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What drives the evolution of preference for young or old red blood cells in malaria parasites?

Khady Gningue[1], Ramsès Djidjou-Demasse[2,3], Sylvain Gandon[4], Quentin Richard[5]

Abstract

Malaria parasites exhibit striking variation in their ability to invade red blood cells (RBCs) of different ages, a trait that differs across *Plasmodium* species and strains and is thought to play a central role in infection success and coexistence. Yet, the evolutionary forces shaping RBC age preference remain poorly understood. Here, we develop an age-structured within-host evolutionary model that links RBC population structure to parasite invasion, replication, and transmission potential. We assume that parasite genotypes are characterized by a continuous preference trait controlling their relative affinity for reticulocytes or normocytes, subject to physiological costs of specialization. We show that evolutionary outcomes are governed by a balance between RBC availability and the reproductive value of the parasite in the two types of RBC, which depend on several within-host parameters like infection efficiency, burst size, and parasite mortality. The evolution of malaria preference for young or old RBCs is driven by the within-host effective reproductive potential. Higher values of this quantity yield a higher equilibrium density of parasites and a lower proportion of normocytes, which drives the evolution of a preference for reticulocytes. This work provides a unified evolutionary explanation for observed species-specific RBC tropism in malaria parasites and highlights how within-host age-structure of RBCs can drive the evolution of malaria preference for different types of host cells.

1 Introduction

Human malaria is caused by several *Plasmodium* species [33], including *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. Among these, *P. falciparum* and *P. vivax* are the most widespread, with *P. falciparum* responsible for the majority of severe cases and malaria-related deaths, whereas *P. vivax* infections are generally less severe [6]. The parasite has a complex life cycle involving sexual reproduction in the mosquito vector [1] and two developmental stages in the human host: a liver stage [13] and a blood stage [5]. Infection begins when an infected mosquito injects sporozoites during a blood meal. Next, the sporozoites rapidly migrate to the liver, where they invade hepatocytes and replicate before releasing merozoites into the bloodstream [13]. The merozoites then invade red blood cells (RBCs), initiating the erythrocytic stage characterized by repeated cycles of replication, cell rupture, and reinvasion of RBCs [29]. *Plasmodium* species exhibit remarkable diversity in their within-host strategies, particularly in their preference for invading rRBCs of different ages, suggesting that RBC age structure is not merely a physiological constraint but a key evolutionary axis shaping parasite adaptation. For example, among human malaria parasites, *P. vivax* and *P. ovale* preferentially invade reticulocytes, *P. malariae* primarily targets mature RBCs, whereas *P. falciparum* can infect RBCs across all age classes [32]. Despite extensive work on within-host competition, the evolutionary forces driving RBC age preference and its role in parasite diversification remain poorly understood.

Indeed, from a theoretical perspective, several mathematical models have been proposed to investigate within-host parasite dynamics in mixed malaria infections [7, 8, 20, 31, 38]. Most of these studies predict competitive exclusion among parasite genotypes of a given species, whereby only one strain persists while the others are driven to extinction [8, 20, 38]. Exceptions arise under specific modelling assumptions regarding the RBC infection rate, which may allow coexistence [7], or species-specific preferences for RBCs of different ages [12, 26, 31]. However,

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these works do not address the evolutionary mechanisms underlying species-specific preferences for RBCs of different ages, nor do they identify the factors shaping such evolutionary strategies. However, RBC tropism is not fixed at the species level and can vary substantially across strains (e.g., [22]), suggesting that it should be treated as a strain-dependent trait. To address this gap, we develop an age-structured within-host model that captures the evolutionary dynamics of malaria parasites in mixed infections. Our framework explicitly accounts for parasite preferences for RBCs of different ages. By linking RBC age structure to parasite replication and invasion strategies, the model provides a mechanistic understanding of the evolutionary drivers behind species-specific infection patterns.

One central result of this work is that parasite evolution is governed by a trade-off between exploitation of young red blood cells (reticulocytes) and mature red blood cells (normocytes), mediated by the effective reproductive potential $\mathcal{R}_{\text{ef}}$. A key contribution is the identification of $\mathcal{R}_{\text{ef}}$ as a unifying evolutionary control parameter governing parasite RBC age preference. This quantity aggregates infection efficiency, burst size, and parasite lifespan. It can thus be interpreted as a proxy for the evolutionary pressure acting at the RBC level, shaping strain-specific targeting strategies. Our analysis shows that RBC age preference is not fixed, but emerges as an adaptive trait shaped by epidemiological and within-host constraints. In particular: (i) low $\mathcal{R}_{\text{ef}}$ selects for preference toward mature RBCs, (ii) high $\mathcal{R}_{\text{ef}}$ favors reticulocyte targeting, and (iii) intermediate regimes generate graded evolutionary transitions. Thus, parasite evolution is organized along a continuous axis of host cell exploitation rather than discrete species-specific strategies. Importantly, variation in $\mathcal{R}_{\text{ef}}$ maps directly onto shifts in RBC tropism across *Plasmodium* species. This suggests that observed differences between species (e.g. *P. falciparum* vs *P. vivax*) can be interpreted as outcomes of continuous evolutionary tuning rather than fixed biological constraints. A non-intuitive result is that parasite reproductive value within a given RBC type is not a reliable predictor of evolutionary preference. In particular, RBC types with higher reproductive value are not necessarily preferred, and host cell abundance and ecological feedbacks can override intrinsic "quality" of the host cell. This decoupling between fitness within a host class and evolutionary preference highlights the importance of ecological context in shaping parasite evolution.

We begin by presenting the mathematical model, including the definitions of its state variables and parameters. Preliminary results are then established, demonstrating the existence of a positive global-in-time solution. We analyze the existence of nontrivial stationary states and characterize the threshold dynamics of the single-genotype system. The invasibility analysis follows, providing a quantitative framework to investigate species-specific evolutionary preferences for RBCs. Finally, we illustrate model predictions and discuss the biological implications and limitations of the modeling assumptions.

2 Model overview

The model describes within-host malaria infection coupled with red blood cells (RBCs) production. Uninfected RBCs (uRBCs) are subdivided into two maturity stages: reticulocytes (young RBCs with density R_r) and normocytes (old RBCs with density R_n). We denote by $\mathcal{J} = \{r, n\}$ the set of RBC maturity stages. The model considers the interaction between malaria parasites and circulating RBCs. We denote by $\mathcal{G}$ the finite set of size N of malaria genotypes $g \in \mathbb{N}$. In the following, however, we focus only on situations where $N = 1$ or $N = 2$. We consider an age-structured dynamics for the parasitized red blood cell (pRBC) stage. Here, the age is a continuous variable representing the time elapsed since an uRBC became parasitized. This continuous age structure makes it possible to track the maturation of pRBCs and thus provides a refined description of pRBC rupture and the associated merozoite release process [8, 12].

The parasite-free dynamics. In the absence of malaria parasites, the dynamics of uRBCs are assumed to follow a discrete maturity-stage structure described by

$$\begin{cases} \dot{R}_r(t) = \Lambda_0 - \theta_r R_r(t), \\ \dot{R}_n(t) = \theta_r R_r(t) - \theta_n R_n(t). \end{cases} \tag{1}$$

The parameters $1/\theta_r$ and $1/\theta_n$ denote the average durations of the reticulocyte and normocyte stages respectively, while Λ_0 represents the production rate of uRBCs. The equilibrium of system (1), hereafter referred to as the parasite-free equilibrium, is given by

$$\bar{R}_j = \frac{\Lambda_0}{\theta_j}, \quad \forall j \in \mathcal{J}. \tag{2}$$

The infection dynamics. In the presence of malaria parasites, we denote by $p_j^g(t, a)$ the size of pRBCs in group $j \in \mathcal{J}$ of genotype $g \in \mathcal{G}$ at time t, where the variable a represents the time elapsed since the RBC was parasitized.

We denote also by $u^g(t)$ the total density of free merozoites of genotype g at time t. Although the production of merozoites is structured according to the type of infected red blood cells $j \in \mathcal{J}$, the free merozoites themselves are not structured, and $u^g(t)$ represents the sum of all contributions arising from each RBC compartment. The model we consider is given by:

$$\begin{cases} \dot{R}_r(t) = \Lambda_0 - \theta_r R_r(t) - \sum_{g\in\mathcal{G}} \beta_r^g u^g(t) R_r(t), \\ \dot{R}_n(t) = \theta_r R_r(t) - \theta_n R_n(t) - \sum_{g\in\mathcal{G}} \beta_n^g u^g(t) R_n(t), \\ p_r^g(t,0) = \beta_r^g u^g(t) R_r(t), \\ p_n^g(t,0) = \beta_n^g u^g(t) R_n(t), \\ (\partial_t + \partial_a)\, p_r^g(t,a) = -(\mu(a) + \theta_r) p_r^g(t,a), \\ (\partial_t + \partial_a)\, p_n^g(t,a) = -(\mu(a) + \theta_n) p_n^g(t,a) + \theta_r p_r^g(t,a), \\ \dot{u}^g(t) = \int_0^\infty \mu(a) \left[m_r^g p_r^g(t,a) + m_n^g p_n^g(t,a) \right] \mathrm{d}a - \delta u^g(t), \end{cases} \tag{3}$$

for each $(t, g, a) \in \mathbb{R}_+ \times \mathcal{G} \times \mathbb{R}_+$, coupled with the initial condition $R_j(0) = R_{j,0} \in \mathbb{R}^+$, $p_j^g(0,\cdot) = p_{j,0}^g \in L^1(\mathbb{R}_+)$ and $u^g(0) = u_0^g \in \mathbb{R}^+$ for each $j \in \mathcal{J}$.

In System (3), β_j^g is the ability of parasites with genotype g to infect RBCs of group j. Malaria parasites, that are the merozoites, become nonviable or die at rate δ. The term $\mu(a)$ represents the rupture rate of pRBCs at time a post-parasitization. The quantity $\int_0^\infty m_j^g \mu(a) p_j^g(t,a)\,\mathrm{d}a$ represents the total production number of merozoites at time t by pRBCs of group j infected with genotype g.

Compared to related studies accounting for differential RBC preferences of *Plasmodium* genotypes (see *e.g.* [12]), the present framework allows each genotype to target all RBC groups with varying infection efficiencies, rather than infection efficiencies to binary values (0 or 1) as assumed in [12].

Moreover, System (3) is studied under the following natural assumption.

Assumption 2.1 *We suppose for each $j \in \mathcal{J}$, $g \in \mathcal{G}$ the following:*

1. $\mu \in L^\infty(\mathbb{R}_+)$, $\Lambda_0 > 0$, $m_j^g > 0$, $\beta_j^g > 0$ *and* $\delta > 0$.
2. *There exist* $a_\mu \geq 0$ *and* $\underline{\mu} > 0$ *such that* $\mu(a) \geq \underline{\mu}$, *f.a.e.* $a \geq a_\mu$.
3. $\theta_r > \theta_n > 0$.

While Assumption 2.1 is fairly general, item 2 implies that pRBCs eventually rupture, whereas item 3 means that normocytes have a longer lifespan than reticulocytes (*i.e.* $1/\theta_n > 1/\theta_r$).

The main variables of Model (3) are listed in Table 1.

Table 1: State variables of the model.

Variable	Description	Unit
$R_r(t)$	Density of young RBCs at time t	cells/mL
$R_n(t)$	Density of mature RBCs at time t	cells/mL
$p_r^g(t,a)$	Density of infected reticulocytes of genotype g and infection age a	cells/mL
$p_n^g(t,a)$	Density of infected normocytes of genotype g and infection age a	cells/mL
$u^g(t)$	Density of free merozoites of genotype g at time t	cells/mL

3 Preliminaries results

Let us define the following quantities:

$$\pi(a,\theta_j) = e^{-\int_0^a (\mu(s)+\theta_j)\mathrm{d}s} \quad \text{and} \quad \rho(\theta_r,\theta_n,a) = \int_0^a \theta_r\, \pi(s,\theta_r)\, e^{-\int_s^a (\mu(\eta)+\theta_n)\mathrm{d}\eta}\mathrm{d}s = \frac{\theta_r}{\theta_r - \theta_n}(\pi(a,\theta_n) - \pi(a,\theta_r)) \tag{4}$$

for each $j \in \mathcal{J}$. In the above expressions, the terms $\pi(a,\theta_r)$ and $\pi(a,\theta_n)$ represent the survival probability of a parasitized reticulocyte (respectively normocyte) up to age a. The term $\theta_r \pi(a,\theta_r)$ represents the probability

that a parasitized reticulocyte survives until infection age s and matures at that age s. Once matured, this RBC survives from age s to age a with probability $e^{-\int_s^a(\mu(\eta)+\theta_n)\mathrm{d}\eta}$. Consequently, since $\theta_r > \theta_n$, we have $\pi(a,\theta_n) > \pi(a,\theta_r), \quad \forall a \geq 0$, which reflects the longer lifespan of mature RBCs compared to reticulocytes. From the expression of $\rho(\theta_r,\theta_n,a)$ in (4), we deduce that $\rho(\theta_r,\theta_n,a) > 0$ for all $a \geq 0$. Biologically, it represents the probability that a parasitized reticulocyte survives long enough to mature into a normocyte before rupture. This highlights the existence of an indirect infection pathway through which parasites initially infecting reticulocytes can complete their development in the normocyte stage.

We define the space $X = \mathbb{R}^2 \times L^1\left(\mathbb{R}_+, \mathbb{R}^{2|\mathcal{G}|}\right) \times \mathbb{R}^{|\mathcal{G}|}$ endowed with the usual norm and X_+ its positive cone, where $|\mathcal{G}| = \mathrm{card}(\mathcal{G})$. The existence and positivity of solutions for system (3) is stated as follows:

Theorem 3.1 *There exists a unique strongly continuous semiflow $\{\Psi(t,\cdot) : X \to X\}_{t\geq 0}$ such that, for each $\varphi_0 = \left(R_{r,0}, R_{n,0}, (p^g_{r,0}, p^g_{n,0})_{g\in\mathcal{G}}, (u^g_0)_{g\in\mathcal{G}}\right) \in X_+$ the map $\Psi(\cdot,\varphi_0) \in \mathcal{C}\left([0,\infty), X_+\right)$ is a mild solution of (3). Furthermore, let $\Psi(\cdot,\varphi_0) = (R_r, R_n, (p^g_r, p^g_n)_{g\in\mathcal{G}}, (u^g)_{g\in\mathcal{G}})$, then:*

1. *For each $g \in \mathcal{G}$, we have*

$$p^g_r(t,a) = \begin{cases} p^g_{r,0}(a-t)\dfrac{\pi(a,\theta_r)}{\pi(a-t,\theta_r)}, & a \geq t, \\ \beta^g_r R_r(t-a)u^g(t-a)\pi(a,\theta_r), & a < t, \end{cases} \tag{5}$$

and

$$p^g_n(t,a) = \begin{cases} p^g_{n,0}(a-t)\dfrac{\pi(a,\theta_n)}{\pi(a-t,\theta_n)} + \theta_r p^g_{r,0}(a-t)e^{-\int_{a-t}^a \mu(\sigma)\mathrm{d}\sigma}\left(\dfrac{e^{-t\theta_n} - e^{-t\theta_r}}{\theta_r - \theta_n}\right), & a \geq t, \\ \beta^g_n R_n(t-a)u^g(t-a)\pi(a,\theta_n) + \beta^g_r u^g(t-a)R_r(t-a)\rho(\theta_r,\theta_n,a), & a < t. \end{cases} \tag{6}$$

2. *Let $m = \max\limits_{g\in\mathcal{G}}\{m^g_r, m^g_n\}$. For all $t \geq 0$, we define the total host populations:*

$$N_r(t) := R_r(t) + \sum_{g\in\mathcal{G}}\int_0^\infty p^g_r(t,a)\,\mathrm{d}a, \quad N_n(t) := R_n(t) + \sum_{g\in\mathcal{G}}\int_0^\infty p^g_n(t,a)\,\mathrm{d}a.$$

Then

$$N_r(t) \leq N_r(0)e^{-\theta_r t} + \frac{\Lambda_0}{\theta_r}(1-e^{-\theta_r t}) \leq \max\left\{R_{r,0} + \sum_{g\in\mathcal{G}}\int_0^\infty p^g_{r,0}(a)\mathrm{d}a, \frac{\Lambda_0}{\theta_r}\right\} =: C_r(\varphi_0) \tag{7}$$

and

$$N_n(t) \leq N_n(0)e^{-\theta_n t} + \frac{\theta_r C_r}{\theta_n}(1-e^{-\theta_n t}) \leq \max\left\{R_{n,0} + \sum_{g\in\mathcal{G}}\int_0^\infty p^g_{n,0}(a)\mathrm{d}a, \frac{\theta_r C_r}{\theta_n}\right\} =: C_n(\varphi_0). \tag{8}$$

Moreover, the parasite load satisfies:

$$\sum_{g\in\mathcal{G}} u^g(t) \leq e^{-\delta t}\sum_{g\in\mathcal{G}} u^g_0 + \frac{m(C_r+C_n)\|\mu\|_{L^\infty}}{\delta}\left(1-e^{-\delta t}\right) \leq \max\left\{\sum_{g\in\mathcal{G}} u^g_0, \frac{m(C_r+C_n)\|\mu\|_{L^\infty}}{\delta}\right\} =: C_u(\varphi_0). \tag{9}$$

Hence $\Psi(t,\varphi_0) \in B_X(0, C_r(\varphi_0) + C_n(\varphi_0) + C_u(\varphi_0))$ for each $t \geq 0$, where $B_X(0,\kappa)$ denotes the ball of X centered at $0 \in X$ with radius κ.

