Global Analysis of New Malaria Intrahost Models with a Competitive Exclusion Principle

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GLOBAL ANALYSIS OF NEW MALARIA INTRAHOST MODELS WITH A COMPETITIVE EXCLUSION PRINCIPLE*

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Abstract. In this paper we propose a malaria within-host model with k classes of age for the parasitized red blood cells and n strains for the parasite. We provide a global analysis for this model. A competitive exclusion principle holds. If $\mathcal{R}_0$, the basic reproduction number, satisfies $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable. On the contrary if $\mathcal{R}_0 > 1$, then generically there is a unique endemic equilibrium which corresponds to the endemic stabilization of the most virulent parasite strain and to the extinction of all the other parasites strains. We prove that this equilibrium is globally asymptotically stable on the positive orthant if a mild sufficient condition is satisfied.

Key words. nonlinear dynamical systems, intrahost models, global stability, *Plasmodium falciparum*, competitive exclusion principle

AMS subject classifications. 34A34, 34D23, 34D40, 92D30

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1. Introduction.

In this paper we consider intrahost models for malaria. These models describe the interaction of a parasite, namely a protozoa *Plasmodium falciparum*, with its target cells, the red blood cells (RBC). During the past decade there has been considerable work on the mathematical modeling of *Plasmodium falciparum* infection [2, 14, 21, 22, 24, 23, 25, 28, 30, 52, 55, 56, 58, 64]. A review has been done by Molineaux and Dietz in [59].

We give a brief review of the features of malaria. Malaria in a human begins with an inoculum of *Plasmodium* parasites (sporozoites) from a female *Anopheles* mosquito. The sporozoites enter the liver within minutes. After a period of asexual reproduction in the liver the parasites (merozoites) are released in the bloodstream where the asexual erythrocyte cycle begins. The merozoites enter RBC, grow, and reproduce over a period of approximately 48 hours after which the erythrocyte ruptures releasing 8–32 "merozoites" daughter parasites that quickly invade a fresh erythrocyte to renew the cycle. This blood cycle can be repeated many times, in the course of which some of the merozoites instead develop in the sexual form of the parasites: gametocytes. Gametocytes are benign for the host and are waiting for the mosquitoes.

The first mathematical model of the erythrocyte cycle was proposed by Anderson, May, and Gupta [3]. This original model has been extended in different directions [2, 3, 21, 25, 28, 30, 64].

The original model [3] is given by the following system:

$$\begin{cases} \dot{x} = \Lambda - \mu_x x - \beta x\, m, \\ \dot{y} = \beta x\, m - \mu_y\, y, \\ \dot{m} = r\, \mu_y\, y - \mu_m\, m - \beta\, x\, m. \end{cases} \tag{1.1}$$

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The state variables are denoted by x, y, and m. The variable x denotes the concentration of uninfected RBC, y the concentration of parasitized red blood cells (PRBC), and m the concentration of the free merozoites in the blood.

We briefly sketch the interpretation of the parameters. Parameters μ_x, μ_y, and μ_m are the death rates of the RBC, PRBC, and free merozoites, respectively. The parameter β is the contact rate between RBC and merozoites. Uninfected blood cells are recruited at a constant rate Λ from the bone marrow and have a natural life-expectancy of $\frac{1}{\mu_x}$ days. Death of a PRBC results in the release of an average number of r merozoites. Free merozoites die or successfully invade a RBC.

This system is isomorphic to numerous systems considered in the mathematical modeling of virus dynamics; see [60, 61, 62] and the references therein. Some authors ignore the loss term $-\beta\, x\, m$ that should appear in the m equation. Indeed without this loss term, merozoites can infect RBC without themselves being absorbed, and this allows one merozoite *to infect more than one RBC*.

The original and the derived malaria models were intended to explain observations, namely parasitaemia, i.e., the concentration y of PRBC and also the decrease of the healthy RBC leading to anaemia. An important characteristic of *Plasmodium falciparum*, the most virulent malaria parasite, is sequestration. At the halfway point of parasite development, the infected erythrocyte leaves the circulating peripheral blood and binds to the endothelium in the microvasculature of various organs where the cycle is completed. A measurement of *Plasmodium falciparum* parasitaemia taken from a blood smear therefore samples young parasites only. Physician treating malaria use the number of parasites in peripheral blood smears as a measure of infection, and this does not give the total parasite burden of the patient. In some respects this is a weak point of the model (1.1). Moreover antimalarial drugs are known to act preferentially on different stages of parasite development. These facts lead some authors to give a general approach to modeling the age structure of *Plasmodium* parasites [22, 23, 24, 57]. Their model is a linear catenary compartmental model. This model is based on a finite number of compartments, each representing a stage of development of the parasite inside the PRBC. The models describe only the dynamics of the morphological stage evolution of the parasites and make no allowance for the dynamics of the healthy RBC.

In this paper we propose a model which combines the advantages of the two approaches. We also consider this model with different strains for the parasites. To encompass the different models of the literature we allow, in this model, to ignore or not the loss term in the m equation. To begin we consider the model with one strain:

$$
\left\{
\begin{array}{l}
\dot{x} = f(x) - \mu_x x - \beta x\, m, \\
\dot{y}_1 = \beta x\, m - \alpha_1\, y_1, \\
\dot{y}_2 = \gamma_1\, y_1 - \alpha_2\, y_2, \\
\dots \\
\dot{y}_k = \gamma_{k-1}\, y_{k-1} - \alpha_k\, y_k, \\
\dot{m} = r\, \gamma_k\, y_k - \mu_m\, m - u\, \beta\, x\, m.
\end{array}
\right. \tag{1.2}
$$

In this system $f(x) - \mu_x\, x$ is the density-dependent growth rate of RBC. The other parameters are positive. In the model of Gravenor et al. [21] $\alpha_i = \gamma_i + \mu_i$, and hence $\alpha_i > \gamma_i$. We do not need this requirement, which implies that our model is not necessarily a catenary compartmental model. In the literature the parameter u takes the values $u = 0$ when the loss of the merozoite when it enters a RBC is ignored or takes $u = 1$ when this loss is not ignored. In our analysis u is simply a nonnegative

parameter. Except for these generalizations this system has already been suggested by Gravenor and Lloyd [21] in their reply to the criticism of Saul [64]. We provide a global analysis of this system related to the basic reproduction ratio $\mathcal{R}_0$ of the considered model.

One problem is how to decide upon the number of parasite compartments in the model. A starting point can be the morphological appearance of the parasite. But if the objective is to reflect the distribution of cycle lengths, the number of compartment can be increased to obtain a gamma distribution. Finally the two approaches can be combined: some compartments are for morphological reasons and others are for behavioral reasons. Then this model can also be interpreted as the application of the method of stages (or the linear chain trick) to the life cycle of PRBC [3, 31, 47, 49, 48, 51]. In other words a chain of compartments is included to generate a distribution of lags. It is also possible to add a class y_{k+1} in order to allow for the production of gametocytes. Different numbers of stages, ranging from 5 to 48, are used in [20, 22, 23, 24].

It is well grounded that a *falciparum* infection consists of distinct parasite genotypes. The model of Anderson, May, and Gupta has been extended in this direction [25, 66]. With regard to such features we propose a model with k stages for the infected RBC, production of gametocytes, and n genotypes, in the population of parasites.

One of the important principles of theoretical ecology is the competitive exclusion principle which states that no two species can indefinitely occupy the same ecological niche [7, 8, 11, 17, 25, 39, 53, 54]. We provide a global analysis of this model and obtain a generic competitive exclusion result within one host individual. This confirms the simulation results obtained in [25]. We compute the basic reproduction ratio $\mathcal{R}_0$ of the model. For this model there is always a disease-free equilibrium (DFE). To put it more precisely this equilibrium corresponds to the extinction of all the parasites, including the free parasites and the intraerythrocyte parasites. We prove that if $\mathcal{R}_0 \leq 1$, then the DFE is globally asymptotically stable (GAS); in other words the parasites are cleared. If $\mathcal{R}_0 > 1$, then, generically, a unique endemic equilibrium exists corresponding to the extinction of all the strains of parasites but one. We prove that this equilibrium is GAS on the positive orthant under a mild condition. For example this condition is automatically satisfied when $u = 0$ and $f(x) = \Lambda - \mu_x\, x$. When $u \neq 0$ the criteria, obtained for deciding the winning strain, differs from other results in the literature. To each i-strain can be associated a basic reproduction number $\mathcal{R}_0^i$ and a threshold $\mathcal{T}_0^i$. It turns out, when $u \neq 0$, that this is precisely this threshold $\mathcal{T}_0^i$ which distinguishes the fate of the strain and not $\mathcal{R}_0^i$ at the difference of [7, 11].

The paper is organized as follows. In section 2 we introduce the model with k stages for the infected RBC and one parasite strain, with and without gametocyte production. We compute the basic reproduction number and provide a stability analysis.

In section 3 we consider the model of Anderson, May, and Gupta with n distinct genotypes and production of gametocytes. This model with a constant recruitment function for the erythrocytes, two strains, and one class of age has been proposed in [25]. We have studied this model in [1]. Here using the computation of section 2, we prove for the general n strain k class of age model that if $\mathcal{R}_0 \leq 1$, then the parasites are cleared and if $\mathcal{R}_0 > 1$, then generically the different genotypes cannot coexist. Namely a unique equilibrium exists, for which only one genotype is positive, and which is GAS on a dense subset of the nonnegative orthant. This result confirms the simulations given in [25].

