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► To cite this version:

Malick Pane, Quentin Richard, Ousmane Seydi, Ramsès Djidjou-Demasse. Mathematical modeling of intra-and inter-species interactions in mixed malaria within-host infections. 2024. hal-04580095

HAL Id: hal-04580095

<https://hal.science/hal-04580095v1>

Preprint submitted on 19 May 2024

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Mathematical modeling of intra- and inter-species interactions in mixed malaria within-host infections

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Abstract

Malaria poses a significant global health challenge, with millions of cases and fatalities reported annually, primarily in the WHO African Region and South-East Asia Region. Mixed-species malaria infections are common but often underestimated, even in regions with low transmission rates. Mathematical models have been instrumental in studying parasite multiplication within hosts during mixed malaria infections, yet existing models typically focus on either intra-species or inter-species dynamics separately. However, both intra- and inter-species diversity are crucial in within-host malaria infection dynamics. In this study, we introduce a mathematical model for intra-species and inter-species interactions between *P. vivax* and *P. falciparum*, exploring their co-infection dynamics within hosts. We establish the properties of the model and conduct invasibility analysis in a multi-species and multi-genotypes framework. We also perform the uniform persistence of parasites over time within the host and discuss several typical scenarios that the model can simulate. Our findings shed light on the complex dynamics of malaria co-infections and their clinical implications.

Keywords: Malaria; Within-host dynamics; Mixed-species infections; Intra- and inter-species interactions; Mathematical modelling; Non-linear dynamical system.

1 Introduction

Malaria continues to pose a major public health challenge, with approximately 247 million cases and 619,000 fatalities reported globally in 2021 [1]. The World Health Organization (WHO) African Region bears the highest malaria burden, followed by the South-East Asia Region. Human malaria, caused by various *Plasmodium* species like *P. falciparum* and *P. vivax*, involves a complex life cycle with stages in both mosquitoes [3] and human or animal hosts [7, 18]. Mosquito bites transmit sporozoites into the bloodstream, which travel to the liver and infect hepatocytes [18]. After replication, merozoites are released into the bloodstream to invade red blood cells, leading to cycles of replication and rupture [33]. Some parasites become gametocytes [38], which complete the life cycle when ingested by mosquitoes. Mixed human malaria parasite infections are widespread globally, occurring even in areas with low transmission rates. A significant proportion of malaria infections within individual hosts involve multiple species of *Plasmodium* simultaneously [30]. Numerous studies have highlighted the prevalence of mixed-species malaria infections in various locations worldwide, e.g. [2, 20, 24, 30, 39]. Despite this prevalence, mixed *Plasmodium* species infections are often overlooked or underestimated [6, 24, 30].

Mathematical models have played a key role in the study of parasite multiplication within hosts during mixed malaria infections. Previous studies have developed various models to explore infection dynamics, with some focusing on multiple genotypes of a single species within a host, e.g. [8, 11, 23, 46], while others investigate mixed-species infection dynamics with single genotypes within a host [17]. If inter-species diversity (e.g. *P. vivax* or *P. falciparum*) has been highlighted by a recent modeling approach as a key factor in maintaining intra-host coinfections due to their distinct ecological trait for RBCs preferences [17], no study combines both this inter-species diversity with intra-species diversity (i.e. multiple genotypes of *P. vivax* and *P. falciparum*) within an intra-host infection.

However, inter-species diversity also plays a crucial role in within-host malaria infection and interaction dynamics. Indeed, intra-species diversity persists due to the numerous antigenic variants, placing substantial pressure on the host immune system and potentially facilitating prolonged parasite infections [36, 41]. Furthermore, both intra- and inter-species are fundamental for our better understanding of *P. vivax* and *P. falciparum* co-infections within the host. In fact, in regions where *P. vivax* and *P. falciparum* coexist, it is often observed that infections with *P. falciparum* are followed by *P. vivax* infections, leading to the hypothesis that *P. falciparum* infections facilitated *P. vivax* infections, e.g. [6] and references therein. The precise nature of the interaction between *P. vivax* and *P. falciparum* in a multi-genotypes setting remains unclear [24, 34]. It is uncertain whether these species compete within the host or if one species provides any degree of protection against the other. These interactions among *Plasmodium* species, both within and between species, can have significant clinical and public health implications. Treating and controlling one species' genotype can affect the clinical epidemiology of the other species, either at the intra-species or inter-species level [24, 30, 39].

We first introduce the mathematical model for the intra-species and inter-species interactions between *P. vivax* and *P. falciparum*. Next, we establish some useful properties including the well-posedness of a positive and global solution of the system. We explore the presence of nontrivial stationary states within the model, showing that the dynamics of the system exhibits a range of behaviors from the persistence of a single species to the coexistence of both species. We precisely determine the conditions for the existence of these nontrivial stationary states, along with the intra-species genotype diversity. Furthermore, we establish the global stability of the parasite-free stationary state. Afterwards, we conduct an invasibility analysis within a multi-species and multi-genotype framework. This analysis is particularly crucial as it enables us to characterize the conditions under which an invading genotype of *P. vivax* or *P. falciparum* species can successfully proliferate within a host initially infected by *P. vivax* or *P. falciparum* under different scenarios. We also perform the parasites uniform persistence over time within the host. Finally, we introduce the model parameterization and discuss several typical simulated scenarios that the model can capture, along with their biological implications.

2 The model description

We introduce a within-host interaction dynamics between young RBCs (reticulocytes), denoted as C_1 , mature RBCs, denoted as C_2 , and two malaria species *P. vivax* and *P. falciparum*. At any given time t , the density of malaria parasites (merozoites) for *P. vivax* and *P. falciparum* are represented by $m_1(t, x)$ and $m_2(t, x)$ respectively where the variable $x \in \mathbb{R}$ is designated as the strain label. The density of parasitized red blood cells by *P. vivax* and *P. falciparum* is denoted by $v_1(t, a, x)$ and $v_2(t, a, x)$, where the structural variable a stands for the time post parasitization. The model we considered then reads :

$$\begin{cases} \frac{dC_1(t)}{dt} = \Lambda - \mu_{1,2}C_1(t) - C_1(t) \int_{\mathbb{R}} \beta_1(x)m_1(t, x)dx - C_1(t) \int_{\mathbb{R}} \beta_2(x)m_2(t, x)dx, \\ \frac{dC_2(t)}{dt} = \mu_{1,2}C_1(t) - \mu_2C_2(t) - C_2(t) \int_{\mathbb{R}} \beta_2(x)m_2(t, x)dx, \\ v_1(t, a = 0, x) = C_1(t)\beta_1(x)m_1(t, x), \\ v_2(t, a = 0, x) = (C_1(t) + C_2(t))\beta_2(x)m_2(t, x), \\ \frac{\partial v_j(t, a, x)}{\partial t} + \frac{\partial v_j(t, a, x)}{\partial a} = -(\mu_2 + \gamma_j(a, x))v_j(t, a, x), \\ \frac{\partial m_j(t, x)}{\partial t} = \int_{\mathbb{R}} k(x-y)p_j(y) \left(\int_0^\infty \gamma_j(a, y)v_j(t, a, y)da \right) dy - (\mu_{m,j} + I_j(x))m_j(t, x). \end{cases} \quad (2.1)$$

In the system (2.1), the parameters $1/\mu_{1,2}$ and $1/\mu_2$ respectively represent the duration of the young and mature stages of RBCs, while Λ denotes the production rate of RBCs from the bone marrow. Contacts between merozoites and uninfected RBCs occur at rate β_j . *P. vivax* exhibits a preference for targeting young RBC stages, whereas *P. falciparum* targets all RBC stages. The parameter $\mu_{m,j}$ represents the natural death rates for merozoites. The functions $\gamma_j(a, x)$ represent the additional death rate of parasitized RBCs by the j -species of strain x at time a post parasitization, resulting in rupture. The rupture, at age a , of parasitized RBCs by the j -species of strain y produce merozoites of strain x at rate $k(x-y)p_j(y)\gamma_j(a, y)$, where $k(x-y)$ is the probability of mutation from strain y to strain x . Hence, mutations randomly shift strains in the phenotype space during each infection generation, following a mutation kernel k . Finally, the effect of the immune system on the j -species of strain x is denoted by $I_j(x)$. We present a summary of state variables and model parameters in Table 1. System (2.1) is coupled with the

Table 1: Withing host model variables and parameters

Param	Description (unit)	Values
State variables		
$C_1(t)$	density of reticulocytes at time t (Cell/ml)	
$C_2(t)$	density of mature RBCs at time t (Cell/ml)	
$v_j(t, a, x)$	density of parasitized RBC –pRBC– by pathogens x of j -species at time t which are parasitized since time a (Cell/ml)	
$m_j(t, x)$	density of merozoites x of j -species at time t (Cell/ml)	
Parameters		
Λ	Production rate of RBC (RBC/h/ml)	1.73×10^6 [5, 31]
$1/\mu_{1,2}$	Duration of the RBC reticulocyte stage (h)	36 [31]
$1/\mu_2$	Duration of the RBC mature stage (days)	116.5 [31]
$\mu_{m,j}$	Decay rates of malaria parasites of the j -species (RBC/day)	48 [22]
τ_j	Erythrocytic cycle duration of the j -species (h)	48 for <i>P. falciparum</i> [37] 48 for <i>P. vivax</i> [37]
p_j^{\max}	Maximal number of merozoites produced per pRBC by the j -species	16 [5, 37]
$p_j(x)$	Number of merozoites with value x produced per pRBC by the j -species	Defined by (8.2)
$\gamma_j(a, x)$	Rupture rate of pRBCs by x of species j since time a	Defined by (8.1)
$I_j(x)$	Cross-immune reaction to parasite x of j -species	Defined by (8.3)
$\beta_1(x)$	Infection rate of pathogens x of the species 1 (RBC/ml/day)	6.27×10^{-7}
$\beta_2(x)$	Infection rate of pathogens x of the species 2 (RBC/ml/day)	6.27×10^{-8}
$\frac{1}{\sigma_j^2}$	Selectivity level within the j -malaria species	$\frac{1}{0.03^2}$
Initial conditions		
$C_{1,0}$	Density of reticulocytes	$\Lambda/\mu_{1,2}$
$C_{2,0}$	Density of of mature RBCs	Λ/μ_2
$v_{j,0}$	Density of pRBCs of the j -species	0

following initial condition:

$$C_j(0) = C_{j,0}, \quad v_j(0, a, x) = v_{j,0}(a, x), \quad m_j(0, x) = m_{j,0}(x).$$

75 3 Model's abstract formulation and overall assumptions

Let us set

$$C(t) = (C_1(t), C_2(t)), \quad m(t, x) = (m_1(t, x), m_2(t, x)), \quad v(t, a, x) = (v_1(t, a, x), v_2(t, a, x)).$$

Then, System (2.1) rewrites as

$$\left\{ \begin{array}{l} \frac{dC(t)}{dt} = \bar{\Lambda} - \mu C(t) - \text{diag} \left(\int_{\mathbb{R}} \kappa_m \beta(y) m(t, y) dy \right) C(t), \\ v(t, a = 0, x) = \text{diag}(\beta(x) m(t, x)) \kappa_m^T C(t), \\ (\partial_t + \partial_a) v(t, a, x) = -(\mu_2 \mathbf{I}_d + \gamma(a, x)) v(t, a, x), \\ \partial_t m(t, x) = \int_{\mathbb{R}} k(x - y) p(y) \int_0^\infty \gamma(a, y) v(t, a, y) da dy - (\nu + I(x)) m(t, x) \end{array} \right. \quad (3.1)$$

78 where $\bar{\Lambda} = (\Lambda, 0)^T$, $\nu = \text{diag}(\mu_{m,j})_{j \in \{1,2\}}$, $\beta = \text{diag}(\beta_j)_{j \in \{1,2\}}$, $I = \text{diag}(I_j)_{j \in \{1,2\}}$, $\gamma = \text{diag}(\gamma_j)_{j \in \{1,2\}}$, $p = \text{diag}(p_j)_{j \in \{1,2\}}$,

$$\mu = \begin{pmatrix} \mu_{1,2} & 0 \\ -\mu_{1,2} & \mu_2 \end{pmatrix}, \quad \kappa_m = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}.$$

Let the Banach space $\mathcal{X} = \mathbb{R}^2 \times L^1(\mathbb{R}, \mathbb{R}^2) \times L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2) \times L^1(\mathbb{R}, \mathbb{R}^2)$, which is endowed with the usual product norm

$$\|(C, f, v, m)^T\|_{\mathcal{X}} = \|C\|_{\mathbb{R}^2} + \|f\|_{L^1(\mathbb{R}, \mathbb{R}^2)} + \|v\|_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)} + \|m\|_{L^1(\mathbb{R}, \mathbb{R}^2)}.$$

Let $A : \mathcal{D}(A) \subset \mathcal{X} \rightarrow \mathcal{X}$ the linear operator defined on the domain $\mathcal{D}(A) := \mathbb{R}^2 \times \{0_{L^1(\mathbb{R}, \mathbb{R}^2)}\} \times \mathcal{D}_v \times L^1(\mathbb{R}, \mathbb{R}^2)$ by

$$A \begin{pmatrix} C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ v \\ m \end{pmatrix} = \begin{pmatrix} -\mu C \\ -v(0, \cdot) \\ -\partial_a v - (\mu_2 \mathbb{1}_d + \gamma)v \\ -(\nu + I)m \end{pmatrix}$$

with

$$\mathcal{D}_v := \{v \in L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2) : v(\cdot, x) \in W^{1,1}(\mathbb{R}_+, \mathbb{R}^2) \text{ a.e } x \in \mathbb{R} \text{ and } \partial_a v \in L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)\}.$$

We then define the set

$$\mathcal{X}_0 = \overline{\mathcal{D}(A)} = \mathbb{R}^2 \times \{0_{L^1(\mathbb{R}, \mathbb{R}^2)}\} \times L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2) \times L^1(\mathbb{R}, \mathbb{R}^2)$$

and we introduce the non-linear map $F : \mathcal{X}_0 \rightarrow \mathcal{X}$ defined by

$$F \begin{pmatrix} C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ v \\ m \end{pmatrix} = \begin{pmatrix} \bar{\Lambda} - \text{diag} \left(\int_{\mathbb{R}} \kappa_m \beta(y) m(y) dy \right) C \\ \text{diag}(\beta m) \kappa_m^T C, \\ 0_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)} \\ \int_{\mathbb{R}} k(\cdot - y) p(y) \int_0^{\infty} \gamma(a, y) v(a, y) da dy \end{pmatrix}. \quad (3.2)$$

Note that $\overline{\mathcal{D}(A)} \neq \mathcal{X}$ hence A is a linear operator with a non-dense domain. Therefore, by identifying $u(t)$ as

$$(C(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, v(t, \cdot, \cdot), m(t, \cdot))^T$$

and letting $u_0 \in \mathcal{X}_0$ the associated initial condition, System (3.1) writes as the following abstract Cauchy problem:

$$\begin{cases} \frac{du(t)}{dt} = Au(t) + F(u(t)), \\ u(0) = u_0. \end{cases} \quad (3.3)$$

81 Let $\mathcal{X}_{0+} = \mathcal{X}_0 \cap \mathcal{X}_+$ with \mathcal{X}_+ the positive cone of \mathcal{X} . System (3.3) is considered under the following quite general assumption

Assumption 3.1.

- 84 1. For each $j \in \{1, 2\}$, the constants Λ , $\mu_{1,2}$, μ_2 , and $\mu_{m,j}$ are positive, while the functions $I_j, \beta_j, p_j \in L_+^\infty(\mathbb{R})$ and $\gamma_j \in L_+^\infty(\mathbb{R}_+ \times \mathbb{R})$.
2. The kernel k is a non-negative function satisfying $k \in L^\infty(\mathbb{R}) \cap L^1(\mathbb{R})$ and $\int_{\mathbb{R}} k(x) dx = 1$.

While Assumption 3.1 guarantees the global well-posedness of the bounded and dissipative semiflow of (3.3), achieving compactness of the trajectories generated by such a semiflow necessitates additional assumptions. Indeed, the compactness of the trajectories is related to the compactness of the linear operator $U : L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2) \rightarrow L^1(\mathbb{R}, \mathbb{R}^2)$

$$U[v](x) = \int_{\mathbb{R}} k(x - y) p(y) \int_0^{\infty} \gamma(a, y) v(a, y) da dy.$$

87 To ensure the compactness of the linear operator U , we shall assume that :

Assumption 3.2.

1. The functions $p_j : \mathbb{R} \rightarrow \mathbb{R}_+$ are continuous, not identically null and $\lim_{|x| \rightarrow \infty} p_j(x) = 0$, for each $j \in \{1, 2\}$.
- 90 2. For each $R > 0$ the function $x \mapsto \sup_{|y| \leq R} k(x + y)$ belongs to $L^1(\mathbb{R})$.

Furthermore, stationary states of System (3.3) are strongly related to the spectral properties of the linear operator $L_j \in \mathcal{L}(L^1(\mathbb{R}))$, defined for each $j \in \{1, 2\}$ by

$$L_j w(x) = \int_{\mathbb{R}} k(x-y) \Gamma_j(y) w(y) dy, \quad \forall w \in L^1(\mathbb{R}) \quad (3.4)$$

93 wherein

$$\Gamma_j(y) = \frac{p_j(y) \beta_j(y)}{\mu_{m,j} + I_j(y)} \times \underbrace{\int_0^{\infty} \gamma_j(a, y) \Pi_j(0, a, y) da}_{\text{average parasite's development period}} \quad (3.5)$$

captures the reproductive value of the parasite of strain y within species j , and where we denote by

$$\Pi_j(a, b, x) = \exp\left(-\int_a^b (\mu_2 + \gamma_j(\ell, x)) d\ell\right)$$

the survival probability of RBCs infected by strain x of species j from time a to b since infection. In general, the compactness property of the linear operator L_j above holds as soon as Assumption 3.2 is replaced by:

96 **Assumption 3.3.**

1. The reproductive functions $\Gamma_j : \mathbb{R} \rightarrow \mathbb{R}_+$ are continuous, not identically null and $\lim_{|x| \rightarrow \infty} \Gamma_j(x) = 0$ for each $j \in \{1, 2\}$.
- 99 2. For each $R > 0$ the function $x \mapsto \sup_{|y| \leq R} k(x+y)$ belongs to $L^1(\mathbb{R})$.

Under Assumption 3.1, it is noteworthy that Assumption 3.2 automatically entails Assumption 3.3. However, it is important to note that while Assumption 3.3 holds, it may not necessarily imply Assumption 3.2.

102 The compactness and irreducibility properties of the linear operator L_j induce the following result that we remember (see [14] for the proof).

Proposition 3.4. *Let $j \in \{1, 2\}$. Under Assumptions 3.1 and 3.3, the linear operator L_j defined by (3.4) is positive, compact and its spectrum $\sigma(L_j) \setminus \{0\}$ is composed of isolated eigenvalues with finite algebraic multiplicity. The spectral radius $r(L_j)$ is a positive algebraically simple eigenvalue associated to the normalized eigenfunction $\phi_j \in L^1(\mathbb{R})$ with $\int_{\mathbb{R}} \phi_j(x) dx = 1$. Moreover, if a nonnegative and non identically null function $\phi \in L^1(\mathbb{R})$ satisfies the equality $L_j(\phi) = \alpha \phi$ for some $\alpha \in \mathbb{R}$, then $\phi > 0$ almost everywhere, $\phi \in \text{span}(\phi_j)$ and $\alpha = r(L_j)$.*

Finally, addressing the concern of uniform persistence of parasites in the proposed model necessitates a technical assumption outlined as follows

Assumption 3.5. Let $j \in \{1, 2\}$. For each $\lambda > 0$ and for almost every $y \in \mathbb{R}$, we have

$$p_j(y) \beta_j(y) \int_s^{\infty} \gamma_j(a, y) e^{-\lambda(a-s)} \Pi_j(s, a, y) da > 0, \quad \forall s \geq 0.$$

111 Essentially, Assumption 3.5 demands that the product $p_j \beta_j$ be almost everywhere positive on \mathbb{R} . However, if, for example, $p_j(y) \beta_j(y) > 0$ holds for nearly every $y \in \Omega$, where Ω is a bounded subset of \mathbb{R} , the model proposed here can straightforwardly be applied to the set Ω , and the methods and outcomes presented here remain valid.

114 4 Global well-posedness, dissipativity and positivity

In this section, we handle the well-posedness of the system (2.1).

4.1 The main result

117 By setting $X := \mathbb{R}^2 \times L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2) \times L^1(\mathbb{R}, \mathbb{R}^2)$, and $X_+ := \mathbb{R}_+^2 \times L_+^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2) \times L_+^1(\mathbb{R}, \mathbb{R}^2)$ its positive cone, the main result of this section reads:

Theorem 4.1. *Let Assumption 3.1 be satisfied. Then,*

120 1. Problem (2.1) generates a globally defined strongly continuous semiflow on X_+ , denoted by Φ and defined by

$$\Phi : \mathbb{R}_+ \times X_+ \ni (t, \hat{u}_0) \mapsto \Phi_t(\hat{u}_0) = (C(t), v(t, \cdot, \cdot), m(t, \cdot)). \quad (4.1)$$

That is, for each $\hat{u}_0 = (C_0, v_0, m_0) \in X_+$, there exists a unique mild solution $(C, v, m) \in \mathcal{C}(\mathbb{R}_+, X_+)$. Furthermore, the set

$$\mathcal{S} := \left\{ (C_0, v_0, m_0) \in X_+ : \begin{cases} C_{1,0} \leq \frac{\Lambda}{\mu_{1,2}}, C_{2,0} \leq \frac{\Lambda}{\mu_2} \\ \sum_{j=1}^2 (C_{j,0} + \|v_{j,0}\|_{L^1(\mathbb{R}_+ \times \mathbb{R})}) \leq \frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \\ \|m_{j,0}\|_{L^1(\mathbb{R})} \leq \frac{\|\gamma_j\|_\infty \|p_j\|_\infty}{\mu_{m,j}} \left(\frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \right), \forall j \in \{1, 2\} \end{cases} \right\} \quad (4.2)$$

is positively invariant with respect to the semi-flow Φ and for each $\hat{u}_0 \in X_+$, the solution defined by (4.1) satisfies

$$\begin{cases} \limsup_{t \rightarrow +\infty} C_1(t) \leq \frac{\Lambda}{\mu_{1,2}} \quad \text{and} \quad \limsup_{t \rightarrow +\infty} C_2(t) \leq \frac{\Lambda}{\mu_2} \\ \limsup_{t \rightarrow +\infty} \sum_{j=1}^2 (C_j(t) + \|v_j(t, \cdot, \cdot)\|_{L^1(\mathbb{R}_+ \times \mathbb{R})}) \leq \frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \end{cases}$$

and for $j \in \{1, 2\}$

$$\limsup_{t \rightarrow +\infty} \|m_j(t, \cdot)\|_{L^1(\mathbb{R})} \leq \frac{\|\gamma_j\|_\infty \|p_j\|_\infty}{\mu_{m,j}} \left(\frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \right).$$

123 2. The semi-flow Φ is point (and bounded) dissipative, i.e. there exists a bounded set $K \subset X_+$, that attracts each point of X_+ (and each bounded set of X_+) i.e. $d_H(\Phi_t(w), K) \xrightarrow{t \rightarrow \infty} 0$ for each $w \in X_+$ (and $d_H(\Phi_t(B), K) \xrightarrow{t \rightarrow \infty} 0$ for any bounded set $B \subset X_+$), where d_H is the Hausdorff semi-distance [21] defined by $d_H(B, K) = \sup_{w \in B} \inf_{v \in K} \|w - v\|_X$.

