^2 la_4(c) + r^4 a_5(c) + 6r^4 l).$$

Setting the ε^3 term equal to zero, we find that either $r = 0$ (in which case we are back to the previous step) or that r satisfies the biquadratic equation

$$a_2(c) + a_4(c)r^2 + r^4 = 0,$$

which is equivalent to

$$2c^3(c-1) + 2c(2c-1)(c^2+2c-1)r^2 + (c^2+2c-1)^2 r^4 = 0.$$

The discriminant of this equation

$$\mathcal{D} = 4c^2(c^2 + 2c - 1)^2 ((2c - 1)^2 - 2c(c - 1)) = 4c^2(c^2 + 2c - 1)^2 (c^2 + (c - 1)^2)$$

is clearly positive, and both roots

$$r^2 = \frac{c}{c^2 + 2c - 1} (-(2c - 1) \pm \sqrt{(2c - 1)^2 - 2c(c - 1)})$$

are strictly negative. Hence, we have two pairs of pure imaginary values for r :

$$r_{1,2} = \pm i \sqrt{\frac{c((2c - 1) + \sqrt{(2c - 1)^2 - 2c(c - 1)})}{c^2 + 2c - 1}},$$

$$r_{3,4} = \pm i \sqrt{\frac{c((2c - 1) - \sqrt{(2c - 1)^2 - 2c(c - 1)})}{c^2 + 2c - 1}}.$$

Substituting each pair into the $\varepsilon^{7/2}$ term and setting it equal to zero, we obtain the corresponding values of l :

$$l_1 = -\frac{a_1(c) + r_{1,2}^2 a_3(c) + r_{1,2}^4 a_5(c)}{2a_2(c) + 4r_{1,2}^2 a_4(c) + 6r_{1,2}^4},$$

$$l_2 = -\frac{a_1(c) + r_{3,4}^2 a_3(c) + r_{3,4}^4 a_5(c)}{2a_2(c) + 4r_{3,4}^2 a_4(c) + 6r_{3,4}^4}.$$

At this point, we have established the existence of six distinct branches of eigenvalues for small $\varepsilon > 0$:

$$z_1 = k_1 \varepsilon + o(\varepsilon),$$

$$z_2 = k_2 \varepsilon + o(\varepsilon),$$

$$z_{3,4} = l_1 \varepsilon + r_{1,2} \varepsilon^{1/2} + o(\varepsilon),$$

$$z_{5,6} = l_2 \varepsilon + r_{3,4} \varepsilon^{1/2} + o(\varepsilon).$$

The first two eigenvalues are real and negative for small $\varepsilon > 0$, so it remains to show that either l_1 or l_2 may be positive for some values of c .

The sign of the expression $2a_2 + 4a_4 r^2 + 6r^4$ can be determined as follows. Consider a cubic polynomial $f(x) = 2x(a_2 + a_4 x + x^2)$ which has three simple zeros at $r_{1,2}^2 < r_{3,4}^2 < 0$. Since $f(x) > 0$ for $x > 0$, we have that $f'(r_{1,2}^2), f'(0) > 0$, and $f'(r_{3,4}^2) < 0$. Thus

$$f'(r_{1,2}^2) = 2a_2(c) + 4r_{1,2}^2 a_4(c) + 6r_{1,2}^4 > 0,$$

$$f'(r_{3,4}^2) = 2a_2(c) + 4r_{3,4}^2 a_4(c) + 6r_{3,4}^4 < 0.$$

Since the denominators of l_1 and l_2 have opposite signs, it suffices to show that the numerators have the same sign. That would imply that one of l_i is positive. We claim that the numerators of l_1 and l_2 are strictly positive for all sufficiently large c . Indeed, let us investigate the asymptotic behavior of the roots of the quadratics $Q_1(x) = a_1(c) + a_3(c)x + a_5(c)x^2$ and $Q_2(x) = a_2(c) + a_4(c)x + x^2$.