3. *Let the set*

$$\mathcal{B} = \left\{\varphi_0 \in X_+ : R_{r,0} + \sum_{g\in\mathcal{G}}\int_0^\infty p^g_{r,0}(a)\mathrm{d}a \leq \frac{\Lambda_0}{\theta_r}, R_{n,0} + \sum_{g\in\mathcal{G}}\int_0^\infty p^g_{n,0}(a)\mathrm{d}a \leq \frac{\Lambda_0}{\theta_n}, \sum_{g\in\mathcal{G}} u^g_0 \leq \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\right\} \tag{10}$$

then the semiflow $\{\Psi(t,\cdot)\}_{t\geq 0}$ is bounded dissipative, that is for any bounded set $B \subset X_+$, we can find $t_0 = t_0(B,\mathcal{B}) \geq 0$ such that $\bar{\Psi}(t,B) \subset \mathcal{B}$ for all $t \geq t_0$.

4. *The semiflow is asymptotically smooth: for any nonempty, closed, bounded and positively invariant set $B \subset X_+$, there exists a compact set $K \subset X_+$ such that $\lim_{t\to\infty} \Delta_H(\Psi(t,B),K) = 0$, where Δ_H is the semi-distance defined by $\Delta_H(K,B) = \sup_{x\in K} \inf_{y\in B} ||x-y||_X$.*

5. *There exists a non-empty compact set $\mathcal{A}$ of X_+, which is invariant under the semiflow $\{\Psi(t,\cdot)\}_{t\geq 0}$, and attracts the bounded subsets of X_+, i.e. for any bounded set $B \subset X_+$, $\lim_{t\to+\infty} \Delta_H(\Psi(t,B),\mathcal{A}) = 0$. The attractor $\mathcal{A}$ satisfies $\mathcal{A} \subset \mathcal{B}$. Moreover, the following sharp bounds hold:*

$$\inf_{\varphi_0\in\mathcal{A}} R_{r,0} > 0, \qquad \inf_{\varphi_0\in\mathcal{A}} R_{n,0} > 0.$$

6. *For each $g \in \mathcal{G}$ we define the sets*

$$\mathcal{W}^g = \{\varphi_0 \in X_+ : \rho^g(\varphi_0) > 0\}, \quad \partial\mathcal{W}^g = X_+ \setminus \mathcal{W}^g \tag{11}$$

where $\rho^g(\varphi_0) = u_0^g + \sum_{j\in\mathcal{J}} \int_0^\infty p_{j,0}^g(a)\mathrm{d}a$ for every $\varphi_0 = (R_{r,0}, R_{n,0}, (p_{r,0}^{g'}, p_{n,0}^{g'})_{g\in\mathcal{G}}, (u_0^{g'})_{g\in\mathcal{G}})$. Then for every $t \geq 0$ we have

$$\Psi(t,\mathcal{W}^g) \subset \mathcal{W}^g, \quad \Psi(t,\partial\mathcal{W}^g) \subset \partial\mathcal{W}^g. \tag{12}$$

Moreover, let $g \in \mathcal{G}$ and $\varphi_0 \in \mathcal{W}^g$ then there exists $t_0 \geq 0$ such that

$$\Psi_u^g(t,\varphi_0) > 0, \qquad \forall t \geq t_0.$$

7. *The semiflow $\{\Psi(t,.)\}_{t\geq 0}$ is state-continuous uniformly in finite time, that is for every $(T,\varphi_0) \in \mathbb{R}_+ \times X_+$ and every $\varepsilon > 0$ there exists $\eta > 0$ such that for every $\widetilde{\varphi}_0 \in X_+$:*

$$\|\varphi_0 - \widetilde{\varphi}_0\|_X \leq \eta \quad \Longrightarrow \quad \|\Psi(t,\varphi_0) - \Psi(t,\widetilde{\varphi}_0)\|_X < \varepsilon, \quad \forall t \in [0,T].$$

Consequently $\mathcal{A}$ is locally asymptotically stable i.e. for every neighborhood V of $\mathcal{A}$, there exists a neighborhood $W \subset V$ of $\mathcal{A}$ such that $\Psi(t,W) \subset V$ for every $t \geq 0$ and there exists moreover a neighborhood V of $\mathcal{A}$ such that $\lim_{t\to\infty} \Delta_H(\Psi(t,V),W) = 0$.

We refer to the section A for the proof of this result.

4 Equilibria and threshold dynamics

Let us consider System (3) with the presence of a single malaria genotype (i.e. $N = 1$) denoted as $g \in \mathbb{N}$. The basic reproduction number $\mathcal{R}_0(g)$ represents the expected number of merozoites generated by one pRBC introduced into a fully healthy RBC population [2, 11]. By the next generation operator approach, we find that

$$\mathcal{R}_0(g) = \mathcal{R}_0^r(g) + \mathcal{R}_0^n(g) + \mathcal{R}_0^{r\to n}(g). \tag{13}$$

Here, $\mathcal{R}_0^r(g)$, $\mathcal{R}_0^n(g)$, and $\mathcal{R}_0^{r\to n}(g)$ denote respectively the total number of merozoites produced: by a parasitized reticulocyte (young RBCs), by a parasitized normocyte (mature RBCs) and by a parasitized reticulocyte for which rupture occurs at the normocyte stage. We have

$$\mathcal{R}_0^r(g) = \beta_r^g \bar{R}_r \frac{m_r^g \Gamma_r}{\delta}, \quad \mathcal{R}_0^{r\to n}(g) = \beta_r^g \bar{R}_r \frac{m_n^g \Gamma_{r\to n}}{\delta}, \quad \mathcal{R}_0^n(g) = \beta_n^g \bar{R}_n \frac{m_n^g \Gamma_n}{\delta},$$

where $\bar{R}_j$ is the parasite-free equilibrium defined by (2) and $\bar{R}_j\beta_j^g$ describes the number of new infections by a merozoite. The quantities $m_r^g\Gamma_r/\delta$, $m_n^g\Gamma_n/\delta$ and $m_n^g\Gamma_{r\to n}/\delta$ represent the contributions of different types of RBC infections to the overall number of merozoites produced by a single merozoite: (i) when infection occurs in reticulocytes and rupture takes place at this same stage; (ii) when infection occurs in normocytes and rupture occurs at this stage; and (iii) when infection occurs in reticulocytes but rupture takes place at the normocyte stage. We refer to Section B.1 for the detailed derivation and computation of this basic reproduction number $\mathcal{R}_0(g)$. The terms Γ_j^s are given by

$$\Gamma_r = \int_0^\infty \pi(a,\theta_r)\mu(a)\,\mathrm{d}a, \quad \Gamma_n = \int_0^\infty \pi(a,\theta_n)\,\mu(a)\,\mathrm{d}a, \quad \Gamma_{r\to n} = \int_0^\infty \rho(\theta_r,\theta_n,a)\mu(a)\,\mathrm{d}a.$$

In the present model, the quantities $\beta_r^g\, m_r^g\, \Gamma_r/\delta$, $\beta_r^g\, m_n\, \Gamma_{r\to n}/\delta$, and $\beta_n^g\, m_n^g\, \Gamma_n/\delta$ are interpreted as pathway-specific *reproductive value*s, since they quantify the expected contribution of an infected RBC to future production of new RBC infections through the corresponding developmental pathway. In particular, they measure the relative long-term contribution of each developmental pathway to future parasite generations. This interpretation is consistent with the classical concept of reproductive value in class-structured populations (see Chapter 10, Section 10.4 of [30]), with its interpretation in structured epidemiological models [10], and with reproductive-value weighting in class-structured populations [23]. The differences between these quantities arise from survival effect. First, survival probabilities depend on the RBC type through the functions $\pi(a,\theta_j)$ and $\rho(\theta_r,\theta_n,a)$. Second, the three terms correspond to distinct infection pathways: Γ_r accounts for parasites completing their development within reticulocytes, Γ_n for those developing within normocytes, and $\Gamma_{r\to n}$ for parasites initially infecting reticulocytes and completing their development after maturation into normocytes. Altogether, these mechanisms lead to potentially different contributions of each RBC compartment. In particular, since $\theta_r > \theta_n$ (Assumption 2.1), it follows that

$$\begin{aligned}
&\Gamma_n = \Gamma_r + (1-\frac{\theta_n}{\theta_r})\Gamma_{r\to n} > \Gamma_r,\\
&(\Gamma_r + \Gamma_{r\to n}) - \Gamma_n = \frac{\theta_n}{\theta_r-\theta_n}\,(\Gamma_n - \Gamma_r) > 0.
\end{aligned} \tag{14}$$

Inequality (14) highlights that RBCs are not equally favorable for parasite development. More precisely, the reproductive values associated with reticulocytes and normocytes are quantified by $\beta_r^g(m_r^g\Gamma_r + m_n^g\Gamma_{r\to n})/\delta$ and $\beta_n^g\, m_n^g\Gamma_n/\delta$, respectively. Therefore, whenever $\theta_r > \theta_n$ (*i.e.* normocytes have a longer lifespan than reticulocytes) and both RBC classes produce the same number of merozoites per infected cell (*i.e.* $m_r^g = m_n^g$) and the merozoites produced from different RBCs are all equally infectious (*i.e.* $\beta_r^g = \beta_n^g$), by (14), reticulocytes provide a higher overall reproductive benefit to the parasite than normocytes, *i.e.* $\Gamma_r + \Gamma_{r\to n} > \Gamma_n$ (Figure 1).

Proposition 4.1 *Let $\mathcal{G} = \{g\}$ and assume that the basic reproduction number $\mathcal{R}_0(g)$ introduced in (13) satisfies $\mathcal{R}_0(g) > 1$. Then, the single-genotype model admits a unique positive equilibrium, denoted by $E^* = \left(R_r^*, R_n^*, p_r^{g,*}, p_n^{g,*}, u^{g,*}\right)$, whose expressions are given by:*

$$\begin{cases}
R_r^* = \dfrac{\theta_r \bar{R}_r}{\theta_r + \beta_r^g u^{g,*}},\\
R_n^* = \dfrac{\theta_r\theta_n \bar{R}_n}{(\theta_r + \beta_r^g u^{g,*})\,(\theta_n + \beta_n^g u^{g,*})},\\
p_r^{g,*}(a) = \beta_r^g u^{g,*} R_r^* \pi(a,\theta_r),\\
p_n^{g,*}(a) = \left[\beta_n^g R_n^* \pi(a,\theta_n) + \beta_r^g R_r^* \rho(\theta_r,\theta_n,a)\right] u^{g,*},
\end{cases} \tag{15}$$

and where $u^{g,*}$ is the unique positive solution of the following equation:

$$\frac{\theta_r}{\theta_r + \beta_r^g u^{g,*}}\left(\mathcal{R}_0^r(g) + \mathcal{R}_0^{r\to n}(g)\right) + \frac{\theta_r}{\theta_r + \beta_r^g u^{g,*}}\cdot\frac{\theta_n}{\theta_n + \beta_n^g u^{g,*}}\mathcal{R}_0^n(g) = 1. \tag{16}$$

The detailed proof of Proposition 4.1 is given in Section C. The next result concerns the global threshold dynamics of the system (3) in the presence of a single genotype.

Theorem 4.2 *Let $\mathcal{G} = \{g\}$.*

1. *The parasite-free equilibrium $E_0 = (\bar{R}_r, \bar{R}_n, 0_{L^1}, 0_{L^1}, 0)$ is globally asymptotically stable in X_+ if $\mathcal{R}_0(g) \le 1$ and in $\partial\mathcal{W}^g$ otherwise.*

2. *If $\mathcal{R}_0(g) > 1$, then there exists a global attractor $\mathcal{A}^g \subset \mathcal{A}$ in $\mathcal{W}^g$ (of compact sets of X_+) that is locally asymptotically stable. In particular, there exists $\eta > 0$, such that for all $\varphi_0 \in \mathcal{W}^g$, we have*

$$\liminf_{t\to\infty}\ \inf_{w\in\partial\mathcal{W}^g} \|\Psi(t,\varphi_0) - w\|_X \ge \eta,$$

where the spaces $\mathcal{W}^g$ and $\partial\mathcal{W}^g$ are defined by (11). That is to say Ψ is ρ^g-strongly uniformly persistent.

The proof of Theorem 4.2 is detailed in Section D.

In the following, we focus on a scenario where two malaria genotypes are present (i.e. $N = 2$ and $\mathcal{G} = \{1,2\}$). Next, we derive the necessary and sufficient conditions for the existence and uniqueness of a positive co-existence equilibrium comprising these two genotypes.

Theorem 4.3 *Suppose that* $\mathcal{G} = \{1, 2\}$,

Case 1. $(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1)) \neq 0$ *and* $(\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)) \neq 0$. *Define*

$$y(2,1) = \frac{\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) - \mathcal{R}_0^r(2) - \mathcal{R}_0^{r\to n}(2)}{\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1)},$$
$$x(2,1) = \frac{1}{\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) + \mathcal{R}_0^n(1)y(2,1)}.$$

Introduce the following condition

$$\begin{cases} 0 < y(2,1) < 1, \\ \mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) + \mathcal{R}_0^n(1)y(2,1) > 1. \end{cases} \tag{17}$$

(i) If condition (17) is not satisfied, then System (3) does not admit any positive equilibrium.

(ii) Assume that condition (17) holds.

- *If* $\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1 = 0$ *then, System (3) admits either no positive equilibrium or infinitely many positive equilibria.*
- *If* $\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1 \neq 0$ *then, System (3) admits a unique positive equilibrium, denoted as* $E^* = \left(R_r^*, R_n^*, p_r^{1,*}, p_n^{1,*}, p_r^{2,*}, p_n^{2,*}, u^{1,*}, u^{2,*}\right)$, *iff*

$$\frac{\theta_n}{\theta_r}\min\left(\frac{\beta_r^1}{\beta_n^1}, \frac{\beta_r^2}{\beta_n^2}\right) < \mathcal{K}(2,1) < \frac{\theta_n}{\theta_r}\max\left(\frac{\beta_r^1}{\beta_n^1}, \frac{\beta_r^2}{\beta_n^2}\right), \tag{18}$$

with $\mathcal{K}(2,1) = \left(\frac{1}{x(2,1)} - 1\right)\left(\frac{1}{y(2,1)} - 1\right)^{-1}$. *Furthermore,*

$$\begin{cases} R_r^* = \dfrac{\theta_r \bar{R}_r}{\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}}, \\ R_n^* = \dfrac{\theta_r\theta_n \bar{R}_n}{\left(\theta_n + \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*}\right)\left(\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}\right)}, \\ p_r^{g,*} = u^{g,*}\beta_r^g R_r^* \pi(a, \theta_r), \quad g \in \mathcal{G}, \\ p_n^{g,*} = u^{g,*}\beta_n^g R_n^* \pi(a, \theta_n) + \beta_r^g u^{g,*} R_r^* \rho(\theta_r, \theta_n, a), \quad g \in \mathcal{G}, \end{cases}$$

and

$$u^{1,*} = \frac{1}{\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1}\left[\theta_r\beta_n^2\left(\frac{1}{x(2,1)} - 1\right) - \theta_n\beta_r^2\left(\frac{1}{y(2,1)} - 1\right)\right],$$
$$u^{2,*} = \frac{1}{\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1}\left[-\theta_r\beta_n^1\left(\frac{1}{x(2,1)} - 1\right) + \theta_n\beta_r^2\left(\frac{1}{y(2,1)} - 1\right)\right].$$

Case 2. Assume that exactly one of the following two equalities holds:

$$\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) = 0, \quad \text{and} \quad (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2))_n \neq 0$$

or

$$\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) \neq 0 \quad \text{and} \quad (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)) = 0.$$

Then, Equation (E6) cannot be satisfied. Hence, System (E5) has no solution, and therefore System (3) admits no positive equilibrium.

Case 3. $(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1)) = 0$ *and* $(\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)) = 0$. *Then, System (3) admits infinitely many positive equilibria.*

In Theorem 4.3, the full coexistence region for the two genotypes is defined by a combination of trade-offs, feasibility, and invasion constraints. Condition (17) define a wedge-shaped region in trait space where the two genotypes exhibit a trade-off in their reproductive pathways: one genotype is more efficient on reticulocytes, while the other is more efficient on normocytes. This ensures that neither genotype dominates all available resources and that both can maintain positive equilibrium densities. Condition (18) further restricts this region by imposing mutual invasibility constraints, ensuring that each genotype can invade the other when rare. Taken together, these four conditions delineate the subset of trait space in which stable coexistence is ecologically feasible.

The detailed proof of Theorem 4.3 is given in Section E.

5 Invasibility analysis

Next, we consider a polymorphic parasite population in which a mutant strain is introduced into a resident population. We will focus on a simplifying scenario where we assume that both types of RBCs produce the same number of merozoites (*i.e.* $m_r^g = m_n^g = m$). Each malaria genotype $g \in \mathcal{G}$ is characterized by a quantitative trait and, we will note, $q_g \in (0,1)$, the value of this trait which measures the probability to invade a reticulocytes ($1 - q_g$ measures the probability to invade a normocyte). Section F provides a mechanistic justification for the definition of this preference trait. In particular, the preference trait is assumed to affect the infection efficiencies β_j^g :

$$\beta_r^g = q_g\, \chi(q_g, c)\, \beta \qquad \text{and} \qquad \beta_n^g = (1 - q_g)\, \chi(q_g, c)\, \beta \tag{19}$$

where β denotes the maximal effectiveness and $\chi(q_g, c)$ is a function that measures the fitness cost of preference. This cost is expected to increase as soon as there is some preference for reticulocytes or nomocytes (*i.e.* when $q_g \neq 1/2$) and the magnitude of the drop in fitness is governed by the parameter $c \in \mathbb{R}_+$:

$$\chi(q_g, c) = e^{-c\left(q_g - \frac{1}{2}\right)^2}. \tag{20}$$

In other words, when $c = 0$, there is no cost associated with a preference, whereas $c > 0$ induces selection toward the no-preference strategy $q = 1/2$.