126 3. In addition to Assumption 3.1, we also require the fulfilment of Assumption 3.2. Then, the semi-flow Φ is asymptotically smooth in X_+ , i.e. for any nonempty, closed, bounded and positively invariant set $B \subset X_+$, there exists a compact set $K \subset X_+$ such that $\lim_{t \rightarrow \infty} d_H(\Phi_t(B), K) = 0$. It follows that there exists a global attractor.

4.2 Proof of Theorem 4.1

132 To prove Theorem 4.1, we need to set a suitable framework for using integrated semigroups (see e.g. [26] and the references therein). We start by giving the following result about the resolvent of A which simply arises from the definition of the linear operator.

Lemma 4.2 (Resolvent). *Suppose that Assumption 3.1 is satisfied. Then for each $\lambda \in \mathbb{C}$ such that $\Re(\lambda) > -\min\{\mu_{1,2}, \mu_2, \mu_{m,1}, \mu_{m,2}\}$, the resolvent of A is given by*

$$(\lambda I_d - A)^{-1} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix} = \begin{pmatrix} C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ v \\ m \end{pmatrix} \in \mathcal{X}_0$$

for every $(u_1, u_2, u_3, u_4)^T \in \mathcal{X}$, with

$$\begin{cases} C = (\lambda I_d + \mu)^{-1} u_1 \\ v(a, x) = e^{-\int_0^a (\lambda I_d + \mu_2 I_d + \gamma(l, x)) dl} u_2(x) + \int_0^a e^{-\int_s^a (\lambda I_d + \mu_2 I_d + \gamma(l, x)) dl} u_3(s, x) ds \\ m(x) = (\lambda I_d + \nu + I(x))^{-1} u_4(x) \end{cases}$$

135 and consequently, A is resolvent positive.

Let $A_0 : \mathcal{D}(A_0) \subset \mathcal{X}_0 \rightarrow \mathcal{X}$ be the part of A on \mathcal{X}_0 , that is the linear operator

$$A_0 u := Au, \quad \forall u \in \mathcal{D}(A_0) = \{u \in \mathcal{D}(A) : Au \in \mathcal{X}_0\}.$$

We also have the following lemma.

Lemma 4.3. *Suppose that Assumption 3.1 is satisfied. Then $A : \mathcal{D}(A) \subset \mathcal{X}_0 \rightarrow \mathcal{X}$ is a Hille-Yosida linear operator. Furthermore, $s(A_0) = s(A) < 0$ with $s(A)$ (resp. $s(A_0)$) the spectral bound of A (resp. A_0), that is for $H \in \{A, A_0\}$*

$$s(H) := \sup\{\Re(\lambda) : \lambda \text{ is in the spectral set of } H\}.$$

Consequently if $\omega_A \in (-s(A_0), 0)$ there exists a constant $M_A \geq 1$ such that

$$\|T_{A_0}(t)\|_{\mathcal{L}(\mathcal{X}_0)} \leq M_A e^{-\omega_A t}, \quad \forall t \geq 0.$$

Proof. Considering the linear operators $A_1 : \mathcal{D}(A) \rightarrow \mathcal{X}$ and $A_2 : \mathcal{X}_0 \rightarrow \mathcal{X}$ as follow

$$A_2 \begin{pmatrix} C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ v \\ m \end{pmatrix} = \begin{pmatrix} -\mu C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ 0_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)} \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \end{pmatrix}, \quad A_1 := A - A_2$$

lead to the decomposition $A = A_1 + A_2$. With Lemma 4.2 we see that

$$\|(\lambda I_d - A_1)^{-1} u\|_{\mathcal{X}} \leq \frac{1}{\lambda + \omega_0} \|u\|_{\mathcal{X}}$$

for each $u \in \mathcal{X}$ and $\lambda \in \mathbb{R}$ with $\lambda \geq -\omega_0$ and $\omega_0 := \min\{\mu_{1,2}, \mu_2, \mu_{m,1}, \mu_{m,2}\}$, leading to $\|(\lambda I_d - A_1)^{-n}\|_{\mathcal{L}(\mathcal{X})} \leq \frac{1}{(\lambda + \omega_0)^n}$ for each $n \geq 1$ so that A_1 is a Hille-Yosida operator. Since A_2 is a bounded linear operator, it follows that A is also a Hille-Yosida linear operator. Consequently, A_0 , the part of A on \mathcal{X}_0 generates a C_0 -semigroup $\{T_{A_0}(t)\}_{t \geq 0}$ with growth bound $\omega(A_0) \in \mathbb{R}$. Next, we note that \mathcal{X}_0 is a AL-space implying that $s(A_0) = \omega(A_0)$ [42, Theorem 3.14]. Recalling that [25, Lemma 2.1] A and A_0 have the same spectral set, we conclude that $s(A_0) = s(A)$. The result follows from Lemma 4.2 and the fact that

$$s(A) = \inf\{\lambda \in \rho(A) : (\lambda - A)^{-1} \mathcal{X}_+ \subset \mathcal{X}_{0+}\}.$$

□

138 4.2.1 Proof of items 1 and 2

The following proposition is devoted to items 1 and 2 of Theorem 4.1.

Proposition 4.4 (Global well-posedness, Boundedness, Dissipativity). *Let Assumption 3.1 be satisfied. Then the*
 141 *Cauchy problem (3.3) generates a globally defined strongly continuous semiflow on \mathcal{X}_{0+} , denoted by U and defined by*

$$U : \mathbb{R}_+ \times X_+ \ni (t, u_0) \mapsto U(t)u_0 = (C_1(t), C_2(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, v_1(t, \cdot, \cdot), v_2(t, \cdot, \cdot), m_1(t, \cdot), m_2(t, \cdot))^T. \quad (4.3)$$

That is, for each $u_0 = (C_{1,0}, C_{2,0}, 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, v_{1,0}, v_{2,0}, m_{1,0}, m_{2,0})^T \in \mathcal{X}_{0+}$, $U(\cdot)u_0 \in \mathcal{C}(\mathbb{R}_+, \mathcal{X}_{0+})$ is the unique mild solution to (3.3). Furthermore, the set \mathcal{S} introduced by (4.2) is positively invariant with respect to the semiflow U and for each $u_0 \in \mathcal{X}_{0+}$, the solution defined by (4.3) satisfies

$$\begin{cases} \limsup_{t \rightarrow +\infty} C_1(t) \leq \frac{\Lambda}{\mu_{1,2}} & \text{and} \quad \limsup_{t \rightarrow +\infty} C_2(t) \leq \frac{\Lambda}{\mu_2} \\ \limsup_{t \rightarrow +\infty} \sum_{j=1}^2 (C_j(t) + \|v_j(t, \cdot, \cdot)\|_{L^1(\mathbb{R}_+ \times \mathbb{R})}) \leq \frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \end{cases}$$

and for $j \in \{1, 2\}$

$$\limsup_{t \rightarrow +\infty} \|m_j(t, \cdot)\|_{L^1(\mathbb{R})} \leq \frac{\|\gamma_j\|_{\infty} \|p_j\|_{\infty}}{\mu_{m,j}} \left(\frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \right).$$

Proof. Thanks to Lemma 4.2 and Lemma 4.3, the linear operator A is resolvent positive and a Hille-Yosida operator. The non-linear map F is clearly continuous and locally Lipschitz due to Assumption 3.1. The local existence then follows from the classical result (see e.g. [27, Theorem 5.2.7, p. 226]). We now claim that

$$\forall \varepsilon > 0, \exists \lambda_{\varepsilon} : F(u) + \lambda_{\varepsilon} u \geq 0, \quad \forall u \in \mathcal{X}_{0+} \cap B_{\mathcal{X}}(0, \varepsilon)$$

wherein $B_{\mathcal{X}}(0, \varepsilon)$ is the open ball in \mathcal{X} centred at 0 with radius ε . Indeed, a sufficient condition for this inequality to hold is to choose λ_ε such that

$$\lambda_\varepsilon \geq \varepsilon (\|\beta_1\|_\infty + \|\beta_2\|_\infty)$$

which proves the claim. It shows that the solution is non-negative due to [26, Proposition 5.3.2, p. 227]. We now prove the global existence. To this end, let $u_0 = (C_0, 0, v_0(\cdot, \cdot), m_0(\cdot))^T \in \mathcal{X}_{0+}$ be given. Then there exists $T_{\max} \in (0, \infty]$ such that if we set

$$U(t)u_0 = (C_1(t), C_2(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, v_1(t, \cdot, \cdot), v_2(t, \cdot, \cdot), m_1(t, \cdot), m_2(t, \cdot)),$$

then for each $t \in [0, T_{\max})$ and almost every $x \in \mathbb{R}$ we have

$$v_j(t, a, x) = \begin{cases} v_{j,0}(a-t, x)\Pi_j(a-t, a, x) & \text{if } t \leq a, \\ \left(\sum_{i=1}^j C_i(t-a)\right) \beta_j(x)m_j(t-a, x)\Pi_j(0, a, x) & \text{if } t > a \end{cases} \quad (4.4)$$

144 and

$$\begin{cases} \frac{dC_1(t)}{dt} = \Lambda - \mu_{1,2}C_1(t) - C_1(t) \int_{\mathbb{R}} \beta_1(x)m_1(t, x)dx - C_1(t) \int_{\mathbb{R}} \beta_2(x)m_2(t, x)dx, \\ \frac{dC_2(t)}{dt} = \mu_{1,2}C_1(t) - \mu_2C_2(t) - C_2(t) \int_{\mathbb{R}} \beta_2(x)m_2(t, x)dx, \\ \frac{\partial m_j(t, x)}{\partial t} = \int_{\mathbb{R}} k(x-y)p_j(y) \left(\int_0^\infty \gamma_j(a, y)v_j(t, a, y)da \right) dy - (\mu_{m,j} + I_j(x))m_j(t, x). \end{cases} \quad (4.5)$$

Note that using the C_1 -equation we obtain

$$\frac{dC_1(t)}{dt} \leq \Lambda - \mu_{1,2}C_1(t), \quad \forall t \in [0, T_{\max})$$

from which we deduce that

$$C_1(t) \leq e^{-\mu_{1,2}t}C_{1,0} + \frac{\Lambda}{\mu_{1,2}}(1 - e^{-\mu_{1,2}t}), \quad \forall t \in [0, T_{\max}) \quad (4.6)$$

so that

$$C_1(t) \leq M_0 := \max\left(C_{1,0}, \frac{\Lambda}{\mu_{1,2}}\right), \quad \forall t \in [0, T_{\max}). \quad (4.7)$$

147 Using (4.7), it follows from the C_2 -equation of (4.5) that

$$\frac{dC_2(t)}{dt} \leq \mu_{1,2}C_1(t) - \mu_2C_2(t) \leq \mu_{1,2}M_0 - \mu_2C_2(t), \quad \forall t \in [0, T_{\max}) \quad (4.8)$$

and by similar arguments we obtain

$$C_2(t) \leq M_1 := \max\left(C_{2,0}, \frac{\mu_{1,2}M_0}{\mu_2}\right), \quad \forall t \in [0, T_{\max}). \quad (4.9)$$

Next, summing the C -equations of (4.5) it follows that

$$\frac{d}{dt} \sum_{j=1}^2 C_j(t) = \Lambda + \mu_2C_1(t) - \mu_2 \sum_{j=1}^2 C_j(t) - \sum_{j=1}^2 \int_{\mathbb{R}} v_j(t, 0, x)dx, \quad \forall t \in (0, T_{\max}).$$

From where we obtain for each $t \in [0, T_{\max})$

$$\sum_{j=1}^2 C_j(t) = e^{-\mu_2 t} \sum_{j=1}^2 C_{j,0} + \int_0^t e^{-\mu_2(t-a)} (\Lambda + \mu_2 C_1(a)) da - \sum_{j=1}^2 \int_0^t e^{-\mu_2(t-a)} \int_{\mathbb{R}} v_j(a, 0, x) dx da. \quad (4.10)$$

150 Next, using (4.4) it follows that for each $t \in [0, T_{\max})$

$$\begin{aligned} \sum_{j=1}^2 \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx &= \sum_{j=1}^2 \int_{\mathbb{R}} \int_0^t \Pi_j(0, a, x) v_j(t-a, 0, x) da dx \\ &+ \sum_{j=1}^2 \int_{\mathbb{R}} \int_t^\infty v_{j,0}(a-t, x) \Pi_j(a-t, a, x) da dx. \end{aligned} \quad (4.11)$$

Recalling that

$$\Pi_j(a, \sigma, x) \leq e^{-\mu_2(\sigma-a)}, \quad \forall \sigma \geq a \geq 0, \quad x \in \mathbb{R}, \quad j \in \{1, 2\}$$

we infer from (4.11) that for each $t \in [0, T_{\max})$

$$\sum_{j=1}^2 \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \leq \sum_{j=1}^2 \int_{\mathbb{R}} \int_0^t e^{-\mu_2(t-a)} v_j(a, 0, x) da dx + e^{-\mu_2 t} \sum_{j=1}^2 \int_{\mathbb{R}} \int_0^\infty v_{j,0}(a, x) da dx. \quad (4.12)$$

Therefore, setting

$$R(t) := \sum_{j=1}^2 \left(C_j(t) + \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \right), \quad \forall t \in [0, T_{\max})$$

and summing (4.10) and (4.12) we obtain

$$R(t) \leq e^{-\mu_2 t} R(0) + \int_0^t e^{-\mu_2(t-a)} (\Lambda + \mu_2 C_1(a)) da, \quad \forall t \in [0, T_{\max}) \quad (4.13)$$

153 so that (4.7) combined with (4.13) implies

$$R(t) \leq M_2 := \max \left(R(0), \frac{\Lambda + \mu_2 M_0}{\mu_2} \right), \quad \forall t \in [0, T_{\max}). \quad (4.14)$$

Thanks to (4.14), Assumption 3.1, and the m_j -equation in (4.5), we have for each $t \in [0, T_{\max})$

$$\frac{d}{dt} \int_{\mathbb{R}} m_j(t, x) dx \leq \|\gamma_j\|_\infty \|p_j\|_\infty M_2 - \mu_{m,j} \int_{\mathbb{R}} m_j(t, x) dx, \quad j \in \{1, 2\}$$

so that

$$\int_{\mathbb{R}} m_j(t, x) dx \leq \max \left(\frac{\|\gamma_j\|_\infty \|p_j\|_\infty M_2}{\mu_{m,j}}, \int_{\mathbb{R}} m_{j,0}(x) dx \right), \quad j \in \{1, 2\}, \quad \forall t \in [0, T_{\max}). \quad (4.15)$$

156 It is now clear from (4.7), (4.9), and (4.15) that for each $u_0 \in \mathcal{X}_{0+}$ we have $T_{\max} := T_{\max}(u_0) = +\infty$. Moreover, the positive invariance of the set \mathcal{S} defined in (4.2) is a direct consequence of the estimates (4.7), (4.9), (4.14) and (4.15). Let us now prove the dissipativity of the semiflow generated by (3.3). To do so we first note that (4.6) implies that

$$\limsup_{t \rightarrow +\infty} C_1(t) \leq \frac{\Lambda}{\mu_{1,2}}. \quad (4.16)$$

159 Next, let $\epsilon > 0$ be given. Thanks to (4.16) there exists $t_0 := t_0(\epsilon, u_0) > 0$ such that

$$C_1(t) \leq \frac{\Lambda}{\mu_{1,2}} + \epsilon, \quad \forall t \geq t_0. \quad (4.17)$$

Consequently, (4.8) and (4.17) imply that

$$\frac{dC_2(t)}{dt} \leq \mu_{1,2} \left(\frac{\Lambda}{\mu_{1,2}} + \epsilon \right) - \mu_2 C_2(t), \quad \forall t \geq t_0$$

that is

$$C_2(t) \leq e^{-\mu_2(t-t_0)} C_2(t_0) + \frac{\mu_{1,2}}{\mu_2} \left(\frac{\Lambda}{\mu_{1,2}} + \epsilon \right) \left(1 - e^{-\mu_2(t-t_0)} \right), \quad \forall t \geq t_0. \quad (4.18)$$

Recalling that $t \rightarrow C_2(t)$ is bounded on $[0, +\infty)$ it follows from (4.18) that

$$\limsup_{t \rightarrow +\infty} C_2(t) \leq \frac{\mu_{1,2}}{\mu_2} \left(\frac{\Lambda}{\mu_{1,2}} + \epsilon \right). \quad (4.19)$$

Since $\epsilon > 0$ is arbitrary in the above estimate (4.19) we conclude that

$$\limsup_{t \rightarrow +\infty} C_2(t) \leq \frac{\Lambda}{\mu_2}.$$

To obtain the dissipativity concerning the v_j -components, we combine (4.7), (4.13), and (4.17) to obtain

$$R(t) \leq e^{-\mu_2 t} R(0) + \int_0^{t_0} e^{-\mu_2(t-a)} (\Lambda + \mu_2 M_0) da + \int_{t_0}^t e^{-\mu_2(t-a)} \left(\Lambda + \mu_2 \left(\frac{\Lambda}{\mu_{1,2}} + \epsilon \right) \right) da, \quad \forall t \geq t_0$$

from where

$$\limsup_{t \rightarrow +\infty} R(t) \leq \frac{\Lambda}{\mu_2} + \frac{\Lambda}{\mu_{1,2}} + \epsilon.$$

162 Since $\epsilon > 0$ can be chosen arbitrarily small we end up with

$$\limsup_{t \rightarrow +\infty} R(t) \leq \frac{\Lambda}{\mu_2} + \frac{\Lambda}{\mu_{1,2}}. \quad (4.20)$$

To complete the proof, we prove that the dissipativity holds along the m_j -components. To this end, we note that (4.20) implies that for each $\eta > 0$, there exists $t_1 := t_1(\eta, u_0) > 0$ such that $R(t) \leq \frac{\Lambda}{\mu_2} + \frac{\Lambda}{\mu_{1,2}} + \eta$ for all $t \geq t_1$. Consequently, we obtain from the m_j -equation that

$$\frac{d}{dt} \int_{\mathbb{R}} m_j(t, x) dx \leq \|\gamma_j\|_{\infty} \|p_j\|_{\infty} \left(\frac{\Lambda}{\mu_2} + \frac{\Lambda}{\mu_{1,2}} + \eta \right) - \mu_{m,j} \int_{\mathbb{R}} m_j(t, x) dx, \quad j \in \{1, 2\}, \quad \forall t \geq t_1.$$

Using similar arguments as above, we obtain

$$\limsup_{t \rightarrow +\infty} \int_{\mathbb{R}} m_j(t, x) dx \leq \frac{\|\gamma_j\|_{\infty} \|p_j\|_{\infty}}{\mu_{m,j}} \left(\frac{\Lambda}{\mu_2} + \frac{\Lambda}{\mu_{1,2}} + \eta \right), \quad \forall \eta > 0.$$

The proof of Proposition 4.4 is completed. \square

4.2.2 Proof of item 3

165 The next proposition is concerned by the asymptotic smoothness of the semiflow generated by (3.3) (or equivalently (2.1)), that is the third item of Theorem 4.1.

Proposition 4.5 (Asymptotic smoothness of the semiflow). *Let Assumptions 3.1 and 3.2 be satisfied. Then the nonlinear semiflow $\{U(t)\}_{t \geq 0}$ generated by (3.3) has the form*

$$U(t) = U_1(t) + U_2(t), \quad \forall t \geq 0$$

with the following properties:

- 168 *i) For each $t > 0$, $U_1(t) : \mathcal{X}_{0+} \rightarrow \mathcal{X}$, maps bounded sets of \mathcal{X}_{0+} into relatively compact sets of \mathcal{X} ;*
ii) There exists $\xi : [0, +\infty) \times [0, +\infty) \rightarrow [0, +\infty)$ such that for each $\epsilon > 0$, $\lim_{t \rightarrow +\infty} \xi(t, \epsilon) \rightarrow 0$ and if $u_0 \in \mathcal{X}_{0+}$ with $\|u_0\|_{\mathcal{X}} \leq \epsilon$ then $\|U_2(t)u_0\|_{\mathcal{X}} \leq \xi(t, \epsilon)$ for all $t \geq 0$.