- Equation $Q_1 = 0$ is equivalent (after dividing through by $2c$) to

$$\frac{2c^3(c - 1)}{(c^2 + 2c - 1)^2} + \frac{3(c - 1/2)(c^3 + 3c^2 + c - 1)}{(c^2 + 2c - 1)^2} x + (1 + 1/c)x^2 = 0.$$

As $c \rightarrow \infty$, the roots of this equation converge to the roots of $2 + 3x + x^2 = 0$, that is, $x = -2$ or $x = -1$. This follows from the continuity of roots.

- Similarly, as $c \rightarrow \infty$, the roots of $Q_2 = 0$ converge to the roots of $2 + 4x + x^2 = 0$, that is, $x = -2 \pm \sqrt{2}$. An equivalent statement is that

$$\lim_{c \rightarrow \infty} r_{1,2}^2 = -2 - \sqrt{2}, \quad \lim_{c \rightarrow \infty} r_{3,4}^2 = -2 + \sqrt{2}.$$

Since $-2 - \sqrt{2} < -2 < -1 < -2 + \sqrt{2}$ (i.e. the roots of Q_1 are located between the roots of Q_2), we conclude that the numerators of l_1 and l_2 are strictly positive for all sufficiently large values of c . Since the denominator of l_1 (respectively, l_2) is positive (respectively, negative), we conclude that $l_1 > 0$ and $l_2 < 0$ for all sufficiently large c . This concludes the proof of Theorem 5.2. \diamond

6. RESULTS ON BOUNDEDNESS OF SOLUTIONS, COMPETITIVE EXCLUSION AND PERSISTENCE

Theorem 6.1. *Suppose that $b, \mu_1, \mu_2 > 0$ and $c_{ii} > 0$ for all $i = 1, \dots, n$. Then all nonnegative solutions of (2.4) – (2.6) are ultimately uniformly bounded.*

Proof. Without loss of generality, we may consider only positive solutions, that is $y_i(t), z_i(t), w_i(t) > 0$. First, it is clear that since $\dot{y}_i \leq y_i$, we have $y_i(t) \leq y_i(0)e^t$. Hence, all solutions are defined for $t \geq 0$. Next, we introduce the quantities $\alpha_i = y_i/(z_i + w_i) > 0$. It follows that

$$\dot{\alpha}_i = \frac{y_i(1 - z_i - w_i)(z_i + w_i) - y_i(y_i + b \sum_{j=1}^n c_{ij}y_j - \mu_1z_i - \mu_2w_i)}{(z_i + w_i)^2}.$$

Clearly, this implies that

$$\dot{\alpha}_i \leq \alpha_i(1 - (1 + bc_{ii})\alpha_i + \frac{\mu_1z_i + \mu_2w_i}{z_i + w_i}).$$

Using the fact that

$$\frac{\mu_1z_i + \mu_2w_i}{z_i + w_i} \leq \max(\mu_1, \mu_2), \quad z_i, w_i > 0,$$

we obtain the inequality

$$\dot{\alpha}_i \leq \alpha_i(1 + \max(\mu_1, \mu_2) - (1 + bc_{ii})\alpha_i).$$

Hence, $\dot{\alpha}_i < 0$ as long as $\alpha_i > \alpha_i^* := \frac{1 + \max(\mu_1, \mu_2)}{1 + bc_{ii}}$. Consequently, $\alpha_i(t) \leq \hat{\alpha}_i := \max(\alpha_i(0), \alpha_i^*)$ for all $t \geq 0$. Equivalently, we have that $y_i(t) \leq \hat{\alpha}_i(z_i(t) + w_i(t))$, which implies that

$$\dot{y}_i \leq y_i(1 - \frac{y_i}{\hat{\alpha}_i}), \quad t \geq 0.$$

Therefore, $y_i(t)$ is bounded for all $t \geq 0$. Finally, we have that

$$\limsup_{t \rightarrow \infty} \alpha_i(t) \leq \alpha_i^*, \quad \limsup_{t \rightarrow \infty} y_i(t) \leq \alpha_i^*, \quad \limsup_{t \rightarrow \infty} z_i(t) \leq \frac{\alpha_i^*}{\mu_1}, \quad \limsup_{t \rightarrow \infty} w_i(t) \leq \frac{b \sum_j c_{ij} \alpha_j^*}{\mu_2}. \quad \diamond$$

6.1. Extinction of some antigenic variants. In this section, we define the matrix

$$(6.1) \quad A := \gamma_1 I_n + \gamma_2 C,$$

where γ_1 and γ_2 are given by (2.7). We will use

$$\langle f(t) \rangle = \frac{1}{t} \int_0^t f(s) ds$$

to denote the average value of $f(t)$ on the interval $[0, t]$.