Global results of stability for the DFE as well for the endemic equilibrium for epidemic models are not so common [26, 27, 33, 43, 65, 67, 68]. Global stability

results for the endemic equilibrium have often been obtained by using monotone system techniques [29, 36]. Usually the Poincaré–Bendixson property of monotone systems in dimension 3 is used [40, 41, 42, 43, 44, 45]. Our results generalize the results of [13].

2. Stability analysis of a one strain model with *k* stages. We consider a general class of systems. The haemopoiesis is a complex system. In the cited references the recruitment of RBC is given by $\Lambda - \mu_x\, x$. In this paper we will use a more general function $\varphi(x)$. In a more complex system the haemopoiesis could be an input coming from another system:

$$\left\{\begin{array}{l} \dot{x} = f(x) - \mu_x x - \beta x\, m = \varphi(x) - \beta\, x\, m, \\ \dot{y}_1 = \beta x\, m - \alpha_1\, y_1, \\ \dot{y}_2 = \gamma_1\, y_1 - \alpha_2\, y_2, \\ \dots \\ \dot{y}_k = \gamma_{k-1}\, y_{k-1} - \alpha_k\, y_k, \\ \dot{m} = r\, \gamma_k\, y_k - \mu_m\, m - u\, \beta\, x\, m. \end{array}\right. \tag{2.1}$$

We denote by y the column vector $(y_1, \dots, y_k)^T$. The parameter u is nonnegative. The reason for this parameter is to encompass some malaria models in which the term $-\beta\, x\, m$ can appear or not. In [2] Anderson has considered a system without the $-\beta\, x\, m$ in the $\dot{m}$ equation. In [60] all the basic models of virus dynamics are also without this term. One feature of *Plasmodium falciparum*, responsible for the deadly case of malaria, is that more than one parasite can invade RBC. In this case u is the mean number of parasites invading RBC and thus disappearing from the circulating blood.

Some authors [25, 56] have included in the model production of gametocytes. In the course of the production of merozoites from bursting erythrocytes, some invading merozoites develop into the sexual, nonreplicating transmission stages known as gametocytes. The gametocytes are benign and transmissible to mosquitoes. We can also, following these authors, include a production of gametocytes in our model. If we denote by y_{k+1} the "concentration of gametocytes," the model becomes

$$\left\{\begin{array}{l} \dot{x} = f(x) - \mu_x x - \beta x\, m = \varphi(x) - \beta\, x\, m, \\ \dot{y}_1 = \beta x\, m - \alpha_1\, y_1, \\ \dot{y}_2 = \gamma_1\, y_1 - \alpha_2\, y_2, \\ \dots \\ \dot{y}_k = \gamma_{k-1}\, y_{k-1} - \alpha_k\, y_k, \\ \dot{y}_{k+1} = \rho\, \gamma_k\, y_k - \alpha_{k+1}\, y_{k+1}, \\ \dot{m} = r\, \gamma_k\, y_k - \mu_m\, m - u\, \beta\, x\, m. \end{array}\right. \tag{2.2}$$

We start to analyze the system with minimal hypothesis on f but nevertheless plausible from the biological point of view. The function f gives the production of erythrocytes from the bone marrow. The function $\varphi(x) = f(x) - \mu_x x$ models the population dynamic of RBC in the absence of parasites. The RBC have a finite lifetime, and then μ_x represents the average per capita death rate of RBC. The function f models in some way homeostasis. In this paper we suppose that f depends only on x. It could be assumed that the recruitment function depends on x and the total population of erythrocytes $x + \sum_i y_i$. In this paper we will analyze the simplified case which is the model considered in all the referenced literature. The rationale behind this simplification is that in a malaria primo-infection typically y is in the order of 10^{-1}

to 10^{-4} of the concentration of healthy erythrocytes x. This can be confirmed from the data of malaria therapy. In the last century neurosyphilitic patients were given malaria therapy, which was routine care at that time. Some of them were infected with *Plasmodium falciparum*. Data were collected at the National Institutes of Health laboratories in Columbia, SC and Milledgeville, GA during the period 1940 to 1963 [12].

We assume that f is a $\mathcal{C}^1$. Since homeostasis is maintained we assume that the dynamic without parasites is asymptotically stable. In other words, for the system

$$\dot{x} = f(x) - \mu_x\, x = \varphi(x)$$

there exists a unique $x^* > 0$ such that

$$\varphi(x^*) = 0, \quad \text{and } \varphi(x) > 0 \quad \text{for } 0 \le x < x^*, \quad \text{and } \varphi(x) < 0 \quad \text{for } x > x^*. \tag{2.3}$$

2.1. Notation. We will rewrite systems (2.1) and (2.2) in a condensed simpler form.

Before we introduce some classical notation.

We identify vectors of $\mathbb{R}^n$ with $n \times 1$ column vectors. $\langle\, |\, \rangle$ denotes the euclidean inner product. $\|z\|_2^2 = \langle\, z \mid z\,\rangle$ is the usual euclidean norm.

The family $\{e_1, \ldots, e_n\}$ denotes the canonical basis of the vector space $\mathbb{R}^n$. For example $e_1 = (1, 0, \ldots, 0)^T$. We denote by e_ω the last vector of the canonical basis, $e_\omega = (0, \ldots, 0, 1)^T$.

If $z \in \mathbb{R}^n$, we denote by z_i the ith component of z. Equivalently $z_i = \langle\, z \mid e_i\,\rangle$.

For a matrix A we denote by $A(i, j)$ the entry at the row i, column j. For matrices A, B we write $A \le B$ if $A(i, j) \le B(i, j)$ for all i and j, $A < B$ if $A \le B$ and $A \ne B$, and $A \ll B$ if $A(i, j) < B(i, j)$ for all i and j.

A^T denotes the transpose of A. Then $\langle\, z_1 \mid z_2\,\rangle = z_1^T\, z_2$. The notation A^{-T} will denote the transpose of the inverse of A.

For this section we rewrite the systems (2.1) and (2.2) under a unique form:

$$\begin{cases} \dot{x} = \varphi(x) - \beta\, x\, \langle\, e_\omega \mid z\,\rangle, \\ \dot{z} = \beta\, x\, \langle\, e_\omega \mid z\,\rangle\, e_1 + A_0\, z - u\, \beta\, x\, \langle\, e_\omega \mid z\,\rangle\, e_\omega. \end{cases} \tag{2.4}$$

In the case of the system (2.1) we have for A_0

$$A_0 = \begin{bmatrix} -\alpha_1 & 0 & 0 & \cdots & 0 & 0 \\ \gamma_1 & -\alpha_2 & 0 & \cdots & 0 & 0 \\ 0 & \gamma_2 & -\alpha_3 & \cdots & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ 0 & \cdots & 0 & \gamma_{k-1} & -\alpha_k & 0 \\ 0 & \cdots & 0 & 0 & r\gamma_k & -\mu_m \end{bmatrix} \tag{2.5}$$

and an analogous formula for (2.2).

We define the matrix $A(x) = A_0 - \beta\, x\, e_\omega\, e_\omega^T$. This a Metzler stable matrix. (A Metzler matrix is a matrix with nonnegative off-diagonal entries [5, 32, 50].)

It is not difficult to check that the nonnegative orthant is positively invariant by (2.4) and that there exists a compact absorbing set K for this system. An absorbing set D is a neighborhood such that a trajectory of the system starting from any initial condition enters and remains in D for a sufficiently large time T.

2.2. Global stability results. We can now give the main result of this section.

THEOREM 2.1. *We consider the system* (2.4) *with the hypothesis* (2.3) *on* φ *satisfied. We define the basic reproduction ratio of the system* (2.1) *and* (2.2) *by*

$$\mathcal{R}_0 = \frac{r\beta x^*}{\mu_m + u\,\beta\,x^*}\,\frac{\gamma_1\cdots\gamma_k}{\alpha_1\cdots\alpha_k}. \tag{2.6}$$

1. *The system* (2.1) *is GAS on* $\mathbb{R}_+^{k+2}$ *(respectively,* (2.2) *on* $\mathbb{R}_+^{k+3}$*) at the DFE* $(x^*, 0, \ldots, 0)$ *if and only if* $\mathcal{R}_0 \le 1$.

2. *If* $\mathcal{R}_0 > 1$*, then the DFE is unstable and there exists a unique endemic equilibrium (EE) in the positive orthant,* $(\bar{x}, \bar{z}) \gg 0$*, given by*

$$\begin{cases} \bar{x} = \dfrac{\mu_m}{\beta\left[r\dfrac{\gamma_1\cdots\gamma_k}{\alpha_1\cdots\alpha_k} - u\right]}, \\ \bar{z} = \varphi(\bar{x})\,(-A_0)^{-1}\,(e_1 - u\,e_\omega). \end{cases} \tag{2.7}$$

Denoting $\alpha^* = -\max_{x\in[0,x^*]}(\varphi'(x))$*, if*

$$u\,\beta\,\varphi(\bar{x}) \le \alpha^*\,\mu_m, \tag{2.8}$$

then the EE is GAS on the nonnegative orthant, except for initial conditions on the x*-axis.*

Proof of Theorem 2.1. To begin we will consider the system (2.1) without gametocytes, i.e., the system (2.4) with A_0 as defined in (2.5). The stability analysis for (2.2) follows easily from the stability analysis of (2.1).