Proof. The proof of Proposition 4.5 will be given in a series of lemma. To this end, let us note that the nonlinear map F defined in (3.2) can be written as $F = F_1 + F_2$ where we have set for each $(C, 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, v, m)^T \in \mathcal{X}_{0+}$

$$F_1 \begin{pmatrix} C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ v \\ m \end{pmatrix} = \begin{pmatrix} \bar{\Lambda} - \text{diag} \left(\int_{\mathbb{R}} \kappa_m \beta(y) m(y) dy \right) C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, \\ 0_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)} \\ \int_{\mathbb{R}} k(\cdot - y) p(y) \int_0^{\infty} \gamma(a, y) v(a, y) da dy \end{pmatrix}$$

171 and

$$F_2 \begin{pmatrix} C \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \\ v \\ m \end{pmatrix} = \begin{pmatrix} 0_{\mathbb{R}^2} \\ \text{diag}(\beta m) \kappa_m^T C \\ 0_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)} \\ 0_{L^1(\mathbb{R}, \mathbb{R}^2)} \end{pmatrix}. \quad (4.21)$$

It is worth noting that if Assumptions 3.1 and 3.3 are satisfied then F_1 maps bounded sets of \mathcal{X}_{0+} into a relatively compact set of \mathcal{X}_0 . Indeed, the first component of F_1 belongs to a finite-dimensional space while the last component

174 of F_1 is a composition of a linear continuous map with a compact linear map which is a consequence of Assumptions
 3.1 and 3.2 (see [14]). In the following, $B \subseteq \mathcal{X}_{0+}$ is a bounded subset of \mathcal{X}_{0+} . Recall that for each $u_0 \in B$, the
 integrated (mild) solution $t \in [0, +\infty) \mapsto U(t)u_0$ of (3.3) is given by

$$U(t)u_0 = T_{A_0}(t)u_0 + \lim_{\lambda \rightarrow +\infty} \int_0^t T_{A_0}(t-s)\lambda(\lambda - A)^{-1}F(U(s)u_0)ds, \quad \forall t \geq 0. \quad (4.22)$$

177 Next, we define for each $u_0 \in B$, the map $t \mapsto \hat{U}(t)u_0$ by

$$\hat{U}(t)u_0 := \lim_{\lambda \rightarrow +\infty} \int_0^t T_{A_0}(t-s)\lambda(\lambda - A)^{-1}F_1(U(s)u_0)ds, \quad t \geq 0. \quad (4.23)$$

We also define the map $t \mapsto \check{U}(t)u_0$ as

$$\check{U}(t)u_0 := T_{A_0}(t)u_0, \quad t \geq 0 \quad (4.24)$$

and the map $t \mapsto \tilde{U}(t)u_0$ as

$$\tilde{U}(t)u_0 := \lim_{\lambda \rightarrow +\infty} \int_0^t T_{A_0}(t-s)\lambda(\lambda - A)^{-1}F_2(U(s)u_0)ds, \quad t \geq 0. \quad (4.25)$$

180 Let us note that the uniqueness of the integrated solution (4.22) together with (4.23), (4.24) and (4.25) imply that
 for each $u_0 \in B$ we have

$$U(t)u_0 = \hat{U}(t)u_0 + \check{U}(t)u_0 + \tilde{U}(t)u_0, \quad \forall t \geq 0. \quad (4.26)$$

183 Note that using similar arguments to the proof of Proposition 4.4, one obtains that there exists $K_0 := K_0(B) > 0$
 such that

$$\sup_{t \geq 0, u_0 \in B} \|U(t)u_0\|_{\mathcal{X}} \leq K_0. \quad (4.27)$$

Moreover, due to Lemma 4.3, the equality (4.24) and the boundedness of B , there exists $K_1 := K_1(B) > 0$ such
 that

$$\sup_{u_0 \in B} \|\check{U}(t)u_0\|_{\mathcal{X}} \leq e^{-\omega_A t} K_1, \quad \forall t \geq 0. \quad (4.28)$$

186 We have the following lemma.

Lemma 4.6. *Let Assumptions 3.1 and 3.2 be satisfied. Then, for each $T > 0$, the set $\mathcal{B} := \{\hat{U}(\cdot)u_0 \in C([0, T], \mathcal{X}_0) : u_0 \in B\}$ is relatively compact in $C([0, T], \mathcal{X}_0)$.*

Proof. Let $T > 0$ be given and define \mathcal{B} as in the Lemma. The proof will be done by using the Arzelà-Ascoli
 theorem. To do so, we have to prove that for each $t \geq 0$, the set $\mathcal{B}(t) := \{\hat{U}(t)u_0 : u_0 \in B\}$ is compact in \mathcal{X}_0 and \mathcal{B}
 is an equicontinuous family. Let us note that $F_1(U(s)u_0) \in \mathcal{X}_0$ for all $s \geq 0$, $u_0 \in B$ so that (4.23) becomes

$$\hat{U}(t)u_0 = \int_0^t T_{A_0}(t-s)F_1(U(s)u_0)ds, \quad \forall t \geq 0, \quad \forall u_0 \in B.$$

Thanks to (4.27) we can define the bounded set

$$B_0 := \{U(t)u_0 : t \geq 0, u_0 \in B\},$$

The compactness of F_1 implies that $F_1(B_0)$ is relatively compact. Recalling that $(s, y) \mapsto T_{A_0}(s)y$ is continuous,
 we deduce that the set

$$\{T_{A_0}(t-s)F_1(U(s)u_0) : s \in [0, t], u_0 \in B\} \subset \{T_{A_0}(t-s)F_1(y) : s \in [0, t], y \in B_0\}$$

is relatively compact. By a theorem by Mazur, we conclude that for each $t > 0$ the set

$$\mathcal{B}(t) = \left\{ \int_0^t T_{A_0}(t-s)F_1(U(s)u_0)ds : u_0 \in B \right\}$$

is relatively compact. This proves that for each $t \geq 0$, the set $\mathcal{B}(t)$ is relatively compact. To complete the proof, we have to prove that \mathcal{B} is equicontinuous. To this end, let $0 \leq t_0 \leq t \leq T$ be given. Then we have

$$\begin{aligned}\hat{U}(t)u_0 - \hat{U}(t_0)u_0 &= \int_{t_0}^t T_{A_0}(t-s)F_1(U(s)u_0)ds + \int_0^{t_0} [T_{A_0}(t-s) - T_{A_0}(t_0-s)]F_1(U(s)u_0)ds \\ &= \int_{t_0}^t T_{A_0}(t-s)F_1(U(s)u_0)ds + \int_0^{t_0} [T_{A_0}(t-t_0+s) - T_{A_0}(s)]F_1(U(t_0-s)u_0)ds\end{aligned}$$

189 proving that

$$\|\hat{U}(t)u_0 - \hat{U}(t_0)u_0\|_{\mathcal{X}} \leq \sup_{y \in B_0} \|F_1(y)\|_{\mathcal{X}} \int_{t_0}^t M_A e^{-\omega_A(t-s)} ds + t_0 \sup_{s \in [0, t_0], y \in F_1(B_0)} \|T_{A_0}(t-t_0+s)y - T_{A_0}(s)y\|_{\mathcal{X}}. \quad (4.29)$$

The equicontinuity of \mathcal{B} follows from (4.29) and the fact that $F_1(B_0)$ is relatively compact. \square

Due to (4.26)-(4.27) and Lemma 4.6, our Proposition 4.5 is a consequence of the following lemma.

Lemma 4.7. *Let Assumptions 3.1 and 3.2 be satisfied. Then, the nonlinear maps $\{\tilde{U}(t)\}_{t \geq 0}$ defined in (4.25) has the form*

$$\tilde{U}(t) = \tilde{V}(t) + \tilde{Z}(t), \quad \forall t \geq 0$$

192 with the following properties:

i) For each $t > 0$, $\tilde{V}(t) : \mathcal{X}_0 \rightarrow \mathcal{X}$, maps B into relatively compact sets of \mathcal{X} ;

ii) There exists a constant $\tilde{K} := \tilde{K}(B) > 0$ such that $\|\tilde{Z}(t)u_0\|_{\mathcal{X}} \leq \tilde{K}(1+t)e^{-\omega_A^+ t}$, for all $t \geq 0$ and $u_0 \in B$.

195 The positive constant $\omega_A^+ > 0$ is defined as $\omega_A^+ := \min\{\omega_A, \mu_2\}$ with ω_A defined in Lemma 4.3.

Proof. Let us set for each $t \geq 0$, $u_0 \in B$

$$U(t)u_0 := (C_1^{u_0}(t), C_2^{u_0}(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, v_1^{u_0}(t, \cdot, \cdot), v_2^{u_0}(t, \cdot, \cdot), m_1^{u_0}(t, \cdot), m_2^{u_0}(t, \cdot))$$

and

$$\begin{cases} \hat{U}(t)u_0 := (\hat{C}_1^{u_0}(t), \hat{C}_2^{u_0}(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, \hat{v}_1^{u_0}(t, \cdot, \cdot), \hat{v}_2^{u_0}(t, \cdot, \cdot), \hat{m}_1^{u_0}(t, \cdot), \hat{m}_2^{u_0}(t, \cdot)) \\ \tilde{U}(t)u_0 := (\tilde{C}_1^{u_0}(t), \tilde{C}_2^{u_0}(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, \tilde{v}_1^{u_0}(t, \cdot, \cdot), \tilde{v}_2^{u_0}(t, \cdot, \cdot), \tilde{m}_1^{u_0}(t, \cdot), \tilde{m}_2^{u_0}(t, \cdot)) \\ \check{U}(t)u_0 := (\check{C}_1^{u_0}(t), \check{C}_2^{u_0}(t), 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, \check{v}_1^{u_0}(t, \cdot, \cdot), \check{v}_2^{u_0}(t, \cdot, \cdot), \check{m}_1^{u_0}(t, \cdot), \check{m}_2^{u_0}(t, \cdot)) \end{cases}$$

so that we get for each $t \geq 0$, $j \in \{1, 2\}$ and $u_0 \in B$:

$$\begin{cases} C_j^{u_0}(t) &= \hat{C}_j^{u_0}(t) + \check{C}_j^{u_0}(t) + \tilde{C}_j^{u_0}(t), \\ m_j^{u_0}(t, \cdot) &= \hat{m}_j^{u_0}(t, \cdot) + \check{m}_j^{u_0}(t, \cdot) + \tilde{m}_j^{u_0}(t, \cdot), \\ v_j^{u_0}(t, \cdot, \cdot) &= \hat{v}_j^{u_0}(t, \cdot, \cdot) + \check{v}_j^{u_0}(t, \cdot, \cdot) + \tilde{v}_j^{u_0}(t, \cdot, \cdot). \end{cases} \quad (4.30)$$

Note that, using (4.28) we have for each $j \in \{1, 2\}$ and $t \geq 0$ the following estimates

$$\begin{cases} \sup_{u_0 \in B} |\check{C}_j^{u_0}(t)| &\leq K_1 e^{-\omega_A t}, \\ \sup_{u_0 \in B} \|\check{m}_j^{u_0}(t, \cdot)\|_{L^1(\mathbb{R})} &\leq K_1 e^{-\omega_A t}, \end{cases} \quad (4.31)$$

198 while (4.27) gives the following estimates

$$\begin{cases} \sup_{u_0 \in B} |C_j^{u_0}(t)| \leq K_0, \quad \forall t \geq 0 \\ \sup_{u_0 \in B} \|m_j^{u_0}(t, \cdot)\|_{L^1(\mathbb{R})} \leq K_0, \quad \forall t \geq 0. \end{cases} \quad (4.32)$$

Using (4.21) and (4.25) it follows that $t \mapsto (\check{C}^{u_0}(t), \check{v}^{u_0}(t, \cdot, \cdot), \check{m}^{u_0}(t, \cdot))$ satisfies, in the mild sense, the following system

$$\begin{cases} \frac{d\check{C}^{u_0}(t)}{dt} = -\mu \check{C}^{u_0}(t), \\ \check{v}^{u_0}(t, a = 0, x) = \text{diag}(\beta(x)m^{u_0}(t, x))\kappa_m^T C^{u_0}(t), \\ (\partial_t + \partial_a)\check{v}^{u_0}(t, a, x) = -(\mu_2 \mathbf{I}_d + \gamma(a, x))\check{v}^{u_0}(t, a, x), \\ \partial_t \check{m}^{u_0}(t, x) = -(\nu + I(x))\check{m}^{u_0}(t, x) \end{cases}$$

with initial conditions $\tilde{C}^{u_0}(0) = 0$, $\tilde{m}^{u_0}(0, \cdot) = 0_{L^1(\mathbb{R}, \mathbb{R}^2)}$ and $\tilde{v}^{u_0}(0, \cdot, \cdot) = 0_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}^2)}$. Consequently, we have

$$\tilde{C}^{u_0}(t) = 0, \quad \tilde{m}^{u_0}(t, \cdot) = 0_{L^1(\mathbb{R}, \mathbb{R}^2)}, \quad \forall u_0 \in B, \quad \forall t \geq 0 \quad (4.33)$$

and for each $j \in \{1, 2\}$, $t \geq 0$, $a \geq 0$ and $u_0 \in B$:

$$\tilde{v}_j^{u_0}(t, a, \cdot) = 1_{[0, t]}(a) \beta_j(\cdot) \Pi_j(0, a, \cdot) \left(\sum_{i=1}^j C_i^{u_0}(t-a) \right) m_j^{u_0}(t-a, \cdot). \quad (4.34)$$

201 Hence, we infer from (4.30) and (4.33) that for each $j \in \{1, 2\}$, $t \geq 0$ and $u_0 \in B$:

$$\begin{cases} m_j^{u_0}(t, \cdot) &= \hat{m}_j^{u_0}(t, \cdot) + \check{m}_j^{u_0}(t, \cdot), \\ C_j^{u_0}(t) &= \hat{C}_j^{u_0}(t) + \check{C}_j^{u_0}(t). \end{cases} \quad (4.35)$$

Moreover, using (4.35) we obtain from (4.31) and (4.32) that for each $j \in \{1, 2\}$ and $t \geq 0$:

$$\sup_{u_0 \in B} |\hat{C}_j^{u_0}(t)| \leq K_0 + K_1. \quad (4.36)$$

Next, note that using (4.34) and (4.35), we have for each $t \geq 0$, $a \geq 0$, $j \in \{1, 2\}$, $x \in \mathbb{R}$ and $u_0 \in B$:

$$\begin{aligned} \tilde{v}_j^{u_0}(t, a, x) &= 1_{[0, t]}(a) \beta_j(x) \Pi_j(0, a, x) \left(m_j^{u_0}(t-a, x) \sum_{i=1}^j \check{C}_i^{u_0}(t-a) + \check{m}_j^{u_0}(t-a, x) \sum_{i=1}^j \hat{C}_i^{u_0}(t-a) \right) \\ &\quad + 1_{[0, t]}(a) \beta_j(x) \Pi_j(0, a, x) \sum_{i=1}^j \hat{C}_i^{u_0}(t-a) \hat{m}_j^{u_0}(t-a, x) \end{aligned}$$

so that for each $t \geq 0$ and $u_0 \in B$:

$$\tilde{v}_j^{u_0}(t, \cdot, \cdot) = \tilde{w}_j^{u_0}(t, \cdot, \cdot) + \tilde{z}_j^{u_0}(t, \cdot, \cdot)$$

where we have set for all $t \geq 0$, $a \geq 0$ and $u_0 \in B$:

$$\begin{aligned} \tilde{w}_j^{u_0}(t, a, x) &= 1_{[0, t]}(a) \beta_j(x) \Pi_j(0, a, x) \left(m_j^{u_0}(t-a, x) \sum_{i=1}^j \check{C}_i^{u_0}(t-a) + \check{m}_j^{u_0}(t-a, x) \sum_{i=1}^j \hat{C}_i^{u_0}(t-a) \right) \\ \tilde{z}_j^{u_0}(t, a, x) &= 1_{[0, t]}(a) \beta_j(x) \Pi_j(0, a, x) \left(\sum_{i=1}^j \hat{C}_i^{u_0}(t-a) \right) \hat{m}_j^{u_0}(t-a, x). \end{aligned}$$

Using (4.31), (4.32) and (4.36) it is easy to prove that there exists a constant $\tilde{K}_1 > 0$, depending only on B such that

$$\|\tilde{w}_j^{u_0}(t, \cdot, \cdot)\|_{L^1} \leq \tilde{K}_1 (1+t) e^{-\min\{\omega_A, \mu_2\}t}, \quad \forall t \geq 0, \quad j \in \{1, 2\}.$$

We now conclude the proof by proving that for each $t > 0$, the set $\{\tilde{z}_j^{u_0}(t, \cdot, \cdot) : u_0 \in B\}$ is relatively compact in $L^1(\mathbb{R}_+ \times \mathbb{R})$. To do so, let $\{\tilde{z}_j^n(t, \cdot, \cdot) : n \in \mathbb{N}\}$ be a bounded sequence in $\{\tilde{z}_j^{u_0}(t, \cdot, \cdot) : u_0 \in B\}$. Thanks to Lemma 4.6, the set $\{\hat{m}_j^n : n \in \mathbb{N}\}$ is compact in $C([0, t], L^1(\mathbb{R}))$ and $\{\hat{C}_j^n : n \in \mathbb{N}\}$ is compact in $C([0, t], \mathbb{R})$. Consequently, there exists $\hat{m}_j^\infty \in C([0, t], L^1(\mathbb{R}))$ and $\hat{C}_j^\infty \in C([0, t], \mathbb{R})$ such that

$$\lim_{n \rightarrow +\infty} \hat{m}_j^n = \hat{m}_j^\infty \quad \text{in } C([0, t], L^1(\mathbb{R}))$$

and

$$\lim_{n \rightarrow +\infty} \hat{C}_j^n = \hat{C}_j^\infty \quad \text{in } C([0, t], \mathbb{R}).$$

Next, setting for each $t \geq 0$, $a \geq 0$, $x \in \mathbb{R}$:

$$\tilde{z}_j^\infty(t, a, x) = 1_{[0, t]}(a) \beta_j(x) \Pi_j(0, a, x) \sum_{i=1}^j \hat{C}_i^\infty(t-a) \hat{m}_j^\infty(t-a, x)$$

it follows easily that

$$\lim_{n \rightarrow +\infty} \tilde{z}_j^n(t, \cdot, \cdot) = \tilde{z}_j^\infty(t, \cdot, \cdot) \quad \text{in } L^1(\mathbb{R}_+ \times \mathbb{R}).$$

□

204 This ends the proof of Proposition 4.5. □

Finally, the simple use of [21, Lemma 3.2.3, p. 37] ends the proof of Theorem 4.1.

5 Stationary states

207 We investigate the existence of stationary states that are solutions $(C_1^*, C_2^*, v_1^*, v_2^*, m_1^*, m_2^*)$ of the following system with $j \in \{1, 2\}$:

$$\begin{cases} 0 = \Lambda - \mu_{1,2}C_1^* - C_1^* \int_{\mathbb{R}} \beta_1(x)m_1^*(x)dx - C_1^* \int_{\mathbb{R}} \beta_2(x)m_2^*(x)dx, \\ 0 = \mu_{1,2}C_1^* - \mu_2C_2^* - C_2^* \int_{\mathbb{R}} \beta_2(x)m_2^*(x)dx, \\ v_j^*(a=0, x) = \left(\sum_{i=1}^j C_i^* \right) \beta_j(x)m_j^*(x), \\ \partial_a v_j^*(a, x) = -(\mu_2 + \gamma_j(a, x))v_j^*(a, x), \\ \int_{\mathbb{R}} k(x-y)p_j(y) \left(\int_0^\infty \gamma_j(a, y)v_j^*(a, y)da \right) dy = (\mu_{m,j} + I_j(x))m_j^*(x). \end{cases} \quad (5.1)$$

The parasite-free equilibrium denoted by E_0 always exists and is defined by

$$E_0 = \left(C_1^{E_0}, C_2^{E_0}, 0, 0, 0, 0 \right), \quad \text{with } C_1^{E_0} = \frac{\Lambda}{\mu_{1,2}}, \quad C_2^{E_0} = \frac{\Lambda}{\mu_2}. \quad (5.2)$$

210 The endemic stationary states rely on the spectral analysis of the linear operators L_j , defined by (3.4) whose properties have been reminded in Proposition 3.4. We define the following thresholds:

$$\mathcal{R}_1 = \frac{\Lambda}{\mu_{1,2}}r(L_1), \quad \mathcal{R}_2 = \left(\frac{\Lambda}{\mu_{1,2}} + \frac{\Lambda}{\mu_2} \right) r(L_2) \quad \text{and} \quad \mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\}. \quad (5.3)$$

We can state the following result:

213 **Theorem 5.1.** *Let Assumptions 3.1 and 3.3 be satisfied.*

1. If $\mathcal{R}_1 > 1$, then System (2.1) has an equilibrium $E_1 = \left(C_1^{E_1}, C_2^{E_1}, v_1^{E_1}, 0_{L^1(\mathbb{R}_+ \times \mathbb{R})}, m_1^{E_1}, 0_{L^1(\mathbb{R})} \right)$ where

$$\begin{aligned} C_1^{E_1} &= \frac{C_1^{E_0}}{\mathcal{R}_1}, \quad C_2^{E_1} = \frac{C_2^{E_0}}{\mathcal{R}_1}, \quad v_1^{E_1}(a, x) = C_1^{E_1} \beta_1(x) m_1^{E_1}(x) \Pi_1(0, a, x), \\ m_1^{E_1}(x) &= \mu_{1,2}(\mathcal{R}_1 - 1) \left(\int_{\mathbb{R}} \frac{\beta_1(z)\phi_1(z)}{\mu_{m,1} + I_1(z)} dz \right)^{-1} \times \frac{\phi_1(x)}{\mu_{m,1} + I_1(x)}. \end{aligned} \quad (5.4)$$

2. If $\mathcal{R}_2 > 1$, then System (2.1) has an equilibrium $E_2 = \left(C_1^{E_2}, C_2^{E_2}, 0_{L^1(\mathbb{R}_+ \times \mathbb{R})}, v_2^{E_2}, 0_{L^1(\mathbb{R})}, m_2^{E_2} \right)$ where

$$\begin{aligned} C_1^{E_2} &= \frac{\Lambda}{\mu_{1,2} + \int_{\mathbb{R}} \beta_2(z)m_2^{E_2}(z)dz}, \quad C_2^{E_2} = \frac{\Lambda}{\mu_{1,2} + \int_{\mathbb{R}} \beta_2(z)m_2^{E_2}(z)dz} \times \frac{\mu_{1,2}}{\mu_2 + \int_{\mathbb{R}} \beta_2(z)m_2^{E_2}(z)dz}, \\ v_2^{E_2}(a, x) &= (C_1^{E_2} + C_2^{E_2})\beta_2(x)m_2^{E_2}(x)\Pi_2(0, a, x), \quad m_2^{E_2}(x) = \frac{\lambda_2}{\mu_{m,2} + I_2(z)}\phi_2(x), \end{aligned} \quad (5.5)$$

where λ_2 is the unique positive solution of the following equation

$$1 = \frac{\mu_{1,2}\Lambda r(L_2)}{\mu_{1,2} + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z)\phi_2(z)}{\mu_{m,2} + I_2(z)} dz} \left(\frac{1}{\mu_{1,2}} + \frac{1}{\mu_2 + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z)\phi_2(z)}{\mu_{m,2} + I_2(z)} dz} \right).$$

3. If the following assumption holds

$$1 < \frac{\mathcal{R}_2}{\mathcal{R}_1} < 1 + \frac{\mu_{1,2}}{\mu_2} \quad \text{and} \quad \mathcal{R}_1 > 1 + \left(1 + \frac{\mu_2}{\mu_{1,2}} \right) \frac{\frac{\mathcal{R}_2}{\mathcal{R}_1} - 1}{1 + \frac{\mu_{1,2}}{\mu_2} - \frac{\mathcal{R}_2}{\mathcal{R}_1}} \quad (5.6)$$

then System (2.1) has a unique positive equilibrium $E^* = (C_1^{E^*}, C_2^{E^*}, v_1^{E^*}, v_2^{E^*}, m_1^{E^*}, m_2^{E^*})$ such that

$$\begin{cases} C_1^{E^*} = \frac{\Lambda}{\mu_{1,2} + \sum_{k=1}^2 \int_{\mathbb{R}} \beta_k(z) m_k^{E^*}(z) dz}, \\ C_2^{E^*} = \frac{\Lambda \mu_{1,2}}{(\mu_{1,2} + \sum_{k=1}^2 \int_{\mathbb{R}} \beta_k(z) m_k^{E^*}(z) dz) (\mu_2 + \int_{\mathbb{R}} \beta_2(z) m_2^{E^*}(z) dz)}, \\ v_1^{E^*}(a, x) = C_1^{E^*} \beta_1(x) m_1^{E^*}(x) \Pi_1(0, a, x), \\ v_2^{E^*}(a, x) = (C_1^{E^*} + C_2^{E^*}) \beta_2(x) m_2^{E^*}(x) \Pi_2(0, a, x), \\ m_1^{E^*}(x) = \frac{\lambda_1}{\mu_{m,1} + I_1(x)} \phi_1(x), \\ m_2^{E^*}(x) = \frac{\lambda_2}{\mu_{m,2} + I_2(x)} \phi_2(x), \end{cases} \quad (5.7)$$

where λ_1 and λ_2 are positive constants given by

$$\lambda_1 = \mu_{1,2} \frac{\mathcal{R}_1 - \left(1 + \frac{\lambda_2}{\mu_{1,2}} \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz\right)}{\int_{\mathbb{R}} \frac{\beta_1(z) \phi_1(z)}{\mu_{m,1} + I_1(z)} dz}, \quad \lambda_2 = \frac{(\mu_{1,2} + \mu_2) \left(\frac{\mathcal{R}_2}{\mathcal{R}_1} - 1\right)}{\left(1 + \frac{\mu_{1,2}}{\mu_2} - \frac{\mathcal{R}_2}{\mathcal{R}_1}\right) \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz}.$$

216 We can observe that the stationary state E_1 corresponds to the scenario where only *P. vivax* is present, whereas only *P. falciparum* is present at the stationary state E_2 . Both species can be found at the positive stationary state E^* , see Figure 1. Note that the condition (5.6) necessarily implies that $\mathcal{R}_2 > \mathcal{R}_1 > 1$.

