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# Differential preferences for RBCs is key for *Plasmodium* species evolutionary diversity within human host

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## Abstract

*Plasmodium* species exhibit differential preferences for red blood cells (RBCs) of different ages. From a fundamental standpoint, we develop an original approach to show that such a differential ecological characteristic of *Plasmodium* species within their human host is fundamental to capture species diversity within the same host. This is based on a within-host malaria infection model coupled with a discrete maturity stage of RBCs production. The parasitized RBCs stage is an age-structured model with a continuous variable representing the time since the concerned RBC is parasitized. We show that with such difference in the RBCs preferences, the long-term coexistence of different species is possible under a certain condition, basically based on a suitable order on the basic reproduction numbers of each species. In particular, we show that the dynamical behavior of the model is not trivial and can range from the extinction of all species, the persistence of a single species, to the coexistence of more than one species. We also describe how our general analysis can be applied in some co-infection configurations including three malaria species: *P. Falciparum*, *P. Vivax*, and/or *P. Malariae*. This improved understanding of the within-host parasite multiplication in a context of mixed *Plasmodium* species interactions.

**Key words.** Malaria; RBC preference; Within-host coexistence; Mathematical modelling; Non-linear dynamical system

## 1 Introduction

Human malaria is caused by diverse species of *Plasmodium* spp. [36] (e.g. *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*). While *P. falciparum* and *P. vivax* are the most common, *P. falciparum* causes the most severe disease and almost all fatalities, whereas *P. vivax* is usually considered to be benign [8]. The malaria parasite has a ‘complex’ life cycle involving sexual reproduction occurring in the insect vector [2] and two stages of infection within a human (or animal host), a liver stage [16] and blood stage [7]. Human infection starts by the bite of an infected mosquito, which injects the sporozoite form of *Plasmodium* during a blood meal. The sporozoites enter the host peripheral circulation, and rapidly transit to the liver where they infect liver cells (hepatocytes) [16]. The parasite replicates within the liver cell before rupturing to release extracellular parasite forms (merozoites), into the host circulation, where they may invade red blood cells (RBCs) to initiate blood stage infection [30]. Then follows a series of cycles of replication, rupture, and re-invasion of the RBC. Some asexual parasite forms commit to an alternative developmental pathway and become sexual forms (gametocytes) [34]. Gametocytes can be taken up by mosquitoes during a blood meal where they undergo a cycle of sexual development to produce sporozoites [2], which completes the parasite life cycle.

The prevalence of mixed human malaria parasite infection is globally widespread. Even in areas of low transmission, a high proportion of within-host malaria infections is with more than one species of *Plasmodium* at the same time [28]. Many studies indicate the distributional prevalence of mixed-species malaria infections in different locations across the world, *e.g.* [1, 18, 23, 28, 37]. Mixed *Plasmodium spp.* infections is then common but often unrecognized or underestimated [23, 28]. From a biological standpoint, this can be explained by both observer error, difficulty in distinguishing the young ring-form parasites of the five malaria species of humans, and that many infections are at densities below the threshold of detection by microscopy [28].

From a fundamental standpoint, several mathematical models have been developed to study the within-host parasite multiplication in a context of mixed malaria infections, *e.g.* [9, 11, 22, 45]. In most cases, those studies highlight the competition exclusion principle amount genotype (or strain) of a given species (*i.e.*, only one strain survives while the other strains go to extinction) [11, 22, 45], except in some configuration where a particular modelling assumption on RBCs infection rate is introduced [9]. Note that such competitive exclusion of mixed-strain infections is also supported by experimental studies, *e.g.* [40, 42]. Furthermore, based on these results, some studies conclude that two species of the malaria parasites cannot co-persist within a single host, *e.g.* [45], which is quite in contradiction with mixed *Plasmodium* species infections developed earlier. One reason of that apparent contradiction is that all those modelling studies tackle the issue of malaria infections with more than one genotype from a particular species within a single host, and not the case of multi-species *Plasmodium* infections within a single host. However, there are several widespread empirical evidences that support the occurrence of within-host malaria infections with more than one species of *Plasmodium* at the same time [1, 18, 23, 28, 28, 37]. Indeed, *Plasmodium spp.* exhibit differential preferences for RBCs of different ages. In the human parasite species, *P. vivax* and *P. ovale* have a predilection for reticulocytes, *P. malariae* for mature RBCs, and *P. falciparum* for all types [32]. Here, we will show that such a differential ecological characteristics of *Plasmodium* species within their vertebrate host is fundamental to capture species diversity within the same host. These *Plasmodium* species interactions have important clinical and public health implications, as treatment and control of one parasite have an effect on the clinical epidemiology of the sympatric species, see *e.g.* [23, 28, 37].

We first introduce the mathematical model and define its parameters. Next, we establish some useful properties that include the existence of a positive global in time solution of the system, the parasite invasion process, and the threshold asymptotic dynamics of the model. We investigate the existence of nontrivial stationary states of the model. In particular, we show that the dynamical behavior of the system is not trivial and can range from the extinction of all species, the persistence of a single species, to the coexistence of more than one species. We also describe how our general analysis can be applied in some co-infection configurations: (i) *P. Falciparum* and *P. Vivax*, (ii) *P. Falciparum* and *P. Malariae*, and (iii) *P. Vivax* and *P. Malariae*. Finally, we discuss some scenarios that can be captured by the model, as well as the biological implications of model assumptions and limitations.

## 2 The model description

We describe the within-host malaria infection coupled with RBCs production. Fig. 1 below presents the flow diagram of the model considered here. This model is an extension of the model previously introduced in [13] for the understanding dynamics of *Plasmodium* gametocytes production. For uninfected RBCs (uRBCs) dynamics, we consider three maturity stages for the RBCs: reticulocyte ( $R_r$ ), mature RBC ( $R_m$ ) and senescent RBC ( $R_s$ ). Here,  $R_j$  refers to the  $j$ -stage RBCs population size and we denote as  $\mathcal{J} = \mathcal{J}$  the set of RBCs maturity stages. All these three maturity stages are vulnerable to *P. falciparum* while *P. Vivax* and *P. Malariae* only target reticulocyte and senescent, respectively. For the parasitized stage, we consider an age-structured dynamics for the parasitized RBCs (pRBC). Here the age is a continuous variable representing the time since the concerned RBC is parasitized. Such a continuous age structure will allow us to track the development and maturity of pRBCs, but also to have a refined

description of the pRBC rupture and of the merozoites release phenomenon.

**Uninfected RBC dynamics.** We denote by  $R_r(t)$ ,  $R_m(t)$  and  $R_s(t)$ , respectively the density of reticulocytes, mature RBCs and senescent RBCs at time  $t$ .

In the absence of malaria parasites, the evolution of circulating red blood cells is assumed to follow a discrete maturity stage system of ordinary differential equations that takes the form

$$\begin{cases} \frac{dR_r(t)}{dt} = \Lambda_0 - \mu_r R_r(t), \\ \frac{dR_m(t)}{dt} = \mu_r R_r(t) - \mu_m R_m(t), \\ \frac{dR_s(t)}{dt} = \mu_m R_m(t) - \mu_s R_s(t). \end{cases} \quad (2.1)$$

The parameters  $1/\mu_r$ ,  $1/\mu_m$  and  $1/\mu_s$  respectively denote the duration of RBC reticulocyte stage, mature stage and senescent stage while  $\Lambda_0$  represents the normal value of the RBC production from marrow source (i.e. the production rate of RBC). System (2.1) can also be found in [29]. Stationary states of (2.1), called hereafter parasite-free equilibrium, is given by

$$R_j^* = \frac{\Lambda_0}{\mu_j}, \quad j \in \mathcal{J}.$$

Defining the total concentration of RBCs by  $R^* = R_r^* + R_m^* + R_s^*$ , we then introduce the proportion of each uRBC stage at the parasite-free equilibrium by

$$q_j^* = \frac{R_j^*}{R^*}, \quad j \in \mathcal{J}.$$

Parameters of this system are selected from [4, 20, 29] (Table 1) so that in the absence of parasite the equilibrium normal distribution is given by

$$(R_r^*; R_m^*; R_s^*) = (62.50; 4853; 83.30) \times 10^6 \text{ cell/ml}.$$

This leads to the normal concentration of RBC  $R^* = (R_r^* + R_m^* + R_s^*)$  around  $4.99 \times 10^9$  cell/ml that corresponds to the usual normal value.

**Multi-species malaria infection dynamics.** Here we consider the interaction between  $n$  malaria species together with the circulating RBCs. We respectively denote by  $u_k(t)$  and  $p_k(t, a)$  the density of merozoites and pRBC at time  $t$  induced by the  $k$ -species. The variable  $a$  denotes the time since the concerned RBC is parasitized. Then the malaria infection dynamics reads as:

$$\begin{cases} \dot{R}_r(t) = \Lambda_0 - \mu_r R_r(t) - \left( \sum_{k=1}^n \gamma_r^k \beta_k u_k(t) \right) R_r(t), \\ \dot{R}_m(t) = \mu_r R_r(t) - \mu_m R_m(t) - \left( \sum_{k=1}^n \gamma_m^k \beta_k u_k(t) \right) R_m(t), \\ \dot{R}_s(t) = \mu_m R_m(t) - \mu_s R_s(t) - \left( \sum_{k=1}^n \gamma_s^k \beta_k u_k(t) \right) R_s(t), \\ p_k(t, 0) = \beta_k u_k(t) \sum_{j \in \mathcal{J}} \gamma_j^k R_j(t), \\ \partial_t p_k(t, a) + \partial_a p_k(t, a) = -(\mu_k(a) + \mu_0) p_k(t, a), \\ \dot{u}_k(t) = \int_0^\infty r_k \mu_k(a) p_k(t, a) da - \mu_{v,k} u_k(t), \text{ with } k = 1, 2, \dots, n, \end{cases} \quad (2.2)$$

coupled with the initial condition

$$R_j(0) = R_{j,0}, p_k(0, a) = p_{k,0}(a), u_k(0) = u_{k,0}. \quad (2.3)$$

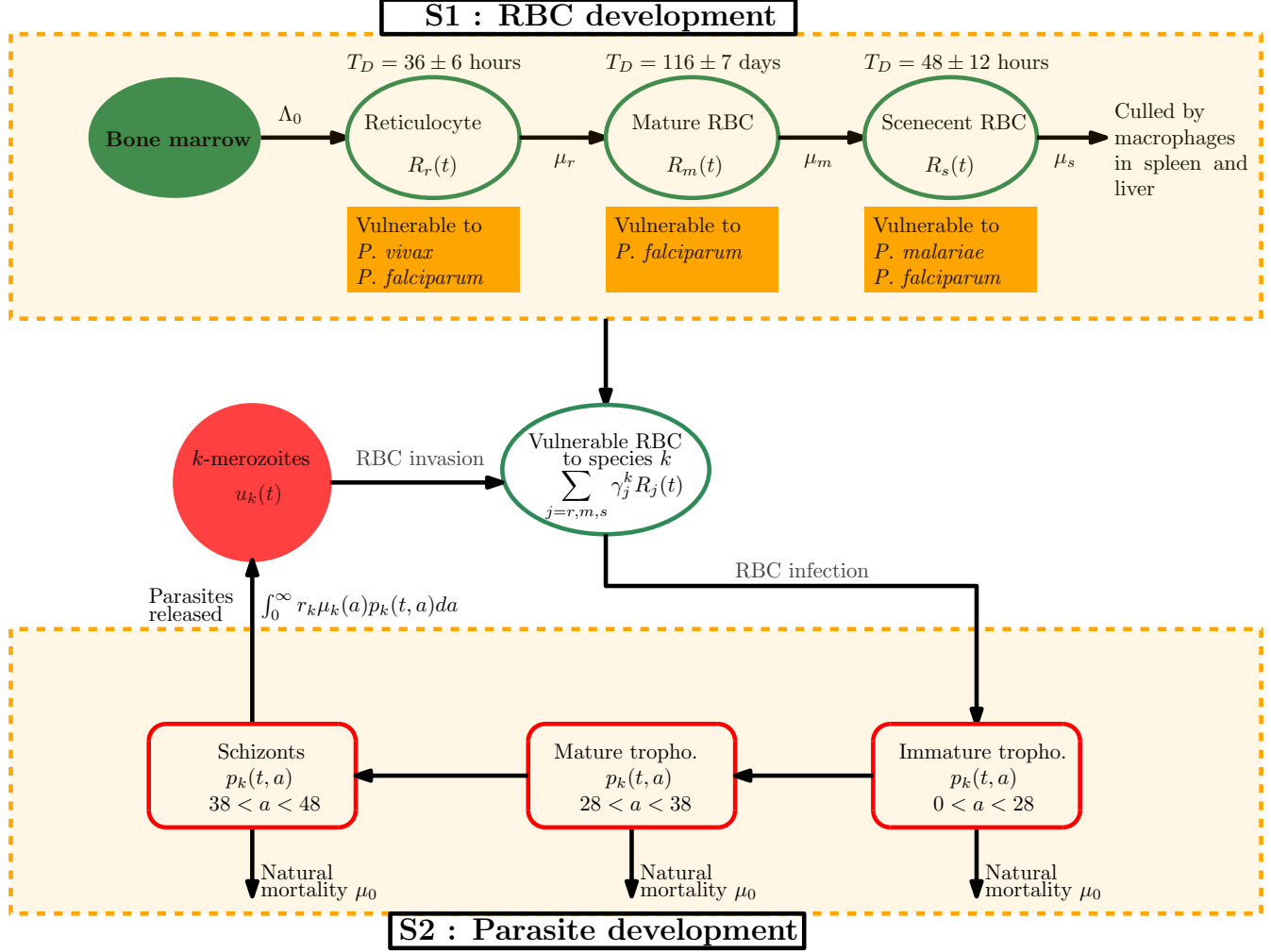


Figure 1: ( $S_1$ ) The RBC development chain, ( $S_2$ ) the parasite development chain.  $T_D$  = average duration of a stage of development.  $\Lambda_0$  is the RBC production rate from the marrow source.  $1/\mu_r$  (resp.  $1/\mu_m$ ,  $1/\mu_s$ ) is the duration of the RBC reticulocyte (resp. mature, senescent) stage. A continuous parameter  $a$  denotes the time since the concerned RBC is parasitized. Immature trophozoite-stage ( $0 < a < 26$  hours), Mature trophozoite-stage ( $26 < a < 38$  hours) and Schizont-stage ( $38 < a < 48$  hours). In the case of *P. Falciparum* infection, one has ( $\gamma_r = \gamma_m = \gamma_s = 1$ ) while for *Vivax* one has ( $\gamma_r = 1$ ,  $\gamma_m = \gamma_s = 0$ ) and for *malariae* ( $\gamma_r = \gamma_m = 0$ ,  $\gamma_s = 1$ ), see e.g. [32].

Table 1: Model variables and parameters

Param.	Description (unit)	Values[source]
<b>State variables</b>		
$R_r(t)$	Density of reticulocytes at time $t$ (Cell/ml)	
$R_m(t)$	Density of mature RBCs at time $t$ (Cell/ml)	
$R_s(t)$	Density of senescent RBCs at time $t$ (Cell/ml)	
$p_k(t, a)$	Density of parasitized RBCs by the $k$ -species at time $t$ , which are parasitized since time $a$ (Cell/ml)	
$u_k(t)$	Density of merozoites at time $t$ due to the $k$ -species (Cell/ml)	
<b>Parameters</b>		
$\Lambda_0$	Production rate of RBC (RBC/h/ml)	$1.73 \times 10^6$ [4, 29]
$1/\mu_r$	Duration of the RBC reticulocyte stage (h)	36 [29]
$1/\mu_m$	Duration of the RBC mature stage (days)	116.5 [29]
$1/\mu_s$	Duration of the RBC senescent stage (h)	48 [29]
$\mu_0$	Natural death rate of uRBC (RBC/day)	0.00833 [4]
$\mu_{v,k}$	Decay rates of malaria parasites of the $k$ -species (RBC/day)	48 [20]
$r_k$	Number of merozoites produced per pRBC by the $k$ -species	16 [4, 32]
$\tau_k$	Erythrocytic cycle duration for the $k$ -species (h)	48 for <i>P. Falciparum</i> [32] 48 for <i>P. Vivax</i> [32] 72 for <i>P. Malariae</i> [32]
$\mathcal{R}_0^k$	Basic reproduction number of the $k$ -species	variable
$\beta_k$	Infection rate of the $k$ -species	Calculated <sup>a</sup>
<b>Initial conditions</b>		
$R_j(0)$	Density of RBCs at the maturity stage $j$	$R_j^*$
$p_k(0, \cdot)$	Density of pRBCs	0
$u_k(0)$	Density of malaria parasites of the $k$ -species	$10^7$
<sup>a</sup> $\beta_{k,s}$ are calculated by (6.1)		

System (2.2) will be considered under the following natural assumption

$$\Lambda_0 > 0, \beta_j > 0, \tau_j > 0, \alpha_j > 0, r_j > 0, \gamma_j^k \geq 0,$$

and

$$\sum_{j \in \mathcal{J}} \gamma_j^k > 0, \forall k = 1, \dots, n.$$

The latter inequality means that the  $k$ -th malaria species can consume at least one RBCs stage, *i.e.* either reticulocytes, mature or senescent.