In a first step we will compute $\mathcal{R}_0$. We use our preceding notation and define $A^* = A(x^*)$, i.e., the matrix computed at the equilibrium x^* of φ, which is a stable Metzler matrix. We will use, repeatedly in what follows, the property that if M is a stable Metzler matrix, then $-M^{-1} \ge 0$ [5]. The expression of $\mathcal{R}_0$ is obtained easily by using the next generation matrix of the system (2.1) [9, 15, 16]. We have for the basic reproduction number

$$\mathcal{R}_0 = \beta\,x^*\left\langle -(A^*)^{-1}\,e_1 \mid e_\omega \right\rangle.$$

If we remark that the matrix A^* is the matrix A_0 modified by a rank-one matrix, namely $A^* = A_0 - u\,\beta\,x^*\,e_\omega\,e_\omega^T$, we can use the Sherman–Morrison–Woodbury formula

$$-(A^*)^{-1} = -A_0^{-1} - \frac{u\,\beta\,x^*}{1 + u\,\beta\,x^*\,e_\omega^T\,(-A_0)^{-1}\,e_\omega}\,(-A_0)^{-1}\,e_\omega\,e_\omega^T\,(-A_0)^{-1}$$

or equivalently

$$-(A^*)^{-1} = -A_0^{-1} - \frac{u\,\beta\,x^*}{\mu_m + \beta\,x^*}\,e_\omega\,e_\omega^T\,(-A_0)^{-1}.$$

This shows that $-(A^*)^{-1}$ is obtained from $-A_0^{-1}$ by multiplying the last line of $-A_0^{-1}$ by $\frac{\mu_m}{\mu_m + u\,\beta\,x^*}$. Then we get

$$\mathcal{R}_0 = \beta\,x^*\,\frac{\mu_m}{\mu_m + u\,\beta\,x^*}\left\langle -(A_0)^{-1}\,e_1 \mid e_\omega \right\rangle,$$

and then in computing the last entry of the first column of A_0 we obtain (2.6).

We remark that $\mathcal{R}_0 > 1$ is equivalent to the following threshold condition:

(2.9)
$$\mathcal{T}_0 = \frac{\beta\, x^*}{\mu_m}\left[\mu_m \left\langle -(A_0)^{-1}\, e_1 \mid e_\omega \right\rangle - u\right] = \beta\, x^* \left\langle -(A_0)^{-1}\, (e_1 - u\, e_\omega) \mid e_\omega \right\rangle > 1.$$

We are now ready to analyze the stability of the DFE.

It is well known that if $\mathcal{R}_0 > 1$, then the DFE is unstable [15], which implies that the condition $\mathcal{R}_0 \leq 1$ is necessary for stability.

To prove the sufficiency, in a second step, we consider the following function defined on the nonnegative orthant:

$$V_{DFE}(z) = \beta\, x^* \langle\, e_\omega \mid (-A_0^{-1})z \,\rangle. \tag{2.10}$$

Its time derivative along the trajectories of system (2.4) is

$$\dot{V}_{DFE} = \beta\, x \langle\, e_\omega \mid z \,\rangle\, \beta\, x^* \langle\, e_\omega \mid (-A_0)^{-1}\, (e_1 - u\, e_\omega) \,\rangle - \beta\, x^* \langle\, e_\omega \mid z \,\rangle$$

or equivalently, using the expression of $\mathcal{T}_0$ given in (2.9),

$$\dot{V}_{DFE} = \beta \langle\, e_\omega \mid z \,\rangle\, (\mathcal{T}_0\, x - x^*)\,. \tag{2.11}$$

Now we take as a candidate Liapunov function, defined on the nonnegative orthant minus the hyperplane face $x = 0$,

$$V = (x - x^* \ln x) - x^*(1 - \ln x^*) + V_{DFE}(z).$$

This function is positive definite (relatively to the DFE) on $\mathbb{R}^{k+2}_{+,x>0} = \{(x, y, m) \in \mathbb{R}^{k+2}_{+} \;:\; x > 0\}$. Its time derivative is given by

$$\dot{V} = \frac{x - x^*}{x}\, \varphi(x) - (x - x^*)\, \beta \langle\, e_\omega \mid z \,\rangle + \beta \langle\, e_\omega \mid z \,\rangle\, (\mathcal{T}_0\, x - x^*)$$

or assuming $\mathcal{R}_0 \leq 1$

$$\dot{V} = \frac{x - x^*}{x}\, \varphi(x) + \beta\, x \langle\, e_\omega \mid z \,\rangle\, (\mathcal{T}_0 - 1) \;\leq\; 0.$$

By assumption (2.3) we have $(x - x^*)\varphi(x) \leq 0$ for all $x \geq 0$. Therefore $\dot{V} \leq 0$ for all $(x, z) \in \mathbb{R}^{k+2}_{+,x>0}$, which proves the stability of the DFE. Its attractivity follows from LaSalle's invariance principle [6, 37, 38], since the largest invariant set contained in $\{(x, z) \in \mathbb{R}^{k+2}_{+,x>0} \;:\; \dot{V} = 0\}$ is reduced to the DFE. On the other hand the vector field is strictly entrant on the face $x = 0$. Hence the whole orthant $\mathbb{R}^{k+2}_{+}$ belongs to the region of attraction of the DFE.

Now we assume that $\mathcal{R}_0 > 1$. The equilibria $(\bar{x}, \bar{z})$ of the system, different from the DFE, are determined by the relations

$$\bar{z} = \beta\, \bar{x} \langle\, \bar{z} \mid e_\omega \,\rangle\, (-A_0)^{-1}\, (e_1 - u\, e_\omega).$$

Replacing $\bar{z}$ in $\langle\, \bar{z} \mid e_\omega \,\rangle$ we obtain

$$\langle\, \bar{z} \mid e_\omega \,\rangle = \beta\, \bar{x} \langle\, \bar{z} \mid e_\omega \,\rangle \langle\, (-A_0)^{-1}\, (e_1 - u\, e_\omega) \mid e_\omega \,\rangle. \tag{2.12}$$

If $\langle\, \bar{z} \mid e_\omega \,\rangle = 0$, then $\varphi(\bar{x}) = 0$, we obtain $\bar{x} = x^*$, and hence $\bar{z} = 0$; i.e., the corresponding equilibrium is the DFE. In the other case, i.e., $\langle\, \bar{z} \mid e_\omega \,\rangle \neq 0$, the relation (2.12) gives

$$\beta\, \bar{x} \left\langle\, (-A_0)^{-1}\, (e_1 - u\, e_\omega) \mid e_\omega \,\right\rangle = 1. \tag{2.13}$$

Using $\langle\, (-A_0)^{-1}\, e_\omega \mid e_\omega \,\rangle = \frac{1}{\mu_m}$ we finally have

$$\bar{x} = \frac{\mu_m}{\beta \left[\mu_m \langle\, (-A_0)^{-1}\, e_1 \mid e_\omega \,\rangle - u\right]} = \frac{x^*}{\mathcal{T}_0}.$$

We deduce that if $\mathcal{R}_0 > 1$, then $0 < \bar{x} < x^*$, and hence $\varphi(\bar{x}) > 0$. Therefore

$$\bar{z} = \varphi(\bar{x})\ (-A_0)^{-1}\, (e_1 - u\, e_\omega).$$

The last component of $\bar{z}$, $\langle\, \bar{z} \mid e_\omega \,\rangle = \bar{m}$, is given by

$$\bar{m} = \frac{\varphi(\bar{x})}{\beta\, \bar{x}} > 0.$$

The k first components of $\bar{z}$ are given by the k first components of $\varphi(\bar{x})\ (-A_0)^{-1}\, e_1$. It is straightforward to check that the first column of $(-A_0)^{-1}$ namely $(-A_0)^{-1}\, e_1 \gg 0$, which proves that $\bar{z} \gg 0$. We have then proved that there is a unique EE in the positive orthant if and only if $\mathcal{R}_0 > 1$.