Theorem 6.2. *Suppose that the following condition holds:*

$$(6.2) \quad \exists r \in \{1, \dots, n\} : \forall \mathbf{x} \geq \mathbf{0}, \mathbf{Ax} \geq \mathbf{1} \Rightarrow (\mathbf{Ax})_r > 1,$$

then for any positive solution $y_i(t), z_i(t), w_i(t) > 0$ of (2.4) – (2.6), we have $\lim_{t \rightarrow \infty} y_r(t) = 0$.

In (6.2), the vector inequalities correspond to the order induced by the standard cone R_+^n .

Proof. For any positive solution of (2.4) – (2.6), we have that

$$\begin{aligned} \langle \dot{y}_i / y_i \rangle &= 1 - \langle z_i \rangle - \langle w_i \rangle, \\ \langle \dot{z}_i \rangle &= \langle y_i \rangle - \mu_1 \langle z_i \rangle, \\ \langle \dot{w}_i \rangle &= b \sum_{j=1}^n c_{ij} \langle y_j \rangle - \mu_2 \langle w_i \rangle, \end{aligned}$$

Theorem 6.1 implies that

$$\begin{aligned} \langle \dot{z}_i(t) \rangle &= \frac{z_i(t) - z_i(0)}{t} \rightarrow 0, \quad t \rightarrow \infty, \\ \langle \dot{w}_i(t) \rangle &= \frac{w_i(t) - w_i(0)}{t} \rightarrow 0, \quad t \rightarrow \infty, \\ \limsup_{t \rightarrow \infty} \langle \dot{y}_i/y_i \rangle &= \limsup_{t \rightarrow \infty} 1 - \langle z_i(t) \rangle - \langle w_i(t) \rangle \leq 0. \end{aligned}$$

Let $\mathbf{y}(t) = (y_1(t), \dots, y_n(t))$. Without loss of generality, there exists a convex compact set $K \subset \mathbb{R}_+^n$ such that $\mathbf{y}(t) \in K$ for all $t \geq 0$. The convexity of K implies that $\langle \mathbf{y}(t) \rangle \in K$ for all $t \geq 0$. Let K' be the compact set

$$K' = \{\mathbf{x} \in K : A\mathbf{x} \geq \mathbf{1}\}.$$

By (6.2), compactness of K' and continuity of solutions, there exists $\varepsilon > 0$ such that $(A\mathbf{x})_r > 1 + \varepsilon$ for all $\mathbf{x} \in K'$. Also by continuity, there exists $\delta > 0$ such that $(A\mathbf{x})_r > 1 + \varepsilon/2$ for all \mathbf{x} in the δ -neighborhood of K' .

Now we analyze the averages more carefully. Since

$$|\langle z_i \rangle - \gamma_1 \langle y_i \rangle| \rightarrow 0, \quad |\langle w_i \rangle - \gamma_2 \sum_{j=1}^n c_{ij} \langle y_j \rangle| \rightarrow 0,$$

we have that

$$\limsup_{t \rightarrow \infty} 1 - \langle z_i(t) \rangle - \langle w_i(t) \rangle = \limsup_{t \rightarrow \infty} 1 - \gamma_1 \langle y_i(t) \rangle - \gamma_2 \sum_{j=1}^n c_{ij} \langle y_j(t) \rangle \leq 0,$$

that is,

$$\liminf_{t \rightarrow \infty} (A\langle \mathbf{y}(t) \rangle)_i \geq 1$$

for all $i = 1, \dots, n$. It follows that there exists $T > 0$ such that $\text{dist}(\langle \mathbf{y}(t) \rangle, K') < \delta$ for all $t > T$. Therefore, $(A\langle \mathbf{y}(t) \rangle)_r > 1 + \varepsilon/2$ for all $t > T$. This in turn implies that there exists $T' > 0$ such that

$$\langle \dot{y}_r(t) \rangle / y_r(t) = 1 - \langle z_r(t) \rangle - \langle w_r(t) \rangle < -\varepsilon/4, \quad t > T',$$

or equivalently,

$$y_r(t) < y_r(0) \exp(-\varepsilon t/4), \quad t > T'.$$

This clearly implies that $\lim_{t \rightarrow \infty} y_r(t) = 0$. ◊

6.2. Partial persistence. We begin with a general result on partial persistence which we will apply to the malaria model (2.4) – (2.6).