We briefly sketch the interpretation of the parameters arising in (2.2). Parameters  $\mu_0$  and  $\mu_{v,k}$ , respectively, denote the natural death rates for pRBC and free  $k$ -merozoites. Function  $\mu_k(a)$  denotes the additional death rate of pRBC due to the  $k$ -parasites at age  $a$  and leading to the rupture. The rupture of pRBC at age  $a$  results in the release of an average number  $r_k$  of merozoites into the blood stream, so that pRBC then produce, at age  $a$ , merozoites at rate  $r_k \mu_k(a)$ . Together with this description, the quantity  $\int_0^\infty r_k \mu_k(a) p_k(t, a) da$  corresponds to the number of merozoites produced by the  $k$ -pRBC at time  $t$ . The parameter  $\beta_k$  describes the contact rate between uRBC and free  $k$ -merozoites. Here the rupture function  $\mu_k(a)$  is taken of the form

$$\mu_k(a) = \begin{cases} 0 & \text{if } a < \tau_k \\ \alpha_k & \text{if } a > \tau_k \end{cases}, \quad (2.4)$$

where  $\tau_k$  is the erythrocytic cycle duration of the  $k$ -species. An important characteristic of *Plasmodium* species is the development of parasites within RBCs. The  $k$ -parasite species within a RBC takes an average of  $\tau_k$  hours to mature and release free merozoites. The development of parasites within RBCs is characterized by the rupture function  $\mu_k$  (2.4). With such formulation, the overall average development period is  $\approx \tau_k$  hours. Indeed, let  $D_k(a) = \exp(-\int_0^a \mu_k(\sigma)d\sigma)$  the probability that a pRBC remains parasitized after  $a$  hours (without taking into account other mechanisms such as the natural mortality). Then, the average parasite's development period is  $\int_0^\infty D_k(a)da = \tau_k + 1/\alpha_k$ . We fix, *e.g.*  $\alpha_k = 10$  for all species, such that  $\int_0^\infty D_k(a)da = \tau_k + 1/\alpha_k \approx \tau_k$ . The value of  $\alpha_k$  is therefore not strictly significant as soon as the last approximation holds.

Next, let us introduce the following notations, for  $a \geq b$ ,

$$\Pi_k(a, b) = e^{-\mu_0(a-b)} \exp\left(-\int_b^a \mu_k(\tau)d\tau\right), k = 1, \dots, n. \quad (2.5)$$

Note that parameters  $\Pi_k$  are finite constants under the model parameter assumption. Furthermore,  $\Pi_k(a, b)$  is the probability that a pRBC by the  $k$ -th species, which is parasitized since  $b$  hours, remains so after  $a$  hours of infection.

Parameters  $\gamma_j^k$  describe the preference of parasites' targets ( $j \in \mathcal{J}$ ) of the  $k$ -species. For example, *P. Falciparum* do not have any preference for RBC so that  $\gamma_r = \gamma_m = \gamma_s = 1$ . For *P. Vivax* infection one has  $\gamma_r = 1$  and  $\gamma_m = \gamma_s = 0$ , so that target RBCs mostly consist in reticulocytes while for *P. Malariae* infection, the target RBCs are mostly senescent cells, that is  $\gamma_r = \gamma_m = 0$  and  $\gamma_s = 1$  [32].

It is useful to write System (2.2) into a more compact form. To that end, we introduce the vectors  $\mathbf{R}(t) = (R_r(t), R_m(t), R_s(t))^T$ ,  $\mathbf{p}(t, a) = (p_1(t, a), \dots, p_n(t, a))^T$  and  $\mathbf{u}(t) = (u_1(t), \dots, u_n(t))^T$ . Here  $x^T$  is set for the transpose of a vector or matrix  $x$ . Then, System (2.2) can be rewritten as

$$\begin{cases} \dot{\mathbf{R}}(t) = \mathbf{\Lambda} - (\mathbf{m}_0 + \boldsymbol{\omega})\mathbf{R}(t) - \text{diag}(\boldsymbol{\gamma}\boldsymbol{\beta}\mathbf{u}(t))\mathbf{R}(t), \\ \mathbf{p}(t, 0) = \text{diag}(\boldsymbol{\beta}\mathbf{u}(t))\boldsymbol{\gamma}^T\mathbf{R}(t), \\ \partial_t \mathbf{p}(t, a) + \partial_a \mathbf{p}(t, a) = -(\boldsymbol{\mu}(a) + \boldsymbol{\mu}_0)\mathbf{p}(t, a), \\ \dot{\mathbf{u}}(t) = \int_0^\infty \mathbf{r}\boldsymbol{\mu}(a)\mathbf{p}(t, a)da - \boldsymbol{\mu}_v\mathbf{u}(t), \end{cases} \quad (2.6)$$

where  $\text{diag}(w)$  is a diagonal matrix with the diagonal elements given by  $w$  and we have formally set

$$\begin{aligned} \mathbf{\Lambda} &= \begin{pmatrix} \Lambda_0 \\ 0 \\ 0 \end{pmatrix}, \quad \boldsymbol{\gamma} = \begin{pmatrix} \gamma_r^1 & \dots & \gamma_r^n \\ \gamma_m^1 & \dots & \gamma_m^n \\ \gamma_s^1 & \dots & \gamma_s^n \end{pmatrix}, \quad \boldsymbol{\omega} = \begin{pmatrix} 0 & 0 & 0 \\ -\mu_r & 0 & 0 \\ 0 & -\mu_m & 0 \end{pmatrix}, \\ \boldsymbol{\beta} &= \text{diag}(\beta_j)_{j=1, \dots, n}, \quad \boldsymbol{\mu}(a) = \text{diag}(\mu_j(a))_{j=1, \dots, n}, \quad \mathbf{m}_0 = \text{diag}(\mu_j)_{j \in \mathcal{J}}, \\ \mathbf{m} &= \mathbf{m}_0 + \boldsymbol{\omega}, \quad \boldsymbol{\mu}_v = \text{diag}(\mu_{v,j})_{j=1, \dots, n}, \quad \mathbf{r} = \text{diag}(r_j)_{j=1, \dots, n}, \quad \boldsymbol{\mu}_0 = \mu_0 I, \end{aligned} \quad (2.7)$$

and where  $I$  is the identity matrix. Furthermore, we set

$$\boldsymbol{\Pi}(a, b) = e^{-\mu_0(a-b)} \exp\left(-\int_b^a \boldsymbol{\mu}(\sigma)d\sigma\right), \quad a \geq b \geq 0,$$

which is the survival probability matrix in which components  $\Pi_{k,s}$  are given by (2.5).

### 3 General remarks

In this section, we establish some useful properties of solutions of (2.2) that include the existence of a positive global in time solution of the system.



We first formulate system (2.6) in an abstract Cauchy problem. For that aim, we introduce the Banach space  $\mathcal{X} = \mathbb{R}^3 \times \mathbb{R}^n \times L^1(0, \infty, \mathbb{R}^n) \times \mathbb{R}^n$  endowed with the usual product norm  $\|\cdot\|_{\mathcal{X}}$  as well as its positive cone  $\mathcal{X}_+$ . Let  $A : D(A) \subset \mathcal{X} \rightarrow \mathcal{X}$  be the linear operator defined by  $D(A) = \mathbb{R}^3 \times \{0_{\mathbb{R}^n}\} \times W^{1,1}(0, \infty, \mathbb{R}^n) \times \mathbb{R}^n$  and

$$A(\mathbf{R}, 0_{\mathbb{R}^n}, \mathbf{p}, \mathbf{u}) = (-\mathbf{m}_0 \mathbf{R}, -\mathbf{p}(0), -\mathbf{p}' - (\boldsymbol{\mu} + \boldsymbol{\mu}_0) \mathbf{p}, -\boldsymbol{\mu}_v \mathbf{u}). \quad (3.1)$$

Finally, let us introduce the non-linear map  $F : \overline{D(A)} \rightarrow \mathcal{X}$  defined by

$$F(\mathbf{R}, 0_{\mathbb{R}^n}, \mathbf{p}, \mathbf{u}) = \left( \boldsymbol{\Lambda} - \boldsymbol{\omega} \mathbf{R} - \text{diag}(\boldsymbol{\gamma} \boldsymbol{\beta} \mathbf{u}) \mathbf{R}, \text{diag}(\boldsymbol{\beta} \mathbf{u}) \boldsymbol{\gamma}^T \mathbf{R}, 0, \int_0^\infty \mathbf{r} \boldsymbol{\mu}(a) \mathbf{p}(a) da \right).$$

By identifying  $\varphi(t)$  together with  $(\mathbf{R}(t), 0_{\mathbb{R}^n}, \mathbf{p}(t, \cdot), \mathbf{u}(t))^T$  and  $\varphi_0$  together with the associated initial condition (2.3), system (2.6) rewrites as the following Cauchy problem

$$\begin{cases} \frac{d\varphi(t)}{dt} = A\varphi(t) + F(\varphi(t)), \\ \varphi(0) = \varphi_0. \end{cases} \quad (3.2)$$

Since system (2.2) is designed to model a biological process, its solutions should remain positive and bounded. By setting  $\mathcal{X}_0 = D(A)$  and  $\mathcal{X}_{0+} = \mathcal{X}_0 \cap \mathcal{X}_+$ , the positivity and boundedness of the solutions of system (2.2) is provided by the following result.

**Theorem 3.1** *There exists a unique strongly continuous semiflow  $\{\Phi(t, \cdot) : \mathcal{X}_0 \rightarrow \mathcal{X}_0\}_{t \geq 0}$  such that for each  $\varphi_0 \in \mathcal{X}_{0+}$ , the map  $\varphi \in \mathcal{C}((0, \infty), \mathcal{X}_{0+})$  defined by  $\varphi = \Phi(\cdot, \varphi_0)$  is a mild solution of (3.2), namely, it satisfies  $\int_0^t \varphi(s) ds \in D(A)$  and  $\varphi(t) = \varphi_0 + A \int_0^t \varphi(s) ds + \int_0^t F(\varphi(s)) ds$  for all  $t \geq 0$ . Moreover,  $\{\Phi(t, \cdot)\}_t$  satisfies the following properties:*

1. Let  $\Phi(t, \varphi_0) = (\mathbf{R}(t), 0_{\mathbb{R}^n}, \mathbf{p}(t, \cdot), \mathbf{u}(t))^T$ ; then the following Volterra formulation holds true

$$\mathbf{p}(t, a) = \begin{cases} \Pi(a, a-t) \mathbf{p}_0(a-t) & \text{if } t \leq a, \\ \Pi(a, 0) \text{diag}(\boldsymbol{\beta} \mathbf{u}(t-a)) \boldsymbol{\gamma}^T \mathbf{R}(t-a) & \text{if } t > a. \end{cases} \quad (3.3)$$

coupled with the  $\mathbf{R}(t)$  and  $\mathbf{m}(t)$  equations of (2.6).

2. For all  $\varphi_0 \in \mathcal{X}_{0+}$  one has for all  $t \geq 0$ ,

$$\sum_{j \in \mathcal{J}} R_j(t) + \sum_{k=1}^n \int_0^\infty p_k(t, a) da \leq \max \left\{ \frac{\Lambda}{c_0}, \sum_{j \in \mathcal{J}} R_{j,0} + \sum_{k=1}^n \int_0^\infty p_{k,0}(a) da \right\}, \quad (3.4)$$

and

$$\sum_{k=1}^n u_k(t) \leq \max \left\{ \frac{r_{\max} \alpha_{\max}}{\mu_{v, \min}} \max \left\{ \frac{\Lambda}{c_0}, \sum_{j \in \mathcal{J}} R_{j,0} + \sum_{k=1}^n \int_0^\infty p_{k,0}(a) da \right\}, \sum_{k=1}^n u_{k,0} \right\}, \quad (3.5)$$

where  $\Lambda = \Lambda_0 + \mu_s \max \left\{ \frac{\Lambda_0}{\mu_r}, R_{r,0} \right\} + \mu_s \max \left\{ \frac{\Lambda_0}{\mu_m}, \frac{\mu_r}{\mu_m} R_{r,0}, R_{m,0} \right\}$  and  $c_0 = \min\{\mu_s, \mu_0\}$ ,  $r_{\max} = \max\{r_j\}_{j=1, \dots, n}$ ,  $\alpha_{\max} = \max\{\alpha_j\}_{j=1, \dots, n}$  and  $\mu_{v, \min} = \min\{\mu_{v,j}\}_{j=1, \dots, n}$ .

3. The semiflow  $\{\Phi(t, \cdot)\}_t$  is bounded dissipative and asymptotically smooth, that is

Bounded dissipative: there exists a bounded set  $\mathcal{B} \subset \mathcal{X}_0$  such that for any bounded set  $U \subset \mathcal{X}_0$ , there exists  $\tau = \tau(U, \mathcal{B}) \geq 0$  such that  $\Phi(t, U) \subset \mathcal{B}$  for  $t \geq \tau$ .

Asymptotically smooth: for any nonempty, closed, bounded set  $U \subset \mathcal{X}_0$ , there exists a nonempty compact set  $J = J(U)$  such that  $J$  attracts  $\{\varphi \in U : \Phi(t, \varphi) \in U, \forall t \geq 0\}$ .



4. There exists a nonempty compact set  $\mathcal{B} \subset \mathcal{X}_{0+}$  such that

(i)  $\mathcal{B}$  is invariant under the semiflow  $\{\Phi(t, \cdot)\}_t$ .

(ii) The subset  $\mathcal{B}$  attracts the bounded sets of  $\mathcal{X}_{0+}$  under the semiflow  $\{\Phi(t, \cdot)\}_t$ .

We recall that a nonempty set  $J \subset \mathcal{X}$  is said to *attract* a nonempty set  $B \subset \mathcal{X}$  if  $\delta_{\mathcal{X}}(\Phi(t, B), J) \rightarrow 0$  as  $t \rightarrow +\infty$ , where  $\delta_{\mathcal{X}}(B, J) = \sup_{u \in B} \inf_{v \in J} \|u - v\|_{\mathcal{X}}$  is a semi-distance on  $\mathcal{X}$ . Moreover, notice that the notion of *asymptotically smooth* is used here within the terminology of Hale, Lasalle and Slemrod [19]. However, this is strictly equivalent to the notion of *asymptotically compact* within the terminology of Ladyzhenskaya [24].

*Proof.* It is easy to check that the operator  $A$  is a Hille-Yosida operator. Then standard results apply to provide the existence and uniqueness of a mild solution to (2.6) (we refer to [25, 41] for more details). The Volterra formulation is also standard and we refer to [21, 44] for more details.

The  $R_r$  equation of (2.2) gives  $\dot{R}_r(t) \leq \Lambda_0 - \mu_r R_r(t)$ , that is

$$R_r(t) \leq \max \left\{ \frac{\Lambda_0}{\mu_r}, R_{r,0} \right\}.$$

Similarly, from the  $R_m$  and  $R_s$  equations of (2.2), we successfully obtain

$$R_m(t) \leq \max \left\{ \frac{\Lambda_0}{\mu_m}, \frac{\mu_r}{\mu_m} R_{r,0}, R_{m,0} \right\}$$

and

$$R_s(t) \leq \max \left\{ \frac{\Lambda_0}{\mu_s}, \frac{\mu_r}{\mu_s} R_{r,0}, \frac{\mu_m}{\mu_s} R_{m,0}, R_{s,0} \right\}.$$

Next, for estimate (3.4), let  $\varphi_0 \in \mathcal{X}_{0+}$ ; then adding up the  $R_{j,s}$  equations together with the  $p_{k,s}$  equations of (2.2) yields

$$\frac{d}{dt} \left( \sum_{j \in \mathcal{J}} R_j(t) + \sum_{k=1}^n \int_0^\infty p_k(t, a) da \right) \leq \Lambda_0 - \mu_s R_s(t) - \mu_0 \sum_{k=1}^n \int_0^\infty p_k(t, a) da,$$

that is

$$\frac{d}{dt} \left( \sum_{j \in \mathcal{J}} R_j(t) + \sum_{k=1}^n \int_0^\infty p_k(t, a) da \right) \leq \Lambda_0 + \mu_s (R_r(t) + R_m(t)) - \mu_s \sum_{j \in \mathcal{J}} R_j(t) - \mu_0 \sum_{k=1}^n \int_0^\infty p_k(t, a) da.$$

Setting  $\Lambda = \Lambda_0 + \mu_s \max \left\{ \frac{\Lambda_0}{\mu_r}, R_{r,0} \right\} + \mu_s \max \left\{ \frac{\Lambda_0}{\mu_m}, \frac{\mu_r}{\mu_m} R_{r,0}, R_{m,0} \right\}$  and  $c_0 = \min\{\mu_s, \mu_0\}$ , it comes

$$\sum_{j \in \mathcal{J}} R_j(t) + \sum_{k=1}^n \int_0^\infty p_k(t, a) da \leq \max \left\{ \frac{\Lambda}{c_0}, \sum_{j \in \mathcal{J}} R_{j,0} + \sum_{k=1}^n \int_0^\infty p_{k,0}(a) da \right\}.$$

From where one deduces estimate (3.4). Finally, by  $u_{k,s}$  equations of (2.2), we have

$$\dot{u}_k(t) \leq r_k \alpha_k \int_0^\infty p_k(t, a) da - \mu_{v,k} u_k(t),$$

that is

$$\sum_{k=1}^n \dot{u}_k(t) \leq \sum_{k=1}^n r_k \alpha_k \int_0^\infty p_k(t, a) da - \sum_{k=1}^n \mu_{v,k} u_k(t).$$

Then, by (3.4) the later inequality leads to

$$\sum_{k=1}^n u_k(t) \leq \max \left\{ \frac{r_{\max} \alpha_{\max}}{\mu_{v,\min}} \max \left\{ \frac{\Lambda}{c_0}, \sum_{j \in \mathcal{J}} R_{j,0} + \sum_{k=1}^n \int_0^\infty p_{k,0}(a) da \right\}, \sum_{k=1}^n u_{k,0} \right\},$$

with  $r_{\max} = \max\{r_j\}_{j=1,\dots,n}$ ,  $\alpha_{\max} = \max\{\alpha_j\}_{j=1,\dots,n}$  and  $\mu_{v,\min} = \min\{\mu_{v,j}\}_{j=1,\dots,n}$ . Estimate (3.5) follows and which ends item 2. of the theorem.