Finally we will prove a sufficient condition for the global asymptotic stability of the EE. To this end we define the following candidate Liapunov function on the positive orthant minus the face corresponding to $x = 0$:

$$V_{EE}(x, y, m) = a(x - \bar{x} \ln x) + \sum_{i=1}^{k} b_i\, (y_i - \bar{y}_i \ln y_i)\ + b_{k+1}\, (m - \bar{m}\ \ln m). \tag{2.14}$$

This function has a unique global minimum in $(\bar{x}, \bar{y}, \bar{m})$. We will choose the coefficients a, b_i, b_{k+1} such that in the computation of $\dot{V}$, the linear terms in y_i and m and the bilinear terms in $x\, m$ cancel. Let us show that it is possible with positive coefficients. To this end we rewrite the function V_{EE} using the notation $z = (y, m)^T$, $\ln z = (\ln z_1, \ln z_2, \ldots, \ln z_{k+1})^T$, and $b = (b_1, \ldots, b_k, b_{k+1})^T$:

$$V_{EE}(x, z) = a(x - \bar{x} \ln x) + \langle\, b \mid z - diag(\bar{z}) \ln z \,\rangle.$$

Consider the block matrix

$$M = \begin{bmatrix} -1 & (e_1 - u\, e_\omega)^T \\ \beta\, \bar{x}\, e_\omega & A_0^T \end{bmatrix}.$$

Using classical Schur complement techniques and the relation (2.13) on $\bar{x}$, we have

$$\begin{aligned} \det(M) &= \det(A_0)[-1 + \beta\, \bar{x} (e_1 - u\, e_\omega)^T\, (-A_0^{-T})\, e_\omega] \\ &= \det(A_0)[-1 + \beta\, \bar{x} \,\langle\, -A_0^{-1}\, (e_1 - u\, e_\omega) \mid e_\omega \,\rangle] = 0. \end{aligned}$$

Since the matrix M is obviously of codimension 1 (A_0 is nonsingular) the kernel of M is of dimension 1. Then there exists $a \in \mathbb{R}$ and $b \in \mathbb{R}^{k+1}$ such that

$$a = (e_1 - u\, e_\omega)^T\, b = \langle\, b \mid e_1 - u\, e_\omega \,\rangle \tag{2.15a}$$

and

$$b = a\,\beta\,\bar{x}\,(-A_0^{-T})\,e_\omega. \tag{2.15b}$$

Since the kernel is one dimensional, a can be chosen arbitrarily. Thanks to the structure of A_0, if $a > 0$, then $b \gg 0$.

The derivative of V along the trajectories of (2.4) is given by

$$\begin{aligned}\dot{V}_{EE} &= a\,\frac{x-\bar{x}}{x}\,\varphi(x) - a\,\beta x\,\langle\, e_\omega \mid z\,\rangle + a\,\beta\,\bar{x}\,\langle\, e_\omega \mid z\,\rangle + \beta\,x\,\langle\, e_\omega \mid z\,\rangle\,\langle\, b \mid e_1 - u\,e_\omega\,\rangle \\ &\quad + \langle\, b \mid A_0 z\,\rangle + \langle\, b \mid \operatorname{diag}(\bar{z})\operatorname{diag}(z)^{-1}\,\dot{z}\,\rangle \\ &= a\,\frac{x-\bar{x}}{x}\,\varphi(x) + \langle\, b \mid \operatorname{diag}(\bar{z})\operatorname{diag}(z)^{-1}\,\dot{z}\,\rangle \\ &\quad + a\,\beta\,\bar{x}\,\langle\, e_\omega \mid z\,\rangle + \langle\, b \mid A_0 z\,\rangle + \beta x\,\langle\, e_\omega \mid z\,\rangle\,\big(\langle\, b \mid e_1 - u\,e_\omega\,\rangle - a\big).\end{aligned}$$

Using the relation (2.15b) we see that

$$\langle\, b \mid A_0\,z\,\rangle = -a\,\beta\,\bar{x}\,\langle\,(A_0^{-T})\,e_\omega \mid A_0 z\,\rangle = -a\,\beta\,\bar{x}\,\langle\, e_\omega \mid z\,\rangle.$$

Therefore the linear terms in z cancel. The same is true for the bilinear terms thanks to the relation (2.15a). Finally we get

$$\dot{V}_{EE} = a\,\frac{x-\bar{x}}{x}\,\varphi(x) + \langle\, b \mid \operatorname{diag}(\bar{z})\operatorname{diag}(z)^{-1}\,\dot{z}\,\rangle.$$

We choose $b_{k+1} = 1 = \langle\, b \mid e_\omega\,\rangle = a\,\beta\,\bar{x}\,\langle\, -A^{-T}\,e_\omega \mid e_\omega\,\rangle = a\,\beta\,\bar{x}\frac{1}{\mu_m}$. In other words $a = \frac{\mu_m}{\beta\,\bar{x}}$. With the hypothesis $\mathcal{R}_0 > 1$ we have $a > 0$, and hence $b \gg 0$ as wanted. With this choice developing $\dot{V}$ gives

$$\begin{aligned}\dot{V}_{EE} &= a\,f(x) - a\mu_x\,x - af(x)\frac{\bar{x}}{x} + a\,\mu_x\,\bar{x} - b_1\,\beta\bar{y}_1\frac{xm}{y_1} - \sum_{i=2}^{k} b_i\gamma_{i-1}y_{i-1}\frac{\bar{y}_i}{y_i} \\ &\quad + \sum_{i=1}^{k} b_i\,\alpha_i\,\bar{y}_i - r\,\gamma_k\,y_k\;\frac{\bar{m}}{m} + u\,\beta\bar{m}x + \mu_m\bar{m}.\end{aligned}$$

We collect some useful relations between our coefficients at the EE. We have from the definitions of a and b, since $b_{k+1} = 1$,

$$\begin{cases} a + u = b_1, \\ b_1\,\alpha_1 = \gamma_1\,b_2, \\ b_2\,\alpha_2 = \gamma_2\,b_3, \\ \cdots \\ b_{k-1}\,\alpha_{k-1} = \gamma_{k-1}\,b_k, \\ b_k\,\alpha_k = r\,\gamma_k. \end{cases} \tag{2.16}$$

From these relations and the properties of the EE $\bar{z}$ we have

$$b_1\,\beta\,\bar{x}\,\bar{m} = b_i\,\alpha_i\,\bar{y}_i = b_i\,\gamma_{i-1}\,\bar{y}_{i-1} = r\,\gamma_k\,\bar{y}_k \tag{2.17}$$

and

$$a\alpha_1\bar{y}_1 = \mu_m\,\bar{m}. \tag{2.18}$$

Replacing, in the expression of $\dot{V}$, $a\mu_x\bar{x}$ by $a\,f(\bar{x}) - a\beta\bar{x}\bar{m} = af(\bar{x}) - a\alpha_1\,\bar{y}_1$ we obtain

$$\dot{V}_{EE} = kr\gamma_k\bar{y}_k + af(\bar{x}) + af(x) + (u\,\beta\bar{x}\bar{m} - a\mu_x\bar{x})\frac{x}{\bar{x}} - af(x)\frac{\bar{x}}{x} - b_1\,\beta\,\bar{x}\,\bar{m}\,\frac{x}{\bar{x}}\,\frac{m}{\bar{m}}\,\frac{\bar{y}_1}{y_1} - \sum_{i=2}^{k} b_i\gamma_{i-1}\bar{y}_{i-1}\frac{y_{i-1}}{\bar{y}_{i-1}}\frac{\bar{y}_i}{y_i} - r\gamma_k\bar{y}_k\frac{y_k}{\bar{y}_k}\frac{\bar{m}}{m}.$$

Using again the relations between the coefficients we get

$$\dot{V}_{EE} = kr\gamma_k\bar{y}_k + af(\bar{x}) + af(x) + (r\gamma_k\bar{y}_k - af(\bar{x}))\frac{x}{\bar{x}} - af(x)\frac{\bar{x}}{x} - r\,\gamma_k\,y_k\,\frac{x}{\bar{x}}\,\frac{m}{\bar{m}}\,\frac{\bar{y}_1}{y_1} - \sum_{i=2}^{k} r\gamma_k\bar{y}_k\frac{y_{i-1}}{\bar{y}_{i-1}}\frac{\bar{y}_i}{y_i} - r\gamma_k\bar{y}_k\frac{y_k}{\bar{y}_k}\frac{\bar{m}}{m}$$

and finally

$$\dot{V}_{EE} = a\left[f(x) + f(\bar{x}) - f(\bar{x})\frac{x}{\bar{x}} - f(x)\frac{\bar{x}}{x}\right] + r\,\gamma_k\,\bar{y}_k\left[k + \frac{x}{\bar{x}} - \frac{x}{\bar{x}}\,\frac{m}{\bar{m}}\,\frac{\bar{y}_1}{y_1} - \sum_{i=2}^{k}\frac{y_{i-1}}{\bar{y}_{i-1}}\frac{\bar{y}_i}{y_i} - \frac{y_k}{\bar{y}_k}\frac{\bar{m}}{m}\right].$$

Now we will use the fact that there exists ξ in the open interval $\xi \in]x, \bar{x}[$ such that $f(x) = f(\bar{x}) + (x - \bar{x})\,f'(\xi)$. Replacing in the preceding expression gives

$$\dot{V}_{EE} = af(\bar{x})\left[2 - \frac{x}{\bar{x}} - \frac{\bar{x}}{x}\right] + a\,f'(\xi)\frac{(x-\bar{x})^2}{x} + r\,\gamma_k\,\bar{y}_k\left[k + \frac{x}{\bar{x}} - \frac{x}{\bar{x}}\,\frac{m}{\bar{m}}\,\frac{\bar{y}_1}{y_1} - \sum_{i=2}^{k}\frac{y_{i-1}}{\bar{y}_{i-1}}\frac{\bar{y}_i}{y_i} - \frac{y_k}{\bar{y}_k}\frac{\bar{m}}{m}\right].$$

Using the relations (2.16)–(2.17) we have

$$af(\bar{x}) = (b_1 - u)f(\bar{x}) = b_1(\mu_x\bar{x} + \beta\bar{x}\bar{m}) - u\,f(\bar{x}) = b_1\,\mu_x\,\bar{x} + r\gamma_k\bar{y}_k - u\,f(\bar{x}).$$