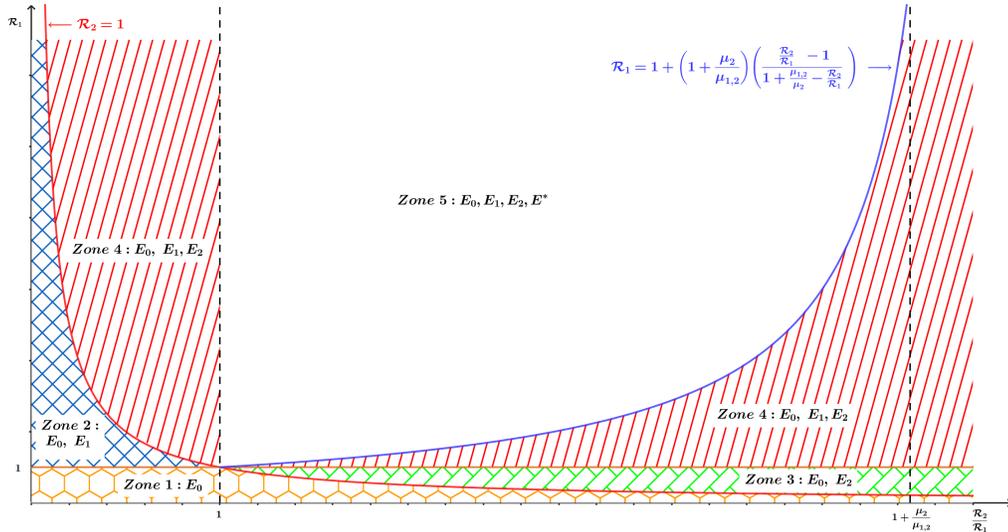


Figure 1: **Qualitative view of areas for the existence of equilibria according to \mathcal{R}_1 and $\frac{\mathcal{R}_2}{\mathcal{R}_1}$.** In zone 1 there is only E_0 since $\mathcal{R}_0 < 1$. Zone 2 is bounded by $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, whence E_0 and E_1 are present. Zone 3 is bounded by $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$, so that E_0 and E_2 exist. In zones 4 and 5, the conditions $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$ are satisfied so that E_0, E_1 and E_2 are present in both zones. However, the condition (5.6) holds in zone 5 but not in zone 4, whence E^* is only present in zone 5.

219 *Proof.*

1. At the stationary state E_1 , System (5.1) rewrites

$$\begin{cases} 0 = \Lambda - \mu_{1,2} C_1^{E_1} - C_1^{E_1} \int_{\mathbb{R}} \beta_1(x) m_1^{E_1}(x) dx, \\ 0 = \mu_{1,2} C_1^{E_1} - \mu_2 C_2^{E_1}, \\ v_1^{E_1}(0, x) = C_1^{E_1} \beta_1(x) m_1^{E_1}(x), \\ \partial_a v_1^{E_1}(a, x) = -(\mu_2 + \gamma_1(a, x)) v_1^{E_1}(a, x), \\ 0 = \int_{\mathbb{R}} k(x-y) p_1(y) \left(\int_0^\infty \gamma_1(a, y) v_1^{E_1}(a, y) da \right) dy - (\mu_{m,1} + I_1(x)) m_1^{E_1}(x). \end{cases} \quad (5.8)$$

The first two equations of (5.8) lead to

$$C_1^{E_1} = C_1^{E_0} \frac{\mu_{1,2}}{\mu_{1,2} + \int_{\mathbb{R}} \beta_1(z) m_1^{E_1}(z) dz}, \quad C_2^{E_1} = C_2^{E_0} \frac{\mu_{1,2}}{\mu_{1,2} + \int_{\mathbb{R}} \beta_1(z) m_1^{E_1}(z) dz}$$

and we have from the v_1 -equation

$$v_1^{E_1}(a, x) = C_1^{E_1} \beta(x) m_1^{E_1}(x) \Pi_1(0, a, x).$$

Substituting the above expressions of $C_1^{E_1}$ and $v_1^{E_1}$ into the last equation of (5.8), it comes

$$\frac{\Lambda}{\mu_{1,2} + \int_{\mathbb{R}} \frac{\beta_1(z)}{\mu_{m,1} + I_1(z)} \bar{m}_1(z) dz} L_1 \bar{m}_1(x) = \bar{m}_1(x), \quad (5.9)$$

222 where we have set $\bar{m}_1 = (\mu_{m,1} + I_1) m_1^{E_1}$ and L_1 is the linear operator introduced by (3.4). Then, by Proposition 3.4 we find from (5.9) that $\bar{m}_1 = \lambda_1 \phi_1$, where λ_1 is a positive constant. Moreover, by (5.9) we have

$$\frac{1}{r(L_1)} = \frac{\Lambda}{\mu_{1,2} + \lambda_1 \int_{\mathbb{R}} \frac{\beta_1(z) \phi_1(z)}{\mu_{m,1} + I_1(z)} dz}.$$

i.e.

$$\lambda_1 = \mu_{1,2} \left(\frac{\Lambda}{\mu_{1,2}} r(L_1) - 1 \right) \left(\int_{\mathbb{R}} \frac{\beta_1(z) \phi_1(z)}{\mu_{m,1} + I_1(z)} dz \right)^{-1}$$

225 from which we obtain the equilibrium E_1 defined by (5.4).

2. Similarly, for the stationary state E_2 we have

$$\begin{aligned} C_1^{E_2} &= \frac{\Lambda}{\mu_{1,2} + \int_{\mathbb{R}} \beta_2(z) m_2^{E_2}(z) dz}, \\ C_2^{E_2} &= \frac{\Lambda}{\mu_{1,2} + \int_{\mathbb{R}} \beta_2(z) m_2^{E_2}(z) dz} \cdot \frac{\mu_{1,2}}{\mu_2 + \int_{\mathbb{R}} \beta_2(z) m_2^{E_2}(z) dz}, \\ v_2^{E_2}(a, x) &= \left(C_1^{E_2} + C_2^{E_2} \right) \beta_2(x) m_2^{E_2}(x) \Pi_2(0, a, x), \end{aligned}$$

and

$$\frac{\Lambda}{\mu_{1,2} + \int_{\mathbb{R}} \frac{\beta_2(z) \bar{m}_2(z)}{\mu_{m,2} + I_2(z)} dz} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \int_{\mathbb{R}} \frac{\beta_2(z) \bar{m}_2(z)}{\mu_{m,2} + I_2(z)} dz} \right) L_2 \bar{m}_2(x) = \bar{m}_2(x) \quad (5.10)$$

228 where we have set $\bar{m}_2 = (\mu_{m,2} + I_2) m_2^{E_2}$ and L_2 is the linear operator defined by (3.4). Again from Proposition 3.4 we find from (5.10) that $\bar{m}_2 = \lambda_2 \phi_2$, where λ_2 is a positive constant. Moreover, by (5.10) we have

$$\frac{1}{r(L_2)} = \frac{\Lambda}{\mu_{1,2} + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz} \right). \quad (5.11)$$

The right-hand side of (5.11) is continuous and strictly decreasing in λ_2 , so a necessary and sufficient condition to have a nontrivial endemic equilibrium is $\frac{1}{r(L_2)} < \frac{\Lambda}{\mu_{1,2}} \left(1 + \frac{\mu_{1,2}}{\mu_2} \right)$, *i.e.* $\mathcal{R}_2 > 1$. This ends the computation of the equilibrium E_2 defined by (5.5). Note that an explicit expression of λ_2 reads

$$\lambda_2 = \frac{\mu_2 + \mu_{1,2} \left(1 - \frac{\Lambda r(L_2)}{\mu_{1,2}} \right) + \sqrt{\left(\mu_2 + \mu_{1,2} \left(1 - \frac{\Lambda r(L_2)}{\mu_{1,2}} \right) \right)^2 + 4\mu_{1,2}\mu_2(\mathcal{R}_2 - 1)}}{2 \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz}.$$

3. From System (5.1), the positive equilibrium E^* is such that

$$C_1^{E^*} = \frac{\Lambda}{\mu_{1,2} + \sum_{k=1}^2 \int_{\mathbb{R}} \beta_k(z) m_k^{E^*}(z) dz},$$

$$C_2^{E^*} = \frac{\Lambda \mu_{1,2}}{(\mu_{1,2} + \sum_{k=1}^2 \int_{\mathbb{R}} \beta_k(z) m_k^{E^*}(z) dz)(\mu_2 + \int_{\mathbb{R}} \beta_2(z) m_2^{E^*}(z) dz)},$$

$$v_1^{E^*}(a, x) = C_1^{E^*} \beta_1(x) m_1^{E^*}(x) \Pi_1(0, a, x), \quad v_2^{E^*}(a, x) = (C_1^{E^*} + C_2^{E^*}) \beta_2(x) m_2^{E^*}(x) \Pi_2(0, a, x).$$

Substituting the above estimates into the last equation of (5.1) we obtain the following system:

$$\begin{cases} \frac{\Lambda}{\mu_{1,2} + \sum_{j=1}^2 \int_{\mathbb{R}} \frac{\beta_j(z)}{\mu_{m,j} + I_j(z)} \bar{m}_j(z) dz} L_1 \bar{m}_1(x) = \bar{m}_1(x), \\ \frac{\Lambda}{\mu_{1,2} + \sum_{j=1}^2 \int_{\mathbb{R}} \frac{\beta_j(z)}{\mu_{m,j} + I_j(z)} \bar{m}_j(z) dz} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \int_{\mathbb{R}} \frac{\beta_2(z)}{\mu_{m,2} + I_2(z)} \bar{m}_2(z) dz} \right) L_2 \bar{m}_2(x) = \bar{m}_2(x) \end{cases} \quad (5.12)$$

where we have set $\bar{m}_j = (\mu_{m,j} + I_j) m_j^{E^*}$. We get $\bar{m}_j = \lambda_j \phi_j$ with positive constants λ_j . Furthermore, (5.12) gives

$$\begin{cases} \frac{1}{r(L_1)} = \frac{\Lambda}{\mu_{1,2} + \sum_{j=1}^2 \lambda_j \int_{\mathbb{R}} \frac{\beta_j(z)}{\mu_{m,j} + I_j(z)} \phi_j(z) dz}, \\ \frac{1}{r(L_2)} = \frac{\Lambda}{\mu_{1,2} + \sum_{j=1}^2 \lambda_j \int_{\mathbb{R}} \frac{\beta_j(z)}{\mu_{m,j} + I_j(z)} \phi_j(z) dz} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z)}{\mu_{m,2} + I_2(z)} \phi_2(z) dz} \right) \end{cases}$$

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i.e.

$$\begin{cases} 1 = \mathcal{R}_1 \frac{\mu_{1,2}}{\mu_{1,2} + \sum_{j=1}^2 \lambda_j \int_{\mathbb{R}} \frac{\beta_j(z)}{\mu_{m,j} + I_j(z)} \phi_j(z) dz}, \\ 1 = \frac{\mathcal{R}_2 \left(\frac{1}{\mu_{1,2}} + \frac{1}{\mu_2} \right)^{-1}}{\mathcal{R}_1 \mu_{1,2}} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z)}{\mu_{m,2} + I_2(z)} \phi_2(z) dz} \right). \end{cases} \quad (5.13)$$

The right-hand side of the second equation of (5.13) is continuous and strictly decreasing in λ_2 . Thus, the necessary and sufficient condition for the existence of $\lambda_2 > 0$ reads:

$$\frac{\mathcal{R}_2 \left(\frac{1}{\mu_{1,2}} + \frac{1}{\mu_2} \right)^{-1}}{\mathcal{R}_1 \mu_{1,2}} \left(1 + \frac{\mu_{1,2}}{\mu_2} \right) > 1 \quad \text{and} \quad \frac{\mathcal{R}_2 \left(\frac{1}{\mu_{1,2}} + \frac{1}{\mu_2} \right)^{-1}}{\mathcal{R}_1 \mu_{1,2}} < 1$$

that is equivalent to

$$1 < \frac{\mathcal{R}_2}{\mathcal{R}_1} < 1 + \frac{\mu_{1,2}}{\mu_2}.$$

Still from the second equation of (5.13), we obtain

$$\lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz = \frac{(\mu_{1,2} + \mu_2) \left(\frac{\mathcal{R}_2}{\mathcal{R}_1} - 1 \right)}{\left(1 + \frac{\mu_{1,2}}{\mu_2} \right) - \frac{\mathcal{R}_2}{\mathcal{R}_1}}.$$

It then remains to find λ_1 . Note that the right-hand side of the first equation of (5.13) is continuous and strictly decreasing in λ_1 . Thus, the necessary and sufficient condition for the existence of $\lambda_1 > 0$ is

$$\frac{\mathcal{R}_1 \mu_{1,2}}{\mu_{1,2} + \lambda_2 \int_{\mathbb{R}} \frac{\beta_2(z) \phi_2(z)}{\mu_{m,2} + I_2(z)} dz} > 1$$

i.e.

$$\mathcal{R}_1 > 1 + \left(1 + \frac{\mu_2}{\mu_{1,2}} \right) \frac{\frac{\mathcal{R}_2}{\mathcal{R}_1} - 1}{1 + \frac{\mu_{1,2}}{\mu_2} - \frac{\mathcal{R}_2}{\mathcal{R}_1}}$$

and we have

$$\lambda_1 = \mu_{1,2} \frac{\mathcal{R}_1 - \left(1 + \frac{\lambda_2}{\mu_{1,2}} \int_{\mathbb{R}} \frac{\beta_2(z)\phi_2(z)}{\mu_{m,2} + I_2(z)} dz\right)}{\int_{\mathbb{R}} \frac{\beta_1(z)\phi_1(z)}{\mu_{m,1} + I_1(z)} dz}.$$

The computation of the positive stationary state E^* , defined by (5.7), concludes here. □

234 6 Basic reproduction numbers and invasion fitness

The basic reproduction number, commonly represented as \mathcal{R}_0 , is defined within this context as the total number of new malaria parasites originating from a single parasite introduced into a parasite-free RBCs environment [4, 12]. In an initially unparasitized RBCs population, this metric can ascertain the potential for a parasite strain to propagate within that RBCs environment. Conversely, when the RBCs population is initially colonized by a resident parasite strain, the invasion fitness is employed to assess whether a new parasite strain can successfully invade this RBCs environment or not. In this context, the calculation of both the \mathcal{R}_0 and the invasion fitness relies on the next-generation operator approach [12, 43] and the standard adaptive dynamics methodology [13, 19, 32, 35].

6.1 The basic reproduction number

243 We have the following result.

Proposition 6.1. *Let Assumption 3.1 holds.*

1. Let $j \in \{1, 2\}$. The basic reproduction number of strain x within the j -species, denoted by $\mathcal{R}_j(x)$, is such that

$$\mathcal{R}_j(x) = \left(\sum_{i=1}^j C_i^{E_0} \right) \int_{\mathbb{R}} k(x-y) \Gamma_j(y) dy, \quad (6.1)$$

246 where Γ_j is the reproduction function introduced by (3.5) and the constants $C_i^{E_0}$ are defined by (5.2).

2. For each $j \in \{1, 2\}$ the threshold quantity \mathcal{R}_j introduced by (5.3) is the basic reproduction number of the j -species, while \mathcal{R}_0 defined by (5.3) is the basic reproduction number of System (2.1).

Proof. Let $j \in \{1, 2\}$. Let us denote by $b_j(t, x)$ the number of parasites, of strain x within the species j , that are newly produced at time t . From (2.1) we get

$$b_j(t, x) = \int_{\mathbb{R}} k(x-y) p_j(y) \left(\int_0^\infty \gamma_j(a, y) v_j(t, a, y) da \right) dy.$$

Then, linearizing the system (2.1) around the parasite-free stationary state E_0 , and using Volterra's formulation, we obtain

$$v_j(t, a, x) = \begin{cases} v_{j,0}(a-t, x) \Pi_j(a-t, a, x) & \text{if } t \leq a, \\ \left(\sum_{i=1}^j C_i^{E_0} \right) \beta_j(x) m_j(t-a, x) \Pi_j(0, a, x) & \text{if } t > a. \end{cases}$$

Therefore,

$$\begin{aligned} b_j(t, x) &= \left(\sum_{i=1}^j C_i^{E_0} \right) \int_{\mathbb{R}} k(x-y) p_j(y) \beta_j(y) \left(\int_0^t \gamma_j(a, y) m_j(t-a, y) \Pi_j(0, a, y) da \right) dy \\ &\quad + \int_{\mathbb{R}} k(x-y) p_j(y) \left(\int_t^\infty \gamma_k(a, y) v_{j,0}(a-t, x) \Pi_j(a-t, a, y) da \right) dy. \end{aligned} \quad (6.2)$$

Furthermore, we have

$$m_j(t, x) = e^{-(\mu_{m,j} + I_j(x))t} m_{j,0}(x) + \int_0^t e^{-(\mu_{m,j} + I_j(x))(t-s)} b_j(s, x) ds.$$

249 By the above expression, (6.2) rewrites as follows

$$b_j(t, x) = \left(\sum_{i=1}^j C_i^{E_0} \right) \int_{\mathbb{R}} k(x-y) p_j(y) \beta_j(y) \int_0^t \gamma_j(a, y) \Pi_j(0, a, y) \int_0^{t-a} e^{-(\mu_{m,j} + I_j(y))(t-a-s)} b_j(s, y) ds da dy + g_j(t, x) \quad (6.3)$$

where $g_j(t, x)$ accounts for the number of parasites produced by the initial condition:

$$g_j(t, x) = \left(\sum_{i=1}^j C_i^{E_0} \right) \int_{\mathbb{R}} k(x-y) p_j(y) \beta_j(y) \left(\int_0^t e^{-(\mu_{m,j} + I_j(y))(t-a)} m_{j,0}(y) \gamma_j(a, y) \Pi_j(0, a, y) da \right) dy \\ + \int_{\mathbb{R}} k(x-y) p_j(y) \left(\int_t^\infty \gamma_k(a, y) v_{j,0}(a-t, x) \Pi_j(a-t, a, y) da \right) dy.$$

Since

$$p_j(y) \beta_j(y) \int_0^t \gamma_j(a, y) \Pi_j(0, a, y) \int_0^{t-a} e^{-(\mu_{m,j} + I_j(y))(t-a-s)} b_j(s, y) ds da = \int_0^t b_j(t-a, y) F_j(a, y) da,$$

wherein

$$F_j(a, y) = e^{-(\mu_{m,j} + I_j(y))a} p_j(y) \beta_j(y) \int_0^a \gamma_j(s, y) \Pi_j(0, s, y) e^{(\mu_{m,j} + I_j(y))s} ds$$

then the equality (6.3) becomes

$$b_j(t, x) = \left(\sum_{i=1}^j C_i^{E_0} \right) \int_0^t \int_{\mathbb{R}} k(x-y) F_j(a, y) b_j(t-a, y) dy da + g_j(t, x).$$

Given the formulation above, the basic reproduction number $\mathcal{R}_j(x)$ of strain x within the j -species is computed as the spectral radius $r(G_j[x])$ of the next-generation operator $G_j[x]$, as defined by:

$$G_j[x] : L^1(\mathbb{R}) \ni v \mapsto \left(\sum_{i=1}^j C_i^{E_0} \right) \int_0^\infty \int_{\mathbb{R}} k(x-y) F_j(a, y) v(y) dy da \in \mathbb{R}.$$

Then it comes that

$$\mathcal{R}_j(x) = \left(\sum_{i=1}^j C_i^{E_0} \right) \int_0^\infty \int_{\mathbb{R}} k(x-y) F_j(a, y) dy da = \left(\sum_{i=1}^j C_i^{E_0} \right) \int_{\mathbb{R}} k(x-y) \Gamma_j(y) dy$$

where the last equality comes from $\int_0^\infty F_j(a, y) da = \Gamma_j(y) < \infty$, with Γ_j the reproduction function introduced by (3.5). We now introduce the linear operator G_j , such that

$$G_j(v)(x) = G_j[x]v, \quad \forall v \in L^1(\mathbb{R}), \quad \forall x \in \mathbb{R}.$$

Observe that $G_j = \left(\sum_{i=1}^j C_i^{E_0} \right) L_j$, where L_j is the linear operator introduced by (3.4). Then, the basic reproduction number of the j -species is calculated as the spectral radius of the next generation operator G_j , *i.e.*

$$r(G_j) = \left(\sum_{i=1}^j C_i^{E_0} \right) r(L_j).$$

Note that the spectral radius of G_j satisfies $r(G_j) = \mathcal{R}_j$, where \mathcal{R}_j is the threshold parameter introduced by (5.3), which proves the first point. In addition, the next generation operator of the overall system is $G = \text{diag}(G_1, G_2)$, so that the basic reproduction number \mathcal{R}_0 of System (2.1) is given by

$$\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\}.$$

□

6.2 Invasion in a parasitized RBCs environment

Let us introduce the notation (x_1, x_2) to represent a parasite population, where x_1 denotes the parasite strain of the first species (*i.e.* $P. vivax$) and x_2 represents the parasite strain of the second species (*i.e.* $P. falciparum$). The notation (x_1, \emptyset) indicates the absence of the second species, whereas (\emptyset, x_2) signifies the absence of the first species. We also denote by $f_{(x_1, x_2)}(y_1, y_2)$ the invasion fitness of a mutant with phenotype (y_1, y_2) in the resident population set by the equilibrium $E^{(x_1, x_2)}$ of phenotype (x_1, x_2) . Then $f_{(x_1, x_2)}(y_1, y_2) = \left(f_{(x_1, x_2)}^1(y_1), f_{(x_1, x_2)}^2(y_2) \right)$, where $f_{(x_1, x_2)}^j(y_j)$ is the invasion fitness of a mutant of strain y_j within j -species in the resident population set by the equilibrium $E^{(x_1, x_2)}$ of strain (x_1, x_2) . Hence, a mutant strain y_j within the j -species in the resident population, as defined by the equilibrium $E^{(x_1, x_2)}$, will spread whenever $f_{(x_1, x_2)}^j(y_j) > 0$. We then have the following results of the invasion fitness:

Proposition 6.2. *Let Assumptions 3.1 and 3.3 be satisfied. Let us define the following thresholds:*

$$\mathcal{R}_1^{x_1} = C_1^{E_0} \Gamma_1(x_1) \quad \text{and} \quad \mathcal{R}_2^{x_2} = \left(C_1^{E_0} + C_2^{E_0} \right) \Gamma_2(x_2).$$

1. *Scenario 1: both species (*i.e.* $P. vivax$ and $P. falciparum$) are the resident. Assume that*

$$1 < \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} < 1 + \frac{\mu_{1,2}}{\mu_2} \quad \text{and} \quad \mathcal{R}_1^{x_1} > 1 + \left(1 + \frac{\mu_2}{\mu_{1,2}} \right) \left(\frac{\frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} - 1}{\left(1 + \frac{\mu_{1,2}}{\mu_2} \right) - \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}}} \right).$$

The above condition ensures the existence of the resident equilibrium $E^{(x_1, x_2)}$ and we have

$$f_{(x_1, x_2)}(y_1, y_2) = \left(\frac{C_1^{(x_1, x_2)}}{C_1^{E_0}} (\mathcal{R}_1^{y_1} - \mathcal{R}_1^{x_1}), \frac{\sum_{i=1}^2 C_i^{(x_1, x_2)}}{\sum_{i=1}^2 C_i^{E_0}} (\mathcal{R}_2^{y_2} - \mathcal{R}_2^{x_2}) \right)$$

with $C_1^{(x_1, x_2)}$ and $C_2^{(x_1, x_2)}$ respectively the size of young and mature RBCs in the environment set by the resident. Hence, we have

$$\text{sign} \left(f_{(x_1, x_2)}^1(y_1) \right) = \text{sign} (\mathcal{R}_1^{y_1} - \mathcal{R}_1^{x_1}) \quad \text{and} \quad \text{sign} \left(f_{(x_1, x_2)}^2(y_2) \right) = \text{sign} (\mathcal{R}_2^{y_2} - \mathcal{R}_2^{x_2}). \quad (6.4)$$

2. *Scenario 2: only the first species (*i.e.* $P. vivax$) is the resident. Assume that $\mathcal{R}_1^{x_1} > 1$ which guarantees the existence of the resident equilibrium $E^{(x_1, \emptyset)}$. Then, we have*

$$f_{(x_1, \emptyset)}(y_1, y_2) = \left(\frac{C_1^{x_1}}{C_1^{E_0}} (\mathcal{R}_1^{y_1} - \mathcal{R}_1^{x_1}), \frac{C_1^{x_1}}{C_1^{E_0}} (\mathcal{R}_2^{y_2} - \mathcal{R}_1^{x_1}) \right)$$

with $C_1^{x_1}$ and $C_2^{x_1}$ respectively the size of young and mature RBCs in the environment set by the resident. We obtain

$$\text{sign}(f_{(x_1, \emptyset)}^1(y_1)) = \text{sign}(\mathcal{R}_1^{y_1} - \mathcal{R}_1^{x_1}), \quad \text{and} \quad \text{sign}(f_{(x_1, \emptyset)}^2(y_2)) = \text{sign}(\mathcal{R}_2^{y_2} - \mathcal{R}_1^{x_1}).$$

3. *Scenario 3: only the second species (*i.e.* $P. falciparum$) is the resident. Assume that $\mathcal{R}_2^{x_2} > 1$, which guarantees the existence of the resident equilibrium $E^{(\emptyset, x_2)}$. We then have*

$$f_{(\emptyset, x_2)}(y_1, y_2) = \left(\frac{C_1^{x_2}}{C_1^{E_0}} \left(\mathcal{R}_1^{y_1} - \frac{\left(\sum_{i=1}^2 C_i^{x_2} \right) / C_1^{x_2}}{\left(\sum_{i=1}^2 C_i^{E_0} \right) / C_1^{E_0}} \mathcal{R}_2^{x_2} \right), \frac{\left(\sum_{i=1}^2 C_i^{x_2} \right)}{\left(\sum_{i=1}^2 C_i^{E_0} \right)} (\mathcal{R}_2^{y_2} - \mathcal{R}_2^{x_2}) \right)$$

with $C_1^{x_2}$ and $C_2^{x_2}$ respectively the size of young and mature RBCs in the environment set by the resident.
Then:

$$\text{sign} \left(f_{(\emptyset, x_2)}^1(y_1) \right) = \text{sign} \left(\mathcal{R}_1^{y_1} - \frac{\left(\sum_{i=1}^2 C_i^{x_2} \right) / C_1^{x_2}}{\left(\sum_{i=1}^2 C_i^{E_0} \right) / C_1^{E_0}} \mathcal{R}_2^{x_2} \right), \quad (6.5)$$

$$\text{sign} \left(f_{(\emptyset, x_2)}^2(y_2) \right) = \text{sign} \left(\mathcal{R}_2^{y_2} - \mathcal{R}_2^{x_2} \right). \quad (6.6)$$

Proof. Scenario 1: both species are resident. Let $E^{(x_1, x_2)}$ be the equilibrium set by the resident population of strain (x_1, x_2) . Such an equilibrium satisfies:

$$E^{(x_1, x_2)} = (C_1^{(x_1, x_2)}, C_2^{(x_1, x_2)}, v_1^{(x_1, x_2)}(\cdot) \delta_{x_1}(\cdot), m_1^{(x_1, x_2)} \delta_{x_1}(\cdot), v_2^{(x_1, x_2)}(\cdot) \delta_{x_2}(\cdot), m_2^{(x_1, x_2)} \delta_{x_2}(\cdot)).$$

At the equilibrium $E^{(x_1, x_2)}$, System (2.1) rewrites

$$\left\{ \begin{array}{l} 0 = \Lambda - C_1^{(x_1, x_2)} \left(\mu_{1,2} + \beta_1(x_1) m_1^{(x_1, x_2)} + \beta_2(x_2) m_2^{(x_1, x_2)} \right) \\ 0 = \mu_{1,2} C_1^{(x_1, x_2)} - C_2^{(x_1, x_2)} \left(\mu_2 + \beta_2(x_2) m_2^{(x_1, x_2)} \right), \\ v_j^{(x_1, x_2)}(0) = \left(\sum_{k=1}^j C_k^{(x_1, x_2)} \right) \beta_j(x_j) m_j^{(x_1, x_2)}, \\ \frac{dv_j^{(x_1, x_2)}}{da}(a) = -(\mu_2 + \gamma_j(a, x_j)) v_j^{(x_1, x_2)}(a), \\ m_j^{(x_1, x_2)} = \frac{p_j(x_j)}{\mu_{m,j} + I_j(x_j)} \int_0^\infty \gamma_j(a, x_j) v_j^{(x_1, x_2)}(a) da \end{array} \right. \quad (6.7)$$

for each $j \in \{1, 2\}$. From (6.7) we deduce that

$$\left\{ \begin{array}{l} C_1^{(x_1, x_2)} = \frac{\Lambda}{\mu_{1,2} + \beta_1(x_1) m_1^{(x_1, x_2)} + \beta_2(x_2) m_2^{(x_1, x_2)}}, \\ C_2^{(x_1, x_2)} = \frac{\Lambda \mu_{1,2}}{\mu_{1,2} + \beta_1(x_1) m_1^{(x_1, x_2)} + \beta_2(x_2) m_2^{(x_1, x_2)}} \times \frac{1}{\mu_2 + \beta_2(x_2) m_2^{(x_1, x_2)}}, \\ v_j^{(x_1, x_2)}(a) = \left(\sum_{k=1}^j C_k^{(x_1, x_2)} \right) \beta_j(x_j) m_j^{(x_1, x_2)} \Pi_j(0, a, x_j). \end{array} \right.$$

Replacing the above expressions into the last equation of (6.7) it comes

$$\left\{ \begin{array}{l} 1 = \frac{\Lambda}{\mu_{1,2} + \beta_1(x_1) m_1^{(x_1, x_2)} + \beta_2(x_2) m_2^{(x_1, x_2)}} \Gamma_1(x_1), \\ 1 = \frac{\Lambda}{\mu_{1,2} + \beta_1(x_1) m_1^{(x_1, x_2)} + \beta_2(x_2) m_2^{(x_1, x_2)}} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \beta_2(x_2) m_2^{(x_1, x_2)}} \right) \Gamma_2(x_2) \end{array} \right.$$

264 *i.e.*

$$\left\{ \begin{array}{l} 1 = \frac{\Lambda}{\mu_{1,2} + \beta_1(x_1) m_1^{(x_1, x_2)} + \beta_2(x_2) m_2^{(x_1, x_2)}} \Gamma_1(x_1), \\ 1 = \frac{\Gamma_2(x_2)}{\Gamma_1(x_1)} \left(1 + \frac{\mu_{1,2}}{\mu_2 + \beta_2(x_2) m_2^{(x_1, x_2)}} \right). \end{array} \right. \quad (6.8)$$

The right-hand side of the second equation of (6.8) is strictly decreasing in $m_2^{(x_1, x_2)}$. Thus, a necessary and sufficient condition for a positive solution $m_2^{(x_1, x_2)}$ is

$$\frac{\Gamma_2(x_2)}{\Gamma_1(x_1)} < 1 \quad \text{and} \quad \frac{\Gamma_2(x_2)}{\Gamma_1(x_1)} \left(1 + \frac{\mu_{1,2}}{\mu_2} \right) > 1. \quad (6.9)$$

267 Observe that

$$\frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} = \frac{C_1^{E_0} + C_2^{E_0}}{C_1^{E_0}} \times \frac{\Gamma_2(x_2)}{\Gamma_1(x_1)} = \left(1 + \frac{\mu_{1,2}}{\mu_2} \right) \frac{\Gamma_2(x_2)}{\Gamma_1(x_1)}.$$

Therefore, conditions (6.9) are equivalent to

$$1 < \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} < 1 + \frac{\mu_{1,2}}{\mu_2}.$$

Still from the system (6.8), the second equation then gives

$$m_2^{(x_1, x_2)} \beta_2(x_2) = \frac{(\mu_{1,2} + \mu_2) \left(\frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} - 1 \right)}{\left(1 + \frac{\mu_{1,2}}{\mu_2} \right) - \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}}}.$$

For $m_1^{(x_1, x_2)}$, the right-hand side of the first equation of (6.8) is strictly decreasing in $m_1^{(x_1, x_2)}$ with limit 0 when $m_1^{(x_1, x_2)} \rightarrow \infty$. So, a necessary and sufficient condition for a positive solution $m_1^{(x_1, x_2)}$ is

$$\frac{\mu_{1,2}}{\mu_{1,2} + \beta_2(x_2) m_2^{(x_1, x_2)}} \mathcal{R}_1^{x_1} > 1 \iff \mathcal{R}_1^{x_1} > 1 + \left(1 + \frac{\mu_2}{\mu_{1,2}} \right) \left(\frac{\frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} - 1}{\left(1 + \frac{\mu_{1,2}}{\mu_2} \right) - \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}}} \right).$$

In summary, the resident equilibrium $E^{(x_1, x_2)}$ exists if and only if the following conditions are satisfied

$$1 < \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} < 1 + \frac{\mu_{1,2}}{\mu_2} \quad \text{and} \quad \mathcal{R}_1^{x_1} > 1 + \left(1 + \frac{\mu_2}{\mu_{1,2}} \right) \left(\frac{\frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}} - 1}{\left(1 + \frac{\mu_{1,2}}{\mu_2} \right) - \frac{\mathcal{R}_2^{x_2}}{\mathcal{R}_1^{x_1}}} \right).$$

We now assume that a mutant with phenotype (y_1, y_2) causes a small perturbation of the system set out by the resident equilibrium $E^{(x_1, x_2)}$. Thus, we set

$$\begin{cases} C_j(t) &= C_j^{(x_1, x_2)} + b_j(t), \\ v_j(t, a, x) &= v_j^{(x_1, x_2)}(a) \delta_{x_j}(x) + g_j(t, a) \delta_{y_j}(x), \\ m_j(t, x) &= m_j^{(x_1, x_2)} \delta_{x_j}(x) + h_j(t) \delta_{y_j}(x) \end{cases}$$

for each $j \in \{1, 2\}$. We remind that by (2.1) we have

$$\begin{cases} v_j(t, 0, x) &= \left(\sum_{k=1}^j C_k(t) \right) \beta_j(x) m_j(t, x), \\ (\partial_t + \partial_a) v_j(t, a, x) &= -(\mu_2 + \gamma_j(a, x)) v_j(t, a, x), \\ \partial_t m_j(t, x) &= \int_{\mathbb{R}} k(x-y) p_j(y) \int_0^\infty \gamma_j(a, y) v_j(t, a, y) da dy - (\mu_{m,j} + I_j(x)) m_j(t, x) \end{cases}$$

for each $j \in \{1, 2\}$. Then, the small perturbations for infection g_1, g_2, h_1 and h_2 , are governed by the following system of equations around $E^{(x_1, x_2)}$, with $x_j \neq y_j$:

$$\begin{cases} g_j(t, 0) &= \left(\sum_{k=1}^j C_k^{(x_1, x_2)} \right) \beta_j(y_j) h_j(t), \\ (\partial_t + \partial_a) g_j(t, a) &= -(\mu_2 + \gamma_j(a, y_j)) g_j(t, a), \\ h_j'(t) \delta_{y_j}(\cdot) &= k(\cdot - y_j) p_j(y_j) \int_0^\infty \gamma_j(a, y_j) g_j(t, a) da + k(\cdot - x_j) p_j(x_j) \int_0^\infty \gamma_j(a, x_j) v_j^{(x_1, x_2)}(a) da \\ &\quad - (\mu_{m,j} + I_j(\cdot)) (m_j^{(x_1, x_2)} \delta_{x_j}(\cdot) + h_j(t) \delta_{y_j}(\cdot)) \end{cases}$$

for each $j \in \{1, 2\}$. By integrating $h_j'(t) \delta_{y_j}(z)$ and since $\int_{\mathbb{R}} k(y-z) dz = 1$, for any y , it comes

$$\begin{cases} g_j(t, 0) &= \left(\sum_{k=1}^j C_k^{(x_1, x_2)} \right) \beta_j(y_j) h_j(t), \\ (\partial_t + \partial_a) g_j(t, a) &= -(\mu_2 + \gamma_j(a, y_j)) g_j(t, a), \\ h_j'(t) &= p_j(y_j) \int_0^\infty \gamma_j(a, y_j) g_j(t, a) da + p_j(x_j) \int_0^\infty \gamma_j(a, x_j) v_j^{(x_1, x_2)}(a) da \\ &\quad - (\mu_{m,j} + I_j(x_j)) m_j^{(x_1, x_2)} - (\mu_{m,j} + I_j(y_j)) h_j(t) \end{cases}$$

for each $j \in \{1, 2\}$. Note that by definition of the resident equilibrium $E^{(x_1, x_2)}$, we have

$$p_j(x_j) \int_0^\infty \gamma_j(a, x_j) v_j^{(x_1, x_2)}(a) da - (\mu_{m,j} + I_j(x_j)) m_j^{(x_1, x_2)} = 0, \quad \forall j \in \{1, 2\}. \quad (6.10)$$

It follows, for each $j \in \{1, 2\}$, that:

$$\begin{cases} g_j(t, 0) &= \left(\sum_{i=1}^j C_i^{(x_1, x_2)} \right) \beta_j(y_j) h_j(t), \\ (\partial_t + \partial_a) g_j(t, a) &= -(\mu_2 + \gamma_j(a, y_j)) g_j(t, a), \\ h'_j(t) &= p_j(y_j) \int_0^\infty \gamma_j(a, y_j) g_j(t, a) da - (\mu_{m,j} + I_j(y_j)) h_j(t). \end{cases} \quad (6.11)$$

Denoting by $M_j^{(x_1, x_2)}(t, y_j)$ the number of newly produced parasites of species j at time t with phenotype y_j in a resident population (x_1, x_2) , we see that

$$M_j^{(x_1, x_2)}(t, y_j) = p_j(y_j) \int_0^\infty \gamma_j(a, y_j) g_j(t, a) da.$$

Through similar computations employed in deriving the reproductive numbers in the proof of Proposition 6.1, it follows that

$$M_j^{(x_1, x_2)}(t, y_j) = \int_0^t F_j^{(x_1, x_2)}(a, y_j) M_j^{(x_1, x_2)}(t - a, y_j) da + H_j(t, y_j),$$

where H_j accounts for the initial condition of (6.11) and

$$F_j^{(x_1, x_2)}(a, y_j) = e^{-(\mu_{m,j} + I_j(y_j))a} \left(\sum_{i=1}^j C_i^{(x_1, x_2)} \right) p_j(y_j) \beta_j(y_j) \int_0^a \gamma_j(s, y_j) \Pi_j(0, s, y_j) e^{(\mu_{m,j} + I_j(y_j))s} ds.$$

As a result of the above formulation, we find that the basic parasitic reproduction number $\mathcal{R}(y_j, E^{(x_1, x_2)})$ of a mutant strain y_j , in the resident population of strain (x_1, x_2) is given by

$$\mathcal{R}(y_j, E^{(x_1, x_2)}) = \int_0^\infty F_j^{(x_1, x_2)}(a, y_j) da = \left(\sum_{i=1}^j C_i^{(x_1, x_2)} \right) \Gamma_j(y_j).$$

270 Therefore, the invasion fitness $f_{(x_1, x_2)}(y_1, y_2)$ of a mutant strain (y_1, y_2) in the resident population $E^{(x_1, x_2)}$ writes

$$f_{(x_1, x_2)}(y_1, y_2) = \left(\frac{\mathcal{R}(y_1, E^{(x_1, x_2)}) - 1}{\mathcal{R}(y_2, E^{(x_1, x_2)}) - 1} \right) = \left(\frac{\frac{C_1^{(x_1, x_2)}}{C_1^{E_0}} \mathcal{R}_1^{y_1} - 1}{\frac{\sum_{i=1}^2 C_i^{(x_1, x_2)}}{\sum_{i=1}^2 C_i^{E_0}} \mathcal{R}_2^{y_2} - 1} \right). \quad (6.12)$$

By (6.10), we have

$$\frac{C_1^{(x_1, x_2)}}{C_1^{E_0}} \mathcal{R}_1^{x_1} = 1 \quad \text{and} \quad \frac{\sum_{i=1}^2 C_i^{(x_1, x_2)}}{\sum_{i=1}^2 C_i^{E_0}} \mathcal{R}_2^{x_2} = 1$$

from where (6.12) rewrites as

$$f_{(x_1, x_2)}(y_1, y_2) = \left(\frac{\frac{C_1^{(x_1, x_2)}}{C_1^{E_0}} (\mathcal{R}_1^{y_1} - \mathcal{R}_1^{x_1})}{\frac{\sum_{i=1}^2 C_i^{(x_1, x_2)}}{\sum_{i=1}^2 C_i^{E_0}} (\mathcal{R}_2^{y_2} - \mathcal{R}_2^{x_2})} \right).$$

Scenario 2: only the first species (*i.e.* $P. vivax$) is resident. Using calculations similar to those of Scenario 1, the equilibrium $E^{(x_1, \emptyset)} = (C_1^{x_1}, C_2^{x_1}, v_1^{x_1}(a) \delta_{x_1}(\cdot), m_1^{x_1} \delta_{x_1}(\cdot), v_2^{x_1} = 0, m_2^{x_1} = 0)$ set by the resident $(x_1, 0)$ exists if and only if $\mathcal{R}_1^{x_1} > 1$ and then we have

$$\begin{cases} C_1^{x_1} &= C_1^{E_0} \frac{\mu_{1,2}}{\mu_{1,2} + \beta_1(x_1) m_1^{x_1}}, \\ C_2^{x_1} &= C_2^{E_0} \frac{\mu_{1,2}}{\mu_{1,2} + \beta_1(x_1) m_1^{x_1}}, \\ v_1^{x_1}(a) &= C_1^{x_1} \beta_1(x_1) m_1^{x_1} \Pi_1(0, a, x_1), \\ m_1^{x_1} &= \frac{\mu_{1,2}}{\beta_1(x_1)} (\mathcal{R}_1^{x_1} - 1). \end{cases}$$

Furthermore, the reproduction number $\mathcal{R}(y_j, E_1^{(x_1, \emptyset)})$ of a mutant with phenotype y_j , in the resident population set by $E_1^{(x_1, \emptyset)}$ is given by

$$\mathcal{R}(y_j, E_1^{(x_1, \emptyset)}) = \int_0^\infty F_j^{x_1}(a, y_j) da = \left(\sum_{i=1}^j C_i^{x_1} \right) \Gamma_j(y_j).$$

Hence the invasion fitness $f(x_1, \emptyset)(y_1, y_2)$ writes

$$f_{(x_1, \emptyset)}(y_1, y_2) = \begin{pmatrix} \frac{C_1^{x_1}}{C_1^{E_0}} (\mathcal{R}_1^{y_1} - \mathcal{R}_1^{x_1}) \\ \frac{C_1^{x_1}}{C_1^{E_0}} (\mathcal{R}_2^{y_2} - \mathcal{R}_1^{x_1}) \end{pmatrix}.$$

Scenario 3: only the second species (*i.e.* *P. falciparum*) is resident. As for the previous scenarios, we find that the resident equilibrium $E^{(\emptyset, x_1)} = (C_1^{x_2}, C_2^{x_2}, v_1^{x_2} = 0, m_1^{x_2} = 0, v_2^{x_2}(a)\delta_{x_2}(\cdot), m_2^{x_2}\delta_{x_2}(\cdot))$ is such that

$$\begin{cases} C_1^{x_2} &= C_1^{E_0} \frac{\mu_{1,2}}{\mu_{1,2} + \beta_2(x_2)m_2^{x_2}}, \\ C_2^{x_2} &= C_2^{E_0} \frac{\mu_{1,2}\mu_2}{(\mu_{1,2} + \beta_2(x_2)m_2^{x_2})(\mu_2 + \beta_2(x_2)m_2^{x_2})}, \\ v_1^{x_2}(a) &= (C_1^{x_2} + C_2^{x_2})\beta_2(x_2)m_2^{x_2}\Pi_2(0, a, x_2), \end{cases}$$

where $m_2^{x_2}$ is the unique positive solution to the following equation (provided that $\mathcal{R}_2^{x_2} > 1$):

$$\frac{\mu_{1,2}}{\mu_{1,2} + \beta_2(x_2)m_2^{x_2}} \left(C_1^{E_0} + C_2^{E_0} \frac{\mu_2}{\mu_2 + \beta_2(x_2)m_2^{x_2}} \right) \Gamma_2(x_2) = 1.$$

Applying the same methodology as in the previous section, we find that the reproduction number $\mathcal{R}(y_j, E_1^{(\emptyset, x_2)})$ of a mutant strain y_j , in the resident population $E_1^{(\emptyset, x_2)}$ is given by

$$\mathcal{R}(y_j, E_2^{(\emptyset, x_2)}) = \left(\sum_{i=1}^j C_i^{x_2} \right) \Gamma_j(y_j).$$

Thus the invasion fitness writes

$$f_{(\emptyset, x_2)}(y_1, y_2) = \begin{pmatrix} \frac{C_1^{x_2}}{C_1^{E_0}} \left(\mathcal{R}_1^{y_1} - \frac{(\sum_{i=1}^2 C_i^{x_2})/C_1^{x_2}}{(\sum_{i=1}^2 C_i^{E_0})/C_1^{E_0}} \mathcal{R}_2^{x_2} \right) \\ \frac{(\sum_{i=1}^2 C_i^{x_2})}{(\sum_{i=1}^2 C_i^{E_0})} (\mathcal{R}_2^{y_2} - \mathcal{R}_2^{x_2}) \end{pmatrix}.$$

Finally, note that

$$(C_1^{x_2} + C_2^{x_2})/C_1^{x_2} = 1 + \frac{C_2^{E_0}}{C_1^{E_0}} \frac{\mu_2}{(\mu_2 + \beta_2(x_2)m_2^{x_2})},$$

whence

$$\frac{(C_1^{x_2} + C_2^{x_2})/C_1^{x_2}}{(C_1^{E_0} + C_2^{E_0})/C_1^{E_0}} = \left(1 + \frac{C_2^{E_0}}{C_1^{E_0}} \frac{\mu_2}{\mu_2 + \beta_2(x_2)m_2^{x_2}} \right) \left(1 + \frac{C_2^{E_0}}{C_1^{E_0}} \right)^{-1} < 1.$$

□

273 7 Parasite's extinction and uniform persistence

In this section, we analyze parasite extinction and persistence in relation to the thresholds \mathcal{R}_j introduced by (5.3). These thresholds are vital in understanding how parasite populations behave over time within the host. We investigate the conditions for complete parasite elimination or persistence.