The bounded dissipativity of the semiflow  $\{\Phi(t, \cdot)\}_t$  is a direct consequence of estimate 2. It remains to prove the asymptotic smoothness. For that end, let  $B$  be a forward invariant bounded subset of  $\mathcal{X}_{0+}$ . According to the results in [35] it is sufficient to show that the semiflow is asymptotically compact on  $B$ . Therefore, let us consider a sequence of solutions  $\{\varphi_q = (\mathbf{R}^q, 0_{\mathbb{R}^n}, \mathbf{p}^q, \mathbf{u}^q)^T\}_{q \geq 0}$  that is equibounded in  $\mathcal{X}_{0+}$  and let consider a sequence  $\{t_q\}_{q \geq 0}$  such that  $t_q \rightarrow +\infty$ . Let us show that the sequence  $\{\varphi_q(t_q)\}_{q \geq 0}$  is relatively compact in  $\mathcal{X}_{0+}$ . For that end, we consider the sequence of map  $\{w_q(t) = \varphi_q(t + t_q)\}_{q \geq 0}$ . Since  $\mathbf{R}^q$  and  $\mathbf{u}^q$  are uniformly bounded in the Lipschitz norm, Arzela-Ascoli theorem implies that, possibly along a sub-sequence, one may assume that  $\mathbf{R}^q(t + t_q) \rightarrow \hat{\mathbf{R}}$  and  $\mathbf{u}^q(t + t_q) \rightarrow \hat{\mathbf{u}}(t)$  locally uniformly for  $t \in \mathbb{R}$ . It remains to deal with the sequence  $\{\mathbf{p}^q(t_q, \cdot)\}_{q \geq 0}$ . Let us denote by  $\tilde{\mathbf{p}}^q(t, \cdot) = \mathbf{p}^q(t + t_q, \cdot)$ . Using the Volterra integral formulation it comes

$$\tilde{p}_k^q(t, a) = \begin{cases} p_{k,0}(a - t - t_q) \Pi_k(a, a - t - t_q), & \text{for } t + t_q < a, \\ \beta_k u_k^q(t + t_q - a) \left( \sum_{j \in \mathcal{J}} \gamma_j^k R_j^q(t + t_q - a) \right) \Pi_k(a, 0), & \text{for } t + t_q \geq a, \end{cases}$$

for all  $k = 1, \dots, n$ .

Finally, since  $\beta_k u_k^q(t + t_q - a) \left( \sum_{j \in \mathcal{J}} \gamma_j^k R_j^q(t + t_q - a) \right) \Pi_k(a, 0)$  converges as  $q \rightarrow \infty$  towards some function  $\xi_k(t, a) = \beta_k \hat{u}_k(t - a) \left( \sum_{j \in \mathcal{J}} \gamma_j^k \hat{R}_j(t - a) \right) \Pi_k(a, 0)$  locally uniformly, one easily concludes that

$$p_k^q(t_q, \cdot) = \tilde{p}_k^q(0, \cdot) \rightarrow \beta_k \hat{u}_k(t - \cdot) \left( \sum_{j \in \mathcal{J}} \gamma_j^k \hat{R}_j(t - \cdot) \right) \Pi_k(\cdot, 0) \text{ in } L^1(0, \infty; \mathbb{R}) \text{ and } \forall k = 1, \dots, n.$$

Item 3. of the theorem then follows.

For item 4., items 2. and 3. show that  $\Phi$  is point dissipative, eventually bounded on bounded sets, and asymptotically smooth. Thus, item 4. follows from Theorem 2.33 of [38].  $\blacksquare$

The next result is concerned with spectral properties of the linearized semiflow  $\Phi$  at a given equilibrium point  $\bar{\varphi} \in \mathcal{X}_{0+}$ . The associated linearized system at the point  $\bar{\varphi}$  reads as

$$\frac{d\varphi(t)}{dt} = (A + B[\bar{\varphi}])\varphi(t),$$

where  $A$  is the linear operator defined in (3.1) while  $B[\bar{\varphi}] \in \mathcal{L}(\mathcal{X}_0, \mathcal{X})$  is the bounded linear operator defined by :

$$B[\bar{\varphi}]\varphi = \begin{pmatrix} -\omega \mathbf{R} - \text{diag}(\gamma \beta \bar{\mathbf{u}}) \mathbf{R} - \text{diag}(\gamma \beta \bar{\mathbf{u}}) \bar{\mathbf{R}} \\ \text{diag}(\beta \bar{\mathbf{u}}) \gamma^T \mathbf{R} + \text{diag}(\beta \bar{\mathbf{u}}) \gamma^T \bar{\mathbf{R}} \\ 0_{L^1(0, \infty, \mathbb{R}^n)} \\ \int_0^\infty \mathbf{r} \mu(a) \mathbf{p}(a) da \end{pmatrix}.$$

We then have the following lemma.

**Lemma 3.2** *Let us set  $\Omega = \{\lambda \in \mathbb{C} : \operatorname{Re}(\lambda) > -\min(\mu_r, \mu_m, \mu_s, \mu_0, \mu_{v,k})\}$ . Then, the spectrum  $\sigma(A + B[\bar{\varphi}]) \cap \Omega \neq \emptyset$ , only consists of the point spectrum and one has*

$$\sigma(A + B[\bar{\varphi}]) \cap \Omega = \{\lambda \in \Omega : \Delta(\lambda, \bar{\varphi}) = 0\},$$

where function  $\Delta(\cdot, \bar{\varphi}) : \Omega \rightarrow \mathbb{C}$  is defined by

$$\Delta(\lambda, \bar{\varphi}) = \det[\mathcal{D}(\lambda, \bar{\varphi})], \quad (3.6)$$

with  $\mathcal{D}(\lambda, \bar{\varphi}) = \operatorname{diag}(\Delta_k(\lambda, \bar{\varphi}))_{k=1, \dots, n}$  such that

$$\Delta_k(\lambda, \bar{\varphi}) = 1 - \frac{\beta_k}{\lambda + \mu_{v,k}} \left( \sum_{j \in \mathcal{J}} \gamma_j^k \bar{R}_j \right) \int_0^\infty r_k \mu_k(a) e^{-\lambda a} \Pi_k(a, 0) da.$$

*Proof.* Let us denote by  $A_0 : D(A_0) \subset \mathcal{X}_0 \rightarrow \mathcal{X}_0$  the part of  $A$  in  $\mathcal{X}_0 = D(A)$ , which is defined by

$$A_0 \varphi = A \varphi, \quad \forall \varphi \in D(A_0) = \{\varphi \in D(A) : A \varphi \in D(A)\}.$$

Then, it is the infinitesimal generator of a  $C_0$ -semigroup on  $\mathcal{X}_0$  denoted by  $\{T_{A_0}(t)\}_{t \geq 0}$ . Let  $\varphi = (\mathbf{R}, 0_{\mathbb{R}^n}, \mathbf{p}(\cdot), \mathbf{u})^T$ . We find that

$$T_{A_0}(t) \varphi = \begin{cases} (e^{-\mathbf{m}_0 t} \mathbf{R}, 0_{\mathbb{R}^n}, \Pi(a, a-t) \mathbf{p}(a-t), e^{-\mu_v t} \mathbf{u})^T, & \forall a \geq t, \\ (e^{-\mathbf{m}_0 t} \mathbf{R}, 0_{\mathbb{R}^n}, 0_{L^1(0, \infty, \mathbb{R}^n)}, e^{-\mu_v t} \mathbf{u})^T, & \forall a < t. \end{cases}$$

Then, for  $t \geq a_0$  we have

$$\|T_{A_0}(t - a_0) \varphi\|_{\mathcal{X}} \leq \exp \left( - \min_{j \in \{\mathcal{J}, 0\}} \mu_j (t - a_0) \right) \|\varphi\|_{\mathcal{X}}, \quad \forall t \geq a_0.$$

We deduce that the growth rate of this semigroup satisfies

$$\omega_0(A_0) := \lim_{t \rightarrow +\infty} \frac{\ln \left( \|T_{A_0}(t)\|_{\mathcal{L}(\mathcal{X})} \right)}{t} \leq - \min_{j \in \{\mathcal{J}, 0\}} \mu_j.$$

Then, since operator  $B[\bar{\varphi}]$  is compact, the results in [6] (pages 691-712) or [14] apply and provided that the essential growth rate of  $\left\{ T_{(A+B[\bar{\varphi}])_0}(t) \right\}_{t \geq 0}$ —the  $C_0$ -semigroup generated by the part of  $(A + B[\bar{\varphi}])$  in  $\mathcal{X}_0$ —satisfies

$$\omega_{0,ess}((A + B[\bar{\varphi}])_0) \leq \omega_{0,ess}(A_0) < \omega_0(A_0) \leq - \min_{j \in \{\mathcal{J}, 0\}} \mu_j.$$

Applying the result in [15, 43], the latter inequality ensures that  $\Omega \cap \sigma(A + B[\bar{\varphi}]) \neq \emptyset$  and it is only composed of point spectrum of  $(A + B[\bar{\varphi}])$ .

It remains to derive the characteristic equation. Let  $\lambda \in \rho(A + B[\bar{\varphi}])$ , where  $\rho(\cdot)$  stands for the resolvent. For  $\phi = (\mathbf{S}, \mathbf{v}, \mathbf{q}, \mathbf{w}) \in \mathcal{X}$ , we have  $(\lambda I - A)\varphi - B[\bar{\varphi}]\varphi = \phi$ , and from where we have the following fixed point equation

$$\varphi = (\lambda I - A)^{-1} \phi + (\lambda I - A)^{-1} B[\bar{\varphi}] \varphi.$$

Then, standard computations apply to obtain (3.6). ■

## 4 Parasite invasion process and threshold dynamics

### 4.1 Basic reproduction number and invasion fitness

The basic reproduction number, usually denoted as  $\mathcal{R}_0$ , is defined as the total number of parasites arising from one newly pRBCs introduced into an uninfected host, see *e.g.* [3, 12]. It can typically be used to study the spread of the  $k$ -th species in an uninfected host. In an environment with  $n$  malaria species, the parasite will spread if  $\mathcal{R}_0 > 1$ , with

$$\mathcal{R}_0 = \max_{k=1, \dots, n} \mathcal{R}_0^k, \quad (4.1)$$

where the quantity

$$\mathcal{R}_0^k = \Psi_k \sum_{j \in \mathcal{J}} \gamma_j^k R_j^*$$

is the basic reproduction number of the  $k$ -th species. This expression involves the disease-free equilibrium of uRBCs  $\sum_{j \in \mathcal{J}} \gamma_j^k R_j^*$  and the fitness function  $\Psi_k$  of the  $k$ -th species are given by

$$\Psi_k = \frac{\beta_k}{\mu_{v,k}} \int_0^{+\infty} r_k \mu_k(a) \Pi_k(a, 0) da, \quad (4.2)$$

for all  $k = 1, \dots, n$ . See Appendix A for details on computation.

The quantity  $\Psi_k$  is the reproductive value of the  $k$ -th species. Note that  $\Pi_k(a, 0)$  is the survival probability of a pRBC until  $a$  hours. Once multiplied by  $r_k \mu_k(a)$  and integrated over all infection ages  $a$  it gives the total number of merozoites truly produced by a pRBC.

With the definition of  $\mu_k$  in (2.4), we obtain

$$\Psi_k = \frac{\beta_k r_k \alpha_k e^{-\mu_0 \tau_k}}{\mu_{v,k} (\alpha_k + \mu_0)}.$$

This equation traduces that (i) during its lifetime  $1/\mu_{v,k}$ , (ii) a merozoite can infects RBCs at rate  $\beta_k$ , (iii) pRBCs survives the erythrocytic cycle duration with probability  $e^{-\mu_0 \tau_k}$ , and (iv) produces  $r_k$  merozoites with a probability  $\alpha_k/(\alpha_k + \mu_0)$ .

The  $\mathcal{R}_0^k$  allows quantifying the invasion capability of the  $k$ -th species in an uninfected (or disease-free) environment, and the  $k$ -th species can invade the disease-free environment if  $\mathcal{R}_0^k > 1$ . However, the spread a new species (let say the  $l$ -th species) in an environment already infected by a resident species (let say the  $k$ -species) is typically studied using adaptive dynamics, see *e.g.* [17, 31]. We calculate the invasion fitness  $f(k, l)$  of the new and rare species  $l$ . The new species  $l$  will invade the resident  $k$  if and only if  $f(k, l) > 0$ . Here, we calculate (Appendix A) the invasion fitness  $f(k, l)$  as

$$f(k, l) = \sum_{j=1}^3 \left( \Psi_l \gamma_j^l - \Psi_k \gamma_j^k \right) \underbrace{R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k}}_{\text{feedback of resident species } k}, \quad (4.3)$$

where we have used the correspondences  $r \equiv 1$ ,  $m \equiv 2$  and  $s \equiv 3$ .

The environmental feedback of the resident species  $k$  conditions the ability of the new invader  $l$  to invade the resident population. It depends on the conditions set out by the resident, in particular on the RBCs resource already taken by the resident species  $k$ .

Accordingly, as soon as the RBCs preferences of parasites' targets do not differ between species (*i.e.*,  $\gamma_j^k = \gamma_j$ , for all species  $k$ ), (4.3) is rewritten

$$f(k, l) = (\Psi_l - \Psi_k) \sum_{j=1}^3 \gamma_j R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k}. \quad (4.4)$$

It follows that the model (2.2) admits an optimisation principle based on  $\mathcal{R}_0$ , because the sign of the invasion fitness  $f(k, l)$  in (4.4) is given by the sign of the difference between  $\mathcal{R}_0^l = \Psi_l \sum_{j \in \mathcal{J}} \gamma_j R_j^*$  and  $\mathcal{R}_0^k = \Psi_k \sum_{j \in \mathcal{J}} \gamma_j R_j^*$ . Conversely, if the RBCs preferences of parasites' targets differ for at least two species (*i.e.*, we can find  $k$  and  $l$  such that  $(\gamma_r^k, \gamma_m^k, \gamma_s^k) \neq (\gamma_r^l, \gamma_m^l, \gamma_s^l)$ ), equation (4.3) does not hold and the optimization principle does not apply. Accordingly, the coexistence of at least species  $k$  and  $l$  is then possible.

## 4.2 Threshold dynamics

This section is devoted to the threshold dynamics result of System (2.2). First, let us introduce some useful notations and remarks. Consider the following metric space

$$\mathcal{M} = \text{int}(\mathbb{R}_+^3) \times L_+^1((0, +\infty), \mathbb{R})^n \times \mathbb{R}_+^n$$

endowed with the distance induced by the norm in  $\mathbb{R}^3 \times L^1((0, +\infty), \mathbb{R})^n \times \mathbb{R}^n$ . Furthermore, for each given species  $k = 1, \dots, n$ , let  $\xi_k : \mathcal{M} \rightarrow \mathbb{R}_+$  be the continuous function defined by

$$\xi_k(\mathbf{R}, \mathbf{p}, \mathbf{u}) = u_k + \int_0^{+\infty} p_k(a) da, \quad \forall (\mathbf{R}, \mathbf{p}, \mathbf{u}) \in \mathcal{M},$$

and the sets

$$\begin{aligned} \mathcal{M}_0^k &= \{(\mathbf{R}, \mathbf{p}, \mathbf{u}) \in \mathcal{M} : \xi_k(\mathbf{R}, \mathbf{p}, \mathbf{u}) > 0\}, \\ \partial \mathcal{M}_0^k &= \{(\mathbf{R}, \mathbf{p}, \mathbf{u}) \in \mathcal{M} : \xi_k(\mathbf{R}, \mathbf{p}, \mathbf{u}) = 0\} = \mathcal{M} \setminus \mathcal{M}_0^k, \\ \mathcal{M}_0 &:= \left\{ (\mathbf{R}, \mathbf{p}, \mathbf{u}) \in \mathcal{M} : \xi(\mathbf{R}, \mathbf{p}, \mathbf{u}) := \sum_{k=1}^n \xi_k(\mathbf{R}, \mathbf{p}, \mathbf{u}) > 0 \right\}, \\ \partial \mathcal{M}_0 &:= \{(\mathbf{R}, \mathbf{p}, \mathbf{u}) \in \mathcal{M} : \xi(\mathbf{R}, \mathbf{p}, \mathbf{u}) = 0\} = \mathcal{M} \setminus \mathcal{M}_0. \end{aligned}$$

Next, we will mainly focus on the proof of the malaria species extinction and persistence below.