Replacing in the preceding expression of $\dot{V}$ gives

$$\dot{V}_{EE} = (b_1\,\mu_x\,\bar{x} - u\,f(\bar{x}))\,\left[2 - \frac{x}{\bar{x}} - \frac{\bar{x}}{x}\right] + a\,f'(\xi)\frac{(x-\bar{x})^2}{x} + r\,\gamma_k\,\bar{y}_k\left[k + 2 - \frac{\bar{x}}{x} - \frac{x}{\bar{x}}\,\frac{m}{\bar{m}}\,\frac{\bar{y}_1}{y_1} - \sum_{i=2}^{k}\frac{y_{i-1}}{\bar{y}_{i-1}}\frac{\bar{y}_i}{y_i} - \frac{y_k}{\bar{y}_k}\frac{\bar{m}}{m}\right].$$

This can also be written

$$\dot{V}_{EE} = \Phi(x, y, m) = -\left[b_1\,\mu_x\,\bar{x} - u\,f(\bar{x}) - a\,\bar{x}\,f'(\xi)\right]\frac{(x-\bar{x})^2}{x\bar{x}} + r\,\gamma_k\,\bar{y}_k\left[k + 2 - \frac{\bar{x}}{x} - \frac{x}{\bar{x}}\,\frac{m}{\bar{m}}\,\frac{\bar{y}_1}{y_1} - \sum_{i=2}^{k}\frac{y_{i-1}}{\bar{y}_{i-1}}\frac{\bar{y}_i}{y_i} - \frac{y_k}{\bar{y}_k}\frac{\bar{m}}{m}\right]. \tag{2.19}$$

The term between brackets in the last expression of $\dot{V}$ is nonpositive by the inequality between the arithmetical mean and the geometrical mean. Then a sufficient condition for $\dot{V} \leq 0$ is

$$b_1 \mu_x \bar{x} - u f(\bar{x}) - a \bar{x} f'(\xi) \geq 0.$$

Moreover with this condition $\dot{V}$ is negative, except at the EE for the system (2.1). This proves the global asymptotic stability of the EE on the positive orthant for the system (2.1).

The vector field associated with the system is strictly entrant on the faces of the orthant, except the x-axis, where it is tangent. The basin of attraction of the EE is then the orthant, except the x-axis, which is the stable manifold of the DFE.

Using the function $\varphi(x) = f(x) - \mu_x x$ the preceding condition is equivalent to

$$u \varphi(\bar{x}) \leq -a \bar{x} \varphi'(\xi),$$

or equivalently, replacing a by its value $a = \frac{\mu_m}{\beta \bar{x}}$, the condition becomes

$$u \beta \varphi(\bar{x}) \leq -\mu_m \varphi'(\xi).$$

Setting $\alpha^* = -\max_{x \in [0,x^*]} \varphi'(x)$ a sufficient condition for global asymptotic stability of the EE is

$$\mathcal{R}_0 > 1 \quad \text{and} \quad u \beta \varphi(\bar{x}) \leq \mu_m \alpha^*.$$

We have proved the theorem for the system without gametocytes. We have seen that $\mathcal{R}_0$ does not depend on the production of gametocytes. If $\mathcal{R}_0 \leq 1$, it is easy, integrating the linear stable y_{k+1} equations of (2.2) from the solutions of (2.1), to see that the DFE is asymptotically stable and that all the trajectories converge to the equilibrium. The same argument is used when $\mathcal{R}_0 > 1$. This ends the proof of Theorem 2.1. □

Remark 1. If this model is a model for a within-host model of malaria, each coefficient α_i is made of the mortality of the i-class and the rate of transmission in the $i+1$-class: $\alpha_i = \mu_i + \gamma_i$. This implies that $\gamma_i \leq \alpha_i$. We do not need this assumption, and our conclusions are valid for our more general model. The only hypothesis is that the parameters of the system are positive.

Remark 2. In the proof of Theorem 2.1 the quantity

$$\beta x^* \left\langle -(A_0)^{-1} (e_1 - u e_\omega) \mid e_\omega \right\rangle,$$

which we have called $\mathcal{T}_0$ when $\mathcal{R}_0 > 1$, plays a prominent role. When $\mathcal{R}_0 \leq 1$ and $u \neq 0$ three cases occur: $0 < \mathcal{T}_0 \leq 1$ or $\mathcal{T}_0 < 0$ or $\mathcal{T}_0 = 0$.

In the two first cases we can define $\bar{x} = \frac{x^*}{\mathcal{T}_0}$, and we obtain an equilibrium $(\bar{x}, \bar{z})$ of the system which is not in the nonnegative orthant (either $\bar{x} < 0$ or $\bar{z} < 0$).

In the third case, the computations, done in the proof of Theorem 2.1, for the research of an equilibrium show that $\langle z \mid e_\omega \rangle = 0$, and hence $z = 0$, and finally the equilibrium is the DFE $(x^*, 0)$.

We introduce a definition of $\mathcal{T}_0$ that will simplify future computations. The case $\mathcal{T}_0 = 0$ is special, since $\mathcal{T}_0 = \frac{x^*}{\bar{x}}$ is no longer true. However this case can be thought,

by convention and misuse of language, as $\bar{x} = +\infty$.

DEFINITION 2.2. *We define for the system* (2.1) *the threshold*

$$\mathcal{T}_0 = \frac{x^*}{\dfrac{\mu_m}{\beta\left[r\dfrac{\gamma_1\cdots\gamma_k}{\alpha_1\cdots\alpha_k} - u\right]}} = \beta\, x^* \left\langle -(A_0)^{-1}\,(e_1 - u\, e_\omega) \mid e_\omega \right\rangle. \tag{2.20}$$

When $\mathcal{T}_0 \neq 0$ *we have also* $\mathcal{T}_0 = \frac{x^*}{\bar{x}}$.

Remark 3. It should be pointed out that the kind of Liapunov function defined by (2.14) has a long history of application to Lotka–Volterra models [18, 19] and was originally discovered by Volterra himself, although he did not use the vocabulary and the theory of Liapunov functions. Since epidemic models are "Lotka–Volterra" like models, the pertinence of this function is not surprising. Similar Liapunov functions have been used in epidemiology [4, 34, 35, 46, 63], although with different parameters. We have already used this kind of function in a simplified version of this paper in [1].

2.3. Comparison with known results. Our stability result improves the one of De Leenheer and Smith [13] in two directions:

1. We introduce n stages for latent classes.
2. Our sufficient condition for the global asymptotic stability of the endemic equilibrium is weaker than the one provided in [13]; for instance the sufficient condition given in Theorem 2.1 is satisfied for malaria parameters given in [3], while the condition of [13] is not satisfied.

2.4. Application to the original AMG model [3]. The original Anderson–May–Guptka model is a three dimensional system (1.1) which has the same form as system (2.1) with $f(x) = \Lambda$. The sufficient condition (2.8) applied to the AMG model (1.1) can be written

$$\beta\Lambda \leq \frac{r}{r-1}\,\mu_x\,\mu_m. \tag{2.21}$$

For the system (1.1), it is possible to give a weaker sufficient stability condition.

PROPOSITION 2.3. *If* $\mathcal{R}_0 > 1$ *and* $\beta\Lambda \leq (\sqrt{r} + \sqrt{r-1})^2\,\mu_x\,\mu_m$, *then the EE is a GAS steady state for system* (1.1) *with respect to initial states not on the x-axis.*

Since in general the parameter r is larger than 2 (see, for instance, [28]), we have $(\sqrt{r} + \sqrt{r-1})^2 > \frac{r}{r-1}$.

Proof. Thanks to the computations done before, we have for system (1.1)

$$\dot{V}_{EE} = (r-1)\Lambda\left[2 - \frac{x}{\bar{x}} - \frac{\bar{x}}{x}\right] + r\,\mu_y\,\bar{y}\left[1 + \frac{x}{\bar{x}} - \frac{y}{\bar{y}}\frac{\bar{m}}{m} - \frac{x}{\bar{x}}\frac{m}{\bar{m}}\frac{\bar{y}}{y}\right].$$

Define $X = \frac{x}{\bar{x}}$ and $S = \frac{y}{\bar{y}}\frac{\bar{m}}{m}$. Then one can write

$$\begin{aligned}\dot{V}_{EE} &= -(r-1)\Lambda\tfrac{(X-1)^2}{X} + r\,\mu_y\,\bar{y}\left(1 + X - S - \tfrac{X}{S}\right)\\ &= -(r-1)\Lambda\tfrac{(X-1)^2}{X} + r\,\mu_y\,\bar{y}\;\Psi(X,S).\end{aligned}$$

We have $\Psi(X,S) \geq 0 \Leftrightarrow X \leq S \leq 1$ or $X \geq S \geq 1$. On the other hand $\Psi(X,S) \leq \Psi(X,\sqrt{X}) = (\sqrt{X}-1)^2$. Therefore

$$\begin{aligned}&\dot{V}_{EE} \leq (r-1)\Lambda(\sqrt{X}-1)^2\left(\tfrac{r\,\mu_y\,\bar{y}}{(r-1)\Lambda} - \left(1 + \tfrac{1}{\sqrt{X}}\right)^2\right),\\ &\dot{V}_{EE} \leq (r-1)\Lambda(\sqrt{X}-1)^2\left(\sqrt{\tfrac{r\,\mu_y\,\bar{y}}{(r-1)\Lambda}} + 1 + \tfrac{1}{\sqrt{X}}\right)\left(\sqrt{\tfrac{r\,\mu_y\,\bar{y}}{(r-1)\Lambda}} - 1 - \tfrac{1}{\sqrt{X}}\right).\end{aligned} \tag{2.22}$$