Let

$$(6.3) \quad \dot{x} = f(x, y)$$

$$(6.4) \quad \dot{y} = g(x, y)$$

be a forward complete system on $X \times Y := \mathbb{R}_+^n \times \mathbb{R}_+^m$. We say that (6.3) – (6.4) is *x-partially (strongly uniformly) persistent* if there is some $\delta > 0$ so that for all $(x, y) \in \text{int}(\mathbb{R}_+^n) \times \text{int}(\mathbb{R}_+^m)$ there holds that

$$\liminf_{t \rightarrow \infty} x_i(t) \geq \delta, \quad i = 1, \dots, n.$$

In what follows, we use ∂X to denote the boundary of the set X .

Inspired by the persistence result in [5] we have

Theorem 6.3. *Assume that $\partial X \times Y$ is forward invariant for (6.3)–(6.4), and suppose $K \subset X \times Y$ is a compact absorbing set (thus every forward solution of (6.3) – (6.4) eventually enters and remains in K). Let $P : X \times Y \rightarrow \mathbb{R}$ be continuously differentiable and the restriction of P to $\partial X \times Y$ be 0, and positive elsewhere. Assume that there is a continuous function $\psi : X \times Y \rightarrow \mathbb{R}$ so that*

$$(6.5) \quad \frac{\dot{P}}{P} = \psi \text{ on } X \times Y \setminus (\partial X \times Y)$$

12 IMMUNE RESPONSE TO A MALARIA INFECTION: PROPERTIES OF A MATHEMATICAL MODEL

If for all $(x, y) \in \partial X \times Y$, there is some $T > 0$ such that:

$$(6.6) \quad \langle \psi(x(T), y(T)) \rangle > 0,$$

then (6.3) – (6.4) is x -partially persistent.

The proof can be found in [3] and is omitted here.

REMARK 6.4. A result similar to Theorem 12.2.2 in [5] holds for system (6.3) – (6.4). Namely, Theorem 6.3 remains true if condition (6.6) holds only for (x, y) that are ω limit points of orbits in $\partial X \times Y$. The proof is exactly the same as in [5].

We will apply Theorem 6.3 to prove a persistence result for the malaria model (2.4) – (2.6), which we re-write here in a more compact form:

$$(6.7) \quad \dot{X} = \text{diag}(X)[\mathbf{1} - (I_n \ I_n)Y],$$

$$(6.8) \quad \dot{Y} = -\text{diag}(\mu)Y + BX,$$

where $\begin{pmatrix} X \\ Y \end{pmatrix} \in \mathbb{R}_+^n \times \mathbb{R}_+^{2n}$, $\mathbf{1} = (1 \dots 1)' \in \mathbb{R}^n$, $\mu = (\mu_1 \dots \mu_1 \ \mu_2 \dots \mu_2)' \in \mathbb{R}^{2n}$ and

$$B = \begin{pmatrix} I_n \\ bC \end{pmatrix}.$$

Note that $\partial\mathbb{R}_+^n \times \mathbb{R}_+^{2n}$ is forward invariant, and that there is a compact absorbing set K in $\mathbb{R}_+^n \times \mathbb{R}_+^{2n}$ by Theorem 6.1. Let

$$A = (I_n \ I_n)\text{diag}^{-1}(\mu)B.$$

We will show the following:

Theorem 6.5. *If there is some $p \in \text{int}(\mathbb{R}_+^n)$ so that*

$$(6.9) \quad p'[\mathbf{1} - A\bar{X}] > 0,$$

for all \bar{X} for which $\begin{pmatrix} \bar{X} \\ \text{diag}^{-1}(\mu)B\bar{X} \end{pmatrix}$ is an equilibrium of (6.7) – (6.8) in $\partial\mathbb{R}_+^n \times \mathbb{R}_+^{2n}$, then system (6.7) – (6.8) is persistent.