**Theorem 4.1** *Let  $k \in \{1, \dots, n\}$  be given. Let  $(\mathbf{R}, \mathbf{u}, \mathbf{p})$  be a mild solution of (2.2) with  $R_j(0) > 0$  for  $j \in \mathcal{J}$ .*

*(Extinction) If either  $\mathcal{R}_0^k < 1$  or  $u_k(0) + \int_0^\infty p_k(0, a) da = 0$ , then*

$$\lim_{t \rightarrow +\infty} u_k(t) = 0 \quad \text{and} \quad \lim_{t \rightarrow +\infty} \int_0^\infty p_k(t, a) da = 0.$$

*Therefore, if  $\mathcal{R}_0 < 1$ , then the parasite-free equilibrium is globally asymptotically stable.*

*(Uniform persistence) If  $\mathcal{R}_0 > 1$ , then the parasite-free equilibrium becomes unstable, and there exists  $\epsilon > 0$  such that for each initial condition in  $\mathcal{M}$  we have*

$$\liminf_{t \rightarrow +\infty} \sum_{k=1}^n \left( u_k(t) + \int_0^{+\infty} p_k(t, a) da \right) \geq \epsilon.$$

We proceed in several steps for the proof of Theorem 4.1. The following result ensures that the metric spaces  $\mathcal{M}$ ,  $\mathcal{M}_0^k$  and  $\partial \mathcal{M}_0^k$  are positively invariant with respect to the semiflow generated by System (2.2).

**Proposition 4.2** *The metric spaces  $\mathcal{M}$ , and the subsets  $\mathcal{M}_0^k$ ,  $\partial \mathcal{M}_0^k$ , for all  $k = 1, \dots, n$ , are positively invariant with respect to the semiflow generated by System (2.2).*

A consequence of Proposition 4.2 is that both  $\mathcal{M}_0$  and  $\partial\mathcal{M}_0$  are positively invariant.

*Proof of Proposition 4.2.* Due to the influx  $\Lambda_0$  in the  $R_r$ -equation, one has from standard arguments that for each given non-negative initial conditions of (2.2),  $R_r(t) > 0$ ,  $\forall t > 0$ . Therefore using successively the  $R_m$ -equation and the  $R_s$ -equation one can easily prove that for all  $t > 0$   $R_s(t) > 0$  and  $R_m(t) > 0$ . This ensures that the metric space  $\mathcal{M}$  is positively invariant with respect to the semiflow generated by (2.2).

It remains to prove the positive invariance of the subsets  $\mathcal{M}_{0,s}^k$  and  $\partial\mathcal{M}_{0,s}^k$ . We first claim below results.

**Claim 4.3** Define, for each  $\lambda > -(\mu_0 + \alpha_k)$ , the map  $a \rightarrow \Theta_k(\lambda, a)$  as

$$\Theta_k(\lambda, a) := \int_a^{+\infty} r_k \mu_k(s) e^{-\lambda(s-a)} \Pi_k(s, a) ds, \quad \forall a \geq 0.$$

Next, let  $\widehat{R}_j > 0$ ,  $j \in \mathcal{J}$  be given and define

$$\mathcal{T}_0^k = \Psi_k \sum_{j \in \mathcal{J}} \gamma_j^k \widehat{R}_j,$$

where  $\Psi_k, s$  are define by (4.2). Then there exists  $\lambda_k > -\min\{\mu_0 + \alpha_k, \mu_{v,k}\}$  such that

1.  $\lambda_k$  and  $\mathcal{T}_0^k - 1$  have the same sign and

$$\Theta_k(\lambda, 0) \beta_k \sum_{j \in \mathcal{J}} \gamma_j^k \widehat{R}_j = \mu_{v,k} + \lambda_k. \quad (4.5)$$

2.  $\Theta_k(\lambda_k, a)' = [\lambda_k + \mu_0 + \mu_k(a)] \Theta_k(\lambda_k, a) - r_k \mu_k(a)$  for almost every  $a \geq 0$ .

3. If  $(\mathbf{R}, \mathbf{u}, \mathbf{p})$  is a mild solution of (2.6) then the map  $t \rightarrow \Gamma_k(t)$  defined as

$$\Gamma_k(t) := u_k(t) + \int_0^\infty \Theta_k(\lambda_k, a) p_k(t, a) da, \quad t \geq 0$$

satisfies

$$\Gamma_k(t) = e^{\lambda_k(t-t_0)} \Gamma_k(t_0) + \int_{t_0}^t e^{\lambda_k(t-s)} \Theta_k(\lambda_k, 0) \beta_k u_k(s) \sum_{j \in \mathcal{J}} \gamma_j^k (R_j(s) - \widehat{R}_j) ds, \quad \forall t \geq t_0 \geq 0. \quad (4.6)$$

We also claim that

**Claim 4.4** Let  $(\mathbf{R}, \mathbf{u}, \mathbf{p})$  be a mild solution of (2.6) with  $u_k(0) \geq 0$ ,  $p_k(0, \cdot) \in L_+^1((0, +\infty), \mathbb{R})$ ,  $k = 1, \dots, n$  and  $R_{j0} > 0$ ,  $j = 1, 2, 3$ . Then there exists  $R_j^\pm > 0$ ,  $j = 1, 2, 3$  such that

$$R_j^- < R_j(t) < R_j^+, \quad \forall t \geq 0.$$

Before proving the above claims, let us complete the proof of the proposition.

Let  $(\mathbf{R}, \mathbf{u}, \mathbf{p})$  be a mild solution of (2.6) with initial condition in  $\mathcal{M}$ . Thus, Claim 4.4 implies that there exist  $R_j^\pm > 0$ ,  $j \in \mathcal{J}$  such that

$$R_j^- \leq R_j(t) \leq R_j^+, \quad \forall t \geq 0.$$

Let  $\widehat{R}_j = R_j^+$  (resp.  $\widehat{R}_j = R_j^-$ ),  $j \in \mathcal{J}$  and  $\lambda_k^+$  (resp.  $\lambda_k^-$ ) be the real value such that Claim 4.3 is satisfied. Thus, using item 3. of Claim 4.3 with

$$\Gamma_k^\pm(t) := u_k(t) + \int_0^\infty \Theta_k(\lambda_k^\pm, a) p_k(t, a) da, \quad t \geq 0,$$

we have

$$\begin{cases} \Gamma_k^+(t) \geq e^{\lambda_k^+ t} \Gamma_k^+(0), & t \geq 0, \\ \Gamma_k^-(t) \leq e^{\lambda_k^- t} \Gamma_k^-(0), & t \geq 0. \end{cases}$$

Therefore,

$$u_k(t) + \int_0^\infty \Theta_k(\lambda_k^+, a) p_k(t, a) da \leq e^{\lambda_k^+ t} \left( u_k(0) + \int_0^\infty \Theta_k(\lambda_k^+, a) p_k(0, a) da \right), \quad \forall t \geq 0 \quad (4.7)$$

and

$$e^{\lambda_k^- t} \left( u_k(0) + \int_0^\infty \Theta_k(\lambda_k^-, a) p_k(0, a) da \right) \leq u_k(t) + \int_0^\infty \Theta_k(\lambda_k^-, a) p_k(t, a) da, \quad \forall t \geq 0. \quad (4.8)$$

The result follows by using (4.7) and (4.8) combined with the fact that

$$\int_0^\infty \Theta_k(\lambda_k^\pm, a) p_k(0, a) da = 0 \Leftrightarrow \int_0^\infty p_k(0, a) da = 0.$$

The proof of Claim 4.4 is rather standard and we refer to [26] for instance. It now remains to prove Claim 4.3.

*Proof of Claim 4.3.* Let us first note that  $a \rightarrow \Theta_k(\lambda, a)$  is well defined for each  $\lambda > -(\mu_0 + \alpha_k)$ . Indeed, it is easy to see that

$$\Theta_k(\lambda, a) = e^{\lambda a} \Pi_k(0, a) \Theta_k(\lambda, 0) - \int_0^a r_k \mu_k(s) e^{-\lambda(s-a)} \Pi_k(s, a) ds, \quad \forall a \geq 0, \quad (4.9)$$

with

$$\Theta_k(\lambda, 0) = \int_0^{+\infty} r_k \mu_k(s) e^{-\lambda s} \Pi_k(s, 0) ds = \frac{r_k \alpha_k e^{-(\mu_0 + \lambda) \tau_k}}{\alpha_k + \mu_0 + \lambda}.$$

This ensures that the  $\Theta_k(\lambda, a)$  is convergent for  $\lambda > -(\alpha_k + \mu_0)$ . To prove item 1., we note that

$$\frac{\Theta_k(\lambda, 0)}{\mu_{v,k} + \lambda} \beta_k \sum_{j \in \mathcal{J}} \gamma_j^k \widehat{R}_j = \frac{r_k \alpha_k e^{-(\mu_0 + \lambda) \tau_k}}{(\mu_{v,k} + \lambda)(\alpha_k + \mu_0 + \lambda)} \beta_k \sum_{j \in \mathcal{J}} \gamma_j^k \widehat{R}_j \quad (4.10)$$

is well defined, positive, decreasing and continuous for  $\lambda > -\widehat{\lambda}$  with  $\widehat{\lambda} = \min\{\mu_0 + \alpha_k, \mu_{v,k}\}$ . Note that for  $\lambda = 0$ , the right hand side of (4.10) is  $\mathcal{T}_0^k$ . The result follows from intermediate values theorem arguments. This completes the proof of item 1. Item 2. is a consequence of (4.9) together with

$$\frac{d}{da} \left( e^{\lambda_k a} \Pi_k(0, a) \right) = [\lambda_k + \mu_0 + \mu_k(a)] e^{\lambda_k a} \Pi_k(0, a), \quad \text{a.e } a \geq 0.$$

Next, we prove that item 3., holds true. To do this, it is sufficient to show that it is satisfied for the set of initial conditions for which  $t \rightarrow \Gamma_k(t)$  is differentiable and proceeds by density. In this case, observe that for each  $t > 0$ ,

$$\begin{aligned} \frac{d\Gamma_k(t)}{dt} &= \dot{u}_k(t) + \int_0^\infty \Theta_k(\lambda_k, a) \partial_t p_k(t, a) da \\ &= \int_0^\infty r_k \mu_k(a) p_k(t, a) da \\ &\quad - \mu_{v,k} u_k(t) - \int_0^\infty \Theta_k(\lambda_k, a) [\partial_a p_k(t, a) + (\mu_k(a) + \mu_0) p_k(t, a)] da \\ &= \int_0^\infty r_k \mu_k(a) p_k(t, a) da - \mu_{v,k} u_k(t) + \Theta_k(\lambda, 0) p_k(t, 0) \\ &\quad + \int_0^\infty [\Theta_k(\lambda_k, a)' - \Theta_k(\lambda, a) (\mu_k(a) + \mu_0)] p_k(t, a) da. \end{aligned}$$



Hence using (4.5), we get

$$\begin{aligned}
\frac{d\Gamma_k(t)}{dt} &= -\mu_{v,k}u_k(t) + \Theta_k(\lambda_k, 0)\beta_k u_k(t) \sum_{j \in \mathcal{J}} \gamma_j^k R_j(t) + \lambda_k \int_0^\infty \Theta_k(\lambda_k, a)p_k(t, a)da \\
&= \lambda_k u_k(t) + \Theta_k(\lambda_k, 0)\beta_k u_k(t) \sum_{j \in \mathcal{J}} \gamma_j^k (R_j(t) - \hat{R}_j) + \lambda_k \int_0^\infty \Theta_k(\lambda_k, a)p_k(t, a)da \\
&= \lambda_k \Gamma_k(t) + \Theta_k(\lambda_k, 0)\beta_k u_k(t) \sum_{j \in \mathcal{J}} \gamma_j^k (R_j(t) - \hat{R}_j), \quad t > 0.
\end{aligned}$$

The result follows by the variation of constants formula. ■

We now turned to the proof of Theorem 4.1. ■

*Proof of Theorem 4.1.*

**Extinction.** If  $u_k(0) + \int_0^\infty p_k(0, a)da = 0$ , then the result follows from the positive invariance of  $\partial\mathcal{M}_0^k$ . Next, assume that  $\mathcal{R}_0^k < 1$ . Let us first recall that  $\mathcal{R}_0^k = \Psi_k \sum_{j \in \mathcal{J}} \gamma_j^k R_j^* < 1$ . Let  $\epsilon > 0$  such that  $\mathcal{T}_0^k = \Psi_k \sum_{j \in \mathcal{J}} \gamma_j^k (R_j^* + \epsilon) < 1$ . Then, setting  $\hat{R}_j = R_j^* + \epsilon$  in Claim 4.3, there exists  $\lambda_k^\epsilon \in \mathbb{R}$  such that  $\text{sign}(\lambda_k^\epsilon) = \text{sign}(\mathcal{T}_0^k - 1) < 0$ . Recalling that  $\limsup_{t \rightarrow +\infty} R_j(t) \leq R_j^*$ , we can find  $t_0 \geq 0$  such that

$$R_j(t) \leq R_j^* + \epsilon, \quad \forall t \geq t_0. \quad (4.11)$$

Next, define

$$\Gamma_k^\epsilon(t) = u_k(t) + \int_0^\infty \Theta_k(\lambda_k^\epsilon, a)p_k(t, a)da, \quad \forall t \geq 0.$$

Then, we deduce from (4.6) that

$$\Gamma_k^\epsilon(t) \leq e^{\lambda_k^\epsilon(t-t_0)} \Gamma_k^\epsilon(t_0), \quad \forall t \geq t_0.$$

Therefore,

$$u_k(t) \leq e^{\lambda_k^\epsilon(t-t_0)} \Gamma_k^\epsilon(t_0), \quad \forall t \geq t_0 \Rightarrow \lim_{t \rightarrow +\infty} u_k(t) = 0. \quad (4.12)$$

Finally, from the Volterra formulation (3.3) we find, for each  $t \geq t_0$ ,

$$\int_0^{+\infty} p_k(t, a)da = \int_0^{t-t_0} \Pi_k(a, 0) \beta_k u_k(t-a) \sum_{j \in \mathcal{J}} \gamma_j^k R_j(t-a)da + \int_{t-t_0}^{+\infty} \Pi_k(a, a-t+t_0)p_k(t_0, a-t+t_0)da$$

so that (4.11) and (4.12) imply

$$\int_0^{+\infty} p_k(t, a)da \leq \int_0^t e^{-\mu_0 a} \beta_k \Gamma_k^\epsilon(t_0) e^{\lambda_k^\epsilon(t-a)} \sum_{j \in \mathcal{J}} \gamma_j^k (R_j^* + \epsilon)da + e^{-\mu_0(t-t_0)} \int_0^{+\infty} p_k(t_0, a)da.$$

The result follows by taking the limit when  $t \rightarrow +\infty$ .

**Uniform persistence.** We first notice that the instability of the parasite-free equilibrium when  $\mathcal{R}_0 > 1$  is a consequence of Lemma 3.2. Indeed, at the parasite-free equilibrium (let say  $\bar{\varphi}_0$ ) the functions  $\Delta_k$  satisfy  $\Delta_k(0, \bar{\varphi}_0) = 1 - \mathcal{R}_0^k < 0$  and  $\Delta_k(\lambda, \bar{\varphi}_0) \rightarrow 1$  as  $\lambda \rightarrow \infty$ . Which ensures the existence of a strictly positive eigenvalue and the instability of  $\bar{\varphi}_0$  with respect to the semiflow follows.