5.1 Invasion fitness and singular preference trait

This parasite will hereafter be referred to as the *resident* parasite. Next, a second genotype (i.e. $g = 2$) with a preference trait q_2, referred to as the *invader*, is introduced into the system at the resident equilibrium $E^*(q_1, c)$. The ability of the mutant parasite to invade the resident is determined by its invasion fitness $\mathcal{R}(q_1, q_2, c)$, which measures the expected number of new RBC infections produced by the invader during the lifetime of an infected RBC (see Section B.2 for the derivation)

$$\mathcal{R}(q_1, q_2, c) = \underbrace{\frac{\beta\, m}{\delta}}_{\substack{\text{reproductive} \\ \text{potential}}} \cdot \Big(q_2 \underbrace{R_r^*(q_1, c)\, (\Gamma_r + \Gamma_{r\to n})}_{\substack{\text{secondary infections from} \\ \text{reticulocytes}}} + (1 - q_2) \underbrace{R_n^*(q_1, c)\Gamma_n}_{\substack{\text{secondary infections} \\ \text{from normocytes}}} \Big) \cdot \underbrace{\chi(q_2, c)}_{\substack{\text{cost of} \\ \text{preference}}}. \tag{21}$$

The above expression can be interpreted as the product of three biological components: (i) the quantitative parameter

$$\mathcal{R}_{\text{ef}} = \frac{\beta\, m}{\delta}, \tag{22}$$

which represents a composite measure of the parasite effective reproductive potential at the RBC level; (ii) the expected number of secondary infections produced through each RBC class; and (iii) the cost of preference $\chi(q_2, c)$.

The expected number of secondary infections itself depends on two complementary properties of the RBC environment. First, the equilibrium densities $R_r^*(q_1, c)$ and $R_n^*(q_1, c)$ quantify the relative quantity (or availability) of reticulocytes and normocytes. Second, the reproductive values $\Gamma_r + \Gamma_{r\to n}$ and Γ_n characterize the relative quality of the two RBC classes, that is, their expected contribution to future parasite reproduction. Consequently, the evolution of parasite preference is expected to result from a trade-off between the quality and the quantity of the two host-cell types.

To characterize these two ecological components, we introduce two quantities. The ratio

$$\Gamma_{r/n} = \frac{\Gamma_r + \Gamma_{r\to n}}{\Gamma_n}, \tag{23}$$

measures the relative quality of reticulocytes compared with normocytes. Moreover, at the equilibrium (15), the proportion of reticulocytes is given by

$$\mathcal{P}_r(q_1) = \frac{R_r^*}{R_r^* + R_n^*} = \left(1 + \frac{\theta_n}{\theta_n + \beta_n^1 u^{1,*}} \cdot \frac{\bar{R}_n}{\bar{R}_r}\right)^{-1}, \tag{24}$$

which measures their relative quantity (or availability).

Table 2: Model parameters and values used in simulations.

Parameter	Biological meaning	Value	Reference
Λ_0	RBCs production rate (RBC/h/mL)	1.73×10^6	[3, 27]
$1/\theta_r$	Reticulocyte lifespan (h)	36	[27]
$1/\theta_n$	Lifespan of mature RBCs (days)	116.5	[27]
m	Number of merozoites produced by pRBCs	$6 - 32$	[18, 32]
τ	Erythrocyte cycle duration (h)	$48 - 72$	[32]
$\mu(a)$	Rupture function of pRBCs	$\mathbf{1}_{[\tau,\infty)}(a)$	–
β	RBCs infection rate (1/h)	variable	–
δ	Rate of degradation of parasites (h^{-1})	48	[18]

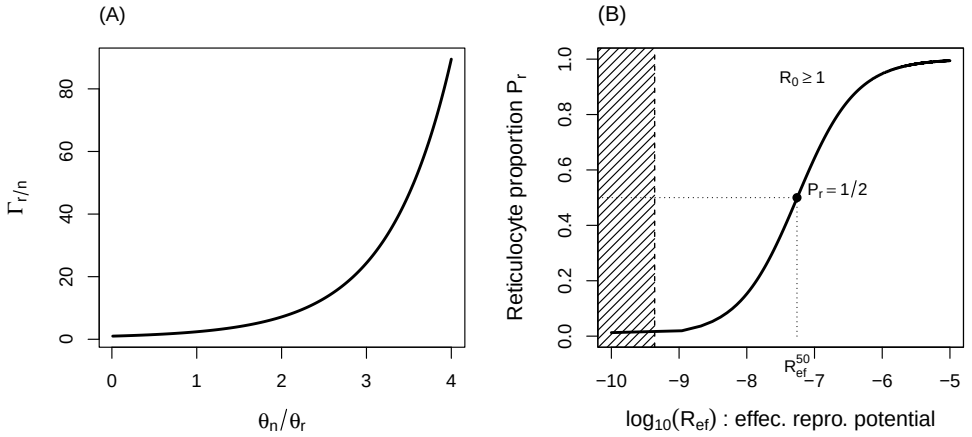


Figure 1: Effects of different within-host parameters on the relative quality (for the parasite) and on the relative quantity of reticulocytes. Panel (A) illustrates that the reproductive value associated with parasites infecting reticulocytes (a measure of the relative *quality* of the reticulocytes for the parasite) is always higher than that associated with parasites infecting normocytes, since the ratio $\Gamma_{r/n}$ in (23), remains greater than one over the whole range of turnover-rate ratios θ_n/θ_r. One may therefore expect the parasite to preferentially infect reticulocytes because these cells provide a higher reproductive return. However, Panel (B) shows that the equilibrium proportion of reticulocytes $\mathcal{P}_r$, defined in (24) (a measure of the relative *quantity* of reticulocytes), increases with the effective reproductive potential $\mathcal{R}_{\text{ef}}$ (illustrated here for $q = 0.5$ and $c = 0$). The hatched region corresponds to parameter values for which $\mathcal{R}_0 < 1$, where the parasite cannot persist. For $\mathcal{R}_0 > 1$, the reticulocyte proportion increases monotonically with $\mathcal{R}_{\text{ef}}$ and reaches $\mathcal{P}_r = 1/2$ at the threshold $\mathcal{R}_{\text{ef}}^{50}$. Hence, parasite evolution is expected to depend not only on the higher quality of reticulocytes but also on their availability.

The preference trait evolution is driven by the selection gradient

$$S(q_1, c) = \left.\frac{\partial \mathcal{R}(q_1, q_2, c)}{\partial q_2}\right|_{q_2=q_1}. \tag{25}$$

Singular strategies are noted q^* and satisfy $S(q^*, c) = 0$. They are characterized by second-order derivatives of the invasion fitness (21),

$$S_{22} = \left.\frac{\partial^2 \mathcal{R}(q_1, q_2, c)}{\partial q_2^2}\right|_{q_1=q_2=q^*}, \quad S_{12} = \left.\frac{\partial^2 \mathcal{R}(q_1, q_2, c)}{\partial q_1 \partial q_2}\right|_{q_1=q_2=q^*}, \quad S_{11} = \left.\frac{\partial^2 \mathcal{R}(q_1, q_2, c)}{\partial q_1^2}\right|_{q_1=q_2=q^*}.$$

A singular strategy is an evolutionary stable strategy (ESS) if $S_{22} < 0$, a convergent stable strategy (CSS) if $S_{12} + S_{22} < 0$, an evolutionary attractor (EA) if both conditions hold, and a branching point if it is a CSS with $S_{22} > 0$ [9, 14, 28]. The existence of a singular preference trait q^* strongly depends on the parameter

$$R = \frac{\theta_r}{\theta_n} \times \frac{\Gamma_n}{\Gamma_r + \Gamma_{r\to n}}.$$

The quantity R is a relative weighting factor that compares the contribution of the reticulocyte and normocyte pathways. It combines the relative residence times of the two stages, through $\theta_r/\theta_n = \theta_n^{-1}/\theta_r^{-1}$, with their relative quality, represented by $\Gamma_n/(\Gamma_r + \Gamma_{r\to n})$. Thus, R measures the relative effective contribution of the reticulocyte pathway compared with the normocyte pathway to the life history of infected RBCs.

Theorem 5.1 *Let $c > 0$ be the cost of preference parameter, and let R be the relative demographic threshold ratio. A necessary and sufficient condition for the existence of a singular strategy q^* (thus satisfying $S(q^*, c) = 0$) is*

$$u^*(q^*, c) = -\frac{\theta_n}{\beta_n(q^*, c)}\left(1 - R\frac{\big(1 - c + 3cq^* - 2c(q^*)^2\big)}{(1 + cq^* - 2c(q^*)^2)}\right) \tag{26}$$

where $u^*(q^*, c)$ is defined by (16). Necessary conditions for the existence of q^* are given below.

1. *If $c < 1$ and $R \geq \dfrac{1}{1-c}$ (or equivalently, $c < \dfrac{R-1}{R}$), there exists at most one solution $q^* \in (0, 1)$ if*

$$\frac{\Lambda_0\, \mathcal{R}_{\rm ef}(\Gamma_r + \Gamma_{r\to n})}{1 - c}\, e^{-c/4} > \theta_r$$

   and no solution otherwise.

2. *If $R \leq 1 - c$ there exists no solution.*

3. *If $c = 1$ or if ($c < 1$ and $1 - c < R < \dfrac{1}{1-c}$), there exists at most one solution $q^* \in (\bar{q}, 1)$ if*

$$\frac{\Lambda_0\, \mathcal{R}_{\rm ef}(\Gamma_r + \Gamma_{r\to n})}{1 - c + 3c\bar{q} - 2c(\bar{q})^2}\, e^{-c(\bar{q}-\frac{1}{2})^2} > \theta_r$$

   where $\bar{q} \in (0, 1)$ is the unique solution of

$$R(1 - c + 3c\bar{q} - 2c(\bar{q})^2) = 1 + c\bar{q} - 2c(\bar{q})^2.$$

   and no solution otherwise.

4. *Case $c > 1$. There exists at most one solution $q^* \in I_c = (q_{\min}(c), q_{\max}(c)) \subset (0, 1)$, where*

$$q_{\min}(c) = \frac{1}{4}\left(3 - \sqrt{1 + \frac{8}{c}}\right), \qquad q_{\max}(c) = \frac{1}{4}\left(1 + \sqrt{1 + \frac{8}{c}}\right).$$

The singular strategy q^* whose existence is established above is always an evolutionarily stable strategy (ESS).

Moreover, since $\lim\limits_{c\to\infty} q_{\min}(c) = \lim\limits_{c\to\infty} q_{\max}(c) = \frac{1}{2}$, the ESS satisfies $q^* \approx \frac{1}{2}$ for large costs c, corresponding to the absence of preferential affinity between RBC classes. Details are provided in Section G.

5.2 Characterization of the evolutionary preference for young or mature RBCs

The ESS q^* introduced above provides a precise characterization of the evolutionary preference of a given malaria genotype for either young or mature RBCs: $q^* < 0.5$ corresponds to a preference for mature RBCs, whereas $q^* > 0.5$ corresponds to a preference for young RBCs. Moreover, when $q^* \approx 0$, $q^* \approx 0.5$, or $q^* \approx 1$, this indicates a strong preference for mature RBCs, no marked preference between the two stages, or a strong preference for young RBCs, respectively.

We then have the following result:

Proposition 5.2 *Let q^* the ESS introduced above. Let us introduce the effective reproductive potential thresholds $\mathcal{R}_{\rm ef}^0$ and $\mathcal{R}_{\rm ef}^{50}$ given by*

$$\begin{aligned}
\mathcal{R}_{\rm ef}^0 &= (1 - c)e^{c/4}\left(\bar{R}_r\left(\Gamma_r + \Gamma_{r\to n}\right)\right)^{-1}, \\
\mathcal{R}_{\rm ef}^{50} &= \left(\bar{R}_r\left(\Gamma_r + \Gamma_{r\to n}\right)\right)^{-1}\left(1 - \frac{\theta_n}{\theta_r} + \Gamma_{r/n}^{-1}\right).
\end{aligned}$$

1. *If* $\mathcal{R}_{\rm ef} < \mathcal{R}_{\rm ef}^{50}$*, then* $q^* < 0.5$*, leading to an evolutionary preference for mature RBCs. In particular,* $q^* = 0$ *when* $\mathcal{R}_{\rm ef} \leq \mathcal{R}_{\rm ef}^{0}$*, leading to a strong evolutionary preference for mature RBCs.*

2. *If* $\mathcal{R}_{\rm ef} > \mathcal{R}_{\rm ef}^{50}$*, then* $q^* > 0.5$*, leading to an evolutionary preference for young RBCs.*

Note that the effective reproductive threshold $\mathcal{R}_{\rm ef}^{0}$ corresponds to values of $\mathcal{R}_{\rm ef}$ below which the ESS q^* favors a strong preference for mature RBCs (Figure 2A,B). This indicates that mature RBCs constitute a more suitable host when the effective reproductive potential of the parasite at the RBC level is not sufficiently strong. By contrast, the threshold $\mathcal{R}_{\rm ef}^{50}$ corresponds to values of $\mathcal{R}_{\rm ef}$ above which the ESS q^* favors a preference for young RBCs (Figure 2). Crucially, we find that parasite preference for reticulocytes at the ESS q^* increases with the effective reproductive potential $\mathcal{R}_{\rm ef}$ (Figure 2). To understand this effect, it is important to notice that the selection gradient depends both on the relative *quality* and the relative *quantity* of the two types of RBCs. On the one hand we showed above that as soon as $\theta_r > \theta_n$ (i.e., normocytes have a longer lifespan than reticulocytes) and assuming identical merozoite production in both RBC classes (i.e., $m_r^g = m_n^g$), it follows from (14) that $\Gamma_{r/n} > 1$. Hence, infecting reticulocytes provide a higher overall reproductive benefit than normocytes. In other words, the relative quality of the reticulocytes is higher (Figure 1A). On the other hand, we have shown that the relative quantity of reticulocytes increases with $\mathcal{R}_{\rm ef}$ (Figure 1B). Indeed, when the effective reproductive potential increases, the density of merozoites increases, more RBCs are infected and are lysed by the parasite which changes the age structure of the RBCs and increases the proportion of reticulocytes. Thus, when $\mathcal{R}_{\rm ef}$ is low, the lower proportion of reticulocytes drives the evolution towards a preference for normocytes (simply because they are more abundant). In contrast, when $\mathcal{R}_{\rm ef}$ is high, the higher quality and the increasing quantity of reticulocytes favors the opposite preference for reticulocytes.

Note that when $\mathcal{P}_r(q^*) = 0.5$ (i.e., there are as many normocytes as reticulocytes), we always have $q^* > 0.5$. Therefore, for $q^* = 0.5$ to hold, there must be a higher abundance of normocytes to compensate for their lower quality, particularly when the fitness cost of preference is low (Figure 1B). In other words, the effective reproductive potential $\mathcal{R}_{\rm ef}$ influences the equilibrium age structure of red blood cells through changes in the proportion of reticulocytes. Since parasite fitness depends on the availability of the different RBC classes, variations in resource composition modify the ecological environment experienced by the parasite.

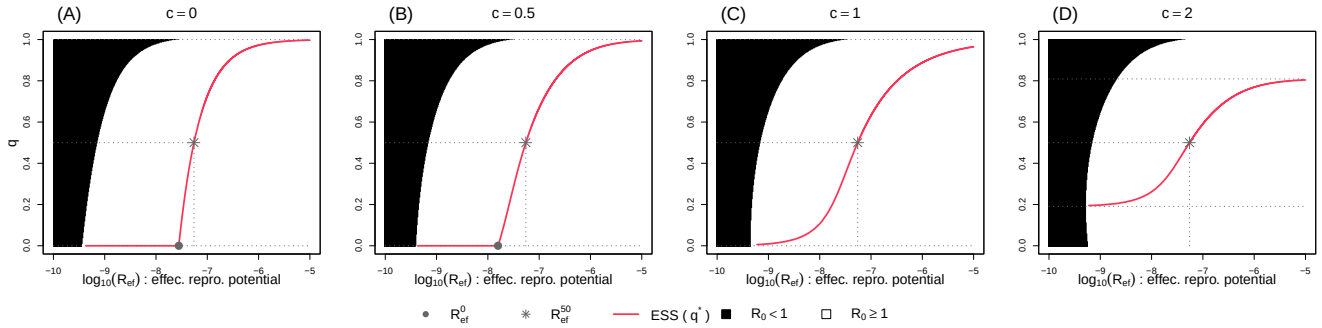


Figure 2: The effective reproductive potential of the parasite $\mathcal{R}_{\rm ef}$ drives the evolution of the preference q^* for reticulocytes. When $\mathcal{R}_{\rm ef} \leq \mathcal{R}_{\rm ef}^{0}$, there is a strong evolutionary preference for mature RBCs, while $\mathcal{R}_{\rm ef}^{0} < \mathcal{R}_{\rm ef} \leq \mathcal{R}_{\rm ef}^{50}$ corresponds to an intermediate evolutionary preference for mature RBCs. By contrast, $\mathcal{R}_{\rm ef} > \mathcal{R}_{\rm ef}^{50}$ corresponds to an evolutionary preference for young RBCs. For low specialization costs ($c \leq 1$), the admissible interval for an interior ESS spans the full range of preference values. When $c > 1$, the ESS is constrained to the interval $(q_{\min}, q_{\max})$ defined in Section 5.1 As the specialization cost increases, $q_{\min}$ and $q_{\max}$ move toward $1/2$, thereby reducing the range of feasible evolutionary outcomes. Here the erythrocyte cycle duration is $\tau = 48$ h, and the other baseline parameter values are summarized in Table 2.