7.1 Technical materials

We explore the properties of a perturbed linear system around the equilibrium E_0 defined in (5.2). We consider $\epsilon \in \mathbb{R}$ to be sufficiently small such that

$$C_i^{E_0} + \epsilon > 0, \quad \forall i \in \{1, 2\}.$$

For $j \in \{1, 2\}$, we examine the linear problem given by

$$\left\{ \begin{array}{l} v_j^\epsilon(t, a = 0, x) = \beta_j(x) m_j^\epsilon(t, x) \left(\sum_{i=1}^j (C_i^{E_0} + \epsilon) \right), \\ \frac{\partial v_j^\epsilon(t, a, x)}{\partial t} + \frac{\partial v_j^\epsilon(t, a, x)}{\partial a} = -(\mu_2 + \gamma_j(a, x)) v_j^\epsilon(t, a, x), \\ \frac{\partial m_j^\epsilon(t, x)}{\partial t} = \int_{\mathbb{R}} k(x-y) p_j(y) \left(\int_0^\infty \gamma_j(a, y) v_j^\epsilon(t, a, y) da \right) dy - (\mu_{m,j} + I_j(x)) m_j^\epsilon(t, x) \end{array} \right. \quad (7.1)$$

with initial conditions $v_j^\epsilon(0, \cdot, \cdot) = v_{j,0} \in L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R})$ and $m_j^\epsilon(0, \cdot) = m_{j,0} \in L^1(\mathbb{R}, \mathbb{R})$. It is noteworthy that these systems are independent of each other as j varies from 1 to 2. For the rest of this section, j is fixed in $\{1, 2\}$. We can express the j -system as the following abstract formulation:

$$\left\{ \begin{array}{l} \frac{d\ell_j(t)}{dt} = (\mathcal{F}_j^\epsilon + \mathcal{V}_j) \ell_j(t), \\ \ell_j(0) = \ell_{j,0} \in \mathcal{Y}_0 \end{array} \right. \quad (7.2)$$

where $\mathcal{Y} = L^1(\mathbb{R}, \mathbb{R}) \times L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}) \times L^1(\mathbb{R}, \mathbb{R})$ and $\mathcal{Y}_0 = \{0_{L^1}\} \times L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}) \times L^1(\mathbb{R}, \mathbb{R})$. The Banach space \mathcal{Y} is endowed with the usual product norm. The bounded linear operator $\mathcal{F}_j^\epsilon : \mathcal{Y}_0 \rightarrow \mathcal{Y}$ is defined as

$$\mathcal{F}_j^\epsilon \begin{pmatrix} 0_{L^1} \\ v_j \\ m_j \end{pmatrix} = \begin{pmatrix} \beta_j m_j \sum_{i=1}^j (C_i^{E_0} + \epsilon) \\ 0_{L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R})} \\ \int_{\mathbb{R}} k(\cdot - y) p_j(y) \int_0^\infty \gamma_j(a, y) v_j(a, y) da dy \end{pmatrix}, \quad \forall \begin{pmatrix} 0_{L^1} \\ v_j \\ m_j \end{pmatrix} \in \mathcal{Y}_0. \quad (7.3)$$

Meanwhile, $\mathcal{V}_j : \mathcal{D}(\mathcal{V}_j) \subset \mathcal{Y}_0 \rightarrow \mathcal{Y}$ is given by

$$\mathcal{V}_j \begin{pmatrix} 0_{L^1} \\ v_j \\ m_j \end{pmatrix} = \begin{pmatrix} -v_j(0, \cdot) \\ -\partial_a v_j - (\mu_2 + \gamma_j) v_j \\ -\mu_{m,j} m_j - I_j m_j \end{pmatrix}, \quad \forall \begin{pmatrix} 0_{L^1} \\ v_j \\ m_j \end{pmatrix} \in \mathcal{D}(\mathcal{V}_j)$$

with $\mathcal{D}(\mathcal{V}_j) = \{0_{L^1}\} \times \mathcal{D}_{j,v} \times L^1(\mathbb{R}, \mathbb{R})$ and

$$\mathcal{D}_{j,v} := \{v \in L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R}) : v(\cdot, x) \in W^{1,1}(\mathbb{R}_+, \mathbb{R}) \text{ a.e } x \in \mathbb{R} \text{ and } \partial_a v \in L^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R})\}.$$

By employing arguments similar to those in Lemma 4.3, it can be shown that the spectral bound $s(\mathcal{V}_j)$ of \mathcal{V}_j satisfies $s(\mathcal{V}_j) < 0$. Furthermore, the linear operator \mathcal{V}_j is resolvent positive, and for each $\lambda > s(\mathcal{V}_j)$, we have

$$(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix} = \begin{pmatrix} 0_{L^1} \\ v_j \\ m_j \end{pmatrix} \in \mathcal{Y}_0$$

for every $(u_1, u_2, u_3)^T \in \mathcal{Y}$, with

$$\left\{ \begin{array}{l} v_j(a, x) = e^{-\lambda a} \Pi_j(0, a, x) u_1(x) + \int_0^a e^{-\lambda(a-s)} \Pi_j(s, a, x) u_2(s, x) ds, \quad a \geq 0, \quad x \in \mathbb{R}, \\ m_j(x) = \frac{1}{\lambda + \mu_{m,j} + I_j(x)} u_3(x), \quad x \in \mathbb{R}. \end{array} \right. \quad (7.4)$$

Therefore, setting

$$\mathcal{T}_{j,\lambda}^\epsilon := r(\mathcal{F}_j^\epsilon (\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1}), \quad \forall \lambda > s(\mathcal{V}_j), \quad (7.5)$$

it follows from [42, Theorem 3.4] that the following sign equality holds true

$$\text{sgn}(\mathcal{T}_{j,\lambda}^\epsilon - 1) = \text{sgn}(-\lambda + s(\mathcal{F}_j^\epsilon + \mathcal{V}_j)), \quad \forall \lambda > s(\mathcal{V}_j).$$

Since $\mathcal{F}_j^\epsilon + \mathcal{V}_j$ and $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$, the part of $\mathcal{F}_j^\epsilon + \mathcal{V}_j$ in \mathcal{Y}_0 have the same spectral set [25, Lemma 2.1], we also have the following equality

$$\operatorname{sgn}(\mathcal{T}_{j,\lambda}^\epsilon - 1) = \operatorname{sgn}(-\lambda + \mathfrak{s}(\mathcal{F}_j^\epsilon + \mathcal{V}_j)) = \operatorname{sgn}(-\lambda + \mathfrak{s}((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)), \quad \forall \lambda > \mathfrak{s}(\mathcal{V}_j). \quad (7.6)$$

Denote by \mathcal{Y}_1 the Banach space

$$\mathcal{Y}_1 = L^1(\mathbb{R}, \mathbb{R}) \times \{0_{L^1}\} \times L^1(\mathbb{R}, \mathbb{R}).$$

288 In the following, we provide a more explicit characterization of $\mathcal{T}_{j,\lambda}^\epsilon$ given by (7.5). To do so, let us first note that using [16, Lemma 2.2] one knows that $\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1}$ has the same spectral radius as its restriction on \mathcal{Y}_1 . Next, observe that for each $\lambda > \mathfrak{s}(\mathcal{V}_j)$ and $(u_1, 0_{L^1}, u_3)^T \in \mathcal{Y}_1$, we have from (7.3) and (7.4)

$$\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1} \begin{pmatrix} u_1 \\ 0_{L^1} \\ u_3 \end{pmatrix} = \begin{pmatrix} \mathcal{G}_{j,\epsilon}^\lambda(u_3) \\ 0_{L^1} \\ \mathcal{H}_j^\lambda(u_1) \end{pmatrix}, \quad (7.7)$$

where we have set for each $u_1, u_3 \in L^1(\mathbb{R}, \mathbb{R})$

$$\mathcal{G}_{j,\epsilon}^\lambda(u_3)(x) := \sum_{i=1}^j (C_i^{E_0} + \epsilon) \frac{\beta_j(x)}{\lambda + \mu_{m,j} + I_j(x)} u_3(x), \quad \forall x \in \mathbb{R}$$

and

$$\mathcal{H}_j^\lambda(u_1)(x) := \int_{\mathbb{R}} k(x-y) p_j(y) \int_0^\infty \gamma_j(a, y) e^{-\lambda a} \Pi_j(0, a, y) da u_1(y) dy, \quad \forall x \in \mathbb{R}.$$

291 From (7.7), it follows that for each $(u_1, 0_{L^1}, u_3)^T \in \mathcal{Y}_1$,

$$(\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1})^2 \begin{pmatrix} u_1 \\ 0_{L^1} \\ u_3 \end{pmatrix} = \begin{pmatrix} \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda(u_1) \\ 0_{L^1} \\ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3) \end{pmatrix}, \quad (7.8)$$

and since $r(\mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda) = r(\mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda)$ and $r((\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1})^2) = r(\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1})^2$, it follows from (7.5) and (7.8) that

$$\mathcal{T}_{j,\lambda}^\epsilon = \sqrt{r((\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1})^2)} = \sqrt{r(\mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda)}, \quad \forall \lambda > \mathfrak{s}(\mathcal{V}_j).$$

Moreover, the linear operator $\mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda : L^1(\mathbb{R}, \mathbb{R}) \rightarrow L^1(\mathbb{R}, \mathbb{R})$ is explicitly given, for $\lambda > \mathfrak{s}(\mathcal{V}_j)$, by

$$(\mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda)w(x) = \sum_{i=1}^j (C_i^{E_0} + \epsilon) \int_{\mathbb{R}} k(x-y) \Gamma_j^\lambda(y) w(y) dy, \quad \forall w \in L^1(\mathbb{R})$$

with

$$\Gamma_j^\lambda(y) := \frac{p_j(y) \beta_j(y)}{\lambda + \mu_{m,j} + I_j(y)} \int_0^\infty \gamma_j(a, y) e^{-\lambda a} \Pi_j(0, a, y) da.$$

From the above discussion, we have the following results.

Proposition 7.1. *Let Assumptions 3.1 and 3.3 be satisfied. Then $\mathfrak{s}(\mathcal{V}_j) < 0$ and we have the following properties:*

- 294 i) $\operatorname{sgn}(\mathcal{T}_{j,\lambda}^\epsilon - 1) = \operatorname{sgn}(-\lambda + \mathfrak{s}(\mathcal{F}_j^\epsilon + \mathcal{V}_j)) = \operatorname{sgn}(-\lambda + \mathfrak{s}((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0))$, for all $\lambda > \mathfrak{s}(\mathcal{V}_j)$.
ii) For each $\lambda > \mathfrak{s}(\mathcal{V}_j)$, the linear operator $(\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1})^2 : \mathcal{Y}_1 \rightarrow \mathcal{Y}_1$ is compact and positive.
iii) For each $\lambda > \mathfrak{s}(\mathcal{V}_j)$, the spectral radius $\mathcal{T}_{j,\lambda}^\epsilon$ of $\mathcal{F}_j^\epsilon(\lambda \mathbf{I}_d - \mathcal{V}_j)^{-1}$ satisfies $\mathcal{T}_{j,\lambda}^\epsilon = \sqrt{r(\mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda)}$.

Next, we establish a key result essential for proving the global asymptotic stability of the equilibrium E_0 and the uniform persistence of the parasites. Prior to proceeding, we note that when $\lambda = 0$ and $\epsilon = 0$, the following equality holds:

$$\mathcal{T}_{j,0}^0 = \sqrt{\mathcal{R}_j}$$

297 where the thresholds \mathcal{R}_j are defined in (5.3).

Lemma 7.2. *Let Assumptions 3.1 and 3.3 be satisfied. Then we have the following properties:*

1. If $\mathcal{R}_j < 1$ then there exists $\epsilon_0 > 0$ such that for each $\epsilon \in [0, \epsilon_0)$ we have $s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) = \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) < 0$ with $\omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)$ the growth bound of the semigroup generated by $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$ (the part of $\mathcal{F}_j^\epsilon + \mathcal{V}_j$ on \mathcal{Y}_0).
2. If $\mathcal{R}_j > 1$ then there exists $\epsilon_0 > 0$ such that for each $\epsilon \in (-\epsilon_0, 0]$ and $i \in \{1, 2\}$ we have $C_i^{E_0} + \epsilon > 0$ and $\mathcal{T}_{j,0}^\epsilon > 1$. Moreover, if Assumption 3.2 is satisfied then $\lambda_j^\epsilon := s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) = \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) > 0$ is an eigenvalue of $\mathcal{F}_j^\epsilon + \mathcal{V}_j$ with eigenvector $\bar{u}_{j\epsilon} \in \mathcal{Y}_{0+} \cap D(\mathcal{V}_j)$.

Proof. Before presenting the proofs of Items 1 and 2, we begin with some remarks. Let $\lambda > s(\mathcal{V}_j)$ be given. Recall from the preceding discussions that for all $\lambda > s(\mathcal{V}_j)$, the linear operator $\mathcal{F}_j^\epsilon(\lambda \text{Id} - \mathcal{V}_j)^{-1}$ has the same spectral radius as its restriction $\mathcal{F}_j^\epsilon(\lambda \text{Id} - \mathcal{V}_j)^{-1} : \mathcal{Y}_1 \rightarrow \mathcal{Y}_1$. Let us set

$$\mathcal{N}_{j,\epsilon}(\lambda) := \mathcal{F}_j^\epsilon(\lambda \text{Id} - \mathcal{V}_j)_{|\mathcal{Y}_1}^{-1} : \mathcal{Y}_1 \rightarrow \mathcal{Y}_1, \quad \forall \lambda > s(\mathcal{V}_j)$$

so that

$$r(\mathcal{N}_{j,\epsilon}(0)) = r(\mathcal{F}_j^\epsilon(-\mathcal{V}_j)^{-1}) \implies \mathcal{T}_{j,0}^\epsilon = r(\mathcal{N}_{j,\epsilon}(0)) = \sqrt{r(\mathcal{N}_{j,\epsilon}(0)^2)}.$$

Moreover, owing to the fact that \mathcal{Y} is an AL-space, we have the following equality [42, Theorem 3.14]:

$$s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) = \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0).$$

With these observations in place, we proceed to complete the proof.

1. Assuming $\mathcal{R}_j < 1$, then $\mathcal{T}_{j,0}^0 = \sqrt{r(\mathcal{N}_{j,0}(0)^2)} < 1$, we observe that $\mathcal{N}_{j,\epsilon}(0)^2$ given by (7.8) for $\lambda = 0$ is compact for each $\epsilon \geq 0$, and the mapping $\epsilon \in [0, +\infty) \mapsto \mathcal{N}_{j,\epsilon}(0)^2 \in \mathcal{L}(\mathcal{Y}_1)$ is continuous. Hence, according to [10, Theorem 2.1], the function $\epsilon \in [0, +\infty) \mapsto r(\mathcal{N}_{j,\epsilon}(0)^2)$ is also continuous. Consequently, there exists $\epsilon_0 > 0$ such that $\mathcal{T}_{j,0}^\epsilon < 1$ for all $\epsilon \in [0, \epsilon_0)$. Using the equality (7.6), we deduce that $s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) < 0$ for all $\epsilon \in [0, \epsilon_0)$.
2. Assume that $\mathcal{R}_j > 1$, then $\mathcal{T}_{j,0}^0 = \sqrt{r(\mathcal{N}_{j,0}(0)^2)} > 1$. Let $\epsilon_1 > 0$ be small enough such that $C_i^{E_0} + \epsilon > 0$ for each $i \in \{1, 2\}$ and $\epsilon \in (-\epsilon_1, 0]$. Using similar arguments as for the first item, it follows that there exists $\epsilon_0 \in [0, \epsilon_1)$ such that

$$\mathcal{T}_{j,0}^\epsilon = \sqrt{r(\mathcal{N}_{j,\epsilon}(0)^2)} > 1, \quad \forall \epsilon \in (-\epsilon_0, 0].$$

If Assumption 3.2 is also satisfied then using similar arguments than in Proposition 4.5 we can prove that

$$T_{(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0}(t) = U_1(t) + U_2(t), \quad t \geq 0$$

where $U_i(t) : \mathcal{Y}_0 \rightarrow \mathcal{Y}_0$, $i \in \{1, 2\}$ are bounded linear operators. Moreover, $U_1(t)$ is compact for each $t > 0$ and $U_2(t)$ satisfies the estimate

$$\|U_2(t)\|_{\mathcal{L}(\mathcal{Y}_0)} \leq K_0(1+t)e^{-\omega_1 t}, \quad \forall t \geq 0$$

for some constants $K_0 > 0$ and $\omega_1 > 0$. Consequently, using the same arguments in [45, Proposition 2.4] we have

$$\omega_{0,ess}((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) \leq \limsup_{t \rightarrow +\infty} \frac{\ln(\|U_2(t)\|_{\mathcal{L}(\mathcal{Y}_0)})}{t} \leq -\omega_1$$

and since $\lambda_j^\epsilon = \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) > 0$ (by using (7.6)) it follows that $\omega_{0,ess}((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) < \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) = \lambda_j^\epsilon = s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)$. The result follows from [45, Proposition 2.5] or [26, Proposition 4.6.5].

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□

The above Lemma 7.2 has the following consequence.

Corollary 7.3. *Let Assumptions 3.1 and 3.3 be satisfied. Let $\epsilon_0 > 0$ be small enough such that the conclusions of Lemma 7.2 hold. If $\mathcal{R}_j < 1$ then for each $\epsilon \in [0, \epsilon_0)$, the zero solution of (7.2) (or equivalently (7.1)) is globally exponentially stable in \mathcal{Y}_0 . Consequently, for each initial conditions $v_j^\epsilon(0, \cdot, \cdot) = v_{j,0} \in L_+^1(\mathbb{R}_+ \times \mathbb{R}, \mathbb{R})$ and $m_j^\epsilon(0, \cdot) = m_{j,0} \in L_+^1(\mathbb{R}, \mathbb{R})$ we have*

$$\lim_{t \rightarrow +\infty} \left(\int_{\mathbb{R}} m_j^\epsilon(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j^\epsilon(t, a, x) da dx \right) = 0.$$

We end this section by proving the asynchronous exponential growth properties of the semigroup generated by $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$.

Proposition 7.4. *Let Assumptions 3.1, 3.2, and 3.5 be satisfied. Let $\epsilon_0 > 0$ be small enough such that the conclusions of Lemma 7.2 hold. If $\mathcal{R}_j > 1$ then for each $\epsilon \in (-\epsilon_0, 0]$ there exists a rank one projector $\mathcal{P}_j^\epsilon : \mathcal{Y}_0 \rightarrow \mathcal{Y}_0$ such that*

$$\mathcal{P}_j^\epsilon T_{(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0}(t) = T_{(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0}(t) \mathcal{P}_j^\epsilon = e^{\lambda_j^\epsilon t} \mathcal{P}_j^\epsilon, \quad \forall t \geq 0, \quad \text{with } \lambda_j^\epsilon = s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) > 0$$

and for each $\ell_{j,0} \in \mathcal{Y}_{0+} \setminus \{0_{\mathcal{Y}_0}\}$ we have $\|\mathcal{P}_j^\epsilon \ell_{j,0}\|_{\mathcal{Y}} > 0$. Moreover, we have $e^{-\lambda_j^\epsilon t} T_{(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0}(t) \rightarrow \mathcal{P}_j^\epsilon$, when $t \rightarrow +\infty$, in the operator norm topology.