Proof. The proof proceeds in two steps. We will first show that system (6.7) – (6.8) is X -partially persistent using Theorem 6.3 and Remark 6.4. Then we will show that the system (6.7) – (6.8) is persistent.

Step 1. Let us first establish X -partial persistence for (6.7) – (6.8). Define the continuously differentiable (perhaps by multiplying the vector p by a sufficiently large positive scalar) function $P : \mathbb{R}_+^n \times \mathbb{R}_+^{2n} \rightarrow [0, \infty)$:

$$P(X, Y) = \prod_{i=1}^n X_i^{p_i},$$

which is 0 on $\partial\mathbb{R}_+^n \times \mathbb{R}_+^{2n}$ and positive elsewhere. Note that (6.5) holds on $\mathbb{R}_+^n \times \mathbb{R}_+^{2n} \setminus (\partial\mathbb{R}_+^n \times \mathbb{R}_+^{2n})$ with

$$\psi(X, Y) = p'[\mathbf{1} - (I_n \ I_n)Y]$$

We claim that for all $Z = (X, Y) \in \partial\mathbb{R}_+^n \times \mathbb{R}_+^{2n}$, there is some $T > 0$ such that:

$$\langle \psi(Z(T)) \rangle > 0,$$

from which X -partial persistence will follow using Theorem 6.3. We will do this by induction on r , the number of non-zero components of X . If $r = 0$, then $X(t) = 0$ for all $t \geq 0$, hence $Y(t) \rightarrow 0$ as $t \rightarrow +\infty$, so that $\omega(Z) = \{0\}$. But since 0 is an equilibrium point of (6.7) – (6.8), (6.9) holds with $\bar{X} = 0$, and therefore our claim follows from Remark 6.4. Assume that the claim has been established for $r = 1, \dots, m - 1$ but that X has m non-zero components (of course, $m < n$). Denote the indices of these components by I , a proper subset of $\{0, 1, \dots, n\}$. There are two cases to consider:

Case 1. Suppose the solution $Z(t)$ converges to the boundary of the set $D = \{(X \ Y) \in \mathbb{R}_+^n \times \mathbb{R}_+^{2n} \mid X_i \neq 0 \text{ for all } i \in I\}$. Then $\omega(Z)$ is contained in part of the boundary of $\mathbb{R}_+^n \times \mathbb{R}_+^{2n}$

where at most $m - 1$ components of X are non-zero. The conclusion of our claim then follows from Remark 6.4 and the induction hypothesis.

Case 2. Suppose the solution $Z(t)$ does not converge to the boundary of D . Then there is some $\epsilon > 0$ and an increasing sequence $t_k \rightarrow \infty$ so that $X_i(t_k) > \epsilon$ for all k and all $i \in I$. For $i \notin I$ we have that $X_i(t) = 0$ for all $t \geq 0$ and thus in particular for all $t = t_k$. Consider the (bounded) sequences of averages $\langle X(t_k) \rangle$ and $\langle Y(t_k) \rangle$, which we may assume -by passing to a subsequence if necessary- converge to limits \tilde{X} and \tilde{Y} with the property that $\tilde{X}_i > 0$ if $i \in I$ and $\tilde{X}_i = 0$ otherwise. Integrating (6.8) between 0 and t_k , dividing by t_k and letting $t_k \rightarrow \infty$ yields:

$$(6.10) \quad 0 = -\text{diag}\tilde{Y} + B\tilde{X}.$$

Consider now the dynamics of the components X_i with $i \in I$ as described by (6.7). In particular, dividing by X_i , integrating between 0 and t_k , dividing by t_k and letting $t_k \rightarrow \infty$, and using (6.10) yields:

$$0 = 1 - (A\tilde{X})_i, \quad i \in I.$$

Since $\tilde{X}_i = 0$ for all $i \notin I$ we see that $\begin{pmatrix} \tilde{X} \\ \text{diag}^{-1}(\mu)B\tilde{X} \end{pmatrix}$ is an equilibrium of (6.7) – (6.8). Finally notice that as $t_k \rightarrow \infty$, we have that:

$$\langle \psi(Z(t_k)) \rangle \rightarrow p'[\mathbf{1} - A\tilde{X}],$$

which is positive by (6.9). This establishes our claim.