6 Discussion

Human malaria is caused by several *Plasmodium* species, including *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. Among these, *P. falciparum* and *P. vivax* are the most prevalent, with *P. falciparum* responsible for most severe cases and deaths. The parasite undergoes a complex life cycle, including sexual reproduction in mosquitoes and liver and blood stages in humans. Mixed infections involving multiple species are common and are partly explained by species-specific preferences for red blood cells (RBCs) of different ages, which influence

coexistence and infection dynamics within the host. Previous mathematical models have investigated within-host dynamics and predicted competitive exclusion among parasite genotypes, but few studies have addressed the evolutionary mechanisms shaping species-specific RBC preferences. We developed an age-structured within-host model that explicitly accounts for parasite preferences for RBCs of different ages, linking RBC age structure to parasite replication and invasion strategies. This model allows us to identify the conditions promoting the within-host coexistence between different parasite genotypes, and yields important insights on the within-host parameters driving the evolution of preference for young RBCs.

Within-host coexistence of different parasitegenotypes. Parasite genotypes coexistence is characterized by the intersection of a set of algebraic constraints in the preference trait space. Condition (17) defines a feasible domain, while Condition (18) further restricts this domain by requiring that the composite quantity $\mathcal{K}(2,1)$ for the set $\mathcal{G} = \{1,2\}$ of competing genotypes lies within a bounded interval determined by their genotype-specific abilities to infect RBCs. In particular, when the ratios of infection abilities satisfy $\frac{\beta_r^2}{\beta_n^2} \approx \frac{\beta_r^1}{\beta_n^1}$, the coexistence of both genotypes becomes unlikely. This is consistent with previous studies highlighting that differences in RBC invasion abilities are a key driver of genotype coexistence (e.g., [12]). Moreover, under the scenario (19) for parasite infection abilities, increasing the cost associated with preferential affinity for RBCs leads to a strong reduction in the coexistence potential of multiple parasite genotypes (Figure 3).

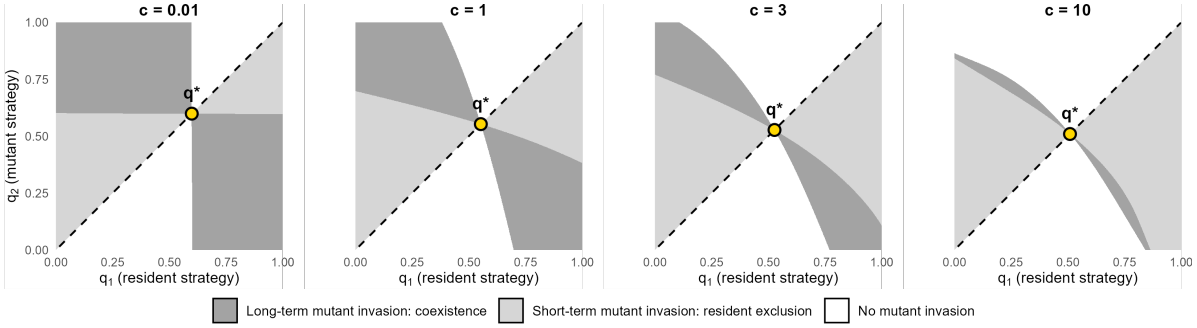


Figure 3: Effect of the cost of preference, c, on the ESS q^* and on the coexistence between multiple parasite genotypes. The yellow dot indicates the ESS value q^* and the gray levels indicate if the mutant can invade and coexist (dark gray), invade and outcompete (light gray), fail to invade a population dominated by the resident strategy.

Evolution of preference for young or old RBCs. Our model reveals the importance of the effective reproductive potential $\mathcal{R}_{\text{ef}}$ (22), which integrates three quantitative parasite traits: infection efficiency (β), the number of merozoites released per burst of infected RBCs (m), and the parasite's average lifespan ($1/\delta$). Variations in $\mathcal{R}_{\text{ef}}$ drive the evolution of different preferences for reticulocytes. Interestingly, this preference varies widely among different *Plasmodium* species: *P. falciparum* exhibits limited RBC selectivity, whereas *P. vivax* preferentially invades reticulocytes and, in contrast, *P. malariae* preferentially targets mature RBCs [32]. Does the variation in $\mathcal{R}_{\text{ef}}$ covaries with the preference for reticulocytes as predicted by our model? It is difficult to answer this question because we failed to obtain good estimates of $\mathcal{R}_{\text{ef}}$ for the different Plasmodium species (Figure 4). Although the burst size (m) is relatively well estimated empirically (e.g., [32]), the other components (i.e. β and δ) contributing to the effective reproductive potential $\mathcal{R}_{\text{ef}}$ are difficult measure. Yet, it is worth mentionning that, as expected from our model, the burst size of *P. malariae* as a significantly lower burst size than the other two *Plasmodium* species. Thus, our model provides a quantitative evolutionary framework to interpret species-specific RBC targeting strategies. This highlights that RBC age structure is not merely a descriptive feature of host cell populations, but also a factor driving adaptive differences among malaria species. Moreover, our results link the evolution of parasite preference to the age distribution of RBCs: a higher abundance of reticulocytes favors the evolution of parasite preference toward reticulocytes, whereas a lower abundance promotes preference toward normocytes.

Limits of the model and perspectives. Although the model proposed here captures key aspects of RBC targeting and parasite dynamics, several assumptions warrant further discussion. In particular, we consider discrete RBC age classes, whereas RBC age is inherently continuous. In addition, we neglect potential feedbacks between RBC

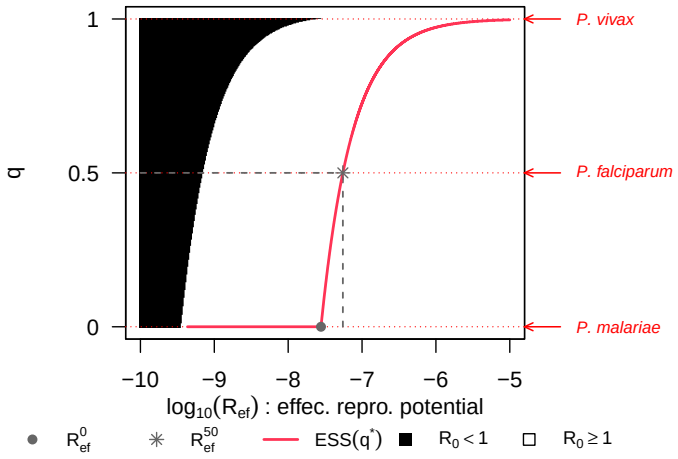


Figure 4: A comparison between our evolutionary predictions and the preference of different *Plasmodium* species for reticulocytes. As discussed in the main text, accurate estimations of $\mathcal{R}_{\text{ef}}$ remain to be obtained for the different *Plasmodium* species.

production in the bone marrow and the density of circulating RBCs. Such feedbacks may be critical, as parasite-induced resource limitation can affect the results obtained under the assumption of a constant RBC production rate. In particular, we have shown that the proportion of each resource class drives the evolution of preference of the parasite for a specific development stage. From (24), the proportions of reticulocytes and normocytes in the presence of parasites are expressed as functions of the ratio $\bar{R}_n/\bar{R}_r$ measured in an infection-free environment. While this ratio is assumed constant in the present framework, it would generally vary when feedbacks between erythropoiesis and circulating RBC densities are taken into account. Extending the present analysis to a framework incorporating such resource limitation mechanisms (e.g. [4]) therefore constitutes a natural and promising direction for future work.

It would be interesting to study the robustness of our results after using alternative formulations for the cost opf preference such as higher order exponential forms inducing sharper penalties, asymmetric costs between red blood cell types, or sigmoidal threshold-like responses, may capture different biological mechanisms and could quantitatively affect evolutionary outcomes. We also assume that the preference trait q^* modulates the infection efficiency β_j, while the number of parasites released upon rupture of infected red blood cells, m_j, remains constant. This choice reflects the hypothesis that host-cell preference primarily influences the invasion process rather than within-cell replication. However, this assumption is not the only plausible one. An alternative modeling framework could let the burst size vary between different types of RBC, thereby capturing potential differences in intracellular development across RBC types while keeping infection efficiency fixed.

Finally, taking into account malaria parasite sexual development (i.e., the process by which asexual parasites stop replicating and differentiate into transmissible male or female gametocytes) may alter host cell quality through the introduction of parasite sexual commitment as a quantitative trait within RBCs. This is particularly relevant since the commitment capability of malaria parasites may differ significantly depending on whether they occupy reticulocytes or normocytes [17]. However, properly accounting for such a process in the analysis developed here would require nesting the within-host dynamics within the epidemiological dynamics, e.g., [25].

Data sharing Statement

All data relevant to this article will are made publicly available. The code (with the R Programming Language) used to simulate the model can be accessed through the Zenodo platform for reproducibility at DOI:10.5281/zenodo.21775048 [15].

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A Proof of Theorem 3.1

Defining the linear operator $A : \mathcal{D}(A) \subset \mathcal{X} \to \mathcal{X}$ by

$$A\begin{pmatrix} R_r \\ R_n \\ 0_{\mathbb{R}^{2|\mathcal{G}|}} \\ \begin{pmatrix} p_r^g(a) \\ p_n^g(a) \end{pmatrix}_{g\in\mathcal{G}} \\ \left(u^g\right)_{g\in\mathcal{G}} \end{pmatrix} = \begin{pmatrix} -\theta_r R_r \\ \theta_r R_r - \theta_n R_n \\ \begin{pmatrix} -p_r^g(0) \\ -p_n^g(0) \end{pmatrix}_{g\in\mathcal{G}} \\ \begin{pmatrix} -\dfrac{\partial p_r^g}{\partial a} - (\mu(a)+\theta_r)p_r^g(a) \\ -\dfrac{\partial p_n^g}{\partial a} - (\mu(a)+\theta_n)p_n^g(a) + \theta_r p_r^g(a) \end{pmatrix}_{g\in\mathcal{G}} \\ \left(-\delta u^g\right)_{g\in\mathcal{G}} \end{pmatrix}$$

with $\mathcal{D}(A) = \mathbb{R}^2 \times \{0\}_{\mathbb{R}^{2|\mathcal{G}|}} \times W^{1,1}(\mathbb{R}_+, \mathbb{R}^{2|\mathcal{G}|}) \times \mathbb{R}^{|\mathcal{G}|}$, $\mathcal{X} = \mathbb{R}^2 \times \mathbb{R}^{2|\mathcal{G}|} \times L^1\left(\mathbb{R}_+, \mathbb{R}^{2|\mathcal{G}|}\right) \times \mathbb{R}^{|\mathcal{G}|}$, then letting $\mathcal{X}_0 = \overline{\mathcal{D}(A)} = \mathbb{R}^2 \times \{0\}_{\mathbb{R}^{2|\mathcal{G}|}} \times L^1(\mathbb{R}_+, \mathbb{R}^{2|\mathcal{G}|}) \times \mathbb{R}^{|\mathcal{G}|}$, its positive cone $\mathcal{X}_{0+} = \mathbb{R}^2_+ \times \{0\}_{\mathbb{R}^{2|\mathcal{G}|}} \times L^1(\mathbb{R}_+, \mathbb{R}^{2|\mathcal{G}|}_+) \times \mathbb{R}^{|\mathcal{G}|}_+$ and the non-linear function $F : \mathcal{X}_0 \to \mathcal{X}$ by

$$F\begin{pmatrix} R_r \\ R_n \\ 0_{\mathbb{R}^{2|\mathcal{G}|}} \\ \begin{pmatrix} p_r^g(a) \\ p_n^g(a) \end{pmatrix}_{g\in\mathcal{G}} \\ \left(u^g\right)_{g\in\mathcal{G}} \end{pmatrix} = \begin{pmatrix} \Lambda_0 - \sum_{g\in\mathcal{G}} \beta_r^g u^g R_r \\ -\sum_{g\in\mathcal{G}} \beta_n^g u^g R_n \\ \begin{pmatrix} \beta_r^g u^g R_r \\ \beta_n^g u^g R_n \end{pmatrix}_{g\in\mathcal{G}} \\ 0_{(L^1(\mathbb{R}_+, \mathbb{R}^{2|\mathcal{G}|}))} \\ \left(\sum_{j\in\{r,n\}} \int_0^\infty m_j^g \mu(a) p_j^g(a) \mathrm{d}a\right)_{g\in\mathcal{G}} \end{pmatrix}$$

then the system (3) can be interpreted as the following semilinear problem

$$\left\{ \begin{array}{rcl} \dfrac{\mathrm{d}u}{\mathrm{d}t}(t) & = & Au(t) + F(u(t)), \quad \forall t > 0, \\ u(0) & = & \varphi_0 \in \mathcal{X}_0. \end{array} \right. \tag{A1}$$

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

$$A_2\begin{pmatrix} R_r \\ R_n \\ 0_{\mathbb{R}^{2|\mathcal{G}|}} \\ \begin{pmatrix} p_r^g(a) \\ p_n^g(a) \end{pmatrix}_{g\in\mathcal{G}} \\ \left(u^g\right)_{g\in\mathcal{G}} \end{pmatrix} = \begin{pmatrix} 0 \\ \theta_r R_r \\ 0_{\mathbb{R}^{2|\mathcal{G}|}} \\ \begin{pmatrix} 0_{L^1(\mathbb{R}_+,\mathbb{R})} \\ \theta_r p_r^g(a) \end{pmatrix}_{g\in\mathcal{G}} \\ 0_{\mathbb{R}^{|\mathcal{G}|}} \end{pmatrix}, \qquad A_1 =: A - A_2$$

so that $A = A_1 + A_2$. Defining $\omega_0 = \min\{\theta_r, \theta_n, \delta\}$ we readily check that

$$\|(\lambda I_d - A_1)^{-1}\varphi_0\|_{\mathcal{X}} \leq \frac{\|\varphi_0\|_{\mathcal{X}}}{\lambda + \omega_0}$$

for every $\varphi_0 \in \mathcal{X}$ and $\lambda \in \mathbb{R}$ with $\lambda > -\omega_0$. It follows that A_1 is a Hille-Yosida operator and since A_2 is a bounded linear operator then A is also a Hille-Yosida operator. Moreover A is resolvent positive, F is locally Lipschitz continuous, *i.e.*

$$\forall \kappa > 0, \exists\, C_\kappa > 0 : \|F(\varphi_0) - F(\widetilde{\varphi}_0)\|_{\mathcal{X}} \leq C_\kappa \|\varphi_0 - \widetilde{\varphi}_0\|_{\mathcal{X}}, \qquad \forall (\varphi_0, \widetilde{\varphi}_0) \in (\mathcal{X}_0 \cap B_{\mathcal{X}}(0,\kappa))^2 \tag{A2}$$

and moreover,

$$\forall \kappa > 0, \exists\, C_\kappa > 0 : \forall \varphi_0 \in \mathcal{X}_{0+} \cap B_{\mathcal{X}}(0,\kappa),\ F(\varphi_0) + C_\kappa \varphi_0 \in \mathcal{X}_+ \text{ and } A - C_\kappa I \text{ is resolvent positive}$$

where $\mathcal{X}_+$ is the positive cone of $\mathcal{X}$. Consequently, standard integrated semigroup approach can be used to ensure the existence and uniqueness of a mild solution (see [24, 35]). We note that the proof of Theorem 3.1 closely follows that of Theorem 3.1 in [8].

Now we handle the proof of Theorem 3.1:

1. The equations (5)-(6) are obtained by using the Volterra integral formulation (see *e.g.* [19, 37]).

2. We derive the uniform bounds for the solutions. For each $g \in \mathcal{G}$, we define the total age-structured populations:

$$N_r^g(t) := \int_0^\infty p_r^g(t,a)\,\mathrm{d}a, \qquad N_n^g(t) := \int_0^\infty p_n^g(t,a)\,\mathrm{d}a. \tag{A3}$$

Integrating (5), we may see that N_r^g is differentiable with respect to t, and the differentiation yields

$$\frac{\mathrm{d}}{\mathrm{d}t}N_r^g(t) = \beta_r^g R_r(t)u^g(t) - \theta_r N_r^g(t) - \int_0^\infty \mu(a)p_r^g(t,a)\,\mathrm{d}a.$$

Summing over $g \in \mathcal{G}$ and using the equation for R_r in (3), we obtain

$$N_r'(t) = \Lambda_0 - \theta_r N_r(t) - \sum_{g\in\mathcal{G}}\int_0^\infty \mu(a)p_r^g(t,a)\,\mathrm{d}a \le \Lambda_0 - \theta_r N_r(t).$$

A simple use of gronwall's lemma lead to (7). Similarly, integrating (6), we see that N_n is differentiable with respect to t and we get

$$N_n'(t) = \theta_r N_r(t) - \theta_n N_n(t) - \sum_{g\in\mathcal{G}}\int_0^\infty \mu(a)p_n^g(t,a)\,\mathrm{d}a \le \theta_r C_r - \theta_n N_n(t) \tag{A4}$$

by using (7). It follows by gronwall's lemma that (8) holds. Next, we bound the parasite load by summing the u^g-equations in (3):

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{g\in\mathcal{G}}u^g(t) = \sum_{g\in\mathcal{G}}\int_0^\infty \mu(a)(m_r^g p_r^g + m_n^g p_n^g)\,\mathrm{d}a - \delta\sum_{g\in\mathcal{G}}u^g(t). \tag{A5}$$

From (7)-(8), we deduce that

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{g\in\mathcal{G}}u^g(t) \le m\|\mu\|_\infty(C_r + C_n) - \delta\sum_{g\in\mathcal{G}}u^g(t).$$

Again, by gronwall's lemma, we get (9).