Proof. The proof relies on the Asynchronous Exponential Growth (AEG) property established by [45, Proposition 2.5], [44, Theorem 3.3] or [9, Theorem 9.10, Theorem 9.11]. Assume that $\mathcal{R}_j > 1$. Thanks to Lemma 7.2 we have the equality $\lambda_j^\epsilon = s((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) = \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) > 0$ for all $\epsilon \in (-\epsilon_0, 0]$. Moreover, by using the same arguments in the proof of Lemma 7.2 we have the strict inequality $\omega_{0,ess}((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0) < \omega((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)$ with $\omega_{0,ess}((\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)$ is the essential growth bound of $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$. Therefore, to obtain the AEG property, we will prove that the semigroup generated by $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$ is positive irreducible. To do so, let us note that for each λ in the resolvent set of $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$ we have from [25, Lemma 2.1]

$$(\lambda \text{Id} - (\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)^{-1} = (\lambda \text{Id} - (\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)^{-1}_{|\mathcal{Y}_0} \quad (7.9)$$

and the semigroup generated by $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$ is positive irreducible if there exists $\lambda_0 \in \mathbb{R}$ such that $(\lambda \text{Id} - (\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)^{-1}$ is irreducible for each $\lambda > \lambda_0$ (see [9, Proposition 7.6]). Next, note that using (7.9) it follows that there exists $\lambda_0 > 0$ large enough such that for each $\lambda \geq \lambda_0$ and $\ell_0 \in \mathcal{Y}_0$ we have

$$(\lambda \text{Id} - (\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)^{-1} \ell_0 = (\lambda \text{Id} - \mathcal{V}_j)^{-1} \sum_{n=0}^{\infty} (\mathcal{F}_j^\epsilon (\lambda \text{Id} - \mathcal{V}_j)^{-1})^n \ell_0. \quad (7.10)$$

Next let $\ell_0 \in \mathcal{Y}_{0+}$ with $\ell_0 = (0_{L^1}, u_2, u_3)^T$ be given. Let us set $\ell_2 = (0_{L^1}, u_2, 0_{L^1})^T$, $\ell_3 = (0_{L^1}, 0_{L^1}, u_3)^T$ and

$$\widehat{\ell}_3 := \mathcal{F}_j^\epsilon (\lambda \text{Id} - \mathcal{V}_j)^{-1} \ell_2.$$

Note that from the resolvent formula (7.3) and (7.4) we have $\widehat{\ell}_3 = (0_{L^1}, 0_{L^1}, \widehat{u}_3)^T$ with

$$\widehat{u}_3(x) := \int_{\mathbb{R}} k(x-y) p_j(y) \int_0^\infty \gamma_j(a, y) \left(\int_0^a e^{-\lambda(a-s)} \Pi_j(s, a, y) u_2(s, y) ds \right) dady$$

that is by the Fubini's theorem

$$\widehat{u}_3(x) := \int_{\mathbb{R}} k(x-y) p_j(y) \int_0^\infty \left(\int_s^\infty \gamma_j(a, y) e^{-\lambda(a-s)} \Pi_j(s, a, y) da \right) u_2(s, y) ds dy. \quad (7.11)$$

Next, using (7.10) we have

$$(\lambda \text{Id} - (\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)^{-1} \ell_0 \geq (\lambda \text{Id} - \mathcal{V}_j)^{-1} \left(\sum_{n=0}^3 (\mathcal{F}_j^\epsilon (\lambda \text{Id} - \mathcal{V}_j)^{-1})^n \ell_3 + \sum_{n=0}^3 (\mathcal{F}_j^\epsilon (\lambda \text{Id} - \mathcal{V}_j)^{-1})^n \widehat{\ell}_3 \right)$$

Moreover using (7.7) and (7.8) we obtain

$$\sum_{n=0}^3 (\mathcal{F}_j^\epsilon (\lambda \text{Id} - \mathcal{V}_j)^{-1})^n \ell_3 = \begin{pmatrix} \mathcal{G}_{j,\epsilon}^\lambda(u_3) + \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3) \\ 0_{L^1} \\ u_3 + \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3) \end{pmatrix}$$

and

$$\sum_{n=0}^3 (\mathcal{F}_j^\epsilon (\lambda \text{Id} - \mathcal{V}_j)^{-1})^n \widehat{\ell}_3 = \begin{pmatrix} \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3) + \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3) \\ 0_{L^1} \\ \widehat{u}_3 + \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3) \end{pmatrix}$$

from which:

$$(\lambda \text{Id} - (\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0)^{-1} \ell_0 \geq (\lambda \text{Id} - \mathcal{V}_j)^{-1} \begin{pmatrix} \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3) + \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3) \\ 0_{L^1} \\ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3) + \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3) \end{pmatrix}. \quad (7.12)$$

330 To conclude the proof, we note that Assumptions 3.1, 3.3, and 3.5 (see [14]) imply that the linear operator $\mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda$ is positive irreducible. Moreover, (7.11) also provides that $\widehat{u}_3 = 0_{L^1}$ if and only if $u_2 = 0_{L^1}$. Consequently if either $u_2 \neq 0_{L^1}$ (i.e. $\widehat{u}_3 \neq 0_{L^1}$) or $u_3 \neq 0_{L^1}$ then we have for almost every $x \in \mathbb{R}$

$$\begin{cases} \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3)(x) + \mathcal{G}_{j,\epsilon}^\lambda \circ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3)(x) > 0 \\ \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(\widehat{u}_3)(x) + \mathcal{H}_j^\lambda \circ \mathcal{G}_{j,\epsilon}^\lambda(u_3)(x) > 0 \end{cases} \quad (7.13)$$

333 Thus, we infer from the resolvent formula of \mathcal{V}_j , (7.12) and (7.13) that the resolvent of $(\mathcal{F}_j^\epsilon + \mathcal{V}_j)_0$ is positive irreducible for all $\lambda \geq \lambda_0$. \square

7.2 Parasite's extinction

336 In this section, we prove that if $\mathcal{R}_j < 1$, then the j -species goes to extinction as times goes to infinity. Consequently, if $\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\} < 1$, then all species extinct as times goes to infinity. Moreover, we also show that if $\mathcal{R}_0 > 1$ then the parasite-free equilibrium state is unstable.

Proposition 7.5. *Let Assumptions 3.1 and 3.3 be satisfied. Let $j \in \{1, 2\}$ be given. If $\mathcal{R}_j < 1$ then for each initial condition $\widehat{u}_0 = (C_0, v_0, m_0)^T \in X_+$, the j -species goes to extinction, that is*

$$\lim_{t \rightarrow +\infty} \left(\int_{\mathbb{R}} m_j(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \right) = 0.$$

Proof. Assume that $\mathcal{R}_j < 1$. Let $\epsilon_0 > 0$ be fixed small enough such that Corollary 7.3 is satisfied for all $\epsilon \in [0, \epsilon_0)$. Let us fix $\epsilon \in [0, \epsilon_0)$. Let $\widehat{u}_0 = (C_0, v_0, m_0) \in X_+$ be any initial condition. Thanks to Proposition 4.4 there exists $t_0 := t_0(\widehat{u}_0, \epsilon) > 0$ such that

$$C_i(t) \leq C_i^{E_0} + \epsilon, \quad \forall t \geq t_0, \quad i = 1, 2.$$

Consequently, we have, in a mild sense, for each $t \geq t_0$

$$\begin{cases} v_j(t, a = 0, x) \leq \beta_j(x) m_j^\epsilon(t, x) \left(\sum_{i=1}^j (C_i^{E_0} + \epsilon) \right), \\ \frac{\partial v_j(t, a, x)}{\partial t} + \frac{\partial v_j(t, a, x)}{\partial a} = -(\mu_2 + \gamma_j(a, x)) v_j(t, a, x) \end{cases}$$

and

$$\frac{\partial m_j(t, x)}{\partial t} = \int_{\mathbb{R}} k(x - y) p_j(y) \left(\int_0^\infty \gamma_j(a, y) v_j(t, a, y) da \right) dy - (\mu_{m,j} + I_j(x)) m_j(t, x).$$

339 Therefore, using the comparison theorem in [28] we obtain for all $t \geq 0$

$$\begin{cases} 0_{L^1} \leq v_j(t + t_0, \cdot, \cdot) \leq v_j^\epsilon(t, \cdot, \cdot) \\ 0_{L^1} \leq m_j(t + t_0, \cdot) \leq m_j^\epsilon(t, \cdot) \end{cases} \quad (7.14)$$

where $t \mapsto (v_j^\epsilon(t, \cdot, \cdot), m_j^\epsilon(t, \cdot))^T$ is the mild solution to (7.1) with initial condition $(v_j(t_0, \cdot, \cdot), m_j(t_0, \cdot))^T$ at time $t = 0$. The result follows from (7.14) and Corollary 7.3. \square

342 **Proposition 7.6.** *Let Assumptions 3.1 and 3.3 be satisfied. The parasite-free equilibrium state is globally asymptotically stable in X_+ if $\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\} < 1$. More precisely, if $\mathcal{R}_0 < 1$ then for each initial condition $\widehat{u}_0 = (C_0, v_0, m_0) \in X_+$, we have*

$$\lim_{t \rightarrow +\infty} \left(\int_{\mathbb{R}} m_j(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \right) = 0, \quad j \in \{1, 2\} \quad (7.15)$$

and

$$\lim_{t \rightarrow +\infty} C_i(t) = C_i^{E_0}, \quad i \in \{1, 2\}.$$

345 If in addition Assumption 3.2 is satisfied, then the parasite-free equilibrium is unstable whenever $\mathcal{R}_0 > 1$.

Proof. If $\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\} < 1$ then (7.15) clearly follows from Proposition 7.5. To prove the convergence of the C_i -components, we note that the boundedness of $t \mapsto C_i(t)$, $i \in \{1, 2\}$ on $[0, +\infty)$ implies that (see [40, Proposition A.14]) there exist sequences (t_n^i) and (s_n^i) with $t_n^i \rightarrow +\infty$ and $s_n^i \rightarrow +\infty$ such that

$$\begin{cases} C_i(t_n^i) \rightarrow C_i^\infty = \limsup_{t \rightarrow +\infty} C_i(t) \\ C_i'(t_n^i) \rightarrow 0 \end{cases} \quad \text{and} \quad \begin{cases} C_i(s_n^i) \rightarrow C_{i,\infty} = \liminf_{t \rightarrow +\infty} C_i(t) \\ C_i'(s_n^i) \rightarrow 0. \end{cases} \quad (7.16)$$

Therefore, using (7.16) and the C_1 -equation in (7.1) it comes

$$0 = \Lambda - \mu_{1,2} C_1^\infty \quad \text{and} \quad 0 = \Lambda - \mu_{1,2} C_{1,\infty} \implies C_1^\infty = C_{1,\infty} = \frac{\Lambda}{\mu_{1,2}}$$

that is

$$\lim_{t \rightarrow +\infty} C_1(t) = \frac{\Lambda}{\mu_{1,2}}. \quad (7.17)$$

Next, using the C_2 -equation in (7.1) combined with (7.16) and (7.17) it follows that

$$0 = \mu_{1,2} \frac{\Lambda}{\mu_{1,2}} - \mu_2 C_2^\infty \quad \text{and} \quad 0 = \mu_{1,2} \frac{\Lambda}{\mu_{1,2}} - \mu_2 C_{2,\infty}.$$

Therefore $C_{2,\infty} = C_2^\infty = \frac{\Lambda}{\mu_2}$ providing that $C_2(t) \rightarrow \frac{\Lambda}{\mu_2}$ when t goes to $+\infty$. The local stability of the parasite-free equilibrium simply follows from the first item of Lemma 7.2 since the linearization of (3.3) around E_0 is (7.2) (up to the C_i -components) with $\epsilon = 0$. Finally, the fact that the parasite-free equilibrium is unstable whenever $\mathcal{R}_0 > 1$ follows from the second item of Lemma 7.2. \square

7.3 Uniform persistence of parasites

In this section, we always assume that $\mathcal{R}_0 > 1$. To obtain the uniform persistence of the parasites, we introduce the maps $\xi : X_+ \rightarrow \mathbb{R}_+$ defined for each $(C_0, v_0, m_0)^T \in X_+$ by

$$\xi(C_0, v_0, m_0) := \sum_{j=1}^2 \left(\int_{\mathbb{R}} m_{j,0}(x) dx + \int_{\mathbb{R}} \int_0^\infty v_{j,0}(a, x) da dx \right).$$

It is clear that ξ is nonnegative and continuous on X_+ . Next, we define the sets

$$\mathbb{M}_0 := \{(C_0, v_0, m_0)^T \in X_+ : \xi(C_0, v_0, m_0) > 0\}$$

and

$$\partial\mathbb{M}_0 := \{(C_0, v_0, m_0)^T \in X_+ : \xi(C_0, v_0, m_0) = 0\}$$

so that $X_+ = \mathbb{M}_0 \cup \partial\mathbb{M}_0$. We first prove the following lemma which states that if $(C_0, v_0, m_0)^T \in \partial\mathbb{M}_0$ then, independently of \mathcal{R}_0 , the parasites-free equilibrium is always globally asymptotically stable on $\partial\mathbb{M}_0$.

Lemma 7.7. *Let Assumptions 3.1 and 3.3 be satisfied. Then for each initial condition $\hat{u}_0 = (C_0, v_0, m_0)^T \in \partial\mathbb{M}_0$, we have*

$$\xi(\Phi_t(\hat{u}_0)) = 0, \quad \forall t \geq 0 \quad \text{and} \quad \lim_{t \rightarrow +\infty} C_i(t) = C_i^{E_0}, \quad i = 1, 2, \quad (7.18)$$

with $\Phi_t(\hat{u}_0) = (C(t), v(t, \cdot, \cdot), m(t, \cdot))$ for all $t \geq 0$.

Proof. The first equality of (7.18) follows from the uniqueness of the solutions of (7.1). The convergence of $C_i(t)$ to $C_i^{E_0}$, for $i = 1, 2$ can then be proven by similar arguments in Proposition 7.6. \square

The main result of this section is the following.

Theorem 7.8. *Let Assumptions 3.1, 3.2, and 3.5 be satisfied. Assume in addition that $1 < \min(\mathcal{R}_1, \mathcal{R}_2) \leq \mathcal{R}_0$. Then, the semiflow $\{\Phi_t\}_{t \geq 0}$ is ξ -strongly uniformly persistent on \mathbb{M}_0 . More precisely, there exists $\eta > 0$ such that for each initial condition $\hat{u}_0 = (C_0, v_0, m_0)^T \in \mathbb{M}_0$ we have*

$$\liminf_{t \rightarrow +\infty} \xi(\Phi_t(\hat{u}_0)) \geq \eta$$

with $\Phi_t(\hat{u}_0) = (C(t), v(t, \cdot, \cdot), m(t, \cdot))$ for all $t \geq 0$.

Proof. Assume that $1 < \min(\mathcal{R}_1, \mathcal{R}_2) \leq \mathcal{R}_0$. Let $\epsilon_0 > 0$ be small enough such the conclusions of Proposition 7.4 hold true for each $\epsilon \in (-\epsilon_0, 0]$ and $j \in \{1, 2\}$. In the following, ϵ is fixed in $\epsilon \in (-\epsilon_0, 0)$. Since $\{\Phi_t\}_{t \geq 0}$ has a compact global attractor, our result is obtained once we prove that the semiflow $\{\Phi_t\}_{t \geq 0}$ is ξ -weakly uniformly persistent on \mathbb{M}_0 [29, 40] that is there exists $\eta_0 > 0$ such that for each initial condition $\widehat{u}_0 = (C_0, v_0, m_0)^T \in \mathbb{M}_0$ we have

$$\limsup_{t \rightarrow +\infty} \xi(\Phi_t(\widehat{u}_0)) \geq \eta_0. \quad (7.19)$$

To prove (7.19), we argue by contradiction. Before proceeding, let us first note that for each initial condition $\widehat{u}_0 = (C_0, v_0, m_0)^T \in \mathbb{M}_0$ that is $\xi(\widehat{u}_0) > 0$, we can prove by standard arguments that

$$\xi(\Phi_t(\widehat{u}_0)) = \sum_{j=1}^2 \left(\int_{\mathbb{R}} m_j(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \right) > 0, \quad \forall t \geq 0. \quad (7.20)$$

Let $\eta_0 > 0$ be small enough such that

$$\begin{cases} \frac{\Lambda}{\mu_{1,2} + 2\eta_0} \geq C_1^{E_0} + \epsilon = \frac{\Lambda}{\mu_{1,2}} + \epsilon \\ \frac{\mu_{1,2}\Lambda}{(\mu_{1,2} + 2\eta_0)(\mu_2 + 2\eta_0)} \geq C_2^{E_0} + \epsilon = \frac{\Lambda}{\mu_2} + \epsilon. \end{cases} \quad (7.21)$$

Let $\widehat{u}_0 \in \mathbb{M}_0$ such that

$$\limsup_{t \rightarrow +\infty} \xi(\Phi_t(\widehat{u}_0)) = \limsup_{t \rightarrow +\infty} \left(\int_{\mathbb{R}} m_j(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \right) < \eta_0. \quad (7.22)$$

Then there exists $t_0 := t_0(\widehat{u}_0) > 0$ such that

$$\left(\int_{\mathbb{R}} m_j(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j(t, a, x) da dx \right) \leq \eta_0, \quad \forall t \geq t_0. \quad (7.23)$$

From (7.23) and the C_i -equations of (7.1) we obtain

$$\begin{cases} C_1'(t) \geq \Lambda - (\mu_{1,2} + \eta_0)C_1(t), \quad t \geq t_0 \\ C_2'(t) \geq \mu_{1,2}C_1(t) - (\mu_2 + \eta_0)C_2(t), \quad t \geq t_0. \end{cases} \quad (7.24)$$

Since $t \rightarrow C_1(t)$ is bounded on $[0, +\infty)$, there exists a sequence (t_n) with $t_n \rightarrow +\infty$ such that $C_1(t_n) \rightarrow C_{1,\infty} = \liminf_{t \rightarrow +\infty} C_1(t)$ and $C_1'(t_n) \rightarrow 0$ (see [40, proposition A.14]). Therefore, using the first equation of (7.24) we obtain

$$\liminf_{t \rightarrow +\infty} C_1(t) = C_{1,\infty} \geq \frac{\Lambda}{\mu_{1,2} + \eta_0}. \quad (7.25)$$

Since $\frac{\Lambda}{\mu_{1,2} + \eta_0} > \frac{\Lambda}{\mu_{1,2} + 2\eta_0}$, the inequality (7.25) implies that there exists $t_1 := t_1(\widehat{u}_0) > t_0$ such that

$$C_1(t) \geq \frac{\Lambda}{\mu_{1,2} + 2\eta_0}, \quad \forall t \geq t_1. \quad (7.26)$$

Consequently, we have from the second equation of (7.24) that

$$C_2'(t) \geq \mu_{1,2} \frac{\Lambda}{\mu_{1,2} + 2\eta_0} - (\mu_2 + \eta_0)C_2(t), \quad t \geq t_1.$$

Using similar arguments as for the C_1 -equation, we obtain

$$C_{2,\infty} := \liminf_{t \rightarrow +\infty} C_2(t) \geq \frac{\mu_{1,2}\Lambda}{(\mu_{1,2} + 2\eta_0)(\mu_2 + \eta_0)}. \quad (7.27)$$

Since $\frac{\mu_{1,2}\Lambda}{(\mu_{1,2} + 2\eta_0)(\mu_2 + \eta_0)} > \frac{\mu_{1,2}\Lambda}{(\mu_{1,2} + 2\eta_0)(\mu_2 + 2\eta_0)}$ we infer from (7.27) that there exists $t_2 := t_2(\widehat{u}_0) > t_1$ such that

$$C_2(t) \geq \frac{\mu_{1,2}\Lambda}{(\mu_{1,2} + 2\eta_0)(\mu_2 + 2\eta_0)}, \quad \forall t \geq t_2. \quad (7.28)$$

381 Thanks to (7.21)-(7.26)-(7.28) we have

$$C_i(t) \geq C_i^{E_0} + \epsilon, \quad \forall t \geq t_2, \quad i = 1, 2. \quad (7.29)$$

The latter inequality (7.29) implies that the m_j and v_j components of (2.1), with $j \in \{1, 2\}$, satisfy for each $t \geq t_2$

$$\begin{cases} v_j(t, a = 0, x) \geq \sum_{i=1}^j (C_i^{E_0} + \epsilon) \beta_j(x) m_j(t, x), \\ \frac{\partial v_j(t, a, x)}{\partial t} + \frac{\partial v_j(t, a, x)}{\partial a} = -(\mu_2 + \gamma_j(a, x)) v_j(t, a, x), \\ \frac{\partial m_j(t, x)}{\partial t} = \int_{\mathbb{R}} k(x-y) p_j(y) \left(\int_0^\infty \gamma_j(a, y) v_j(t, a, y) da \right) dy - (\mu_{m,j} + I_j(x)) m_j(t, x). \end{cases}$$

Thus we obtain by comparison principles in [28] that

$$0 \leq v_j^\epsilon(t, \cdot, \cdot) \leq v_j(t + t_2, \cdot, \cdot), \quad j \in \{1, 2\} \quad \text{and} \quad 0 \leq m_j^\epsilon(t, \cdot) \leq m_j(t + t_2, \cdot), \quad j \in \{1, 2\}$$

for all $t \geq 0$ where $t \mapsto (v_j^\epsilon(t, \cdot, \cdot), m_j^\epsilon(t, \cdot))$ is the mild solution to (7.1) with initial condition $v_j^\epsilon(0, \cdot, \cdot) = v_j(t_2, \cdot, \cdot)$ and $m_j^\epsilon(0, \cdot) = m_j(t_2, \cdot)$. Setting for each $t \geq 0$ and $j \in \{1, 2\}$, $\ell_j^\epsilon(t) := (0_{L^1}, v_j^\epsilon(t, \cdot, \cdot), m_j^\epsilon(t, \cdot))$ and $\ell_{j,0}^\epsilon := (0_{L^1}, v_j^\epsilon(t_0, \cdot, \cdot), m_j^\epsilon(t_0, \cdot))$ it comes

$$\ell_j^\epsilon(t) = T_{(\mathcal{F}_j^\epsilon + \nu_j)_0}(t) \ell_{j,0}^\epsilon, \quad \forall t \geq 0, \quad j \in \{1, 2\}.$$

Since $\mathcal{R}_j > 1$ for $j \in \{1, 2\}$, we infer from Proposition 7.4 that $\lambda_j^\epsilon > 0$ for $j \in \{1, 2\}$ and

$$\lim_{t \rightarrow +\infty} e^{-\lambda_j^\epsilon t} \|T_{(\mathcal{F}_j^\epsilon + \nu_j)_0}(t) \ell_{j,0}^\epsilon\| = \|\mathcal{P}_j^\epsilon \ell_{j,0}^\epsilon\|. \quad (7.30)$$

Since

$$\|\ell_{j,0}^\epsilon\| = \int_{\mathbb{R}} m_j(t_0, x) dx + \int_{\mathbb{R}} \int_0^\infty v_j(t_0, a, x) da dx, \quad j \in \{1, 2\}$$

it follows from (7.20) and Proposition 7.4 that $\|\mathcal{P}_1^\epsilon \ell_{1,0}^\epsilon\| + \|\mathcal{P}_2^\epsilon \ell_{2,0}^\epsilon\| > 0$. Without loss of generality, assume that $\|\mathcal{P}_1^\epsilon \ell_{1,0}^\epsilon\| > 0$. Then (7.30) implies that

$$\|T_{(\mathcal{F}_1^\epsilon + \nu_1)_0}(t) \ell_{1,0}^\epsilon\| = \int_{\mathbb{R}} m_1(t, x) dx + \int_{\mathbb{R}} \int_0^\infty v_1(t, a, x) da dx \xrightarrow{t \rightarrow +\infty} +\infty$$

which is a contradiction to (7.22). The proof is completed. \square

384 8 Parameterization of the model and its typical simulation dynamics

For the numerical simulations, the ruptured functions γ_j are taken as

$$\gamma_j(a, x) = \begin{cases} 0 & \text{if } a < \tau_j, \\ \alpha_j & \text{if } a \geq \tau_j, \end{cases} \quad (8.1)$$

where τ_j is the erythrocytic cycle duration of the j -species (see Table 1 for given values). We fix $\alpha_j = 10$ for all species such that the average parasite's development period: $\int_0^\infty \exp(-\int_0^a \gamma_j(\sigma, x) d\sigma) da = \tau_j + 1/\alpha_j \approx \tau_j$.