We have $\frac{\mu_y\,\bar{y}}{\Lambda} = \frac{\Lambda-\mu_x\bar{x}}{\Lambda} < 1$. Hence for $X \le X^* = \frac{x^*}{\bar{x}} = \frac{(r-1)\beta}{\mu_m}x^*$ we have the following: $\sqrt{\frac{r\,\mu_y\,\bar{y}}{(r-1)\Lambda}} - 1 - \frac{1}{\sqrt{X}} < \sqrt{\frac{r}{(r-1)}} - \frac{\sqrt{\mu_m}}{\sqrt{(r-1)\beta x^*}} - 1 \le 0$, since by assumption $\frac{\beta x^*}{\mu_m} = \frac{\beta\Lambda}{\mu_x\mu_m} \le (\sqrt{r}+\sqrt{r-1})^2$. Therefore, the derivative of V_{EE} along the trajectories of system (1.1) is negative definite on the set $\mathcal{D}_0 = \{(x,y,m) \in \mathbb{R}^3_+ \ : \ 0 < x \le x^*,\ y > 0,\ m > 0\}$. By continuity, there exists $\epsilon > 0$ such that $\dot{V}_{EE}$ is negative definite on the set $\mathcal{D}_\epsilon = \{(x,y,m) \in \mathbb{R}^3_+ \ : \ 0 < x < x^* + \epsilon,\ y > 0,\ m > 0\}$. The global asymptotic stability of the EE follows from the fact that $\mathcal{D}_\epsilon$ is an absorbing set for system (1.1). □

3. The general case: n strains with k classes of parasitized erythrocytes. We define the following system with k classes and n parasite strains:

$$
\left\{
\begin{array}{l}
\dot{x} = f(x) - \mu_x x - \ x \displaystyle\sum_{i=1}^{n} \beta_i\, m_i = \varphi(x) - \ x \displaystyle\sum_{i=1}^{n} \beta_i\ m_i \\
\text{and for } i = 1, \ldots, n, \\
\dot{y}_{1,i} = \beta_i x\, m_i - \alpha_{1i}\, y_{1,i}, \\
\dot{y}_{2,i} = \gamma_{1,i}\, y_{1,i} - \alpha_{2,i}\, y_{2,i}, \\
\ldots \\
\dot{y}_{k,i} = \gamma_{k-1,i}\, y_{k-1,i} - \alpha_{k,i}\, y_{k,i}, \\
\dot{g}_i = \delta_i\, y_{k,i} - \mu_{g_i}\, g_i, \\
\dot{m}_i = r_i\, \gamma_{k,i}\, y_{k,i} - \mu_{m_i}\, m_i - u\, \beta_i\, x\, m_i.
\end{array}
\right. \tag{3.1}
$$

As in preceding sections we rewrite the system as

$$
\left\{
\begin{array}{l}
\dot{x} = \varphi(x) - \ x \displaystyle\sum_{i=1}^{n} \beta_i \left\langle\, z_i \mid e_{i,\omega} \,\right\rangle \\
\text{and for } i = 1, \ldots, n, \\
\dot{z}_i = x\, \beta_i \left\langle\, z_i \mid e_{i,\omega} \,\right\rangle e_{i,1} + A_i\, z_i - u\, x\, \beta_i \left\langle\, z_i \mid e_{i,\omega} \,\right\rangle e_{i,\omega},
\end{array}
\right. \tag{3.2}
$$

where the matrix A_i is the analogous of the matrix A_0 defined in section 2.2, but corresponding to the genotype i, and the vectors $e_{i,1}$ and $e_{i,\omega}$ are defined accordingly. We drop the index 0 in A for readability.

THEOREM 3.1. *We consider the system* (3.1) *with the hypotheses* (2.3) *satisfied. We define the basic reproduction ratio* $\mathcal{R}_0$ *of the system* (3.1) *by*

$$\mathcal{R}_0^i = \frac{r_i \beta_i x^*}{\mu_{m_i} \ + u\, \beta_i\, x^*} \frac{\gamma_{1,i} \cdots \gamma_{k,i}}{\alpha_{1,i} \cdots \alpha_{k,i}}$$

and

$$\mathcal{R}_0 = \max_{i=1,\ldots,n} \mathcal{R}_0^i.$$

1. *The system* (3.1) *is GAS on* $\mathbb{R}_+$ *at the DFE* $(x^*, 0, \ldots, 0)$ *if and only if* $\mathcal{R}_0 \le 1$.

2. *If* $\mathcal{R}_0 > 1$, *then the DFE is unstable. If* $R_0^i > 1$, *there exists an EE in the nonnegative orthant corresponding to the genotype* i, *the value for the other indexes*

$j \neq i$ are $y_j = m_j = 0$, and

$$\text{(3.3)} \qquad \begin{cases} \bar{x}_i = \dfrac{\mu_{m_i}}{\beta_i \left[r_i \dfrac{\gamma_{1,i} \cdots \gamma_{k,i}}{\alpha_{1,i} \cdots \alpha_{k,i}} - u \right]}, \\ \bar{z}_i = \varphi(\bar{x}_i)\ (-A_i)^{-1} (e_{i,1} - u\, e_{i,\omega}), \\ \bar{g}_i = \dfrac{\delta_i}{\mu_{g_i}} \bar{z}_{i,k}, \end{cases}$$

where we denote by $\bar{z}_{i,k}$ the kth *component of $\bar{z}_i$.*

3. *We assume $\mathcal{R}_0 > 1$. We define $\mathcal{T}_0^i$ as in Definition* 2.2. *We assume that the generic conditions $\mathcal{T}_0^i \neq \mathcal{T}_0^j$ are satisfied for $i \neq j$. We suppose that the genotypes have been indexed such that*

$$\mathcal{T}_0^1 > \mathcal{T}_0^2 \geq \cdots \geq \mathcal{T}_0^n.$$

Then the EE corresponding to $\bar{x}_1$ is asymptotically stable and the EEs corresponding to $\bar{x}_j$ for $j \neq 1$ (for those which are in the nonnegative orthant) are unstable.

4. *We assume that the preceding hypothesis $\mathcal{T}_0^1 > \mathcal{T}_0^j$ is satisfied with $\mathcal{R}_0 > 1$. We denote it by $\alpha^* = -\max_{x \in [0, x^*]} (\varphi'(x))$. Then if*

$$u\, \beta_1\, \varphi(\bar{x}_1) \leq \mu_{m_1}\, \alpha^*,$$

the equilibrium $(\bar{x}_1, \bar{y}_1, \bar{m}_1, \bar{g}_1, 0, \ldots, 0)$ is GAS on the orthant minus the x-axis and the faces of the orthant defined by $y_1 = m_1 = g_1 = 0$. In other words the most virulent strain is the winner and the other strains go extinct.

Proof. As in Theorem 2.1 there exists a forward invariant compact absorbing set in the nonnegative orthant for the system (3.1), and hence all the forward trajectories are bounded. The variables g_i do not affect the dynamical evolution of the variables x, $y_{i,j}$, m_i, and so we can consider the system without the production of gametocytes. We use the Liapunov function

$$V_{DFE}(z) = \sum_{i=1}^{n} V_{DFE}(z_i) = \sum_{i=1}^{n} \beta_i\, x^*\, \langle\, e_{i,\omega} \mid (-A_i^{-1}) z_i \,\rangle.$$

Using the system written as (3.2) and the computation (2.11) we easily obtain

$$\dot{V}_{DFE} = \sum_{i=1}^{n} \beta_i \,\langle\, e_{i,\omega} \mid z_i \,\rangle\, \left(\mathcal{T}_0^i\, x - x^* \right).$$

Now we define the Liapunov function on the nonnegative orthant minus the hyperplane face $x = 0$

$$V(x, z) = (x - x^*\, \ln x) - x^*(1 - \ln x^*) + \sum_{i=1}^{n} V_{DFE}(z_i)$$

which gives

$$\begin{aligned} \dot{V} &= \frac{x - x^*}{x}\, \varphi(x) + \sum_{i=1}^{n} x^* \beta_i \,\langle\, z_i \mid e_{i,\omega} \,\rangle - \sum_{i=1}^{n} x \beta_i \,\langle\, z_i \mid e_{i,\omega} \,\rangle \\ &\quad + \sum_{i=1}^{n} \beta_i \,\langle\, e_{i,\omega} \mid z_i \,\rangle\, (\mathcal{T}_0^i\, x - x^*) \\ &= \frac{x - x^*}{x}\, \varphi(x) + \sum_{i=1}^{n} \beta_i \,\langle\, e_{i,\omega} \mid z_i \,\rangle\, x\, \left(\mathcal{T}_0^i\, - 1 \right). \end{aligned}$$

Since $\mathcal{R}_0^i \leq 1$ for all index i, we have $\mathcal{T}_0^i \leq 1$, and hence $\dot{V} \leq 0$. The conclusion follows by Lasalle's invariance principle and consideration of the boundary of the positive orthant.

Now we assume $\mathcal{R}_0 > 1$. The instability of the DFE follows from the properties of $\mathcal{R}_0$ [15]. We assume that the genotypes are indexed such that their corresponding threshold are in decreasing order $\mathcal{T}_0^1 > \mathcal{T}_0^2 \geq \cdots \geq \mathcal{T}_0^n$.