For the uniform persistence, recall that, by Proposition 4.2,  $\mathcal{M}_0$ ,  $\partial\mathcal{M}_0$  and  $\mathcal{M}$  are positively invariant with respect to the semiflow generated by System (2.2). Then, the semiflow restricted to  $\mathcal{M}$  possesses a compact global attractor. Thus, to prove the uniform persistence of the parasites with respect to the decomposition  $(\mathcal{M}_0, \partial\mathcal{M}_0)$ , it is sufficient to prove that  $\partial\mathcal{M}_0$  is  $\xi$ -ejective [27, 38]. We then claim that

**Claim 4.5** *If  $\mathcal{R}_0 > 1$ , then  $\partial\mathcal{M}_0$  is  $\xi$ -ejective; i.e. there exists  $\eta > 0$  such that if*

$$0 < \xi(\mathbf{R}(0), \mathbf{u}(0), \mathbf{p}(0, \cdot)) < \eta,$$

*then there exists  $t_0 > 0$  such that*

$$\xi(\mathbf{R}(t_0), \mathbf{u}(t_0), \mathbf{p}(t_0, \cdot)) \geq \eta.$$

*Proof of Claim 4.5.* Since  $\mathcal{R}_0 = \max(\mathcal{R}_0^k)_k > 1$ , there exists  $k \in \{1, \dots, n\}$  such that  $\mathcal{R}_0^k = \Psi_k \sum_{j \in \mathcal{J}, \gamma_j^k R_j^*} > 1$ . First, observe that

$$\lim_{\delta \rightarrow 0^+} \Psi_k \sum_{i=1}^3 \prod_{j=1}^i \frac{\mu_j}{\mu_j + \delta} \gamma_i^k R_i^* = \mathcal{R}_0^k > 1,$$

where we have used the correspondences  $r \equiv 1$ ,  $m \equiv 2$  and  $s \equiv 3$ . Thus, by continuity, there exists  $\delta_1 > 0$  such that

$$\Psi_k \sum_{i=1}^3 \prod_{j=1}^i \frac{\mu_j}{\mu_j + \delta} \gamma_i^k R_i^* > 1, \quad \forall \delta \in [0, \delta_1]. \quad (4.13)$$

Next, we argue by contradiction. Let  $\delta_0 \in (0, \delta_1)$  be given and fixed such that

$$0 \leq \xi(\mathbf{R}(t), \mathbf{u}(t), \mathbf{p}(t)) < \eta, \quad \forall t \geq 0 \Rightarrow 0 \leq \sum_{k=1}^n \left( u_k(t) + \int_0^{+\infty} p_k(t, a) da \right) < \eta, \quad \forall t \geq 0, \quad (4.14)$$

with

$$\eta := \delta_0 \left( \max_{l=1, \dots, n} \beta_l \right)^{-1}.$$

Then, we have

$$\sum_{l=1}^n \gamma_j^l \beta_l u_l(t) \leq \max_{l=1, \dots, n} \beta_l \sum_{l=1}^n u_l(t) \leq \delta_0, \quad j = 1, 2, 3,$$

so that

$$\begin{cases} \dot{R}_1(t) \geq \Lambda_0 - \mu_1 R_1(t) - \delta_0 R_1(t), & t > 0, \\ \dot{R}_2(t) \geq \mu_1 R_1(t) - \mu_2 R_2(t) - \delta_0 R_2(t), & t > 0, \\ \dot{R}_3(t) \geq \mu_2 R_2(t) - \mu_3 R_3(t) - \delta_0 R_3(t), & t > 0. \end{cases}$$

Thus, we deduce that

$$\liminf_{t \rightarrow +\infty} R_1(t) \geq \frac{\Lambda_0}{\mu_1 + \delta_0} = \frac{\mu_1}{\mu_1 + \delta_0} R_1^*, \quad \liminf_{t \rightarrow +\infty} R_2(t) \geq \frac{\Lambda_0}{\mu_2 + \delta_0} \frac{\mu_1}{\mu_1 + \delta_0} = \frac{\mu_2}{\mu_2 + \delta_0} \frac{\mu_1}{\mu_1 + \delta_0} R_2^*$$

and

$$\liminf_{t \rightarrow +\infty} R_3(t) \geq \frac{\Lambda_0}{\mu_3 + \delta_0} \frac{\mu_2}{\mu_2 + \delta_0} \frac{\mu_1}{\mu_1 + \delta_0} = \frac{\mu_3}{\mu_3 + \delta_0} \frac{\mu_2}{\mu_2 + \delta_0} \frac{\mu_1}{\mu_1 + \delta_0} R_3^*.$$

Because

$$\prod_{j=1}^i \frac{\mu_j}{\mu_j + \delta_0} R_i^* > \prod_{j=1}^i \frac{\mu_j}{\mu_j + \delta_1} R_i^*, \quad \forall i = 1, 2, 3,$$

there exists  $t_0 \geq 0$  such that for each  $i = 1, 2, 3$ ,

$$R_i(t) \geq \prod_{j=1}^i \frac{\mu_j}{\mu_j + \delta_1} R_i^*, \quad \forall t \geq t_0. \quad (4.15)$$

Hence, setting  $\widehat{R}_i = \prod_{j=1}^i \frac{\mu_j}{\mu_j + \delta_1} R_i^*$ ,  $i = 1, 2, 3$ , in Claim 4.3, from (4.13) it follows that

$$\mathcal{T}_0^k = \Psi_k \sum_{j=1}^3 \gamma_j^k \widehat{R}_j > 1.$$

This provides that the  $\lambda_k$  in Claim 4.3 have the sign of  $\text{sign}(\mathcal{T}_0^k - 1) > 0$ . Furthermore, (4.15) implies that the map  $t \rightarrow \Gamma_k(t)$  provided by Claim 4.3 satisfies

$$\begin{aligned} \Gamma_k(t) &= e^{\lambda_k(t-t_0)} \Gamma_k(t_0) + \int_{t_0}^t e^{\lambda_k(t-s)} \Theta_k(\lambda_k, 0) \beta_k u_k(s) \sum_{j=1}^3 \gamma_j^k (R_j(s) - \widehat{R}_j) ds, \quad t \geq t_0 \\ &\geq e^{\lambda_k(t-t_0)} \Gamma_k(t_0), \quad t \geq t_0. \end{aligned}$$

Hence,

$$\lim_{t \rightarrow +\infty} \Gamma_k(t) = +\infty \Leftrightarrow \lim_{t \rightarrow +\infty} \left( u_k(t) + \int_0^{+\infty} \Theta_k(\lambda_k, a) p_k(t, a) da \right) = +\infty.$$

Because  $a \rightarrow \Theta_k(\lambda_k, a)$  belongs to  $L_+^\infty((0, +\infty), \mathbb{R})$ , the foregoing limit contradict (4.14). ■ ■

## 5 Nontrivial equilibrium of System (2.2)

Here, we provide some useful results and remarks on the nontrivial equilibrium of System (2.2), *i.e.*, other equilibria than the parasite-free equilibrium. To simplify the presentation, in this section we use the correspondences  $\mathcal{J} \equiv (1, 2, 3)$  for the uRBCs stages.

**Lemma 5.1** *Let  $(\bar{\mathbf{R}}, \bar{\mathbf{u}}, \bar{\mathbf{p}})$  is a nonnegative equilibrium of System (2.2), with  $\bar{\mathbf{R}} = (\bar{R}_j)_{j=1,2,3}$ ,  $\bar{\mathbf{u}} = (\bar{u}_k)_{k=1,\dots,n}$ ,  $\bar{\mathbf{p}} = (\bar{p}_k)_{k=1,\dots,n}$ . Then,*

1. *We have the following fixed point problem*

$$\begin{cases} \mathbf{R} = \mathbf{R}^* - \mathbf{m}^{-1} \text{diag}(\gamma \beta \bar{\mathbf{u}}) \bar{\mathbf{R}}, \\ \bar{\mathbf{u}} = \left[ \boldsymbol{\mu}_v^{-1} \mathbf{r} \int_0^{+\infty} \boldsymbol{\mu}(a) \Pi(a, 0) da \text{diag}(\gamma^T \mathbf{R}^*) \beta \right] \bar{\mathbf{u}}, \end{cases} \quad (5.1)$$

where

$$\bar{\mathbf{p}}(a) = \Pi(a, 0) \text{diag}(\beta \bar{\mathbf{u}}) \gamma^T \bar{\mathbf{R}} = \Pi(a, 0) \text{diag}(\gamma^T \bar{\mathbf{R}}) \beta \bar{\mathbf{u}}. \quad (5.2)$$

2. *The equilibrium  $(\bar{\mathbf{R}}, \bar{\mathbf{u}}, \bar{\mathbf{p}})$  satisfies*

$$\begin{cases} \bar{R}_i = R_i^* - \frac{1}{\mu_i} \sum_{j=1}^i \sum_{k=1}^n \beta_k \bar{u}_k \gamma_j^k \bar{R}_j, \quad i = 1, 2, 3, \\ \bar{u}_k \sum_{j=1}^3 \gamma_j^k R_j^* = \bar{u}_k \mathcal{R}_0^k \sum_{j=1}^3 \gamma_j^k \bar{R}_j, \quad k = 1, \dots, n, \\ \bar{p}_k(a) = \frac{1}{\mathcal{R}_0^k} \Pi_k(a, 0) \beta_k \bar{u}_k \sum_{j=1}^3 \gamma_j^k R_j^*, \quad k = 1, \dots, n. \end{cases} \quad (5.3)$$

3. *Let  $k \in \{1, \dots, n\}$  be a given species. If  $\mathcal{R}_0^k < 1$  then, the  $k$ -th component of the equilibrium  $(\bar{\mathbf{R}}, \bar{\mathbf{u}}, \bar{\mathbf{p}})$  is such that  $\bar{u}_k = 0$  and  $\bar{p}_k \equiv 0$ .*

*Proof.* The proof of item 1. is straightforward and directly comes from System (2.6). Item 2. is the explicit formulation of (5.1)-(5.2) and the definition of  $\mathcal{R}_0^k$ s in (4.1). For Item 3, assume that  $\mathcal{R}_0^k < 1$ . Since the map  $\mathbf{R} \rightarrow \mathbf{M}(\mathbf{R})$  is increasing, from (5.1), it comes  $\mathbf{R} \leq \mathbf{R}^*$  and

$$\mathbf{u} \leq \mathbf{M}(\mathbf{R}^*)\mathbf{u} \Rightarrow u_k \leq \mathcal{R}_0^k u_k \Rightarrow u_k = 0.$$

Since  $\Pi(a, 0)\text{diag}(\gamma^T \mathbf{R})\beta$  is an invertible diagonal matrix, from (5.2), it follows that  $p_k \equiv 0$ .  $\blacksquare$

Next, let us introduce  $\mathcal{S}$  and  $\mathcal{S}'$  subsets of index  $\{1, \dots, n\}$  such that

$$\begin{aligned} k \in \mathcal{S} &\Leftrightarrow \mathcal{R}_0^k \leq 1, \\ k \in \mathcal{S}' &\Leftrightarrow \mathcal{R}_0^k > 1. \end{aligned}$$

The following result holds.

**Theorem 5.2** *Let  $(\bar{\mathbf{R}}, \bar{\mathbf{u}}, \bar{\mathbf{p}})$  is a non-negative equilibrium of System (2.2), with  $\bar{\mathbf{R}} = (\bar{R}_j)_{j=1,2,3}$ ,  $\bar{\mathbf{u}} = (\bar{u}_k)_{k=1, \dots, n}$ ,  $\bar{\mathbf{p}} = (\bar{p}_k)_{k=1, \dots, n}$ . Then,*

1. *For all  $k \in \mathcal{S}$ ,  $\bar{u}_k = 0$  and  $\bar{p}_k \equiv 0$ . Consequently, when  $\mathcal{R}_0 \leq 1$  the parasite-free equilibrium is the unique equilibrium of (2.2).*

2. *If  $\bar{u}_k > 0$  then, the following properties hold*

(i)  $\bar{p}_k(a) > 0$  for all  $a \geq 0$ , and  $\bar{p}_k(a) = \frac{1}{\mathcal{R}_0^k} \Pi_k(a, 0) \beta_k \bar{u}_k \sum_{j=1}^3 \gamma_j^k R_j^*$ .

(ii) For each  $i = 1, 2, 3$ ;  $\bar{R}_i = \prod_{j=1}^i \frac{\mu_j}{\mu_j + \bar{x}_j} R_i^*$ , with  $\bar{x}_i := \sum_{k \in \mathcal{S}'} \beta_k \bar{u}_k \gamma_i^k$ .

(iii)  $\frac{1}{\mathcal{R}_0^k} \sum_{i=1}^3 \gamma_i^k R_i^* = \sum_{i=1}^3 \gamma_i^k \prod_{j=1}^i \frac{\mu_j}{\mu_j + \bar{x}_j} R_i^*$ .

3.  $(\bar{\mathbf{R}}, \bar{\mathbf{u}}, \bar{\mathbf{p}})$  is a positive equilibrium with the  $k$ -th component  $\bar{u}_k > 0$  if and only if  $(\bar{x}_i = \sum_{l \in \mathcal{S}'} \beta_l \bar{u}_l \gamma_i^l)_{i=1,2,3}$  is a solution of

$$\frac{1}{\mathcal{R}_0^k} \sum_{i=1}^3 \gamma_i^k R_i^* = \sum_{i=1}^3 \gamma_i^k \prod_{j=1}^i \frac{\mu_j}{\mu_j + \bar{x}_j} R_i^*.$$

*Proof.* We start with the proof of Item 1. If  $\mathcal{R}_0^k < 1$ , then we infer from Lemma 5.1 that  $\bar{u}_k = 0$  and  $\bar{p}_k \equiv 0$ . Denote by  $\partial\mathcal{S}$  the subset of  $\mathcal{S}$  such that

$$k \in \partial\mathcal{S} \Leftrightarrow \mathcal{R}_0^k = 1.$$

Next, we argue by contradiction. Suppose that there is a non-empty set of index  $\mathcal{V} \subset \partial\mathcal{S}$  such that  $\mathcal{R}_0^k = 1$  and  $u_k > 0$  for all  $k \in \mathcal{V}$ . Thus, we infer from (5.3) that

$$\mathcal{R}_0^k = 1, \forall k \in \mathcal{V} \Leftrightarrow \sum_{i=1}^3 \gamma_i^k R_i^* = \sum_{i=1}^3 \gamma_i^k \bar{R}_i, \forall k \in \mathcal{V} \quad (5.4)$$

and

$$\bar{R}_i = R_i^* - \frac{1}{\mu_i} \sum_{j=1}^i \sum_{k \in \mathcal{V}} \beta_k \bar{u}_k \gamma_j^k \bar{R}_j, \quad i = 1, 2, 3. \quad (5.5)$$

Hence, multiplying (5.5) by  $\gamma_i^k$  and summing up to  $i = 3$  we get

$$\sum_{i=1}^3 \gamma_i^k \bar{R}_i = \sum_{i=1}^3 \gamma_i^k R_i^* - \sum_{i=1}^3 \frac{\gamma_i^k}{\mu_i} \sum_{j=1}^i \sum_{k \in \mathcal{V}} \beta_k \bar{u}_k \gamma_j^k \bar{R}_j. \quad (5.6)$$

Combining (5.6) together with (5.4), we obtain

$$\sum_{i=1}^3 \frac{\gamma_i^k}{\mu_i} \sum_{j=1}^i \sum_{k \in \mathcal{V}} \beta_k \bar{u}_k \gamma_j^k \bar{R}_j = 0 \Rightarrow \sum_{k \in \mathcal{V}} \beta_k \bar{u}_k \frac{\gamma_i^k}{\mu_i} \gamma_i^k \bar{R}_i = 0, \quad i = 1, 2, 3.$$

Since  $\gamma_i^k \gamma_i^k = \gamma_i^k$ , we obtain

$$\sum_{k \in \mathcal{V}} \beta_k \bar{u}_k \gamma_i^k \bar{R}_i = 0, \quad i = 1, 2, 3 \Rightarrow \sum_{k \in \mathcal{V}} \beta_k \bar{u}_k \sum_{i=1}^3 \gamma_i^k \bar{R}_i = 0.$$

Hence

$$\beta_k \bar{u}_k \sum_{i=1}^3 \gamma_i^k \bar{R}_i = 0, \quad k \in \mathcal{V}.$$

Thus, using the fact that  $\sum_{i=1}^3 \gamma_i^k \bar{R}_i = \sum_{i=1}^3 \gamma_i^k \bar{R}_i^* > 0$ , we conclude that  $\bar{u}_k = 0$  for all  $k \in \mathcal{V}$ . This gives a contradiction and the proof of Item 1. is completed.

Next, for Item 2., we only need to prove (ii) because the properties (i) and (iii) are consequences of (ii) and Lemma 5.1. Let  $\bar{x}_i$  be defined by  $\bar{x}_i = \sum_{k \in \mathcal{S}'} \beta_k \bar{u}_k \gamma_i^k$ ,  $i = 1, 2, 3$ . Since  $\bar{u}_k = 0$  for all  $k \notin \mathcal{S}'$  we also have  $\bar{x}_i = \sum_{k=1}^n \beta_k \bar{u}_k \gamma_i^k$ ,  $i = 1, 2, 3$ . Then (5.3) ensures that

$$\bar{R}_i = R_i^* - \frac{1}{\mu_i} \sum_{j=1}^i \bar{x}_j \bar{R}_j, \quad i = 1, 2, 3.$$

For  $i = 1$ , we have

$$\bar{R}_1 = R_1^* - \frac{1}{\mu_1} \bar{x}_1 \bar{R}_1 \Leftrightarrow \bar{R}_1 = \frac{\mu_1}{\mu_1 + \bar{x}_1} R_1^*$$

and for  $i = 2$ ,

$$\bar{R}_2 = R_2^* - \frac{1}{\mu_2} (\bar{x}_1 \bar{R}_1 + \bar{x}_2 \bar{R}_2) \Leftrightarrow \bar{R}_2 = \frac{1}{\mu_2 + \bar{x}_2} (\mu_2 R_2^* - \bar{x}_1 \bar{R}_1) = \frac{1}{\mu_2 + \bar{x}_2} \left( \mu_2 R_2^* - \frac{\bar{x}_1}{\mu_1 + \bar{x}_1} \mu_1 R_1^* \right).$$

From the equality  $\mu_2 R_2^* = \mu_1 R_1^*$ , we get

$$\bar{R}_2 = \frac{\mu_2 R_2^*}{\mu_2 + \bar{x}_2} \left( 1 - \frac{\bar{x}_1}{\mu_1 + \bar{x}_1} \right) = \frac{\mu_2}{\mu_2 + \bar{x}_2} \frac{\mu_1}{\mu_1 + \bar{x}_1} R_2^*.$$

For  $i = 3$ ,

$$\bar{R}_3 = R_3^* - \frac{1}{\mu_3} (\bar{x}_1 \bar{R}_1 + \bar{x}_2 \bar{R}_2 + \bar{x}_3 \bar{R}_3) \Leftrightarrow \bar{R}_3 = \frac{1}{\mu_3 + \bar{x}_3} [\mu_3 R_3^* - \bar{x}_1 \bar{R}_1 - \bar{x}_2 \bar{R}_2].$$

Hence

$$\bar{R}_3 = \frac{1}{\mu_3 + \bar{x}_3} \left[ \mu_3 R_3^* - \frac{\bar{x}_1}{\mu_1 + \bar{x}_1} \mu_1 R_1^* - \frac{\bar{x}_2}{\mu_2 + \bar{x}_2} \frac{\mu_1}{\mu_1 + \bar{x}_1} \mu_2 R_2^* \right]$$

and recalling that  $\mu_3 R_3^* = \mu_2 R_2^* = \mu_1 R_1^*$ , we obtain

$$\begin{aligned} \bar{R}_3 &= \frac{\mu_3 R_3^*}{\mu_3 + \bar{x}_3} \left[ 1 - \frac{\bar{x}_1}{\mu_1 + \bar{x}_1} - \frac{\bar{x}_2}{\mu_2 + \bar{x}_2} \frac{\mu_1}{\mu_1 + \bar{x}_1} \right] \\ &= \frac{\mu_3 R_3^*}{\mu_3 + \bar{x}_3} \left[ \frac{\mu_1}{\mu_1 + \bar{x}_1} - \frac{\bar{x}_2}{\mu_2 + \bar{x}_2} \frac{\mu_1}{\mu_1 + \bar{x}_1} \right] \\ &= \frac{\mu_3 R_3^*}{\mu_3 + \bar{x}_3} \frac{\mu_1}{\mu_1 + \bar{x}_1} \left[ 1 - \frac{\bar{x}_2}{\mu_2 + \bar{x}_2} \right] \\ &= \frac{\mu_3}{\mu_3 + \bar{x}_3} \frac{\mu_1}{\mu_1 + \bar{x}_1} \frac{\mu_2}{\mu_2 + \bar{x}_2} R_3^*, \end{aligned}$$

which ends the proof of Item 2.