3. Let $B \subset X_+$ be a bounded set and let $\varphi_0 \in B$. From (7), we see that $\limsup_{t\to+\infty} N_r(t) \le \dfrac{\Lambda_0}{\theta_r}$ uniformly in $\varphi_0 \in B$. Let $\varepsilon > 0$ then there exists $T > 0$ (independent of φ_0) such that $N_r(t) \le \dfrac{\Lambda_0}{\theta_r} + \varepsilon$ for every $t \ge T$. From (A4) it follows that

$$N_n'(t) \le \theta_r\left(\frac{\Lambda_0}{\theta_r} + \varepsilon\right) - \theta_n N_n(t), \quad \forall t \ge T$$

leading to

$$N_n(t) \le N_n(T)e^{-\theta_n(t-T)} + \left(\frac{\Lambda_0 + \varepsilon\theta_r}{\theta_n}\right)\left(1 - e^{-\theta_n(t-T)}\right), \quad \forall t \ge T$$

and then $\limsup_{t\to+\infty} N_n(t) \le \dfrac{\Lambda_0 + \varepsilon\theta_r}{\theta_n}$ with $\varepsilon > 0$ as small as necessary, whence $\limsup_{t\to+\infty} N_n(t) \le \dfrac{\Lambda_0}{\theta_n}$ uniformly in $\varphi_0 \in B$. Similarly, let $\varepsilon > 0$, then there exists $T > 0$ such that $N_r(t) \le \dfrac{\Lambda_0}{\theta_r} + \varepsilon$ and $N_n(t) \le \dfrac{\Lambda_0}{\theta_n} + \varepsilon$ for every $t \ge T$. From (A5) it follows that

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{g\in\mathcal{G}}u^g(t) \le m\|\mu\|_{L^\infty}\left[\left(\frac{\Lambda_0}{\theta_r} + \varepsilon\right) + \left(\frac{\Lambda_0}{\theta_n} + \varepsilon\right)\right] - \delta\sum_{g\in\mathcal{G}}u^g(t), \quad \forall t \ge T.$$

It comes

$$\sum_{g\in\mathcal{G}} u^g(t) \le e^{-\delta(t-T)}\left(\sum_{g\in\mathcal{G}} u_0^g\right) + \frac{m\|\mu\|_{L^\infty}}{\delta}\left(\frac{\Lambda_0}{\theta_r}+\frac{\Lambda_0}{\theta_n}+2\varepsilon\right)\left(1-e^{-\delta(t-T)}\right)$$

and finally

$$\limsup_{t\to+\infty}\sum_{g\in\mathcal{G}} u^g(t) \le \frac{m\|\mu\|_{L^\infty}}{\delta}\left(\frac{\Lambda_0}{\theta_r}+\frac{\Lambda_0}{\theta_n}\right) \le \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}$$

uniformly in $\varphi_0 \in B$. In conclusion the semiflow is bounded dissipative.

4. To prove that the semiflow is asymptotically smooth, we decompose the semiflow as

$$\Psi = (\Psi_{R_r}, \Psi_{R_n}, (\Psi^g_{p_r}, \Psi^g_{p_n})_{g\in\mathcal{G}}, (\Psi^g_u)_{g\in\mathcal{G}}).$$

Let $t > 0$. The operators $\Psi_{R_r}(t,.)$, $\Psi_{R_n}(t,.)$ and $\Psi^g_u(t,.)$ are compact for each $g \in \mathcal{G}$ since they are finite dimensional. Now, for each $(g,j) \in \mathcal{G}\times\mathcal{J}$ we decompose the operator $\Psi^g_{p_j}$ as

$$\Psi^g_{p_j} = \Psi^g_{p_j,\mathrm{ini}} + \Psi^g_{p_j,\mathrm{comp}}$$

where

$$\Psi^g_{p_j,\mathrm{ini}}(t,\varphi_0)(a) = \Psi^g_{p_j}(t,\varphi_0)(a)\mathbf{1}_{[t,\infty)}(a), \qquad \Psi^g_{p_j,\mathrm{comp}}(t,\varphi_0)(a) = \Psi^g_{p_j}(t,\varphi_0)(a)\mathbf{1}_{[0,t)}(a)$$

for every $(a,\varphi_0) \in \mathbb{R}_+\times X_+$. From (5), we have

$$\|\Psi^g_{p_r,\mathrm{ini}}(t,\varphi_0)\|_{L^1} \le e^{-\theta_r t}\|p^g_{r,0}\|_{L^1} \le e^{-\theta_n t}\|p^g_{r,0}\|_{L^1}$$

and from (6) we have

$$\|\Psi^g_{p_n,\mathrm{ini}}(t,\varphi_0)\|_{L^1} \le e^{-\theta_n t}\|p^g_{n,0}\|_{L^1} + e^{-\theta_n t}\frac{\theta_r}{\theta_r-\theta_n}\|p^g_{r,0}\|_{L^1}.$$

It follows that the function $\eta : \mathbb{R}_+\times\mathbb{R}_+ \ni (t,\kappa) \longmapsto \kappa\left(1+\frac{\theta_r}{\theta_r-\theta_n}\right)e^{-\theta_n t}$ satisfies

$$\forall\kappa>0 : \lim_{t\to+\infty}\eta(t,\kappa) = 0$$

and

$$\|(0,0,(\Psi^g_{p_r,\mathrm{ini}}(t,\varphi_0),\Psi^g_{p_n,\mathrm{ini}}(t,\varphi_0))_{g\in\mathcal{G}},0)\|_X \le \eta(t,\kappa), \quad \forall(t,\varphi_0,\kappa)\in\mathbb{R}_+\times X_+\times\mathbb{R}_+^* \text{ such that } \|\varphi_0\|_X\le\kappa.$$

Let $g \in \mathcal{G}$. We want to prove that the operators $\Psi^g_{p_j,\mathrm{comp}}(t,.)$ are compact for each $j \in \mathcal{J}$. Let $B \subset X_+$ be a bounded subset, $\kappa = \sup_{\varphi_0\in B}\|\varphi_0\|_X$ and define

$$\overline{C} = \sup_{\varphi_0\in B}(C_r(\varphi_0)+C_n(\varphi_0)+C_u(\varphi_0)).$$

We use the Riesz-Fréchet-Kolmogorov theorem [39, Thm X.1, p.275] to prove that $\{\Psi^g_{p_j,\mathrm{comp}}(t,\varphi_0), \varphi_0\in B\}$ is relatively compact in L^1 for each $j \in \mathcal{J}$. First, using (7)-(8) we have

$$\sup_{\varphi_0\in B}\|\Psi^g_{p_j,\mathrm{comp}}(t,\varphi_0)\|_{L^1} \le \overline{C} < +\infty, \quad \forall j\in\mathcal{J}.$$

Secondly, from (5)-(6) we have

$$\sup_{\varphi_0\in B}\int_h^{+\infty}\Psi^g_{p_j,\mathrm{comp}}(t,\varphi_0)(a)\mathrm{d}a \underset{h\to+\infty}{\longrightarrow} 0, \quad \forall j\in\mathcal{J}$$

since $\Psi^g_{p_j,\mathrm{comp}}(t,\varphi_0)(a) = 0$ for $a > t$. Thirdly, let $h > 0$ such that $h < t$. From (3) we have

$$|R_r'(t)| \le \Lambda_0+\theta_r\overline{C}+\overline{C}^2\sum_{g\in\mathcal{G}}\beta^g_r =: c_1,\ |R_n'(t)| \le \theta_r\overline{C}+\theta_n\overline{C}+\overline{C}^2\sum_{g\in\mathcal{G}}\beta^g_n =: c_2,\ \frac{\mathrm{d}}{\mathrm{d}t}u^g(t) \le 2m\overline{C}\|\mu\|_{L^\infty}+\delta\overline{C} = c_3$$

for every $t \geq 0$. We deduce that

$$\begin{aligned}
&\int_{\mathbb{R}} |\Psi^g_{p_r,\mathrm{comp}}(t,\varphi_0)(a+h) - \Psi^g_{p_r,\mathrm{comp}}(t,\varphi_0)(a)|\mathrm{d}a \\
&\leq \int_0^{t-h} |\Psi^g_{p_r,\mathrm{comp}}(t,\varphi_0)(a+h) - \Psi^g_{p_r,\mathrm{comp}}(t,\varphi_0)(a)|\mathrm{d}a + \int_{t-h}^{t} \Psi^g_{p_r,\mathrm{comp}}(t,\varphi_0)(a)\mathrm{d}a + \int_{-h}^{0} \Psi^g_{p_r,\mathrm{comp}}(t,\varphi_0)(a+h)\mathrm{d}a \\
&\leq \frac{\beta^g_r \overline{C}}{\theta_r}\left(hc_1 + hc_3 + \overline{C}(1 - e^{-(\|\mu\|_{L^\infty}+\theta_r)h})\right) + 2h\overline{C} \underset{h\to 0}{\longrightarrow} 0
\end{aligned}$$

uniformly in $\varphi_0 \in B$. Similar computations show that

$$\int_{\mathbb{R}} |\Psi^g_{p_n,\mathrm{comp}}(t,\varphi_0)(a+h) - \Psi^g_{p_n,\mathrm{comp}}(t,\varphi_0)(a)|\mathrm{d}a \underset{h\to 0}{\longrightarrow} 0$$

uniformly in $\varphi_0 \in B$. It follows that the operators $\Psi^g_{p_j,\mathrm{comp}}(t,.)$ are compact for each $(g,j) \in \mathcal{G} \times \mathcal{J}$. Consequently [16, Lemma 3.2.6, p.38] applies and the semiflow $\{\Psi(t,.)\}_{t\geq 0}$ is asymptotically smooth.

5. From the second point, we can check that orbits of bounded sets are bounded. Then [16, Thm 3.4.6, p.39] applies and lead to the existence of a global compact attractor $\mathcal{A} \subset X_+$ (of bounded sets) for the semiflow $\{\Psi(t,.)\}_{t\geq 0}$. Since $\mathcal{A}$ is a compact invariant and since $\{\Psi(t,.)\}_{t\geq 0}$ is bounded dissipative then

$$\Delta_H(\mathcal{A},\mathcal{B}) = \Delta_H(\Psi(t,\mathcal{A}),\mathcal{B}) \underset{t\to+\infty}{\longrightarrow} 0$$

so $\mathcal{A} \subset \mathcal{B}$. For the last point, let $\varphi_0 \in \mathcal{A}$. By invariance of $\mathcal{A}$ there exists a complete orbit $\{\phi(t), t \in \mathbb{R}\} \subset \mathcal{A} \subset \mathcal{B}$ through φ_0, hence $\phi(0) = \varphi_0$. From (3) we have

$$\frac{\mathrm{d}}{\mathrm{d}t}\Psi_{R_r}(t,\phi(\xi)) \geq \Lambda_0 - \left(\theta_r + \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\sum_{g\in\mathcal{G}}\beta^g_r\right)\Psi_{R_r}(t,\phi(\xi)), \quad \forall (t,\xi) \in \mathbb{R}_+ \times \mathbb{R}$$

leading to

$$\Psi_{R_r}(t,\phi(\xi)) \geq \frac{\Lambda_0}{\theta_r + \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\sum_{g\in\mathcal{G}}\beta^g_r}\left(1 - e^{-(\theta_r + \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\sum_{g\in\mathcal{G}}\beta^g_r)t}\right)$$

where the right term goes to

$$c_1 := \frac{\Lambda_0}{\theta_r + \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\sum_{g\in\mathcal{G}}\beta^g_r} > 0$$

as $t \longrightarrow +\infty$ uniformly in $\xi \in \mathbb{R}$. Let $\varepsilon > 0$, then there exists $T > 0$ such that $\Psi_{R_r}(t,\phi(\xi)) \geq c_1 - \varepsilon$ for every $t \geq T$ and every $\xi \in \mathbb{R}$. Considering $\xi = -T$ implies that

$$R_{r,0} = \Psi_{R_r}(0,\phi(0)) = \Psi_{R_r}(T,\phi(-T)) \geq c_1 - \varepsilon$$

with $\varepsilon > 0$ as small as necessary whence $R_{r,0} \geq c_1 > 0$ for every $\varphi_0 \in \mathcal{A}$.

Similarly, we have

$$\frac{\mathrm{d}}{\mathrm{d}t}\Psi_{R_n}(t,\phi(\xi)) \geq c_1\theta_r - \left(\theta_n + \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\sum_{g\in\mathcal{G}}\beta^g_n\right)\Psi_{R_n}(t,\phi(\xi)), \quad \forall (t,\xi) \in \mathbb{R}_+ \times \mathbb{R}$$

leading to

$$\liminf_{t\to+\infty}\Psi_{R_n}(t,\phi(\xi)) \geq \frac{c_1\theta_r}{\theta_n + \frac{2m\Lambda_0\|\mu\|_{L^\infty}}{\delta\theta_n}\sum_{g\in\mathcal{G}}\beta^g_n} =: c_2 > 0$$

and consequently $R_{n,0} \geq c_2 > 0$ for every $\varphi_0 \in \mathcal{A}$.

6. Let $g \in \mathcal{G}$ and $\varphi_0 \in \mathcal{W}^g$. If $u^g_0 > 0$, then it follows from (3) that

$$\Psi^g_u(t,\varphi_0) \geq e^{-\delta t}u^g_0 > 0, \qquad \forall t \geq 0.$$

Hence $\Psi(t,\varphi_0)\in\mathcal{W}^g$ for every $t\geq 0$. Assume now that $u_0^g=0$. Since $\varphi_0\in\mathcal{W}^g$, we necessarily have

$$\sum_{j\in\mathcal{J}}\int_0^\infty p_{j,0}^g(a)\,\mathrm{d}a>0.$$

By Assumption 2.1 (item 2) and using (5)-(6) we see that

$$\int_0^\infty \mu(a)\sum_{j\in\mathcal{J}} m_j^g\Psi_{p_j}^g(a_\mu,\varphi_0)(a)\,\mathrm{d}a\geq \underline{\mu}\int_{a_\mu}^\infty\sum_{j\in\mathcal{J}} m_j^g\Psi_{p_j}^g(a_\mu,\varphi_0)(a)\mathrm{d}a\geq \underline{\mu}\sum_{j\in\mathcal{J}} m_j^g\left(\int_0^\infty p_{j,0}^g(a)\mathrm{d}a\right)e^{-a_\mu\theta_j}>0.$$

Using (3), we get

$$\frac{\mathrm{d}}{\mathrm{d}t}\Psi_u^g(a_\mu,\varphi_0)>0.$$

This point combined with the argument used in the previous case lead to

$$\Psi_u^g(t,\varphi_0)>0,\quad \forall t>a_\mu.$$

Consequently, $\Psi(t,\varphi_0)\in\mathcal{W}^g$ for every $t\geq 0$ and $\mathcal{W}^g$ is positively invariant. It remains to prove the positive invariance of $\partial\mathcal{W}^g$. Let $\varphi_0\in\partial\mathcal{W}^g$, then

$$u_0^g=0,\qquad N_r^g(0)=0,\qquad N_n^g(0)=0$$

where N_r^g and N_n^g are defined in (A3). Set

$$Y^g(t):=m\left(N_r^g(t)+N_n^g(t)\right)+u^g(t).$$

Integrating (5)-(6), using the definition of m and the bounds (7)-(8), we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}Y^g(t)\leq m\left(\beta_r^gC_r(\varphi_0)+\beta_n^gC_n(\varphi_0)\right)Y^g(t).$$

Since $Y^g(0)=0$, gronwall's lemma gives

$$Y^g(t)=0,\qquad \forall t\geq 0$$

and then $\Psi(t,\varphi_0)\in\partial\mathcal{W}^g$ for every $t\geq 0$. This concludes the proof.