Step 2. In Step 1 we have shown that (6.7) – (6.8) is X -partially persistent, so that for all solutions starting in $\text{int}(\mathbb{R}_+^n) \times \text{int}(\mathbb{R}_+^{2n})$ there is some $\delta > 0$ such that

$$\liminf_{t \rightarrow \infty} X(t) \geq \delta \mathbf{1},$$

where the above vector inequality should be interpreted componentwise. Then (6.8) implies that for all large t , we have that

$$\dot{Y} \geq -\text{diag}(\mu)Y + \frac{\delta}{2}B\mathbf{1}.$$

This implies that:

$$\liminf_{t \rightarrow \infty} Y(t) \geq \frac{\delta}{2}\text{diag}^{-1}(\mu)B\mathbf{1},$$

where the vector on the right-hand side has positive components, which establishes persistence of (6.7) – (6.8). \diamond

6.3. Comparison with a Lotka-Volterra model. It is interesting to compare our competitive exclusion result (Theorem 6.2) and our persistence result (Theorem 6.5) obtained in the previous subsections to corresponding results for the following lower dimensional Lotka-Volterra system:

$$(6.11) \quad \dot{X} = \text{diag}(X)[\mathbf{1} - AX]$$

For this system we can easily prove the following competitive exclusion result, using similar arguments as those in the proof of Theorem 6.2.

Lemma 6.6. *Suppose that (6.2) holds for system (6.11). Then for any solution $x(t)$ of (6.11) in $\text{int}(\mathbb{R}_+^n)$, there holds that $x_r(t) \rightarrow 0$ as $t \rightarrow \infty$.*

For system (6.11), there is the following persistence result [5].

Lemma 6.7. *If there is some $p \in \text{int}(\mathbb{R}_+^n)$ such that (6.9) holds for all \bar{X} which are equilibria of (6.11) in $\partial\mathbb{R}_+^n$, then system (6.11) is persistent.*

In other words, our conditions under which system (6.7) – (6.8) exhibits competitive exclusion (see Theorem 6.2), respectively persistence (see Theorem 6.5) holds, are the same as for the reduced order system (6.11).

Finally, we can interpret conditions (6.2) and (6.9) geometrically, and will see that they are not mutually exclusive. This implies that there are examples of system (6.7) – (6.8) which don't fit our conditions for either competitive exclusion or persistence.

In \mathbb{R}^n , define the closed convex set

$$D = \{\mathbf{x} \in \mathbb{R}^n \mid \mathbf{1} - A\mathbf{x} \leq 0\}.$$

The boundary of D is given by those points \mathbf{x} in D for which $1 - (A\mathbf{x})_i = 0$ for some i . In this case we say that constraint i is active for \mathbf{x} . Condition (6.2) says that there must be a constraint r which is never active in \mathbb{R}_+^n .

Although a geometric interpretation of condition (6.9) is not immediately clear, it has been shown in [5] that (6.9) is equivalent to the following condition which does have a clear geometric meaning.

$$(6.12) \quad C \cap D_+ = \emptyset,$$

where C is the convex hull of the set of equilibria of (6.11) in $\partial\mathbb{R}_+^n$ and $D_+ = D \cap \mathbb{R}_+^n$.

To see that the exclusion condition (6.2) and (6.9) (or the equivalent (6.12)) are not mutually exclusive, consider a system (6.11) with $n = 2$ with nullclines given in Fig. 1. Clearly neither condition (6.2) nor condition (6.12) hold. It is well-known that this is an example of a bistable Lotka-Volterra system. The equilibrium in $\text{int}(\mathbb{R}_+^2)$ is a saddle and every solution in $\text{int}(\mathbb{R}_+^2)$ not on the stable manifold of the interior equilibrium converges to either E_1 or E_2 .