Finally, Item 3. is a consequence of Item 2, and this completes the proof of the theorem. ■

## 6 Applications

This section describes how our general analysis can be applied in some configurations : (FV-model) co-infection by *P. Falciparum* and *P. Vivax*, (FM-model) co-infection model by *P. Falciparum* and *P. Malariae*, (VM-model) co-infection model by *P. Vivax* and *P. Malariae*, and (FVM-model) co-infection by the three malaria species. Due to our general model formulation (2.2), to explore a given scenario we only need to define the parasites preference targets matrix  $\gamma$  introduced by (2.7) and apply results in Section 5. Furthermore, By Theorems 4.1 and 5.2, the parasite-free equilibrium is the unique equilibrium of the general model (2.2) when  $\mathcal{R}_0 < 1$ . Moreover, the parasite-free equilibrium is globally asymptotically stable when  $\mathcal{R}_0 < 1$  and unstable when  $\mathcal{R}_0 > 1$ . We now focus on the equilibria of different models scenarios derived from the general model formulation when  $\mathcal{R}_0 > 1$ .

Next, for all simulations, the infection rates  $(\beta_{k,s})$  are estimated thanks to the basic reproduction number  $(\mathcal{R}_{0,k})$ . Indeed, by (4.1)-(4.2) we have for each  $k$ -species

$$\beta_k = \mathcal{R}_0^k \left[ \frac{r_k \alpha_k e^{-\mu_0 \tau_k}}{\mu_{v,k}(\alpha_k + \mu_0)} \sum_{j \in \mathcal{J}} \gamma_j^k R_j^* \right]^{-1}. \quad (6.1)$$

Finally, all other model parameters and initial conditions are summarized in Table 1.

### 6.1 FV-model: co-infection by *P. Falciparum* and *P. Vivax*

With the parasites preference targets matrix  $\gamma = \begin{pmatrix} 1 & 1 \\ 1 & 0 \\ 1 & 0 \end{pmatrix}$ , the general Model (2.2) leads to the FV-model

where subscripts  $k = F, V$  stand for *Falciparum* and *Vivax* respectively. Recalling the definition of  $\mathcal{R}_0$  and  $\mathcal{R}_0^k$  ( $k = F, V$ ) given by (4.1) we have the following results on the equilibria of the FV-model.

**Theorem 6.1** 1. If  $\mathcal{R}_0^F > 1$  and  $\mathcal{R}_0^V \leq 1$  then, the FV-model has two equilibria : the parasite-free equilibrium and the boundary equilibrium with  $\bar{u}_V = 0$ ,  $\bar{p}_V \equiv 0$ ,  $\bar{x}_r = \beta_F \bar{u}_F$  and

$$\begin{aligned} \bar{R}_r &= \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^*, \quad \bar{R}_m = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} R_m^*, \quad \bar{R}_s = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} \frac{\mu_s}{\mu_s + \bar{x}_r} R_s^*, \\ \bar{p}_F(a) &= \frac{1}{\mathcal{R}_0^F} \bar{x}_r \Pi_F(a, 0) \sum_{j \in \mathcal{J}} R_j^*, \quad \forall a \geq 0, \end{aligned}$$

where  $\bar{x}_r > 0$  is the unique solution of

$$1 = \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} \left[ q_r^* + \frac{\mu_m}{\mu_m + \bar{x}_r} q_m^* + \frac{\mu_m}{\mu_m + \bar{x}_r} \frac{\mu_s}{\mu_s + \bar{x}_r} q_s^* \right].$$

2. If  $\mathcal{R}_0^F \leq 1$  and  $\mathcal{R}_0^V > 1$  then, the FV-model has two equilibria : the parasite-free equilibrium and the boundary equilibrium with  $\bar{u}_F = 0$ ,  $\bar{p}_F \equiv 0$  and

$$\begin{aligned} \beta_V \bar{u}_V &= \mu_r (\mathcal{R}_0^V - 1), \quad \bar{R}_j = \frac{R_j^*}{\mathcal{R}_0^V}, \quad j \in \mathcal{J}, \\ \bar{p}_V(a) &= \frac{\beta_V \bar{u}_V}{\mathcal{R}_0^V} \Pi_V(a, 0) R_r^*, \quad \forall a \geq 0. \end{aligned}$$

3. The FV-model has two equilibria : the parasite-free equilibrium and the positive equilibrium with  $\bar{u}_F > 0$ ,  $\bar{u}_V > 0$  if and only if

$$\mathcal{R}_0^F > \mathcal{R}_0^V > 1, \quad (6.2)$$

and

$$1 > \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} \left[ q_r^* + \frac{\mu_m}{\mu_m + \mu_r (\mathcal{R}_0^V - 1)} \left( q_m^* + \frac{\mu_s}{\mu_s + \mu_r (\mathcal{R}_0^V - 1)} q_s^* \right) \right]. \quad (6.3)$$

Furthermore, by setting  $\bar{x}_r = \beta_F \bar{u}_F + \beta_V \bar{u}_V$  and  $\bar{x}_m = \beta_F \bar{u}_F$ , we have  $\beta_V \bar{u}_V = \mu_r (\mathcal{R}_0^F - 1) - \bar{x}_m$  and

$$\begin{aligned} \bar{R}_r &= \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^*, \quad \bar{R}_m = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} R_m^*, \quad \bar{R}_s = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} \frac{\mu_s}{\mu_s + \bar{x}_m} R_s^*, \\ \bar{p}_j(a) &= \frac{1}{\mathcal{R}_0^j} \Pi_j(a, 0) \beta_i \bar{u}_i \sum_{i \in \mathcal{I}} \gamma_j^i R_i^*, \quad \forall a \geq 0, \quad i = F, V, \end{aligned}$$

where  $\bar{x}_m \in ]0, \mu_r (\mathcal{R}_0^F - 1)[$  is the unique solution of

$$1 = \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} \left[ q_r^* + \frac{\mu_m}{\mu_m + \bar{x}_m} q_m^* + \frac{\mu_m}{\mu_m + \bar{x}_m} \frac{\mu_s}{\mu_s + \bar{x}_m} q_s^* \right].$$

Finally, if (6.2) is satisfied and not (6.3), the positive equilibrium does not exist and we have a boundary equilibrium with  $\bar{u}_F = 0$ ,  $\bar{p}_F \equiv 0$ . Similarly, if  $\mathcal{R}_0^V > \mathcal{R}_0^F > 1$ , the positive equilibrium does not exist and we have a boundary equilibrium with  $\bar{u}_V = 0$ ,  $\bar{p}_V \equiv 0$ .

## 6.2 FM-model: co-infection by *P. Falciparum* and *P. Malariae*

With the parasites preference targets matrix  $\gamma = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 1 \end{pmatrix}$ , the general Model (2.2) leads to the FM-model

where subscripts  $k = F, M$  stand for *Falciparum* and *Malariae* respectively. Recalling the definition of  $\mathcal{R}_0$  and  $\mathcal{R}_0^k$  ( $k = F, M$ ) given by (4.1) we have the following results on the equilibrium of the FM-model.

**Theorem 6.2** 1. If  $\mathcal{R}_0^F > 1$  and  $\mathcal{R}_0^M \leq 1$  then, the FM-model has two equilibria : the parasite-free equilibrium and the boundary equilibrium with  $\bar{u}_M = 0$ ,  $\bar{p}_M \equiv 0$ ,  $\bar{x}_r = \beta_F \bar{u}_F$  and

$$\begin{aligned} \bar{R}_r &= \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^*, \quad \bar{R}_m = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} R_m^*, \quad \bar{R}_s = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} \frac{\mu_s}{\mu_s + \bar{x}_r} R_s^*, \\ \bar{p}_F(a) &= \frac{1}{\mathcal{R}_0^F} \bar{x}_r \Pi_F(a, 0) \sum_{j \in \mathcal{I}} R_j^*, \quad \forall a \geq 0, \end{aligned}$$

where  $\bar{x}_r > 0$  is the unique solution of

$$\frac{1}{\mathcal{R}_0^F} = \frac{\mu_r}{\mu_r + \bar{x}_r} q_r^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} q_m^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} \frac{\mu_s}{\mu_s + \bar{x}_r} q_s^*.$$

2. If  $\mathcal{R}_0^F \leq 1$  and  $\mathcal{R}_0^M > 1$  then, the FM-model has two equilibria : the parasite-free equilibrium and the boundary equilibrium with  $\bar{u}_F = 0$ ,  $\bar{p}_F \equiv 0$ ,  $\beta_M \bar{u}_M = \mu_s (\mathcal{R}_0^M - 1)$  and

$$\begin{aligned} \bar{R}_r &= R_r^*, \quad \bar{R}_m = R_m^*, \quad \bar{R}_s = \frac{R_s^*}{\mathcal{R}_0^M}, \\ \bar{p}_M(a) &= \mu_s \frac{\mathcal{R}_0^M - 1}{\mathcal{R}_0^M} \Pi_M(a, 0) R_s^*, \quad \forall a \geq 0. \end{aligned}$$

3. The FM-model has two equilibria : the parasite-free equilibrium and the positive equilibrium with  $\bar{u}_F > 0$ ,  $\bar{u}_M > 0$  if and only if

$$\mathcal{R}_0^F > 1, \quad \mathcal{R}_0^M > 1, \quad (6.4)$$



and

$$\frac{\mu_r}{\mu_r + \bar{x}_r^{max}} q_r^* + \frac{\mu_r}{\mu_r + \bar{x}_r^{max}} \frac{\mu_m}{\mu_m + \bar{x}_r^{max}} q_m^* + \frac{1}{\mathcal{R}_0^M} q_s^* < \frac{1}{\mathcal{R}_0^F} < q_r^* + q_m^* + \frac{1}{\mathcal{R}_0^M} q_s^*, \quad (6.5)$$

where  $\bar{x}_r^{max} = \mu_s(\mathcal{R}_0^M - 1)q_s^*$ . Furthermore, we have  $\bar{x}_r = \beta_F \bar{u}_F$ ,  $\bar{x}_s = \beta_F \bar{u}_F + \beta_M \bar{u}_M$  and

$$\begin{aligned} \bar{R}_r &= \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^*, \quad \bar{R}_m = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} R_m^*, \quad \bar{R}_s = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} \frac{\mu_s}{\mu_s + \bar{x}_s} R_s^*, \\ \beta_M \bar{u}_M &= \mu_s(\mathcal{R}_0^M - 1) - \frac{1}{q_s^*} \frac{\mathcal{R}_0^M}{\mathcal{R}_0^F} \bar{x}_r, \\ \bar{p}_j(a) &= \frac{1}{\mathcal{R}_0^j} \Pi_j(a, 0) \beta_i \bar{u}_i \sum_{i \in \mathcal{I}} \gamma_j^i R_i^*, \quad \forall a \geq 0, \quad i = F, M, \end{aligned}$$

where  $\bar{x}_r \in ]0, \bar{x}_r^{max}[$  is the unique solution of

$$\frac{1}{\mathcal{R}_0^F} = \frac{\mu_r}{\mu_r + \bar{x}_r} q_r^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} q_m^* + \frac{1}{\mathcal{R}_0^M} q_s^*.$$

Finally, if (6.4) is satisfied and not (6.5), the positive equilibrium does not exist and we have a boundary equilibrium either with  $\bar{u}_F = 0$ ,  $\bar{p}_F \equiv 0$ , or with  $\bar{u}_M = 0$ ,  $\bar{p}_M \equiv 0$ .

### 6.3 VM-model: co-infection by *P. Vivax* and *P. Malariae*

With the parasites preference targets matrix  $\gamma = \begin{pmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{pmatrix}$ , the general Model (2.2) leads to the VM-model where subscripts  $k = V, M$  stand for *Vivax* and *Malariae*, respectively. Recalling the definition of  $\mathcal{R}_0$  and  $\mathcal{R}_0^k$  ( $k = V, M$ ) given by (4.1), we have the following results on the equilibrium of the VM-model.

- Theorem 6.3** 1. If  $\mathcal{R}_0^V \leq 1 < \mathcal{R}_0^M$ , then the VM-model admits two non-negative equilibria, namely, the parasite-free equilibrium and a boundary equilibrium  $(\bar{R}_r, \bar{R}_m, \bar{R}_s, 0, \bar{p}_M(a), 0, \bar{u}_M)$ .
2. If  $\mathcal{R}_0^M \leq 1 < \mathcal{R}_0^V$ , then the VM-model admits two non-negative equilibria, namely, the parasite-free equilibrium and the boundary equilibrium  $(\bar{R}_r, \bar{R}_m, \bar{R}_s, \bar{p}_V(a), 0, \bar{u}_V, 0)$ .
3. If  $1 < \mathcal{R}_0^V < \mathcal{R}_0^M$ , then VM-model admits two non-negative equilibria, namely, the parasite-free equilibrium and the coexistence equilibrium  $(\bar{R}_r, \bar{R}_m, \bar{R}_s, \bar{p}_V(a), \bar{p}_M(a), \bar{u}_V, \bar{u}_M)$ .
- Finally, the components of these equilibria are given by

$$\begin{aligned} \bar{R}_m &= \frac{\mu_r}{\mu_m} \bar{R}_r = \frac{\mu_s}{\mu_m} \frac{\mathcal{R}_0^M}{\mathcal{R}_0^V} \bar{R}_s = \frac{\mu_r}{\mu_m} \frac{R_r^*}{\mathcal{R}_0^V}, \quad \bar{u}_V = \frac{\mu_r}{\beta_V} (\mathcal{R}_0^V - 1), \quad \bar{u}_M = \frac{\mu_s}{\beta_M} \left( \frac{\mathcal{R}_0^M}{\mathcal{R}_0^V} - 1 \right), \\ \bar{p}_V(a) &= \frac{R_r^*}{\mathcal{R}_0^V} \beta_V \bar{u}_V \Pi_V(a, 0), \quad \bar{p}_M(a) = \frac{R_s^*}{\mathcal{R}_0^M} \beta_M \bar{u}_M \Pi_M(a, 0). \end{aligned}$$

Theorems 6.1, 6.2 and 6.3 allow, respectively, in summarizing the qualitative dynamics of the FV-, FM-, and VM-models with respect to the basic reproduction numbers  $\mathcal{R}_{0,s}^k$  ( $k = F, V, M$ ). These dynamics range from the extinction of both species, the persistence of one of those species, to the coexistence of both species for each model, FV-model (Figure 2), FM-model (Figure 3), and VM-model (Figure 4). We refer to Section B for the proof of Theorem 6.1. The proof of Theorems 6.2 and 6.3 is very similar to the proof of Theorem 6.1.