7. Since A is a Hille-Yosida operator then on one hand it generates a locally Lipschitz continuous integrated semigroup $\{S_A(t)\}_{t\geq 0}$ (see [21, Theorem 2.4]) and on the other hand its part A_0 in $\mathcal{X}_0$ generates a $\mathcal{C}_0$-semigroup $\{T_{A_0}(t)\}_{t\geq 0}$ on $\mathcal{X}_0$ with growth bound $\omega(A_0)\in\mathbb{R}$. We note that $\mathcal{X}_0$ is a AL-space leading to $\omega(A_0)=s(A_0)$ by [36, Theorem 3.14] (where $s(A_0)$ denotes the the spectral bound of A_0). Also, A and A_0 have the same spectral set by [24, Lemma 2.2.10, p. 65] hence $s(A_0)=s(A)=-\omega_0$ and there exists a constant $M_A\geq 1$ such that

$$\|T_{A_0}(t)\|_{\mathcal{L}(\mathcal{X}_0)}\leq M_Ae^{-\omega_0 t},\quad \forall t\geq 0.$$

Let $\varphi_0\in\mathcal{X}_{0+}$, $T>0$ and $\varepsilon>0$. Recalling (7)-(8)-(9), we define

$$\kappa=\sup_{\widetilde{\varphi}_0\in B_{\mathcal{X}}(\varphi_0,\varepsilon)\cap\mathcal{X}_{0+}}\{C_r(\widetilde{\varphi}_0)+C_n(\widetilde{\varphi}_0+C_u(\widetilde{\varphi}_0)\}>0,\quad \eta=\frac{\varepsilon}{M_A}e^{-C_\kappa M_AT}$$

where C_κ is defined by (A2). Let $\widetilde{\varphi}_0\in\mathcal{X}_{0+}$ such that $\|\varphi_0-\widetilde{\varphi}_0\|_{\mathcal{X}}\leq\eta$, then $\widetilde{\varphi}_0\in B_{\mathcal{X}}(\varphi_0,\varepsilon)$. Using the expression of the mild solution, it follows that

$$\Psi(t,\varphi_0)-\Psi(t,\widetilde{\varphi}_0)=T_{A_0}(t)(\varphi_0-\widetilde{\varphi}_0)+\frac{d}{dt}\left(S_A*\left(F(\Psi(\cdot,\varphi_0))-F(\Psi(\cdot,\widetilde{\varphi}_0))\right)\right)(t)$$

for every $t\in[0,T]$ where $*$ denotes the convolution product. Since $\Psi(.,\varphi_0)$ and $\Psi(.\widetilde{\varphi}_0)$ belong to $\mathcal{C}_0(\mathbb{R}_+,\mathcal{X}_{0+})$ and since F is Lipschitz continuous then both functions belong to $L^1((0,T),\mathcal{X})$. By the Kellermann-Hieber Theorem (see [21] or [24, Theorem 3.6.2, p.133]) it comes

$$\|\Psi(t,\varphi_0)-\Psi(t,\widetilde{\varphi}_0)\|_{\mathcal{X}}\leq M_A\|\varphi_0-\widetilde{\varphi}_0\|_{\mathcal{X}}+M_A\int_0^t\|F(\Psi(s,\varphi_0))-F(\Psi(s,\widetilde{\varphi}_0))\|_{\mathcal{X}}\mathrm{d}s$$

for every $t \in [0,T]$. From the second item, we know that $\Psi(t,\varphi_0)$ and $\Psi(t,\widetilde{\varphi}_0)$ belong to $B_{\mathcal{X}}(0,\kappa)$ for every $t \in [0,T]$. Using the Lipschitz property of F (see (A2)), we obtain

$$\|\Psi(t,\varphi_0) - \Psi(t,\widetilde{\varphi}_0)\|_{\mathcal{X}} \leq \eta M_A + C_\kappa M_A \int_0^t \|\Psi(s,\varphi_0) - \Psi(s,\widetilde{\varphi}_0)\|_{\mathcal{X}}\, \mathrm{d}s$$

for every $t \in [0,T]$. Applying gronwall's inequality, we deduce the following estimate:

$$\|\Psi(t,\varphi_0) - \Psi(t,\widetilde{\varphi}_0)\|_{\mathcal{X}} \leq \eta M_A\, e^{M_A C_\kappa t} \leq \varepsilon, \quad \forall t \in [0,T].$$

Finally, by using [34, Theorem 2.39 p. 47], the attractor $\mathcal{A}$ is locally asymptotically stable. This ends the proof of Theorem 3.1.

B Computation of the basic reproduction number and of the invasion fitness

B.1 The computation of $\mathcal{R}_0(g)$

In the case of a single genotype g, we consider System (3) with $\mathcal{G} = \{g\}$. Around the Disease-Free Equilibrium (DFE), the densities of uninfected RBCs are fixed at $R_r = \bar{R}_r$ and $R_n = \bar{R}_n$. Let $b^g(t)$ be the total number of merozoites produced at time t:

$$b^g(t) = \int_0^\infty \mu(a)\left[m_r^g p_r^g(t,a) + m_n^g p_n^g(t,a)\right] \mathrm{d}a.$$

By linearizing System (3) around the DFE for a single genotype, we obtain the following reduced system for the infected populations:

$$\begin{cases} p_r^g(t,0) = \beta_r^g u^g(t)\bar{R}_r, \\ p_n^g(t,0) = \beta_n^g u^g(t)\bar{R}_n, \\ (\partial_t + \partial_a)\, p_r^g(t,a) = -(\mu(a)+\theta_r)p_r^g(t,a), \\ (\partial_t + \partial_a)\, p_n^g(t,a) = -(\mu(a)+\theta_n)p_n^g(t,a) + \theta_r p_r^g(t,a), \end{cases}$$

By the method of characteristics, we have:

$$p_r^g(t,a) = \begin{cases} \beta_r^g u^g(t-a)\bar{R}_r e^{-\int_0^a (\mu(s)+\theta_r)\mathrm{d}s}, & \text{if} \quad a < t, \\ p_r^g(0,a-t)e^{-\int_{a-t}^a (\mu(s)+\theta_r)\mathrm{d}s}, & \text{if} \quad a \geq t. \end{cases}$$

and

$$p_n^g(t,a) = \begin{cases} p_n^g(0,a-t)e^{-\int_{a-t}^a (\mu(\eta)+\theta_n)\mathrm{d}\eta} + \theta_r p_r^g(0,a-t)\displaystyle\int_{a-t}^a e^{-\int_{a-t}^\sigma (\mu(\eta)+\theta_r)\mathrm{d}\eta} e^{-\int_\sigma^a (\mu(\eta)+\theta_n)\mathrm{d}\eta}\mathrm{d}\sigma, & \text{if} \quad t < a, \\ \beta_n^g\, \bar{R}_n u^g(t-a)e^{-\int_0^a (\mu(\eta)+\theta_n)\mathrm{d}\eta} + \beta_r^g u^g(t-a)\bar{R}_r \rho(\theta_r,\theta_n,a), & \text{if} \quad t > a. \end{cases}$$

We then have

$$\begin{aligned} b^g(t) = &\int_0^t \left[m_r^g\beta_r^g\bar{R}_r e^{-\int_0^a (\mu(\eta)+\theta_r)\mathrm{d}\eta} + m_n^g\beta_n^g\bar{R}_n e^{-\int_0^a (\mu(\eta)+\theta_n)\mathrm{d}\eta}\right] u^g(t-a)\mu(a)\,\mathrm{d}a \\ &+ \int_0^t m_n^g \rho(\theta_r,\theta_n,a)\beta_r^g\bar{R}_r u^g(t-a)\mu(a)\,\mathrm{d}a + f_0(t), \end{aligned} \tag{B1}$$

where f_0 is accounting for the initial data. The u^g-equation of (3) with $\mathcal{G} = \{g\}$ gives

$$u^g(t-a) = u^g(0)e^{-\delta(t-a)} + \int_0^{t-a} b^g(\eta)e^{-\delta(t-a-\eta)}\,\mathrm{d}\eta.$$

Substituting this equality into (B1), we get:

$$b^g(t) = \int_0^t \int_0^{t-a} \left[\beta_r^g\bar{R}_r\left(m_r^g\pi(a,\theta_r) + m_n^g\rho(\theta_r,\theta_n,a)\right) + m_n^g\beta_n^g\bar{R}_n\pi(a,\theta_n)\right]\mu(a)b(\eta)e^{-\delta(t-a-\eta)}\,\mathrm{d}\eta\,\mathrm{d}a + f_0(t).$$

It comes

$$b^g(t) = \int_0^t \int_0^\ell \Pi^g(\ell)\, b(\ell - a)\mathrm{d}\ell\, \mathrm{d}a + f_0(t),$$

with

$$\Pi^g(\ell) = \left[m_r^g \beta_r^g \bar{R}_r \pi(a,\theta_r) + m_n^g \beta_n^g \bar{R}_n \pi(a,\theta_n) + m_n^g \beta_r^g \bar{R}_r f\rho(\theta_r,\theta_n,a)\right] \mu(a) e^{-\delta(\ell-a)}\, \mathrm{d}\ell\, \mathrm{d}a.$$

Thus, the basic reproduction number $\mathcal{R}_0(g)$ is the spectral radius $r(\mathcal{O}^g)$ of the next-generation operator $\mathcal{O}^g$ (which is a scalar operator in this case), defined by:

$$\mathcal{O}^g : \mathbb{R} \ni v \longmapsto \left(\int_0^\infty \Pi^g(\ell)\, \mathrm{d}\ell\right) v \in \mathbb{R}.$$

This gives:

$$\begin{aligned}
\mathcal{R}_0(g) &= \int_0^\infty \Pi^g(\ell)\, \mathrm{d}\ell, \\
&= \int_0^\infty \int_0^\ell \left[\beta_r^g \bar{R}_r \left(m_r^g \pi(a,\theta_r) + m_n^g \rho(\theta_r,\theta_n,a)\right) + m_n^g \beta_n^g \bar{R}_n \pi(a,\theta_n)\right] \mu(a) e^{-\delta(\ell-a)} \mathrm{d}a\, \mathrm{d}\ell, \\
&= \int_0^\infty \left[\beta_r^g \bar{R}_r \left(m_r^g \pi(a,\theta_r) + m_n^g \rho(\theta_r,\theta_n,a)\right) + m_n^g \beta_n^g \bar{R}_n \pi(a,\theta_n)\right] \mu(a) \int_a^\infty e^{-\delta(\ell-a)} \mathrm{d}\ell\, \mathrm{d}a.
\end{aligned}$$

By Fubini's theorem, we have:

$$\mathcal{R}_0(g) = \frac{1}{\delta} \int_0^\infty \left[m_r^g \beta_r^g \bar{R}_r \pi(a,\theta_r) + m_n^g \beta_n^g \bar{R}_n \pi(a,\theta_n) + m_n^g \beta_r^g \bar{R}_r \rho(\theta_r,\theta_n,a)\right] \mu(a)\, \mathrm{d}a.$$

This proves (13).

B.2 The computation of the invasion fitness $f_{q_1}(q_2, c)$

Linearizing the system (3) at the equilibrium composed solely by the resident with trait q_1, we find that

$$\begin{cases}
\dot{R}_r(t) = -\theta_r R_r(t) - \beta_r^1 u^{1,*} R_r(t) - \beta_r^1 R_r^*(q_1,c) u^1(t) - \beta_r^2 R_r^*(q_1,c) u^2(t), \\
\dot{R}_n(t) = \theta_r R_r(t) - \theta_n R_n(t) - \beta_n^1 u^{1,*} R_n(t) - \beta_n^1 R_n^*(q_1,c) u^1(t) - \beta_n^2 R_n^*(q_1,c) u^2(t), \\
p_r^1(t,0) = \beta_r^1 u^{1,*} R_r(t) + \beta_r^1 R_r^*(q_1,c) u^1(t), \\
p_n^1(t,0) = \beta_n^1 u^{1,*} R_n(t) + \beta_n^1 R_n^*(q_1,c) u^1(t), \\
p_r^2(t,0) = \beta_r^2 R_r^*(q_1,c) u^2(t), \\
p_n^2(t,0) = \beta_n^2 R_n^*(q_1,c) u^2(t), \\
(\partial_t + \partial_a)\, p_r^1(t,a) = -(\mu(a) + \theta_r) p_r^1(t,a), \\
(\partial_t + \partial_a)\, p_n^1(t,a) = \theta_r p_r^1(t,a) - (\mu(a) + \theta_n) p_n^1(t,a), \\
\dot{u}^{q_1}(t) = \displaystyle\int_0^\infty \mu(a) \left[m_r^1 p_r^1(t,a) + m_n^1 p_n^1(t,a)\right] \mathrm{d}a - \delta u^1(t),
\end{cases}$$

which, for the mutant counterpart (the q_2-component) gives for $j \in \{r, n\}$:

$$\begin{cases}
p_r^2(t,0) = \beta_r^2 R_r^*(q_1,c) u^2(t), \\
p_n^2(t,0) = \beta_n^2 R_n^*(q_1,c) u^2(t), \\
(\partial_t + \partial_a)\, p_r^2(t,a) = -(\mu(a) + \theta_r) p_r^2(t,a), \\
(\partial_t + \partial_a)\, p_n^2(t,a) = \theta_r p_r^2(t,a) - (\mu(a) + \theta_n) p_n^2(t,a), \\
\dot{u}^2(t) = \displaystyle\int_0^\infty \mu(a) \left[m_r^2 p_r^2(t,a) + m_n^2 p_n^2(t,a)\right] \mathrm{d}a - \delta u^2(t).
\end{cases} \tag{B2}$$

To analyze the evolution of the above perturbation, we derive a renewal equation for $M^{q_1}(q_2,t)$, the number of newly produced parasites at time t with trait q_2 arising in a resident parasite population characterized by trait q_1. More precisely, this quantity is defined by:

$$M^{q_1}(q_2,t)=\int_0^\infty \mu(a)\Big[m_r^2 p_r^2(t,a)+m_n^2 p_n^2(t,a)\Big]\,da.$$

By (B2), we have

$$u^2(t)=\int_0^t M^{q_1}(q_2,s)e^{-\delta(t-s)}\,ds+u^2(0)e^{-\delta t},$$

$$p_r^2(t,a)=\begin{cases}\exp\Big(-\int_{a-t}^a(\mu(\sigma)+\theta_r)\,d\sigma\Big)\,p_{r,0}^2(a-t), & a\geq t,\\ \pi(a,\theta_r)\beta_r^2R_r^*(q_1,c)u^2(t-a), & a<t.\end{cases}$$

Similarly,

$$p_n^2(t,a)=\begin{cases}e^{-\int_{a-t}^a(\mu(\sigma)+\theta_n)\,d\sigma}p_{n,0}^2(a-t)+\int_{a-t}^a\theta_r e^{-\int_\ell^a(\mu(\sigma)+\theta_n)\,d\sigma}p_r^2(t-a+\ell,\ell)\,d\ell, & a\geq t,\\ \pi(a,\theta_n)\beta_n^2R_n^*(q_1,c)u^2(t-a)+\rho(\theta_r,\theta_n,a)\beta_r^2R_r^*(q_1,c)u^2(t-a), & a<t.\end{cases}$$

Consequently, $M^{q_1}(q_2,t)$ satisfies the following renewal equation:

$$\begin{aligned}M^{q_1}(q_2,t)&=\int_0^t\mu(a)\Big[m_r^2\,\pi(a,\theta_r)\,\beta_r^2R_r^*(q_1,c)+m_n^2\,\pi(a,\theta_n)\,\beta_n^2R_n^*(q_1,c)+m_n^2\,\rho(\theta_r,\theta_n,a)\,\beta_r^2R_r^*(q_1,c)\Big]\\&\quad\times\Big(\int_0^{t-a}M^{q_1}(q_2,s)e^{-\delta(t-a-s)}\,ds\Big)\,da+b(t,q_1,q_2)\\&=\int_0^t B^{q_1}(q_2,a)M^{q_1}(q_2,t-a)\,da+b(t,q_1,q_2),\end{aligned}$$

where $b(t,q_1,q_2)$ represents the initial data. The function $B^{q_1}(q_2,a)$ denotes the expected number of new parasites produced per unit of time in the environment established by the resident parasite with trait q_1, by pRBCs that have been infected for a units of time by parasites of trait q_2:

$$\begin{aligned}B^{q_1}(q_2,a)=\int_0^a\mu(s)\Big[&m_r^2\,\pi(s,\theta_r)\,\beta_r^2R_r^*(q_1,c)+m_n^2\,\pi(s,\theta_n)\,\beta_n^2R_n^*(q_1,c)\\&+m_n^2\,\rho(\theta_r,\theta_n,s)\,\beta_r^2R_r^*(q_1,c)\Big]e^{\delta(s-a)}\,ds.\end{aligned}$$

Following the above formulation and classical adaptive dynamics [14, 28], the number of parasites of a mutant of trait q_2 in a resident population q_1, denoted $\mathcal{R}(q_1,q_2,c)$, is given by:

$$\begin{aligned}\mathcal{R}(q_1,q_2,c)&=\int_0^\infty B^{q_1}(q_2,a)\mathrm{d}a\\&=\delta^{-1}\int_0^\infty\mu(s)\Big[m_r^2\,\pi(s,\theta_r)\,\beta_r^2R_r^*(q_1,c)+m_n^2\,\pi(s,\theta_n)\,\beta_n^2R_n^*(q_1,c)\Big]\mathrm{d}s\\&+\delta^{-1}\int_0^\infty\mu(s)m_n^2\,\rho(\theta_r,\theta_n,s)\,\beta_r^2R_r^*(q_1,c)\mathrm{d}s\\&=\delta^{-1}\Big[m_r^2\,\beta_r^2R_r^*(q_1,c)\int_0^\infty\pi(s,\theta_r)\mu(s)\mathrm{d}s+m_n^2\,\beta_n^2R_n^*(q_1,c)\int_0^\infty\pi(s,\theta_n)\mu(s)\mathrm{d}s\Big]\\&+\delta^{-1}m_n^2\,\beta_r^2R_r^*(q_1,c)\int_0^\infty\rho(\theta_r,\theta_n,s)\mu(s)\mathrm{d}s,\end{aligned}$$

with

$$\rho(\theta_r,\theta_n,a)=\int_0^a\theta_r\,\pi(s,\theta_r)\,e^{-\int_s^a(\mu(\eta)+\theta_n)\mathrm{d}\eta}\,\mathrm{d}s=\frac{\theta_r}{\theta_n-\theta_r}\left(e^{-\theta_r a}-e^{-\theta_n a}\right).$$

Then, the invasion fitness $f_{q_1}(q_2, c)$ is given by

$$f_{q_1}(q_2, c) = \mathcal{R}(q_1, q_2, c) - 1.$$

Note that $\mathcal{R}(q_1, q_2, c)$ can be rewritten as

$$\mathcal{R}(q_1, q_2, c) = \delta^{-1}\Big(R_r^*(q_1, c)\beta_r^2\left(m_r^2\Gamma_r + m_n^2\Gamma_{r\to n}\right) + R_n^*(q_1, c)\beta_n^2 m_n^2\Gamma_n\Big). \tag{B3}$$

C Proof of Proposition 4.1

Let $E^* = (R_r^*, R_n^*, p_r^{g,*}, p_n^{g,*}, u^{g,*})$ denote the positive equilibrium of the single-species model. Then

$$\begin{cases} 0 = \Lambda_0 - \theta_r R_r^* - \beta_r^g R_r^* u^{g,*}, \\ 0 = \theta_r R_r^* - \theta_n R_n^* - \beta_n^g R_n^* u^{g,*} \\ p_r^{g,*}(0) = \beta_r^g R_r^* u^{g,*}, \\ p_n^{g,*}(0) = \beta_n^g R_n^* u^{g,*}, \\ (p_r^{g,*})'(a) = -(\mu(a) + \theta_r) p_r^{g,*}(a), \\ (p_n^{g,*})'(a) = -(\mu(a) + \theta_n) p_n^{g,*}(a) + \theta_r p_n^{g,*}(a), \\ 0 = \displaystyle\int_0^\infty \mu(a)(m_r^g\, p_r^{g,*}(a) + m_n^g\, p_n^{g,*}(a))\,\mathrm{d}a - \delta u^{g,*} \end{cases}$$

i.e.

$$R_r^* = \frac{\theta_r \bar{R}_r}{\theta_r + \beta_r^g u^{g,*}}, \qquad R_n^* = \frac{\theta_r\theta_n \bar{R}_n}{(\theta_r + \beta_r^g u^{g,*})(\theta_n + \beta_n^g u^{g,*})}$$

$$p_r^{g,*}(a) = \beta_r^g u^{g,*} R_r^* \pi(a, \theta_r), \qquad p_n^{g,*}(a) = \beta_n^g u^{g,*} R_n^* \pi(a, \theta_n) + \beta_r^g u^{g,*} R_r^* \rho(\theta_r, \theta_n, a)$$

and $u^{g,*} > 0$ is solution of

$$\Phi(u^{g,*}) := \frac{\theta_r}{\theta_r + \beta_r^g u^{g,*}}\left(\mathcal{R}_0^r(g) + \mathcal{R}_0^{r\to n}(g)\right) + \left(\frac{\theta_r}{\theta_r + \beta_r^g u^{g,*}}\right)\cdot\left(\frac{\theta_n}{\theta_n + \beta_n^g u^{g,*}}\right)\mathcal{R}_0^n(g) = 1.$$

Since the function Φ is decreasing and $\lim_{u\to\infty}\Phi(u) = 0$, the equation $\Phi(u) = 1$ admits a positive solution if and only if $\Phi(0) = \mathcal{R}_0(g) > 1$, in which case the solution is unique.