We will define a Liapunov function on the nonnegative orthant minus the manifold defined by the equations $x = y_1 = m_1 = 0$. For this we need to recall the definition of the function $V_{EE}(x, y_1, m_1)$ defined in (2.14):

$$V_{EE}(x, y, m) = a(x - \bar{x} \ln x) + \sum_{i=1}^{k} b_{1,i} \left(y_{1,i} - \bar{y}_{1,i} \ln y_{1,i}\right) + b_{1,k+1} \left(m_1 - \bar{m}_1 \ln m_1\right).$$

The coefficients $(a, b_{1,i})$ are positive and defined from A_1 as in the proof of Theorem 2.1 from section 2.2. We also use the function V_{EE} defined in (2.10) to consider

$$V(x, z) = \mathcal{T}_0^1 \, V_{EE}(x, z_1) + a \sum_{i=2}^{n} V_{DFE}(z_i)$$

or equivalently

$$V(x, z) = \mathcal{T}_0^1 \, V_{EE}(x, z_1) + a \sum_{i=2}^{n} \beta_i \, x^* \left\langle \, e_{i,\omega} \mid (-A_i^{-1}) \, z_i \, \right\rangle.$$

Using the relation (2.19) and (2.11), we can compute the derivative of V along the trajectories of (3.2):

$$\begin{aligned} \dot{V} = \mathcal{T}_0^1 \Phi(x, z_1) + \, & a \, \mathcal{T}_0^1 \sum_{i=2}^{n} \beta_i \, \bar{x}_1 \left\langle \, e_{i\omega} \mid z_i \, \right\rangle - a \, \mathcal{T}_0^1 \sum_{i=2}^{n} \beta_i \, x \left\langle \, e_{i\omega} \mid z_i \, \right\rangle \\ & + a \sum_{i=2}^{n} \beta_i \left\langle \, z_i \mid e_{i,\omega} \, \right\rangle \left(\mathcal{T}_0^i \, x - x^*\right). \end{aligned}$$

Using $\mathcal{T}_0^1 \, \bar{x}_1 = x^*$ from the Definition 2.2 for the threshold we get

$$\dot{V} = \mathcal{T}_0^1 \Phi(x, z_1) + a \sum_{i=2}^{n} \beta_i \left\langle \, z_i \mid e_{i,\omega} \, \right\rangle x \, \left(\mathcal{T}_0^i - \mathcal{T}_0^1\right) \leq 0.$$

By Liapunov theorem this ends the proof for the stability. The global asymptotic stability is obtained by a straightforward use of LaSalle's invariance principle, which ends the proof of Theorem 3.1. □

Remark 4. In the nongeneric case it can be shown, with the help of the Liapunov functions used in the theorem, that there exists a continuum of stable EE. We omit the proof.

In the generic case, the dynamics of the system are completely determined. The nonnegative orthant is stratified in the union of stable manifolds corresponding to the different equilibria. Only the equilibrium corresponding to the winning strain has a basin of attraction with a nonempty interior.

Remark 5. We have proved that the most virulent strain, that is, the strain which maximizes its respective threshold $\mathcal{T}_0^i$, eliminates the other. We obtain the

same kind of result as in [7], where the authors consider a SIR model with n strains of parasite. They consider that infection by one parasite strain excludes superinfection by other strains (this is also our case) and induces permanent immunity against all strains in case of recovery. They also guarantee limited population by considering a recruitment depending on the density in a monotone decreasing way. They find that the strain which maximizes the basic reproduction ratio eliminates the others. In the case considered by the authors, actually, using our notation, $\mathcal{R}_0 = \frac{x^*}{\bar{x}}$. In fact in this model $\mathcal{T}_0$ and $\mathcal{R}_0$ coincide. This is also the case in our model when $u = 0$. Hence our result compares with the result of [7]. However in the case $u \neq 0$ this is $\mathcal{T}_0^i$, and not $\mathcal{R}_0^i$, which distinguishes the fate of the strain. Our result is then different from [7], where this role is devoted to $\mathcal{R}_0$. The same kind of remarks apply to [10] and [11].

Remark 6. In our model the chains are of equal length for each strain. If the chains are of unequal length, the proof is unchanged. We use equal length for notational convenience. A reason to have unequal length could be to model different behavior for two different strains of the parasite.

4. Conclusion. In this article we have given a parasitic within-host model and have provided a stability analysis of this model.

This model incorporates a number k of compartments for the parasitized target cells and considers n strains for the parasite. The rationale for including multicompartments can be multiple. One reason is to take into account biological reasons, e.g., consideration of morphological or age classes. The second is for behavioral modeling reasons, e.g., to model delays described by gamma distribution functions.

This model has been conceived from malaria infection, since it is well grounded that malaria is a multistrain infection. However other parasitic infections can be considered by this model.

We prove that if the basic reproduction number satisfies $\mathcal{R}_0 \leq 1$, then the DFE is GAS; i.e., the parasite is cleared from the host. Our stability result when $\mathcal{R}_0 > 1$ can be summarized as a competitive exclusion principle. To each i-strain we associate an individual threshold condition $\mathcal{T}_0^i$ as in Definition 2.2. If $\mathcal{R}_0 > 1$, if one strain has its individual threshold strictly larger than the thresholds of the other strains and if a mild sufficient condition is satisfied (for a constant recruitment, i.e., $f(x) = \Lambda$, this condition is simply $u\beta\Lambda \leq \frac{r}{r-u}\,\mu_x\mu_m$), then there exists a GAS equilibrium on the positive orthant. This equilibrium corresponds to the extinction of all strains, except the strain with the largest threshold. This winning strain maximizes the threshold and not its individual basic reproduction number, which is different from previous analogous results of the literature.

REFERENCES

[1] P. Adda, J. L. Dimi, A. Iggidr, J. C. Kamgang, G. Sallet, and J. J. Tewa, *General models of host-parasite systems. Global analysis*, Discrete Contin. Dyn. Syst. Ser. B, to appear.

[2] R. M. Anderson, *Complex dynamic behaviours in the interaction between parasite population and the host's immune system*, Int. J. Parasitol, 28 (1998), pp. 551–566.

[3] R. M. Anderson, R. M. May, and S. Gupta, *Non-linear phenomena in host-parasite interactions*, Parasitology, 99 (1989), pp. 59–79.

[4] A. Beretta and V. Capasso, *On the general structure of epidemic systems. Global asymptotic stability*, Comput. Math. Appl. Ser. A, 12 (1986), pp. 677–694.

[5] A. Berman and R. J. Plemmons, *Nonnegative Matrices in the Mathematical Sciences*, SIAM, Philadelphia, 1994.

[6] N. P. Bhatia and G. P. Szegö, *Dynamical Systems: Stability Theory and Applications*, Springer-Verlag, Berlin, New York, 1967.