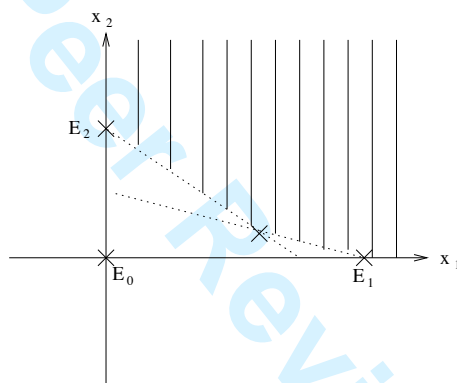


FIGURE 1. An example of system (6.11) with $n = 2$. Nullclines are the dashed lines. The region D_+ is indicated by all parallel vertical lines. The crosses represent the equilibria, the triangle with vertices E_0 , E_1 , E_2 represents C , hence $C \cap D_+ \neq \emptyset$.

7. CONCLUSIONS

In this paper, we presented several mathematical results concerning a model of the within-host malaria infection originally formulated by Recker et al. [7]. We have proved global stability of the model in several special cases: the case of a single antigenic variant, the case of no cross-reactive immunity, and the case of perfect cross-reactive immunity. We have presented a specific example to demonstrate that partial cross-immunity may lead to destabilization of the disease equilibrium provided that the average durations of the specific immunity and the cross-reactive immunity are sufficiently different. This result shows that the dynamics of the malaria model can be much richer than thought previously [8].

We showed that in some cases, one or more antigenic variants become extinct and presented sufficient conditions for such extinction. A given variant will become extinct provided that it is effectively eliminated by any static combination of immune responses that controls all antigenic variants (condition (6.2) of Theorem 6.2). We also presented sufficient conditions for the long-term persistence of all antigenic variants (Theorem 6.5). We could not easily interpret the biological meaning of the persistence condition. Finally, we compared the extinction/persistence dynamics of the malaria model to the dynamics of the corresponding lower dimensional Lotka-Volterra competition model.

Acknowledgment. We thank the anonymous reviewers for their comments and suggestions.

REFERENCES

- [1] R. Antia, M.A. Nowak, and R.M. Anderson, *Antigenic variation and the within-host dynamics of parasites*, Proc. Natl. Acad. Sci. USA 93, 1996, pp. 985-989.
- [2] A. D. Campbell, *A note on Newton's diagram for approximating plane algebraic curves and surfaces*, The American Mathematical Monthly, Vol. 36, No. 4, 1929, pp. 204-208, doi:10.2307/2299296.
- [3] P. De Leenheer and S.S. Pilyugin, *Multi-strain virus dynamics with mutations: a global analysis*, submitted.
- [4] M.B. Gravenor, and A. L. Lloyd, *Reply to : Models for the in-host dynamics of malaria revisited: errors in some basic models lead to large over-estimates of growth rates*, Parasitology 117, 1998, pp. 409-410.
- [5] J. Hofbauer, and K. Sigmund, *Evolutionary Games and Population Dynamics*, Cmbridge University Press, Cambridge, UK, 1998.
- [6] A. Iggidr, J.-C. Kamgang, G. Sallet, and J.-J. Tewa, *Global analysis of new malaria intrahost models with a competitive exclusion principle*, SIAM J. Appl. Math. 67, 2006, pp. 260-278.
- [7] M. Recker, S. Nee, P. C. Bull, S. Kinyanjui, K. Marsh, C. Newbold, and S. Gupta, *Transient cross-reactive immune responses can orchestrate antigenic variation in malaria*, Let. Nature 429, 2004, pp. 555-558.
- [8] M. Recker and S. Gupta, *Conflicting immune responses can prolong the length of infection in Plasmodium falciparum malaria*, Bull. Math. Biol. 68, 2006, pp. 821-835.
- [9] A. Saul, *Models for the in-host dynamics of malaria revisited: errors in some basic models lead to large over-estimates of growth rates*, Parasitology 117, 1998, pp. 405-407.
- [10] H. L. Smith and P. Waltman, *The Theory of the Chemostat*, Cambridge University Press, Cambridge, 1995