D Proof of Theorem 4.2

Let $\mathcal{G} = \{g\}$.

D.1 Proof of the first item

We start with the first item of Theorem 4.2. Suppose first that $\mathcal{R}_0(g) > 1$ and let $\varphi_0 \in \partial\mathcal{W}^g$. From (12), we have $\Psi(t, \varphi_0) \in \partial\mathcal{W}^g$ for every $t \geq 0$ and in particular $\Psi_u^g(t, \varphi_0) = 0$ for every $t \geq 0$. From (5) it comes

$$\|\Psi_{p_r}^g(t, \varphi_0)\|_{L^1(\mathbb{R}_+)} \leq \|p_{r,0}^g\|_{L^1(\mathbb{R}_+)} e^{-t\theta_r}, \quad \|\Psi_{p_n}^g(t, \varphi_0)\|_{L^1(\mathbb{R}_+)} \leq \|p_{n,0}^g\|_{L^1(\mathbb{R}_+)} e^{-t\theta_n} + \frac{\theta_r}{\theta_r - \theta_n}\|p_{r,0}\|_{L^1(\mathbb{R}_+)} e^{-t\theta_n}$$

for every $t \geq 0$. Then (3) implies

$$\Psi_{R_r}(t, \varphi_0) = \bar{R}_r + (R_{r,0} - \bar{R}_r)e^{-\theta_r t}$$

and

$$\Psi_{R_n}(t, \varphi_0) = \bar{R}_n + (R_{n,0} - \bar{R}_n)e^{-\theta_n t} + \frac{\theta_r}{\theta_r - \theta_n}(R_{r,0} - \bar{R}_r)e^{-\theta_n t}\left(1 - e^{-(\theta_r - \theta_n)t}\right).$$

It follows that

$$\|\Psi(t, \varphi_0) - E_0\|_X \leq e^{-\theta_n t}\left(1 + \frac{\theta_r}{\theta_r - \theta_n}\right)\|\varphi_0 - E_0\|_X \underset{\to+\infty}{\longrightarrow} 0$$

which proves the first point.

Suppose now that $\mathcal{R}_0(g) \leq 1$. We introduce the functional

$$L_0 : \varphi_0 \longmapsto \psi_r(0)\overline{R}_r h\left(\frac{R_{r,0}}{\bar{R}_r}\right) + \int_0^\infty \psi_r(a) p^g_{r,0}(a)\,\mathrm{d}a + \int_0^\infty \psi_n(a) p^g_{n,0} a)\,\mathrm{d}a + u^g_0$$

for every $\varphi_0 := (R_{r,0}, R_{n,0}, p^g_{r,0}, p^g_{n,0}, u^g_0) \in X_+$ where

$$\begin{cases} h : \mathbb{R}^*_+ \ni a \longmapsto a - \ln(a) - 1, \\ \psi_n : \mathbb{R}_+ \ni a \longmapsto m^g_n \displaystyle\int_a^\infty \mu(\sigma) e^{-\int_a^\sigma (\mu(\xi)+\theta_n)\mathrm{d}\xi} \mathrm{d}\sigma \in \mathbb{R}_+, \\ \psi_r : \mathbb{R}_+ \ni a \longmapsto m^g_r \displaystyle\int_a^\infty \mu(\sigma) e^{-\int_a^\sigma (\mu(\xi)+\theta_r)\mathrm{d}\xi} + m^g_n \int_a^\infty \mu(\sigma) \int_a^\sigma \theta_r e^{-\int_a^\xi (\mu(\eta)+\theta_r)\mathrm{d}\eta} e^{-\int_\xi^\sigma (\mu(\eta)+\theta_n)\mathrm{d}\eta} \mathrm{d}\xi \mathrm{d}\sigma \in \mathbb{R}_+. \end{cases}$$

By Theorem 3.1 item 5, L_0 is well-defined on $\mathcal{A}$ where we remind that $\mathcal{A}$ is the attractor of bounded sets of X_+. Let $\varphi_0 \in \mathcal{A}$. In order to compute the derivative of the function $t \longmapsto L_0(\Psi(t, \varphi_0))$, we first assume that $\widehat{\varphi}_0 \in \mathcal{D}((A+F)_0) \cap \mathcal{X}_{0+}$ where we defined

$$\widehat{\varphi}_0 = \left(R_{r,0}, R_{n,0}, 0, 0, p^g_{r,0}, p^g_{n,0}, u^g_0\right)^T$$

and where $(A+F)_0$ is the part of the nonlinear generator

$$(A+F)\widehat{\varphi}_0 = A\widehat{\varphi}_0 + F(\widehat{\varphi}_0),\ \forall \widehat{\varphi}_0 \in \mathcal{D}(A)$$

in $\mathcal{X}_0$ with $D((A+F)_0) = \{\widehat{\varphi}_0 \in \mathcal{D}(A) : (A+F)\widehat{\varphi}_0 \in \mathcal{X}_0\}$. It follows from [24, Theorem 5.6.6, p. 242] that the mild solution of (A1) is classical and we can compute the derivative. Let $t \geq 0$. Firstly we have

$$\begin{aligned} \frac{\mathrm{d}}{dt}\left(\psi_r(0)\bar{R}_r g\left(\frac{\Psi_{R_r}(t,\varphi_0)}{\bar{R}_r}\right)\right) &= \psi_r(0)\left(1 - \frac{\bar{R}_r}{\Psi_{R_r}(t,\varphi_0)}\right)\left(\Lambda_0 - \theta_r \Psi_{R_r}(t,\varphi_0) - \beta^g_r\, \Psi^g_u(t,\varphi_0)\, \Psi_{R_r}(t,\varphi_0)\right) \\ &= -\frac{\theta_r \psi_r(0)}{\Psi_{R_r}(t,\varphi_0)}\left(\Psi_{R_r}(t,\varphi_0) - \bar{R}_r\right)^2 + \psi_r(0)\beta^g_r \Psi^g_u(t,\varphi_0)(\bar{R}_r - \Psi_{R_r}(t,\varphi_0)) \end{aligned} \tag{D1}$$

Secondly we compute

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty \psi_r(a)\Psi^g_{p_r}(t,\varphi_0)(a)\,\mathrm{d}a &= -\int_0^\infty \psi_r(a)\left[\partial_a \Psi^g_{p_r}(t,\varphi_0)(a) + (\mu(a)+\theta_r)\Psi^g_{p_r}(t,\varphi_0)(a)\right]\mathrm{d}a \\ &= \psi_r(0)\beta^g_r \Psi^g_u(t,\varphi_0)\Psi_{R_r}(t,\varphi_0) + \int_0^\infty \Big(\psi'_r(a) - (\mu(a)+\theta_r)\psi_r(a)\Big)\Psi^g_{p_r}(t,\varphi_0)(a)\mathrm{d}a \\ &= \psi_r(0)\beta^g_r \Psi^g_u(t,\varphi_0)\Psi_{R_r}(t,\varphi_0) - \int_0^\infty \Big(\theta_r \psi_n(a) + m^g_r \mu(a)\Big)\Psi^g_{p_r}(t,\varphi_0)(a)\mathrm{d}a \end{aligned} \tag{D2}$$

by using the equality $\psi'_r(a) = \left(\mu(a)+\theta_r\right)\psi_r(a) - \theta_r\,\psi_n(a) - m^g_r\,\mu(a)$. Thirdly we compute

$$\begin{aligned} &\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty \psi_n(a)\Psi^g_{p_n}(t,\varphi_0)(a)\,\mathrm{d}a \\ &= -\int_0^\infty \psi_n(a)\left[\partial_a \Psi^g_{p_n}(t,\varphi_0)(a) + (\mu(a)+\theta_n)\Psi^g_{p_n}(t,\varphi_0)(a) - \theta_r \Psi^g_{p_r}(t,\varphi_0)(a)\right]\mathrm{d}a \\ &= \psi_n(0)\beta^g_n \Psi^g_u(t,\varphi_0)\Psi_{R_n}(t,\varphi_0) + \int_0^\infty \Big(\psi'_n(a) - (\mu(a)+\theta_n)\psi_n(a)\Big)\Psi^g_{p_n}(t,\varphi_0)(a) + \theta_r\psi_n(a)\Psi^g_{p_r}(t,\varphi_0)(a)\mathrm{d}a \\ &= \psi_n(0)\beta^g_n \Psi^g_u(t,\varphi_0)\Psi_{R_n}(t,\varphi_0) - \int_0^\infty m^g_n \mu(a)\Psi^g_{p_n}(t,\varphi_0)(a)\mathrm{d}a + \theta_r\int_0^\infty \psi_n(a)\Psi^g_{p_r}(t,\varphi_0)(a)\mathrm{d}a \end{aligned} \tag{D3}$$

by using the equality $\psi'_n(a) = \left(\mu(a)+\theta_n\right)\psi_n(a) - m_n\,\mu(a)$. We also have

$$\frac{d}{dt}\Psi^g_u(t,\varphi_0) = \int_0^\infty \mu(a)\Big(m^g_r \Psi^g_{p_r}(t,\varphi_0)(a) + m^g_n \Psi^g_{p_n}(t,\varphi_0)(a)\Big)\mathrm{d}a - \delta\Psi^g_u(t,\varphi_0). \tag{D4}$$

It follows from (D1)-(D2)-(D3)(D4) that

$$\frac{\mathrm{d}L_0(\Psi(t,\varphi_0))}{\mathrm{d}t} = -\frac{\theta_r\psi_r(0)}{\Psi_{R_r}(t,\varphi_0)}\left(\Psi_{R_r}(t,\varphi_0)-\bar{R}_r\right)^2+\left(\psi_r(0)\beta_r^g\bar{R}_r+\psi_n(0)\beta_n^g\Psi_{R_n}(t,\varphi_0)-\delta\right)\Psi_u^g(t,\varphi_0),\ \forall t\geq 0. \quad \text{(D5)}$$

If $\widehat{\varphi}_0 \notin \mathcal{D}((A+F)_0)$ then we may argue by density of $\mathcal{D}((A+F)_0)\cap\mathcal{X}_{0+}$ into $\mathcal{X}_{0+}$ (see [24, Lemma 5.6.7, p. 243]) combined with the fact that the semiflow $\{\Psi(t,.)\}_{t\geq 0}$ is state-continuous uniformly in finite time (see Theorem 3.1, item 7) to prove the formula (D5) for any $\widehat{\varphi}_0 \in \mathcal{X}_{0+}$ (hence any $\varphi_0 \in X_+$). By invariance of $\mathcal{A}$ we have $\Psi(t,\varphi_0)\in\mathcal{A}$ for every $t\geq 0$, and by using Theorem 3.1 item 5, we know that $\mathcal{A}\subset\mathcal{B}$ (where $\mathcal{B}$ is defined by (10)) hence $\Psi_{R_n}(t,\varphi_0)\leq \bar{R}_n$ for every $t\geq 0$. We deduce from (D5) that

$$\begin{aligned}\frac{\mathrm{d}L_0(\Psi(t,\varphi_0))}{\mathrm{d}t} &\leq -\frac{\theta_r\psi_r(0)}{\Psi_{R_r}(t,\varphi_0)}\left(\Psi_{R_r}(t,\varphi_0)-\bar{R}_r\right)^2+\left(\psi_r(0)\beta_r^g\bar{R}_r+\psi_n(0)\beta_n^g\bar{R}_n-\delta\right)\Psi_u^g(t,\varphi_0),\\ &\leq -\frac{\theta_r\psi_r(0)}{\Psi_{R_r}(t,\varphi_0)}\left(\Psi_{R_r}(t,\varphi_0)-\bar{R}_r\right)^2+\delta\left(\mathcal{R}_0(g)-1\right)\Psi_u^g(t,\varphi_0) \quad \text{(D6)}\end{aligned}$$

by using (13). Since $\mathcal{R}_0(g)\leq 1$ then the derivative is non-positive and L_0 is a Lyapunov function on $\mathcal{A}$. We state the following result.

Lemma D.1 *Let $\varphi_0\in\mathcal{A}$ and $\{\phi(t),t\in\mathbb{R}\}\subset\mathcal{A}$ be a complete orbit through φ_0. If L_0 is constant on $\{\phi(t),t\in\mathbb{R}\}$ then $\phi(t)=E_0$ for every $t\in\mathbb{R}$.*

Proof. Let $\varphi_0 := (R_{r,0},R_{n,0},p_{r,0}^g,p_{n,0}^g,u_0^g)\in\mathcal{A}$ and $\{\phi(t),t\in\mathbb{R}\}\subset\mathcal{A}$ be a complete orbit through φ_0. Suppose that L_0 is constant on $\{\phi(t),t\in\mathbb{R}\}$ then from (D6) it comes

$$\Psi_{R_r}(t,\phi(\sigma))=\bar{R}_r,\quad \forall(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}.$$

In particular $R_{r,0}=\bar{R}_r$. From the R_r-equation of (3) it follows that $\Phi_u^g(t,\phi(\sigma))=0$ for every $(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}$, hence $u_0^g=0$. From the R_n-equation of (3) we get

$$\frac{\mathrm{d}\Psi_{R_n}}{\mathrm{d}t}(t,\phi(\sigma))=\theta_r\bar{R}_r-\theta_n\Psi_{R_n}(t,\phi(\sigma)),\quad \forall(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}.$$

We deduce that

$$\Psi_{R_n}(t,\phi(\sigma))=\Psi_{R_n}(0,\phi(\sigma))e^{-\theta_n t}+\frac{\theta_r\bar{R}_r}{\theta_n}\left(1-e^{-\theta_n t}\right).$$

Since $\mathcal{A}\subset\mathcal{B}$ then $\Psi_{R_n}(0,\phi(\sigma))\leq\bar{R}_n$ for every $\sigma\in\mathbb{R}$ and it follows that $\lim_{t\to+\infty}\Psi_{R_n}(t,\phi(\sigma))=\bar{R}_n$ uniformly in $\sigma\in\mathbb{R}$. Consequently, for any $\varepsilon>0$, there exists $T>0$ such that $|\Psi_{R_n}(t,\phi(\sigma))-\bar{R}_n|\leq\varepsilon$ for every $\sigma\in\mathbb{R}$ and every $t\geq T$. Since $\{\phi(t),t\in\mathbb{R}\}$ is a complete orbit then

$$\Psi_{R_n}(t,\phi(\sigma))=\Psi_{R_n}(T,\phi(\sigma+t-T)),\quad \forall(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}$$

and $|\Psi_{R_n}(t,\phi(\sigma)-\bar{R}_n|\leq\varepsilon$ for every $(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}$. Considering ε as small as necessary then we obtain

$$\Psi_{R_n}(t,\phi(\sigma))=\bar{R}_n,\quad \forall(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}$$

and in particular $R_{n,0}=\bar{R}_n$. Now, we use the expression (5) to state $\Psi_{p_r}^g(t,\phi(\sigma))(a)=0$ for every $(t,\sigma,a)\in\mathbb{R}_+\times\mathbb{R}\times[0,t)$. For $a\geq t$, it suffices to see that

$$\Psi_{p_r}^g(t,\phi(\sigma))(a)=\Psi_{p_r}^g(a+\varepsilon,\phi(\sigma+t-a-\varepsilon))(a)=0$$

for any $\varepsilon>0$ since $a<a+\varepsilon$. We deduce that $\Psi_{p_r}^g(t,\phi(\sigma))=0_{L^1}$ for every $(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}$. Exploiting the relation (6) it follows that $\Psi_{p_n}^g(t,\phi(\sigma))=0_{L^1}$ for every $(t,\sigma)\in\mathbb{R}_+\times\mathbb{R}$ which ends the proof of Lemma D.1 ∎

We now return to the proof of the first item of Theorem 4.2. Let $\varphi_0\in\mathcal{A}$, then there exists $\{\phi(t),t\in\mathbb{R}\}\subset\mathcal{A}$ a complete orbit through φ_0. Since L_0 is a Lyapunov functional on the complete orbit then we deduce from [34, Proposition 2.51, p.53] that L_0 is constant on the alpha-limit set $\alpha(\phi)$ and on the omega-limit set $\omega(\varphi_0)$ (see [16] or [34] for definitions). Since $\{\phi(t),t\in\mathbb{R}\}\subset\mathcal{A}$ which is compact, then $\{\phi(s),s\leq 0\}$ is relatively compact on X and non empty. From [34, Theorem 2.48, p.52] the set $\alpha(\phi)$ is nonempty, compact, invariant, connected and

$\lim_{t\to-\infty} \Delta_H(\phi(t),\alpha(\phi)) = 0$. Since L_0 is constant on $\alpha(\phi)$ then it is constant on every complete orbit on $\alpha(\phi)$ and by Lemma D.1, we get $\alpha(\phi) = \{E_0\}$. It follows that

$$\lim_{s\to-\infty} \Delta_h(\phi(s),\{E_0\}) = 0.$$

Using the facts that $L_0(E_0) = 0$ and that L_0 is a Lyapunov function on $\{\phi(t), t \in \mathbb{R}\}$, then we necessarily get $L_0(\phi(s)) = 0$ for every $s \in \mathbb{R}$. Finally $\{\phi(s), s \in \mathbb{R}\}) \subset \mathcal{A}$ is a complete orbit through $\varphi_0 \in \mathcal{A}$ on which L_0 is constant. Using again Lemma D.1, we get $\varphi_0 = E_0$. In conclusion $\mathcal{A} = \{E_0\}$ which is gAS on X_+ and the first item of Theorem 4.2 is proved.