[7] H. J. Bremermann and H. R. Thieme, *A competitive exclusion principle for pathogen virulence*, J. Math. Biol., 27 (1989), pp. 179–190.
[8] G. J. Butler, H. S. B. Hsu, and P. Waltman, *Coexistence of competing predator in a chemostat*, J. Math. Biol., 17 (1983), pp. 133–151.
[9] C. Castillo-Chavez, Z. Feng, and W. Huang, *On the computation of R_0 and its role on global stability*, in Mathematical Approaches for Emerging and Reemerging Infectious Diseases: An Introduction (Minneapolis, MN, 1999), IMA Vol. Math. Appl. 125, Springer-Verlag, New York, 2002, pp. 229–250.
[10] C. Castillo-Chavez, W. Huang, and J. Li, *Competitive exclusion in gonorrhea models and other sexually transmitted diseases*, SIAM J. Appl. Math., 56 (1996), pp. 494–508.
[11] C. Castillo-Chavez, W. Huang, and J. Li, *Competitive exclusion and coexistence of multiple strains in an SIS STD model*, SIAM J. Appl. Math., 59 (1999), pp. 1790–1811.
[12] W. E. Collins and G. M. Jeffery, *A retrospective examination of the patterns of recrudescence in patients infected with plasmodium falciparum*, Am. J. Trop. Med. Hyg., 61 (1999), pp. 44–48.
[13] P. De Leenheer and H. L. Smith, *Virus dynamics: A global analysis*, SIAM J. Appl. Math., 63 (2003), pp. 1313–1327.
[14] H. H. Diebner, M. Eichner, L. Molineaux, W. E. Collins, G. M. Jeffery, and K. Dietz, *Modelling the transition of asexual blood stages of Plasmodium falciparum to gametocytes*, J. Theoret. Biol., 202 (2000), pp. 113–127.
[15] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., 28 (1990), pp. 365–382.
[16] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *Mathematical Epidemiology of Infectious Diseases Model Building, Analysis and Interpretation*, Wiley Ser. Math. Comput. Biol., John Wiley and Sons, Chichester, 2000.
[17] K. Dietz, *Epidemiologic interference of virus population*, J. Math. Biol., 8 (1979), pp. 291–300.
[18] B. S. Goh, *Global stability in two species interactions*, J. Math. Biol., 3 (1976), pp. 313–318.
[19] B. S. Goh, *Global stability in many-species systems*, Amer. Natur., (1977), pp. 135–143.
[20] M. B. Gravenor and D. Kwiatkowski, *An analysis of the temperature effects of fever on the intra-host population dynamics of plasmodium falciparum*, Parasitology, 117 (1998), pp. 97–105.
[21] 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.
[22] M. B. Gravenor, A. L. Lloyd, P. G. Kremsner, M. A. Missinou, M. English, K. Marsh, and D. Kwiatkowski, *A model for estimating total parasite load in falciparum malaria patients*, J. Theoret. Biol., 217 (2002), pp. 137–48.
[23] M. B. Gravenor, A. R. McLean, and D. Kwiatkowski, *The regulation of malaria parasitaemia: Parameter estimates for a population model*, Parasitology, 110 (1995), pp. 115–122.
[24] M. B. Gravenor, M. B. van Hensbroek, and D. Kwiatkowski, *Estimating sequestered parasite population dynamics in cerebral malaria*, Proc. Natl. Acad. Sci. USA, 95 (1998), pp. 7620–7624.
[25] B. Hellriegel, *Modelling the immune response to malaria with ecological concepts: Short-term behaviour against long-term equilibrium*, Proc. R. Soc. Lond. Ser. B Biol. Sci., 250 (1992), pp. 249–256.
[26] H. W. Hethcote and H. R. Thieme, *Stability of the endemic equilibrium in epidemic models with subpopulations*, Math. Biosci., 75 (1985), pp. 205–227.
[27] H. W. Hethcote, *The mathematics of infectious diseases*, SIAM Rev., 42 (2000), pp. 599–653.
[28] C. Hetzel and R. M. Anderson, *The within-host cellular dynamics of bloodstage malaria: Theoretical and experimental studies*, Parasitology, 113 (1996), pp. 25–38.
[29] M. W. Hirsch, *The dynamical systems approach to differential equations*, Bull Amer. Math. Soc. (N.S.), 11 (1984), pp. 1–64.
[30] M. B. Hoshen, R. Heinrich, W. D. Stein, and H. Ginsburg, *Mathematical modelling of the within-host dynamics of Plasmodium falciparum*, Parasitology, 121 (2001), pp. 227–235.
[31] J. A. Jacquez, *Compartmental Analysis in Biology and Medicine*, Biomedware, Ann Arbor, MI, 1996.
[32] J. A. Jacquez and C. P. Simon, *Qualitative theory of compartmental systems*, SIAM Rev., 35 (1993), pp. 43–79.
[33] J. A. Jacquez, C. P. Simon, and J. Koopman, *Core groups and the R_0s for subgroups in heterogeneous SIS and SI models*, in Epidemics Models: Their Structure and Relation to Data, D. Mollison, ed., Cambridge University Press, Cambridge, UK, 1996, pp. 279–301.

[34] A. Korobeinikov and G. C. Wake, *Lyapunov functions and global stability for SIR and SIRS and SIS epidemiolgical models*, Appl. Math. Lett., 15 (2002), pp. 955–961.
[35] A. Korobeinikov and P. K. Maini, *A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence*, Math. Biosci. Eng., 1 (2004), pp. 57–60.
[36] A. Lajmanovich and J. A. Yorke, *A deterministic model for gonorrhea in a nonhomogeneous population*, Math. Biosci., 28 (1976), pp. 221–236.
[37] J. P. LaSalle and S. Lefschetz, *Stability by Liapunov's Direct Method with Applications*, Academic Press, New York, 1961.
[38] J. P. LaSalle, *The Stability of Dynamical Systems*, CBMS-NSF Regional Conf. Ser. in Appl. Math. 25, SIAM, Philadelphia, 1976.
[39] S. A. Levin and D. Pimentel, *Selection of intermediate rates increase in parasite-host systems*, Amer. Natur., (1981), pp. 308–315.
[40] M. Y. Li, J. R. Graef, L. Wang, and J. Karsai, *Global dynamics of a SEIR model with varying total population size*, Math. Biosci., 160 (1999), pp. 191–213.
[41] M. Y. Li, J. S. Muldowney, and P. van den Driessche, *Global stability for the SEIR model in epidemiology*, Math. Biosci., 125 (1995), pp. 155–164.
[42] M. Y. Li, J. S. Muldowney, and P. van den Driessche, *Global stability of SEIRS models in epidemiology*, Can. Appl. Math. Q., 7 (1999), pp. 409–425.
[43] M. Y. Li and J. S. Muldowney, *Global stability for the SEIR model in epidemiology*, Math. Biosci., 125 (1995), pp. 155–164.
[44] M. Y. Li and J. S. Muldowney, *A geometric approach to global-stability problems*, SIAM J. Math. Anal., 27 (1996), pp. 1070–1083.
[45] M. Y. Li, H. L. Smith, and L. Wang, *Global dynamics of an SEIR epidemic model with vertical transmission*, SIAM J. Appl. Math., 62 (2001), pp. 58–69.
[46] X. Lin and J. W.-H. So, *Global stability of the endemic equilibrium and uniform persistence in epidemic models with subpopulations*, J. Aust. Math. Soc. Ser. B, 34 (1993), pp. 282–295.
[47] A. L. Lloyd, *The dependence of viral parameter estimates on the assumed viral life cycle: Limitations of studies of viral load data*, Proc. R. Soc. Lond. Ser. B Biol. Sci., (2001), pp. 847–854.
[48] A. L. Lloyd, *Destabilization of epidemic models with the inclusion of realistic distributions of infectious periods*, Proc. R. Soc. Lond. Ser. B Biol. Sci., 268 (2001), pp. 985–993.
[49] A. L. Lloyd, *Realistic distributions of infectious periods in epidemic models: Changing patterns of persistence and dynamics*, Theor. Popul. Biol., 60 (2001), pp. 59–71.
[50] D. G. Luenberger, *Introduction to dynamic systems. Theory, models, and applications*, John Wiley and Sons, New York, 1979.
[51] N. MacDonald, *Time Lags in Biological Models*, Springer-Verlag, Berlin, New York, 1978.
[52] D. P. Mason, F. E. McKenzie, and W. H. Bossert, *The blood-stage dynamics of mixed plasmodium malariae-plasmodium falciparum infections*, J. Theoret. Biol., 198 (1999), pp. 549–566.
[53] R. M. May and R. M. Anderson, *Epidemiology and genetics in the coevolution of parasites and hosts*, Proc. R. Soc. Lond. Ser. B. Biol. Sci., 219 (1983), pp. 281–313.
[54] J. Maynard Smith, *Models in Ecology*, Cambridge University Press, Cambridge, UK, 1974.
[55] F. E. McKenzie and W. H. Bossert, *The dynamics of plasmodium falciparum blood-stage infection*, J. Theoret. Biol., 188 (1997), pp. 127–140.
[56] F. E. McKenzie and W. H. Bossert, *The optimal production of gametocytes by plasmodium falciparum*, J. Theoret. Biol., 193 (1998), pp. 419–428.
[57] P. G. McQueen and F. E. McKenzie, *Age-structured red blood cell susceptibility and the dynamics of malaria infections*, Proc. Natl. Acad. Sci. USA, 101 (2004), pp. 9161–9166.
[58] L. Molineaux, H. H. Diebner, M. Eichner, W. E. Collins, G. M. Jeffery, and K. Dietz, *Plasmodium falciparum parasitaemia described by a new mathematical model*, Parasitology, 122 (2001), pp. 379–391.
[59] L. Molineaux and K. Dietz, *Review of intra-host models of malaria*, Parassitologia, 41 (2000), pp. 221–231.
[60] M. A. Nowak and R. M. May, *Virus Dynamics. Mathematical Principles of Immunology and Virology*, Oxford University Press, Oxford, UK, 2000.
[61] A. S. Perelson, D. E. Kirschner, and R. De Boer, *Dynamics of HIV infection of CD4+ T cells*, Math. Biosci., 114 (93), pp. 81–125.
[62] A. S. Perelson and P. W. Nelson, *Mathematical analysis of HIV-1 dynamics in vivo*, SIAM Rev., 41 (1999), pp. 3–44.
[63] J. Prüss, L. Pujo-Mejouet, G. F. Webb, and R. Zacher, *Analysis of a model for the dynamics of prions*, Discrete Contin. Dyn. Syst. Ser. B, 6 (2006), pp. 225–235.

[64] 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, 409–410.

[65] C. P. Simon, J. A. Jacquez, and J. S. Koopman, *A Lyapunov function approach to computing* R_0, in Models for Infectious Human Diseases: Their Structure and Relation to Data, V. Isham and G. Medley, eds., Cambridge University Press, Cambridge, UK, 1996, pp. 311–314.

[66] J. Swinton, *The dynamics of blood-stage malaria: Modelling strain specific and strain transcending immunity*, in Models for Infectious Human Diseases: Their Structure and Relation to Data, V. Isham and G. Medley, eds., Cambridge University Press, Cambridge, UK, 1996, pp. 210–212.

[67] H. R. Thieme, *Global asymptotic stability in epidemic models*, in Equadiff 82, Lecture Notes in Math 1017, W. Knobloch and K. Schmitt, eds., Springer-Verlag, Berlin, 1983, pp. 608–615.

[68] H. R. Thieme, *Mathematics in Population Biology*, Princeton Ser. Theor. Comput. Biol., Princeton University Press, Princeton, NJ, 2003.