We assume the mutation kernel is described by a Gaussian distribution $k(x) = k_\epsilon(x) = (2\pi\epsilon^2)^{-\frac{1}{2}} e^{-\frac{1}{2}(\frac{x}{\epsilon})^2}$ for the mutation kernel, where $\epsilon > 0$ represents the standard deviation of the Gaussian mutation kernel within the phenotypic space. Malaria parasites infection efficiencies β_j are assumed independent of the phenotypic values x , such that $\beta_j(x) = \beta_j$ for all x . For each simulated scenario, we assume that both the production rate p_j and the immune response I_j depend on the phenotypic trait x . More precisely, we define

$$p_j(x) = p_j^{\max} \times \mathcal{N}(x_j^*, \sigma_j)(x), \quad (8.2)$$

$$I_j(x) = I_j^{\max} \times \mathcal{N}(x_j^*, s_j)(x), \quad (8.3)$$

where x_j^* is the dominant parasite phenotype within the j -malaria species. The constants p_j^{\max} and I_j^{\max} are respectively the maximal production rates and the maximal effect of the immune system on the dominant phenotype.

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The parameter σ_j allows quantifying the selectivity level ($\frac{1}{\sigma_j^2}$) within the j -malaria species, while s_j accounts for the cross immunity effect. Finally, $\mathcal{N}(x_j^*, s_j)$ is set for the normal probability density distribution with mean x_j^* and standard deviation s_j .

Model (2.1) can then be used to illustrate various dynamics depending on the specific scenario of interest. Here we illustrate the typical dynamics simulated with the model for two scenarios.

The first scenario is when the immune system is inefficient on both malaria species (*P. vivax* for species 1, and *P. falciparum* for species 2). Clearly, in the absence of the immune system effect, the dominant parasite phenotype, x_1^* , within *P. vivax* can grow because $\mathcal{R}_1(x_1^*)|I_1 \equiv 0 > 1$ (Figure 2A). This is also the case for the dominant parasite phenotype, x_2^* , within *P. falciparum* (Figure 2B). However, although reducing the basic reproduction numbers of both species, the immune system is not sufficiently efficient to keep the dominant parasite phenotypes below the growth threshold and we still have $\mathcal{R}_j(x_j^*) > 1$ with the effect of the immune system (Figure 2C). The model depicts the evolutionary dynamics of interactions between *P. vivax* and *P. falciparum* in the presence of the immune system (Figures 2D,E,F). Malaria parasites of both species entirely evade control by the immune system. Figure 2D depicts the dynamics of malaria parasites and RBCs, while Figures 2E and F illustrate the evolutionary dynamics of malaria parasites for *P. vivax* and *P. falciparum*, respectively. In this scenario, although both species coexist in equilibrium in the long term, with *P. falciparum* dominating (Figure 3), the short-term dynamics, crucial for promptly addressing infected hosts, present a contrasting configuration. Indeed, when the initial presence of both species is nearly equal, there ensues a phase where *P. vivax* predominates almost exclusively for a some duration (Figure 2D). This short-term dynamic aligns closely with the period it takes to treat a case of malaria from the onset of infection to the manifestation of symptoms.

In the second scenario, the immune system is inefficient on *P. falciparum*, species 2, and efficient on *P. vivax*, species 1. As a result, at the end, only *P. vivax* is under control because $\mathcal{R}_1(x_1^*) < 1$, while *P. falciparum* remains uncontrolled because $\mathcal{R}_2(x_2^*) > 1$ (Figures 4 and 5).

9 Conclusion and discussion

Human malaria is caused by various species of *Plasmodium*, such as *P. falciparum* and *P. vivax*. Mixed infections with multiple *Plasmodium* species are common globally but often go unrecognized or underestimated [24, 30]. Mathematical models have been developed to study parasite multiplication within hosts during mixed malaria infections [8, 11, 17, 23, 46]. However, these models typically address infection dynamics separately, focusing on either multiple genotypes of a single species within a host [8, 11, 23, 46], or mixed-species infection dynamics with single genotype within a host [17]. Both the within-species and inter-species diversity play crucial roles in the dynamics of malaria infection within the host. Indeed, different *Plasmodium* species have varying preferences for RBCs, and such ecological characteristics is fundamental to capture species diversity within the same host [17]. Furthermore, the within-species diversity is sustained by a large number of antigenic variants, exerting significant pressure on the host's immune system and which can facilitate the establishment of prolonged infections by the parasite [36, 41].

Here, we present a within-host malaria infection model incorporating the dynamics of RBCs production. We account for uninfected RBCs, including reticulocytes and mature RBCs, as well as an age-structured dynamics for parasitized RBCs. This age structure represents the time since the RBC was parasitized, allowing for a continuous description of the parasitized RBC population. The model, formulated using partial differential equations (PDEs), enables tracking of the development and maturation of parasitized RBCs, as well as a detailed depiction of the rupture of parasitized RBCs and the release of merozoites [15]. The proposed model accounts for the influence of the immune system through the parameter function I_j , considering both the selectivity within malaria species and the cross-immunity effect. However, the model formulation explicitly allows for the introduction of the effects of interventions targeting either *P. falciparum* or *P. vivax* for treatment interventions.

We prove that the basic reproduction number $\mathcal{R}_j(x)$ for strain x within the j -species can be explicitly determined using (6.1). However, deriving an explicit formula for the basic reproduction number \mathcal{R}_j at the species level for the j -species is more challenging. The estimate of \mathcal{R}_j given by (5.3) is essentially determined by the principal eigenvalue of the linear operator L_j defined by (3.4) for any probability kernel k satisfying Assumption 3.3. Though, a more explicit estimation of \mathcal{R}_j can be accurately given when the mutation kernel k depends on a small positive parameter (say $\varepsilon \ll 1$) with the scaling form:

$$k_\varepsilon(x) = \varepsilon^{-1} k(\varepsilon^{-1} x).$$

The parameter $\varepsilon > 0$ can be interpreted as the variance of mutations in the phenotypic space. More precisely, let

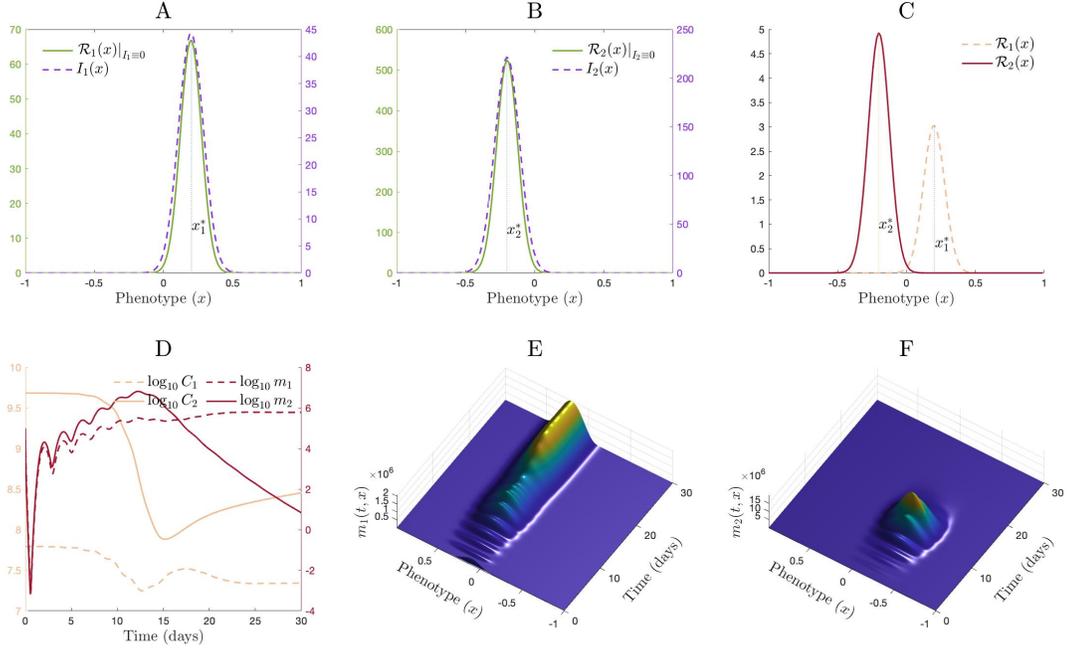


Figure 2: **Typical evolutionary dynamics considering the inefficiency of immune system on both malaria species (Figure 1, zone 5).** (A-B) The immune system $I_j(x)$ and the basic reproduction numbers $\mathcal{R}_j(x)$ without the effect of immune system for *P. vivax*, species 1, and *P. falciparum*, species 2. (C) The basic reproduction numbers with the effect of immune system. (D) Time evolution of young RBCs C_1 and mature RBCs C_2 . (E-F) Distribution of the malaria parasites $m_1(t, x)$ and $m_2(t, x)$ with respect to time t and the phenotypic trait x . Here, parameter values are $(I_1^{\max}, I_2^{\max}) = (10, 50)$, $(s_1, s_2) = (0.09, 0.09)$, $m_1(0, x) = 10^5 \mathcal{N}(0.1, 0.1)(x)$, $m_2(0, x) = 10^5 \mathcal{N}(-0.1, 0.1)(x)$, or default as shown in Table 1.

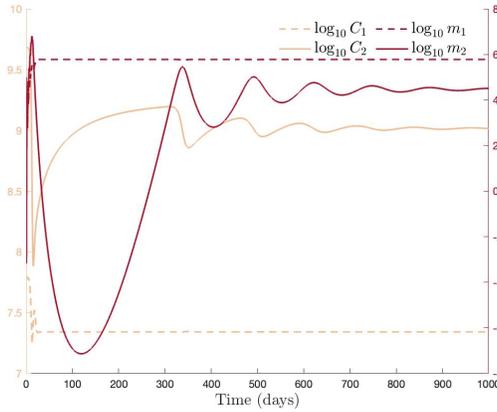


Figure 3: **The long-term dynamics depicted in Figure 2 reveal a stable coexistence of both species, with *P. falciparum* exhibiting dominance of parasites.**

us introduce the set

$$\mathcal{S}_j = \{x \in \mathbb{R} : \Gamma_j(x) = \|\Gamma_j\|_\infty\}.$$

This set is commonly known as the set of Evolutionary Attractors (or dominant phenotypic values) as described in

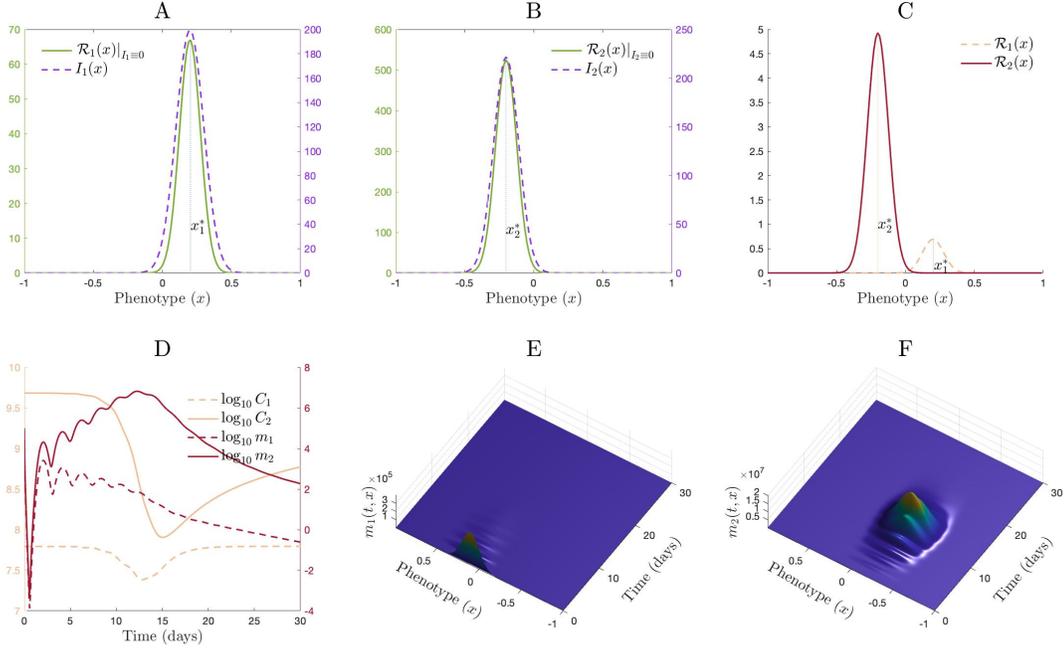


Figure 4: **Typical evolutionary dynamics considering the inefficiency of immune system on *P. falciparum* and its efficiency on *P. vivax* (Figure 1, zone 2).** Panels A-F are same as to those presented in Figure 2. Here, parameter values are $(I_1^{\max}, I_2^{\max}) = (50, 50)$, $(s_1, s_2) = (0.1, 0.09)$, $m_1(0, x) = 10^5 \mathcal{N}(0.1, 0.1)(x)$, $m_2(0, x) = 10^5 \mathcal{N}(-0.1, 0.1)(x)$, or default as shown in Table 1.

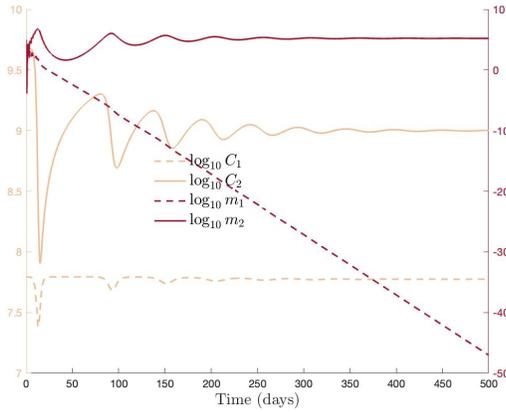


Figure 5: **The long-term dynamics depicted in Figure 4 reveal a stable persistence of only *P. falciparum*.**

classical adaptive dynamics theory (*e.g.* [19, 32]). Indeed, when $\varepsilon > 0$ is small and the reproductive function Γ_j is at least of class \mathcal{C}^1 with a finite number of maxima, it has been demonstrated in [14, Theorem 2.2] that these dominant phenotypic values coincide with the set \mathcal{S}_j . Moreover, let us denote by L_j^ε the operator L_j , see (3.4), with the kernel k replaced by k_ε , results in [14, Theorem 2.2] indicate that the spectral radius $r(L_j^\varepsilon)$ of L_j^ε satisfies, for sufficiently small ε ,

$$r(L_j^\varepsilon) = \Gamma_j(x^*) + \mathcal{O}(\varepsilon), \quad \text{for all } x^* \in \mathcal{S}_j.$$

Based on the aforementioned estimation, we have

$$\mathcal{R}_j = \left(\sum_{i=1}^j C_i^{E_0} \right) \Gamma_j(x^*) + \mathcal{O}(\varepsilon),$$

432 for all $x^* \in \mathcal{S}_j$. Moreover, if $\varepsilon \ll 1$, the profile of the endemic equilibrium E_j , with respect to $x \in \mathbb{R}$, can be more precisely determined. Indeed, if $\mathcal{S}_j = \{x_j^*\}$ and $\left(\sum_{i=1}^j C_i^{E_0} \right) \Gamma_j(x_j^*) > 1$, then the unique positive stationary state $E_j \equiv E_j^\varepsilon$ is concentrated around the evolutionary attractor x_j^* in the phenotypic space \mathbb{R} . For further details on
435 this concentration phenomenon, we refer to [14, Theorem 2.3].

Through our analysis, we have determined the condition (5.6) under which *P. vivax* (species 1) and *P. falciparum* (species 2) can coexist. Note that the estimate (5.6) highlights a significant advantage of *P. vivax* when coexisting
438 with *P. falciparum*, as the coexistence condition always implies $\mathcal{R}_1 < \mathcal{R}_2$. We further determine the invasion fitness of a mutant in a resident population. Such invasibility analysis allows us to determine the invasibility capability for various scenarios at both the within- and between-species scales. According to Proposition 6.2, we observe
441 that an optimization principle based on the reproduction numbers \mathcal{R}_j is applicable either when both *P. vivax* and *P. falciparum* are the resident, or when only *P. vivax* is the resident, see (6.4). Indeed, in such a scenarios, the coexistence of multiple strains of the same species, whether *P. vivax* or *P. falciparum*, is not possible, and
444 an intraspecies competitive exclusion principle prevails. However, the situation becomes more intricate when only *P. falciparum* serves as the resident. In the scenario where only *P. falciparum* is the resident, the coexistence of multiple strains of *P. falciparum* becomes unattainable, see (6.6). In such a configuration, the emergence of an
447 initially rare mutant strain y_1 within the *P. vivax* species takes place when the reproductive capability $\mathcal{R}_1^{y_1}$ of the mutant strain on young RBCs and the reproductive capability $\mathcal{R}_2^{x_2}$ of the resident strain on young RBCs satisfy the condition $\mathcal{R}_1^{y_1} > \frac{(C_1^{x_2} + C_2^{x_2})/C_1^{x_2}}{(C_1^{E_0} + C_2^{E_0})/C_1^{E_0}} \mathcal{R}_2^{x_2}$, see (6.5). In this latter inequality, it is worth noting that the quantity
450 $\frac{(C_1^{x_2} + C_2^{x_2})/C_1^{x_2}}{(C_1^{E_0} + C_2^{E_0})/C_1^{E_0}}$ is always less than unity. It means that the proportion of young RBCs in a parasite-free environment is smaller than the proportion of young red blood cells in the environment set by the resident strain.

As an example of the invasibility analysis in a multi-species and multi-genotypes setting, one may consider the
453 scenario where *P. falciparum* has established an equilibrium, resulting in a resident parasite population primarily dominated by the phenotypic value x_2 , where $\mathcal{R}_2^{x_2} > 1$ (Figure 6A). Now, suppose an initially rare mutant population of *P. vivax* is introduced, characterized by a dominant phenotype y_1 (Figure 6A). The ability of this mutant
456 population to invade is determined by the sign of the invasion fitness $f_{(\emptyset, x_2)}^1(y_1)$ as defined in (6.5). More precisely, in the first invasibility scenario, the mutant population induced by the dominant phenotype y_1 satisfies $\mathcal{R}_1^{y_1} < \frac{(C_1^{x_2} + C_2^{x_2})/C_1^{x_2}}{(C_1^{E_0} + C_2^{E_0})/C_1^{E_0}} \mathcal{R}_2^{x_2}$ (Figure 6A). Consequently, since $f_{(\emptyset, x_2)}^1(y_1) < 0$, this mutant population fails to invade the
459 initial resident population (Figure 6B). Conversely, in the second invasibility scenario, the mutant population satisfies $\mathcal{R}_1^{y_1} > \frac{(C_1^{x_2} + C_2^{x_2})/C_1^{x_2}}{(C_1^{E_0} + C_2^{E_0})/C_1^{E_0}} \mathcal{R}_2^{x_2}$ (Figure 6C). As a result, since $f_{(\emptyset, x_2)}^1(y_1) > 0$, this mutant population succeeds in invading the initial resident population (Figure 6D). It is noteworthy that the threshold $\frac{(C_1^{x_2} + C_2^{x_2})/C_1^{x_2}}{(C_1^{E_0} + C_2^{E_0})/C_1^{E_0}} \mathcal{R}_2^{x_2}$,
462 above which the mutant population with the dominant strain y_1 can proliferate in the environment established by the resident population, is consistently greater than unity. Therefore, merely having a mutant with $\mathcal{R}_1^{y_1} > 1$ is insufficient to ensure invasibility (Figures 6 A,B). A similar invasibility analysis can be designed for the case where
465 *P. vivax* is the resident population. Such invasibility analysis particularly highlights the importance of interactions between *P. falciparum*, *P. vivax* and the acquisition of immunity in the context of malaria within-host infections [6].

468 Acknowledgements

MP was funded by the project ACoMVeC (INV-047049). RDD receive support from the ANR (<https://anr.fr/en/>) grant QUASAR (ANR-21-CE45-0004). The funders had no role in study design, data collection and analysis,
471 decision to publish, or preparation of the manuscript.

Conflict of interest

We declare no conflict of interest.

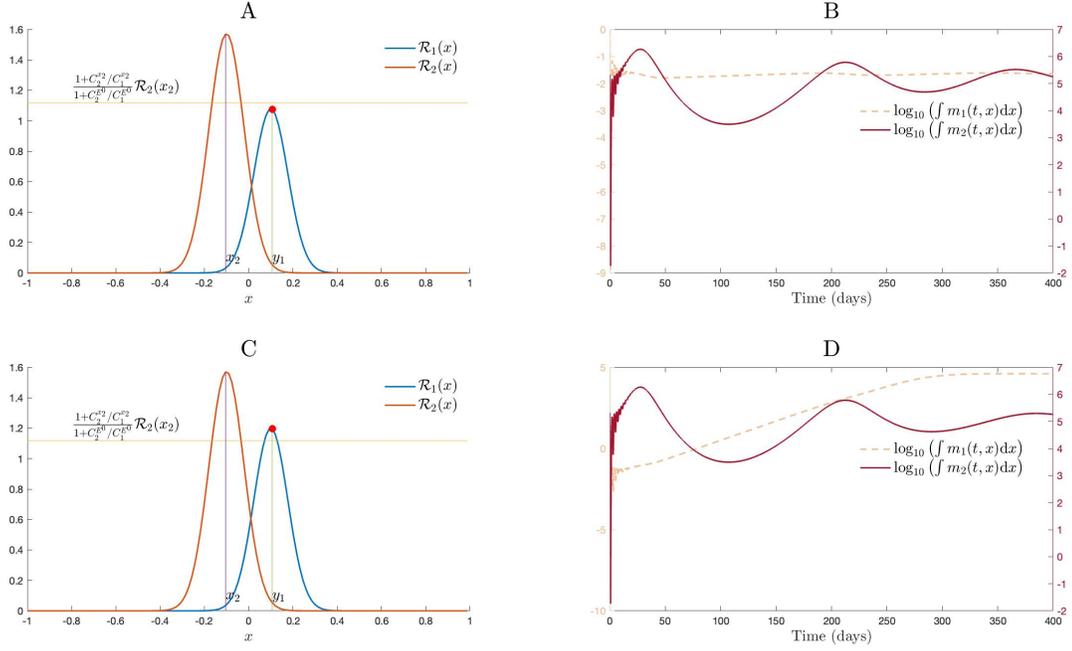


Figure 6: **Invasibility of a *P. vivax* population in a feedback environment set by a *P. falciparum* population.** A-B: $(I_1^{\max}, I_2^{\max}) = (29, 100)$ and the mutant fails in invading. C-D: $(I_1^{\max}, I_2^{\max}) = (26, 100)$ and the mutant succeed in invading. Other parameter values are $(s_1, s_2) = (0.09, 0.05)$, or default as shown in Table 1. For the initial condition, we undertake a two-step process. In Step 1, we initially simulate the model considering only species 2 (*P. falciparum*), setting the initial conditions as follows: $m_1(0, x) = 0$, $m_2(0, x) = 10^5 \mathcal{N}(-0.1, 0.1)(x)$. In Step 2, with species 2 already at equilibrium as established in Step 1, we introduce a mutant of species 1 (*P. vivax*) with initial conditions given by $m_1(0, x) = \mathcal{N}(y_1, 0.1)(x)$, where y_1 is maximising \mathcal{R}_1 .

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