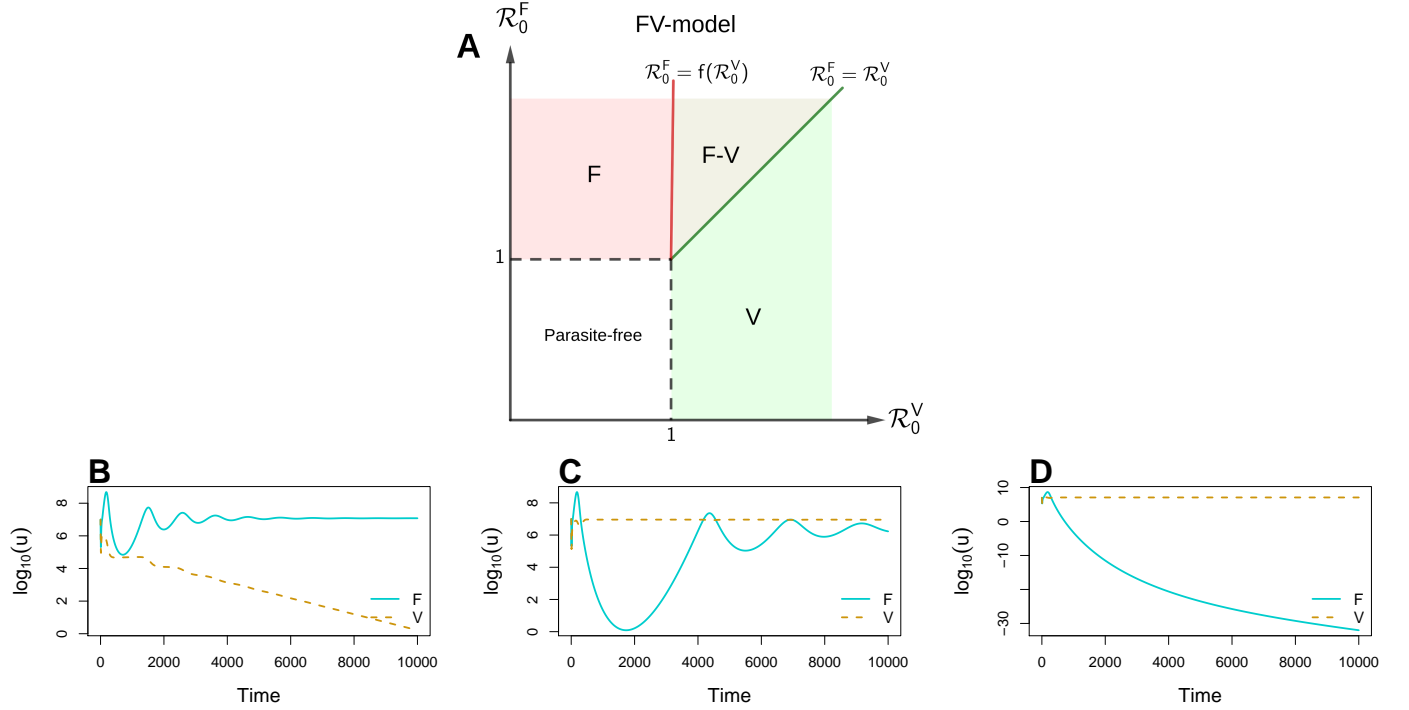


Figure 2: **Overview of the FV-model qualitative dynamics.** (A) Possible equilibria of the FV-model with respect to  $\mathcal{R}_0^F$  and  $\mathcal{R}_0^V$ . (B) Exclusion of species V, with  $(\mathcal{R}_0^F, \mathcal{R}_0^V) = (7, 1.01)$ . (C) Coexistence of both species F and V, with  $(\mathcal{R}_0^F, \mathcal{R}_0^V) = (7, 3)$ . (D) Exclusion of species F, with  $(\mathcal{R}_0^F, \mathcal{R}_0^V) = (7, 8)$ . The function  $f$  is defined by  $f(x) = x \left[ q_r^* + \frac{\mu_m}{\mu_m + \mu_r(x-1)} \left( q_m^* + \frac{\mu_s}{\mu_s + \mu_r(x-1)} q_s^* \right) \right]^{-1}$ , and other model parameters are given by Table 1.

## 7 Discussion

Human malaria is caused by diverse species of *Plasmodium spp.* [36] (e.g., *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*). The prevalence of mixed human malaria parasite infection is globally widespread, and mixed *Plasmodium spp.* infections is then common but often unrecognized or underestimated [23, 28]. From a fundamental standpoint, several mathematical models have been developed to study the within-host parasite multiplication in the context of mixed malaria infections, e.g. [9, 11, 22, 45]. These studies mostly tackle the issue of malaria infections with more than one genotype from a particular species within a single host, and not the case mixed-species *Plasmodium* infection within a single host. By ignoring the phenotypic plasticity in red blood cells (RBCs) preference, which is fundamental in the context of mixed-species *Plasmodium* infections, those studies can somewhat lead to a quite confusive conclusion with respect to the copersistence of multiple *Plasmodium* species within the same host. Indeed, *Plasmodium spp.* exhibit differential preferences for RBCs of differing ages. In human parasite species, *P. vivax* and *P. ovale* have a predilection for reticulocytes, *P. malariae* for mature RBCs, and *P. falciparum* for all types [32].

Here, we show that such a differential ecological characteristics of *Plasmodium* species within their vertebrate host is fundamental to capture species diversity within the same host. For that end, we formulate a within-host malaria infection coupled with RBCs production. For uninfected RBCs (uRBCs) dynamics, we consider the reticulocyte, mature RBC and senescent RBC. For the parasitized stage, we consider an age-structured dynamics for the parasitized RBCs (pRBC). Here, the age is a continuous variable representing the time since the concerned RBC is parasitized. Such a continuous age structure will allow us to track the development and maturity of pRBCs, but also to have a refined description of

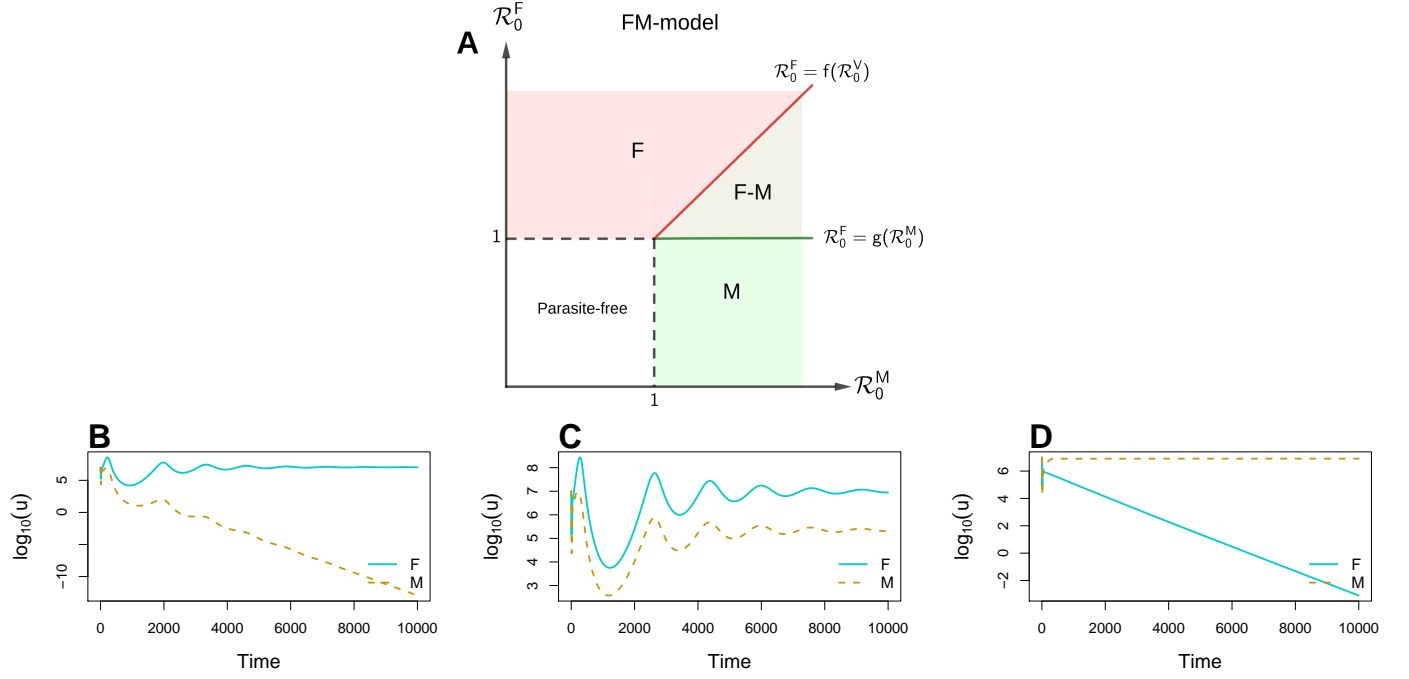


Figure 3: **Overview of the FM-model qualitative dynamics.** (A) Possible equilibria of the FM-model with respect to  $\mathcal{R}_0^F$  and  $\mathcal{R}_0^M$ . (B) Exclusion of species M, with  $(\mathcal{R}_0^F, \mathcal{R}_0^M) = (5, 4)$ . (C) Coexistence of both species F and M, with  $(\mathcal{R}_0^F, \mathcal{R}_0^M) = (3.5, 4)$ . (D) Exclusion of species F, with  $(\mathcal{R}_0^F, \mathcal{R}_0^M) = (0.9, 2.5)$ . The functions  $f$  and  $g$  are defined by  $f(x) = \left[ \frac{q_s^*}{x} + \frac{\mu_r}{\mu_r + \mu_s(x-1)q_s^*} \left( q_r^* + \frac{\mu_m}{\mu_m + \mu_s(x-1)q_s^*} q_m^* \right) \right]^{-1}$ ,  $g(x) = \left( q_r^* + q_m^* + \frac{q_s^*}{x} \right)^{-1}$ , and other model parameters are given by Table 1.

the pRBC rupture and of the merozoites release phenomenon [13].

By equality (4.4), we have shown that without any difference for the RBCs preferences, the general Model (2.2) admits an optimisation principle based on  $\mathcal{R}_0$ . Therefore, in such configurations, Model (2.2) is actually for a multistrains infection of the same species. Furthermore, the long-term coexistence of different strains is not possible and the model exhibits a competitive exclusion principle, *i.e.*, only the strain with the highest  $\mathcal{R}_0$  survives while the others go to extinction. This is in accordance with the results in [11, 22, 40, 42, 45] for instance.

Our analysis suggests that the co-existence of *Plasmodium* species can be characterized as soon as the basic reproduction numbers  $\mathcal{R}_{0,s}^k$  are known. *E.g.*, the co-existence of *P. Vivax* and *P. Malariae* is guarantee by the simple inequality  $(1 < \mathcal{R}_0^V < \mathcal{R}_0^M)$ , Figure 4. For the co-infection model by *P. Falciparum* and *P. Vivax*, the persistence of both species at equilibrium is ensured by conditions (6.2)-(6.3). However, based on the model's parameters in Table 1, the condition (6.3) is almost always satisfied. Consequently, the simpler condition  $(\mathcal{R}_0^F > \mathcal{R}_0^V > 1)$  can be a good approximation of (6.2)-(6.3) ensuring the co-existence of both species at equilibrium (Figure 2A). Similarly, condition (6.4)-(6.5) for the co-existence of *P. Falciparum* and *P. Malariae* can be simply approximate by  $(\mathcal{R}_0^M > \mathcal{R}_0^F > 1)$ , Figure 3.

Furthermore, the competitive advantage of a given species in mixed malaria infections within the host is then determined by the RBCs age preference and the basic reproduction number of the individual species. Species with a higher basic reproduction number, a wider age preference for RBCs and an earlier age preference for RBCs will have a better competitive ability (*i.e.*, either by exclusion of other species or by coexistence with them). Indeed, for the FV-model, *P. Vivax* has wider age preference for reticulocytes compared to *P. Falciparum* such that the former is associated with a broader region of competitive ability in the plane  $\mathcal{R}_0^V$ - $\mathcal{R}_0^F$  (Figure 2A). Similarly, *P. Falciparum* and *P. Vivax* have a broader region of

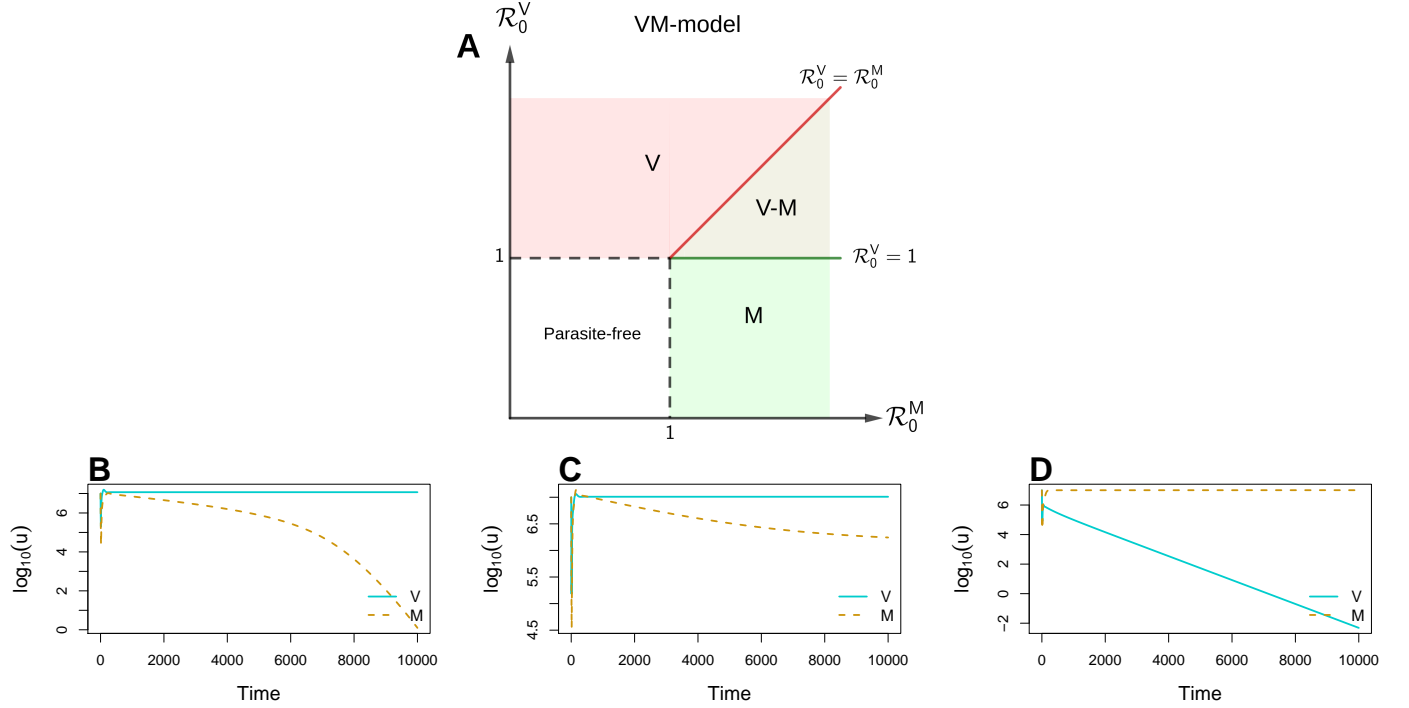


Figure 4: **Overview of the VM-model qualitative dynamics.** (A) Possible equilibria of the VM-model with respect to  $\mathcal{R}_0^V$  and  $\mathcal{R}_0^M$ . (B) Exclusion of species M, with  $(\mathcal{R}_0^V, \mathcal{R}_0^M) = (7, 4)$ . (C) Coexistence of both species V and M, with  $(\mathcal{R}_0^V, \mathcal{R}_0^M) = (4, 7)$ . (D) Exclusion of species V, with  $(\mathcal{R}_0^V, \mathcal{R}_0^M) = (0.9, 4)$ . Other model parameters are given by Table 1.

better competitive ability, respectively, in the configurations of the FM-model (Figure 3A) and VM-model (Figure 4A). Such competitive advantage, depending on the RBCs age preference and growing capacity, is also pointed in [5] for the case of rodent malaria.

The general model formulation (2.2) allows considering a variety of *Plasmodium* species interactions within the host. For example, it can be interesting to determine conditions for the co-existence of *P. Falciparum*, *P. Vivax* and *P. Malariae* within the same host (the FVM-model). Such FVM-model is

obtained with the parasite preference targets matrix  $\gamma = \begin{pmatrix} 1 & 1 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & 1 \end{pmatrix}$ . By similar argument as for other

co-infection configurations, we find that evolutionary co-existence of the three species is guaranteed if the following sufficient conditions hold

$$\begin{aligned} \mathcal{R}_0^M &> \mathcal{R}_0^V \prod_{j=m,s} \left( 1 + \frac{\mu_r}{\mu_j} (\mathcal{R}_0^V - 1) \right), \\ 1 < \mathcal{R}_0^V < \mathcal{R}_0^F &\leq \mathcal{R}_0^V + \mathcal{R}_0^V \frac{\mu_r (\mathcal{R}_0^V - 1)}{\mu_m + \mu_r (\mathcal{R}_0^V - 1)} (q_m^* + q_s^*). \end{aligned} \quad (7.1)$$

Such co-existence evolutionary dynamics of the FVM-model is illustrated with  $\mathcal{R}_0^V = 1.2$ ,  $\mathcal{R}_0^M = 1.01 \times \mathcal{R}_0^V \prod_{j=m,s} \left( 1 + \frac{\mu_r}{\mu_j} (\mathcal{R}_0^V - 1) \right) \approx 25.4$ , and  $\mathcal{R}_0^F = 0.5 \times \left( 2\mathcal{R}_0^V + \mathcal{R}_0^V \frac{\mu_r (\mathcal{R}_0^V - 1)}{\mu_m + \mu_r (\mathcal{R}_0^V - 1)} (q_m^* + q_s^*) \right) \approx 1.8$ , such that (7.1) is satisfied (Figure 5).

These *Plasmodium* species evolutionary coexistence within the same host have important clinical and public health implications. While there is little evidence to guide the treatment of mixed infections, malaria treatment and vaccination targeted at one malaria species could affect the clinical epidemiology

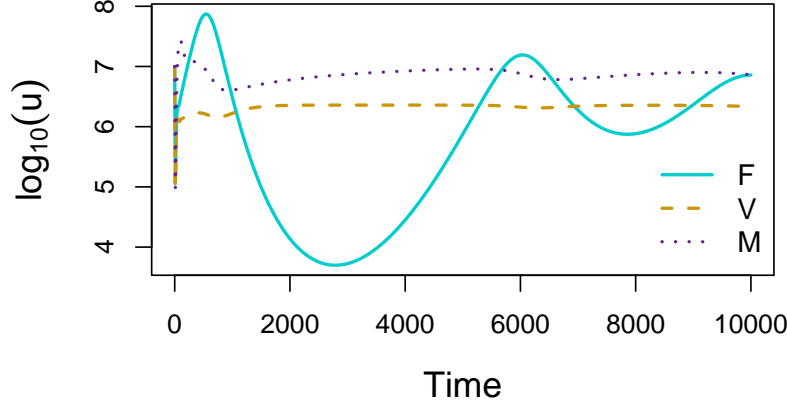


Figure 5: **Coexistence of the three species F, V and M.** Here we fix  $\mathcal{R}_0^V = 1.2$ ,  $\mathcal{R}_0^M = 1.01 \times \mathcal{R}_0^V \prod_{j=m,s} \left(1 + \frac{\mu_r}{\mu_j} (\mathcal{R}_0^V - 1)\right) \approx 25.4$ , and  $\mathcal{R}_0^F = 0.5 \times \left(2\mathcal{R}_0^V + \mathcal{R}_0^V \frac{\mu_r (\mathcal{R}_0^V - 1)}{\mu_m + \mu_r (\mathcal{R}_0^V - 1)} (q_m^* + q_s^*)\right) \approx 1.8$ , such that (7.1) is satisfied. Other model parameters are given by Table 1.

of sympatric *Plasmodium spp.*, see *e.g.* [23, 28, 37]. Therefore, identifying patients with mixed infections is crucial for therapeutic decisions, prompt treatment, and effective patient management [10, 23, 33, 37, 39]. Our analysis suggest that quantifying the reproduction numbers  $\mathcal{R}_0^k$  of each species gives suitable information on the potential co-existence of those species within the same host, and can then be helpful to design appropriate treatment/control measures. Furthermore, the  $\mathcal{R}_0$  aggregates all basic life-history quantitative traits of pathogenicity (generally well characterized from a biological standpoint) into a single fitness metric.

The model proposed here does not take into account immune-mediated parasite killing, which is a potential limitation. Immunity can be considered to target merozoites, parasitized red blood cells and/or immature gametocytes. However, here we do not explicitly model the gametocytes dynamics, and as pointed in [13], immune-mediated parasite killing targeting merozoites has very little impact on the overall model dynamics, probably because merozoites are only short-lived. Finally, immunity targeting parasitized red blood cells raises the question of model parameterization, particularly within our age-structured formulation.

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## A Invasion process

### A.1 Basic reproduction number

Let  $b_k(t)$  be the density of newly produced merozoites at time  $t$  by the species  $k$ . Then, from (2.6) one has

$$\mathbf{b}(t) = \int_0^\infty \mathbf{r}\boldsymbol{\mu}(a)\mathbf{p}(t, a)da, \quad \forall t \geq 0.$$

Linearizing the Volterra formulation (3.3) at the parasite-free equilibrium, it comes

$$\mathbf{p}(t, a) = \begin{cases} \Pi(a, a-t)\mathbf{p}_0(a-t) & \text{if } t \leq a, \\ \Pi(a, 0) \operatorname{diag}(\boldsymbol{\beta}\mathbf{u}(t-a))\boldsymbol{\gamma}^T\mathbf{R}^* & \text{if } t > a. \end{cases}$$

From where together with the equality  $\operatorname{diag}(\boldsymbol{\beta}\mathbf{u}(t-a))\boldsymbol{\gamma}^T\mathbf{R}^* = \operatorname{diag}(\boldsymbol{\gamma}^T\mathbf{R}^*)\boldsymbol{\beta}\mathbf{u}(t-a)$ ,

$$\mathbf{b}(t) = \int_0^t \mathbf{r}\boldsymbol{\mu}(a)\Pi(a, 0)\operatorname{diag}(\boldsymbol{\gamma}^T\mathbf{R}^*)\boldsymbol{\beta}\mathbf{u}(t-a)da + \int_t^{+\infty} \mathbf{r}\boldsymbol{\mu}(a)\Pi(a, a-t)\mathbf{p}_0(a-t)da, \quad \forall t \geq 0.$$

On the other hand, it follows from the  $\mathbf{u}$ -component of (2.6) that

$$\dot{\mathbf{u}}(t) = \mathbf{b}(t) - \boldsymbol{\mu}_v\mathbf{u}(t), \quad t \geq 0,$$

that re-writes as

$$\mathbf{u}(t) = e^{-\boldsymbol{\mu}_v t} \mathbf{u}(0) + \int_0^t e^{-\boldsymbol{\mu}_v(t-s)} \mathbf{b}(s) ds, \quad \forall t \geq 0.$$

As a consequence  $t \rightarrow \mathbf{b}(t)$  satisfies the following renewal equation :

$$\begin{aligned} \mathbf{b}(t) &= \int_0^t \int_0^{t-a} e^{-\boldsymbol{\mu}_v(t-a-s)} \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, 0) \text{diag}(\boldsymbol{\gamma}^T \mathbf{R}^*) \boldsymbol{\beta} \mathbf{b}(s) ds da \\ &\quad + \int_0^t \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, 0) e^{-\boldsymbol{\mu}_v(t-a)} \text{diag}(\boldsymbol{\gamma}^T \mathbf{R}^*) \boldsymbol{\beta} \mathbf{u}(0) da \\ &\quad + \int_t^{+\infty} \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, a-t) \mathbf{p}_0(a-t) da \\ &= \int_0^t \left[ \int_0^{t-s} e^{-\boldsymbol{\mu}_v(t-a-s)} \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, 0) \text{diag}(\boldsymbol{\gamma}^T \mathbf{R}^*) \boldsymbol{\beta} da \right] \mathbf{b}(s) ds \\ &\quad + \int_0^t \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, 0) e^{-\boldsymbol{\mu}_v(t-a)} \text{diag}(\boldsymbol{\gamma}^T \mathbf{R}^*) \boldsymbol{\beta} \mathbf{u}(0) da \\ &\quad + \int_t^{+\infty} \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, a-t) \mathbf{p}_0(a-t) da. \end{aligned}$$

Due to the above formulation, the basic reproduction number  $\mathcal{R}_0$  is calculated as the spectral radius of the diagonal matrix

$$\mathbf{M}(\mathbf{R}^*) := \int_0^{+\infty} \left[ \int_0^l e^{-\boldsymbol{\mu}_v(l-a)} \mathbf{r} \boldsymbol{\mu}(a) \Pi(a, 0) da \right] dl \text{diag}(\boldsymbol{\gamma}^T \mathbf{R}^*) \boldsymbol{\beta}$$

which, by using Fubini's theorem, is also given by

$$\mathbf{M}(\mathbf{R}^*) = \boldsymbol{\mu}_v^{-1} \mathbf{r} \int_0^{+\infty} \boldsymbol{\mu}(a) \Pi(a, 0) da \text{diag}(\boldsymbol{\gamma}^T \mathbf{R}^*) \boldsymbol{\beta}.$$

Therefore, the basic reproduction number  $\mathcal{R}_0^k$  of species  $k$  is calculated as the  $k$ -th diagonal element of  $\mathbf{M}(\mathbf{R}^*)$  that is

$$\begin{aligned} \mathcal{R}_0^k &= \frac{r_k \beta_k}{\mu_{v,k}} \int_0^{+\infty} \mu_k(a) \Pi_k(a, 0) da \sum_{j \in \mathcal{J}} \gamma_j^k R_j^* \\ &= \frac{\beta_k r_k \alpha_k e^{-\mu_0 \tau_k}}{\mu_{v,k} (\alpha_k + \mu_0)} \sum_{j \in \mathcal{J}} \gamma_j^k R_j^*. \end{aligned}$$

## A.2 Invasion fitness

Let us assume that System (2.2), composed only by the  $k$ -th species, reaches the equilibrium  $\bar{E}^k = (\bar{R}_r^k, \bar{R}_m^k, \bar{R}_s^k, \bar{p}_k(\cdot), \bar{u}_k)$  before a new species, let say  $l$ , occurs. Note that  $\bar{E}^k$  is the environmental feedback of the resident species  $k$ . By Theorem 5.2, we have  $\bar{u}_k > 0$  and

$$\begin{cases} \bar{R}_j^k = R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k}, \\ \bar{p}_k(\cdot) = \beta_k \bar{u}_k \Pi(\cdot, 0) \frac{1}{\mathcal{R}_0^k} \sum_{j=1}^3 \gamma_j^k R_j^*, \\ 1 = \Psi_k \sum_{j \in \mathcal{J}} \gamma_j^k R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k}. \end{cases}$$

We introduce a small perturbation in (2.2), due to the species  $l$ , so that the evolution of the system reads as follows:  $R_j(t) = \bar{R}_j^k + B_j(t)$  and for all  $z \in \{1, \dots, n\}$ ,

$$p_z(t, a) = \bar{p}_k(a) \delta_k^z + g(t, a) \delta_l^z \quad \text{and} \quad u_z(t) = \bar{u}_k \delta_k^z + h(t) \delta_l^z,$$

where  $\delta_i$  is the Kronecker delta. Therefore, the perturbations  $g$  and  $h$  are governed by the below linearized system of equations around  $\bar{E}^k$

$$\begin{cases} g(t, 0) = \beta_l h(t) \sum_{j \in \mathcal{J}} \gamma_j^l \bar{R}_j^k, \\ (\partial_t + \partial_a) g(t, a) = -(\mu_l(a) + \mu_0) g(t, a), \\ \dot{h}(t) = \int_0^\infty r_l \mu_k(a) g(t, a) da - \mu_{v,l} h(t). \end{cases} \quad (\text{A.1})$$

Denoting by  $b_k^l(t)$  the density of newly produced merozoites at time  $t$  by the  $l$ -species in a resident population of  $k$ -species, a similar argument as in Section A.1 gives

$$\begin{aligned} b_k^l(t) &= \int_0^t \left[ \int_0^{t-s} e^{-\mu_{v,l}(t-a-s)} \beta_l r_l \mu_l(a) \Pi_l(a, 0) \sum_{j \in \mathcal{J}} \gamma_j^l \bar{R}_j^k da \right] b_k^l(s) ds \\ &+ \int_0^t \beta_l r_l \mu_l(a) \Pi_l(a, 0) e^{-\mu_{v,l}(t-a)} \sum_{j \in \mathcal{J}} \gamma_j^l \bar{R}_j^k h(0) da + \int_t^{+\infty} r_l \mu_l(a) \Pi_l(a, a-t) g(0, a-t) da. \end{aligned}$$

From where, the number of merozoites,  $\mathcal{R}(l, \bar{E}^k)$ , of the  $l$ -species in the resident population of  $k$ -species is given by

$$\begin{aligned} \mathcal{R}(l, \bar{E}^k) &= \int_0^{+\infty} \left[ \int_0^s e^{-\mu_{v,l}(s-a)} \beta_l r_l \mu_l(a) \Pi_l(a, 0) da \right] ds \sum_{j \in \mathcal{J}} \gamma_j^l \bar{R}_j^k \\ &= \frac{\beta_l r_l \alpha_l e^{-\mu_0 \tau_l}}{\mu_{v,l}(\alpha_l + \mu_0)} \sum_{j \in \mathcal{J}} \gamma_j^l \bar{R}_j^k = \Psi_l \sum_{j \in \mathcal{J}} \gamma_j^l R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k}. \end{aligned}$$

Then, the invasion fitness  $f(k, l)$  of the new  $l$ -species in a resident population of  $k$ -species is given by

$$\begin{aligned} f(k, l) &= \mathcal{R}(l, \bar{E}^k) - 1 = \Psi_l \sum_{j \in \mathcal{J}} \gamma_j^l R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k} - 1 \\ &= \Psi_l \sum_{j \in \mathcal{J}} \gamma_j^l R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k} - \Psi_k \sum_{j \in \mathcal{J}} \gamma_j^k R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k} \\ &= \sum_{j \in \mathcal{J}} \left( \gamma_j^l \Psi_l - \gamma_j^k \Psi_k \right) R_j^* \prod_{i=1}^j \frac{\mu_i}{\mu_i + \gamma_i^k \beta_k \bar{u}_k}. \end{aligned}$$

## B Proof of Theorem 6.1

For Item 1., by Theorem 5.2, we first conclude that  $\bar{u}_V = 0$  and  $\bar{p}_V \equiv 0$ . Since  $\mathcal{S}' = \{F\}$ , by Theorem 5.2,  $\bar{u}_F > 0$ . Furthermore, we have  $\bar{x}_r = \beta_F \bar{u}_F = \bar{x}_m = \bar{x}_s$  and  $\bar{x}_r$  is a positive solution of

$$\frac{1}{\mathcal{R}_0^F} (R_r^* + R_m^* + R_s^*) = \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} R_m^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_r} \frac{\mu_s}{\mu_s + \bar{x}_r} R_s^*. \quad (\text{B.1})$$

Let  $\bar{x}_r \rightarrow f(\bar{x}_r)$  be defined as the right hand side of (B.1). Notice that  $f$  is a continuous decreasing map on  $[0, +\infty)$  with

$$f(0) = R_r^* + R_m^* + R_s^* > \frac{1}{\mathcal{R}_0^F} (R_r^* + R_m^* + R_s^*)$$

and  $f(+\infty) = 0$ . Therefore, there exists a unique  $\bar{x}_r > 0$ , solution of (B.1).

For Item 2., by Theorem 5.2, we first conclude that  $\bar{u}_F = 0$  and  $\bar{p}_F \equiv 0$ . Since  $\mathcal{S}' = \{V\}$ , Theorem 5.2 gives  $\bar{u}_V > 0$ . Furthermore, we have  $\bar{x}_r = \beta_V \bar{u}_V$  and  $\bar{x}_m = \bar{x}_s = 0$  and  $\bar{x}_r > 0$  is a solution of

$$\frac{1}{\mathcal{R}_0^V} R_r^* = \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^*.$$

Therefore, we have  $\bar{x}_r = \beta_V \bar{u}_V = \mu_r (\mathcal{R}_0^V - 1)$ . By Lemma 5.1, we have

$$\bar{p}_V(a) = \frac{1}{\mathcal{R}_0^V} \Pi_V(a, 0) \beta_V \bar{u}_V R_r^* = \frac{\mu_r (\mathcal{R}_0^V - 1)}{\mathcal{R}_0^V} \Pi_V(a, 0) R_r^*, \quad \forall a \geq 0,$$

and

$$\bar{R}_r = \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^* = \frac{1}{\mathcal{R}_0^V} R_r^*.$$

Again by Lemma 5.1, it comes

$$\bar{R}_m = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} R_m^* = \frac{\mu_r}{\mu_r + \bar{x}_r} R_m^* = \frac{1}{\mathcal{R}_0^V} R_m^*$$

and

$$\bar{R}_s = \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} \frac{\mu_s}{\mu_s + \bar{x}_s} R_s^* = \frac{\mu_r}{\mu_r + \bar{x}_r} R_s^* = \frac{1}{\mathcal{R}_0^V} R_s^*.$$

Finally for Item 3., Theorem 5.2 ensures that there exists a co-existence equilibrium if and only if there exists  $\bar{u}_F > 0$ ,  $\bar{u}_V > 0$  such that

$$\bar{x}_r = \beta_F \bar{u}_F + \beta_V \bar{u}_V \quad \text{and} \quad \bar{x}_m = \beta_F \bar{u}_F = \bar{x}_s$$

satisfy the following system

$$\begin{cases} \frac{1}{\mathcal{R}_0^F} (R_r^* + R_m^* + R_s^*) = \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} R_m^* + \frac{\mu_r}{\mu_r + \bar{x}_r} \frac{\mu_m}{\mu_m + \bar{x}_m} \frac{\mu_s}{\mu_s + \bar{x}_s} R_s^*, \\ \frac{1}{\mathcal{R}_0^V} R_r^* = \frac{\mu_r}{\mu_r + \bar{x}_r} R_r^*. \end{cases}$$

Therefore, there exists a co-existence equilibrium if and only if there exist  $u_F > 0$ ,  $u_V > 0$  such that

$$\begin{cases} R_r^* + R_m^* + R_s^* = \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} \left[ R_r^* + \frac{\mu_m}{\mu_m + \beta_F \bar{u}_F} R_m^* + \frac{\mu_m}{\mu_m + \beta_F \bar{u}_F} \frac{\mu_s}{\mu_s + \beta_F \bar{u}_F} R_s^* \right], \\ \beta_F \bar{u}_F + \beta_V \bar{u}_V = \mu_r (\mathcal{R}_0^V - 1). \end{cases}$$

The map

$$x \rightarrow f(x) = \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} \left[ R_r^* + \frac{\mu_m}{\mu_m + x} R_m^* + \frac{\mu_m}{\mu_m + x} \frac{\mu_s}{\mu_s + x} R_s^* \right]$$

is continuous and decreasing in  $[0, +\infty)$ . Thus, there exists a unique solution  $\bar{u}_F > 0$ ,  $\bar{u}_V > 0$  and only if  $\mathcal{R}_0^V > 1$  and

$$f(\mu_r (\mathcal{R}_0^V - 1)) < R_r^* + R_m^* + R_s^* < f(0),$$

that is

$$\begin{cases} R_r^* + R_m^* + R_s^* > \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} \left[ R_r^* + \frac{\mu_m}{\mu_m + \mu_r (\mathcal{R}_0^V - 1)} \left( R_m^* + \frac{\mu_s}{\mu_s + \mu_r (\mathcal{R}_0^V - 1)} R_s^* \right) \right], \\ R_r^* + R_m^* + R_s^* < \frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} [R_r^* + R_m^* + R_s^*]. \end{cases}$$

The proof is complete since the second inequality of the above system holds true if and only if  $\frac{\mathcal{R}_0^F}{\mathcal{R}_0^V} > 1$ .