D.2 Proof of the second item

We now start the proof of the second item of Theorem 4.2. We define the set

$$\Omega = \bigcup_{\varphi_0\in\partial\mathcal{W}^g} \omega(\varphi_0)$$

which reduces to $\{E_0\}$ by using the item 1 of Theorem 4.2. Clearly the set $\{E_0\}$ is invariant, disjoint and compact.

Let $K \subset \partial\mathcal{W}^g$ be a compact invariant. We will show that $K = \{E_0\}$. Indeed, let $\varphi_0 \in K$. By invariance of K there exists a complete orbit $\{\phi(t), t \in \mathbb{R}\} \subset K$ through φ_0. From (D6) we see that L_0 is a Lyapunov function on K. The same arguments used for the first item apply and show that L_0 is constant on $\alpha(\phi)$. By Lemma D.1 we get $\alpha(\phi) = \{E_0\}$. We deduce that L_0 is constant on $\{\phi(t), t \in \mathbb{R}\}$ and by Lemma D.1 we get $\varphi_0 = E_0$ whence $K = \{E_0\}$.

It follows that $\{E_0\}$ is isolated in $\partial\mathcal{W}^g$ (we refer to [34] for the definitions). Also, the set Ω is acyclic since, otherwise, there would exist a complete homoclinic orbit $\{\phi(t), t \in \mathbb{R}\} \subset \partial\mathcal{W}^g$ that connects E_0 to itself with $\phi(0) \neq E_0$. This orbit is an invariant set, which is absurd since $\{E_0\}$ is the only compact invariant set by the previous claim.

We now show that $\{E_0\}$ is uniformly weakly ρ^g-repelling *i.e.* there exists $\varepsilon > 0$ such that

$$\limsup_{t\to+\infty} \|\Psi(t,\varphi_0) - E_0\|_X \geq \varepsilon, \quad \forall\varphi_0 \in \mathcal{W}^g.$$

Let $\varphi_0 \in \mathcal{W}^g$. We consider the functional $\widetilde{L}_0$ defined by

$$\widetilde{L}_0(\Psi(t,\varphi_0)) = \int_0^\infty \psi_r(a)\Psi^g_{p_r}(t,\varphi_0)(a)\,\mathrm{d}a + \int_0^\infty \psi_n(a)\Psi^g_{p_n}(t,\varphi_0)(a)\,\mathrm{d}a + \Psi^g_u(t,\varphi_0)$$

where the weights $\psi_j(a)$ are those of the functional L_0. We may prove that the function $\mathbb{R}^*_+ \ni t \longmapsto \widetilde{L}_0(\Psi(t,\varphi_0))$ is well-defined since

$$\frac{\mathrm{d}}{\mathrm{d}t}\Psi_{R_r}(t,\varphi_0) > 0, \qquad \frac{\mathrm{d}}{\mathrm{d}t}\Psi_{R_n}(t,\varphi_0) > 0$$

for every $t > 0$ by using the two first equations of (3) and the fact that the solution is bounded by Theorem 3.1. The same arguments than for L_0 show that the derivative of $\mathbb{R}^*_+ \ni t \longmapsto \widetilde{L}_0(\Psi(t,\varphi_0))$ can be computed as:

$$\frac{d}{dt}\widetilde{L}_0(\Psi(t,\varphi_0)) = \left(\psi_r(0)\beta^g_r\Psi_{R_r}(t,\varphi_0) + \psi_n(0)\beta^g_n\Psi_{R_n}(t,\varphi_0) - \delta\right)\Psi^g_u(t,\varphi_0).$$

by using the equations (D2)-(D3)-(D4). Since $\mathcal{R}_0(g) > 1$ then by definition (13), we can find $\varepsilon > 0$ small enough such that:

$$C_{\mathcal{R}} := \mathcal{R}_0(g) - \frac{\varepsilon}{\delta}\left(\psi_r(0)\beta^g_r + \psi_n(0)\beta^g_n\right) > 1.$$

Suppose by contradiction that there exists $\varphi_0 \in \mathcal{W}^g$ such that $\limsup_{t\to+\infty} \|\Psi(t,\varphi_0) - E_0\|_X < \varepsilon$. Then there exists $\widetilde{t} > 0$ such that $\Psi_{R_j}(t,\varphi_0) \geq \overline{R}_j - \varepsilon$ for each $j \in \mathcal{J}$ and every $t \geq \widetilde{t}$ for every $t \geq \widetilde{t}$. It follows that

$$\frac{d}{dt}\widetilde{L}_0(\Psi(t,\varphi_0)) \geq \delta\left(\mathcal{R}_0(g) - \frac{\varepsilon}{\delta}(\psi_r(0)\beta^g_r + \psi_n(0)\beta^g_n) - 1\right)\Psi^g_u(t,\varphi_0) = \delta(\Gamma - 1)\Psi^g_u(t,\varphi_0).$$

Since $\Gamma > 1$ and since $\Psi^g_u(t,\varphi_0) > 0$ for every $t \geq t_0$ where t_0 is defined in Theorem 3.1 (item 6), then the derivative of $\widetilde{L}_0$ is positive for every $t \geq \max\{t_0,\widetilde{t}\}$. The fact that $\Psi(t,\varphi_0) \in \mathcal{W}^g$ for every $t \geq 0$ ensures that $\widetilde{L}_0(\Psi(t,\varphi_0)) > 0$ for every $t > 0$. Consequently $\lim_{t\to+\infty} \widetilde{L}_0(\Psi(t,\varphi_0)) = +\infty$. This contradicts the assumption.

From [34, Theorem 8.20, p.189] it follows that Ψ is uniformly weakly ρ^g-persistent and even uniformly strongly ρ^g-persistent by combining with [34, Theorem 5.2, p.126]. Finally a simple use of [34, Theorem 5.19, p.138] gives the existence of the global attractor $\mathcal{A}^g$ in $\mathcal{W}^g$ that is locally asymptotically stable.

E The coexistence equilibrium

Consider two genotypes and let $\mathcal{G} = \{1, 2\}$. At equilibrium, System (3) yields:

$$\begin{cases} 0 = \Lambda_0 - \theta_r R_r^* - \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*} R_r^*, \\ 0 = \theta_r R_r^* - \theta_n R_n^* - \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*} R_n^*, \\ p_r^{g,*}(0) = \beta_r^g u^{g,*} R_r^*, \quad g \in \mathcal{G}, \\ p_n^{g,*}(0) = \beta_n^g u^{g,*} R_n^*, \quad g \in \mathcal{G}, \\ (p_r^{g,*})'(a) = -(\mu(a) + \theta_r) p_r^{g,*}(a), \quad g \in \mathcal{G}, \\ (p_n^{g,*})'(a) = -(\mu(a) + \theta_n) p_n^{g,*}(a) + \theta_r p_r^{g,*}(a), \quad g \in \mathcal{G}, \\ 0 = \int_0^\infty \mu(a) \left[m_r^g p_r^{g,*}(a) + m_n^g p_n^{g,*}(a) \right] \mathrm{d}a - \delta u^{g,*}, \quad g \in \mathcal{G}, \end{cases} \tag{E1}$$

i.e.

$$\begin{cases} R_r^* = \dfrac{\Lambda_0}{\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}}, \\ R_n^* = \dfrac{\theta_r R_r^*}{\theta_n + \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*}} = \dfrac{\theta_r \Lambda_0}{\left(\theta_n + \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*}\right)\left(\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}\right)}, \\ p_r^{g,*}(a) = u^{g,*} \beta_r^g R_r^* \pi(a, \theta_r), \\ p_n^{g,*}(a) = \beta_n^g u^{g,*} R_n^* \pi(a, \theta_n) + \beta_r^g u^{g,*} R_r^* \rho(\theta_r, \theta_n, a). \end{cases} \tag{E2}$$

Thus, by (E2), the $(u^{1,*}, u^{2,*})$ equations of (E1) lead to

$$\delta u^{g,*} = u^{g,*} \beta_r^g R_r^* \int_0^\infty \mu(a) \left[m_r^g \pi(a, \theta_r) + m_n^g \rho(\theta_r, \theta_n, a) \right] \mathrm{d}a + u^{g,*} \beta_n^g R_n^* \int_0^\infty \mu(a) m_n^g \pi(a, \theta_n) \, \mathrm{d}a, \quad \forall g \in \mathcal{G}.$$

Since we look for $u^{g,*} > 0$ for each $g \in \{1, 2\}$, then it comes

$$\begin{aligned} \delta = & \frac{\Lambda_0 \beta_r^g}{\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}} \int_0^\infty \mu(a) \left[m_r^g \pi(a, \theta_r) + m_n^g \rho(\theta_r, \theta_n, a) \right] \mathrm{d}a \\ & + \frac{\theta_r \Lambda_0 \beta_n^g}{\left(\theta_n + \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*}\right)\left(\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}\right)} \int_0^\infty \mu(a) m_n^g \pi(a, \theta_n) \, \mathrm{d}a, \quad \forall g \in \mathcal{G} \end{aligned}$$

i.e.

$$\frac{\theta_r}{\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}} \left(\mathcal{R}_0^r(g) + \mathcal{R}_0^{r\to n}(g) \right) + \frac{\theta_r \theta_n}{\left(\theta_n + \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*}\right)\left(\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}\right)} \mathcal{R}_0^n(g) = 1, \quad \forall g \in \mathcal{G}. \tag{E3}$$

Let

$$x = \frac{\theta_r}{\theta_r + \sum_{g\in\mathcal{G}} \beta_r^g u^{g,*}} > 0 \quad \text{and} \quad y = \frac{\theta_n}{\theta_n + \sum_{g\in\mathcal{G}} \beta_n^g u^{g,*}} > 0, \tag{E4}$$

then (E3) becomes

$$\begin{cases} 1 = \left(\mathcal{R}_0^r(g) + \mathcal{R}_0^{r\to n}(g) \right) x + \mathcal{R}_0^n(g) xy, \\ 1 = \left(\mathcal{R}_0^r(q_2) + \mathcal{R}_0^{r\to n}(q_2) \right) x + \mathcal{R}_0^n(q_2) xy. \end{cases} \tag{E5}$$

Solving the equations of System (E5), we obtain (since $x \neq 0$)

$$\left(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) \right) y = \left(\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) \right) - \left(\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2) \right). \tag{E6}$$

Case 1: $\left(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) \right) \neq 0$ and $\left(\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) \right) - \left(\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2) \right) \neq 0$. Then, by (E6)

$$y = \frac{\left(\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) \right) - \left(\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2) \right)}{\left(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) \right)},$$

and (E5) gives

$$x = \frac{1}{\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) + \mathcal{R}_0^n(1)y} = \frac{1}{\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2) + \mathcal{R}_0^n(q_2)y}, \quad \text{as soon as} \quad y > 0.$$

Therefore, we have $0 < x < 1$ and $0 < y < 1$ iff

$$\begin{cases} 0 < y(2,1) =: \dfrac{(\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2))}{(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1))} < 1, \\ \mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1) + \mathcal{R}_0^n(1)y(2,1) = \mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2) + \mathcal{R}_0^n(2)y(2,1) > 1. \end{cases} \tag{E7}$$

Under the above conditions and by (E4) we have

$$\begin{cases} \beta_r^1\, u^{1,*} + \beta_r^2\, u^{2,*} = \theta_r \left(\dfrac{1}{x} - 1\right), \\ \beta_n^1\, u^{1,*} + \beta_n^2\, u^{2,*} = \theta_n \left(\dfrac{1}{y} - 1\right). \end{cases} \tag{E8}$$

From where:

$$\begin{cases} u^{1,*} = & \dfrac{1}{\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1} \left[\theta_r\beta_n^2 \left(\dfrac{1}{x} - 1\right) - \theta_n\beta_r^2 \left(\dfrac{1}{y} - 1\right)\right], \\ u^{2,*} = & \dfrac{1}{\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1} \left[-\theta_r\beta_n^1 \left(\dfrac{1}{x} - 1\right) + \theta_n\beta_r^1 \left(\dfrac{1}{y} - 1\right)\right], \end{cases} \tag{E9}$$

provided that $\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1 \neq 0$. If $\beta_n^2\beta_r^1 - \beta_r^2\beta_n^1 = 0$, then the two equations of System (E8) are linearly dependent on the left-hand side. Therefore, System (E8) admits infinitely many solutions if the right-hand side satisfies the compatibility condition

$$\beta_n^1\theta_r \left(\frac{1}{x} - 1\right) = \beta_r^1\theta_n \left(\frac{1}{y} - 1\right),$$

or equivalently,

$$\beta_n^2\theta_r \left(\frac{1}{x} - 1\right) = \beta_r^2\theta_n \left(\frac{1}{y} - 1\right).$$

If this compatibility condition is not satisfied, then System (E8) admits no solution.

Finally, by (E7) and (E9), we then have $u^{1,*} > 0$ and $u^{2,*} > 0$ iff

$$\frac{\theta_n}{\theta_r} \min\left(\frac{\beta_r^2}{\beta_n^2}, \frac{\beta_r^1}{\beta_n^1}\right) < \left(\frac{1}{x} - 1\right)\left(\frac{1}{y} - 1\right)^{-1} < \frac{\theta_n}{\theta_r} \max\left(\frac{\beta_r^2}{\beta_n^2}, \frac{\beta_r^1}{\beta_n^1}\right).$$

Case 2: Assume that exactly one of the two differences in (E6) is zero. First, suppose that

$$\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) = 0 \quad \text{and} \quad (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)) \neq 0.$$

Substituting $\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) = 0$ into the left-hand side of Equation (E6) yields:

$$0 = (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)),$$

which directly contradicts the assumption that this difference is non-zero. Hence, no solution exists in this case. Conversely, suppose that

$$\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) \neq 0 \quad \text{and} \quad (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)) = 0.$$

Then, Equation (E6) reduces to:

$$(\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1))\, y = 0.$$

Since we require a positive equilibrium where $y > 0$ (by (E4)), this implies that $\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) = 0$, which contradicts the assumption that this term is non-zero. Consequently, if exactly one of the two conditions holds, System (E5) has no solution. Therefore, the main System (3) cannot admit any coexistence equilibrium under these circumstances.

Case 3: Assume that

$$\mathcal{R}_0^n(2) - \mathcal{R}_0^n(1) = 0 \quad \text{and} \quad (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1)) - (\mathcal{R}_0^r(2) + \mathcal{R}_0^{r\to n}(2)) = 0.$$

Then, Equation (E6) is automatically satisfied. So that the two equations in (E5) coincide and reduce to

$$1 = (\mathcal{R}_0^r(1) + \mathcal{R}_0^{r\to n}(1))\, x + \mathcal{R}_0^n(1)xy.$$

Consequently, infinitely many pairs $((x, y))$ satisfy (E5), and therefore this system admits infinitely many positive solutions.

F What is preference?

In the present framework, we assume that parasite *preference* for RBCs of a given age primarily affects the early invasion stage preceding the rupture of pRBCs. This reflects the idea that, during blood-stage infection, merozoites repeatedly encounter RBCs of different ages and may transiently attach to them before either successfully invading or detaching. In this scenario, we model a transient pairing P_j between a merozoite and an RBC of type R_j. Pair formation occurs at rate β_j, followed by either detachment at rate Γ_j or invasion at rate δ_j:

$$\begin{cases} \dot{R}_r(t) = \Lambda_0 - \theta_r R_r(t) - \beta_r u(t) R_r(t) + \Gamma_r P_r(t), \\ \dot{R}_n(t) = \theta_r R_r(t) - \theta_n R_n(t) - \beta_n u(t) R_n(t) + \Gamma_n P_n(t), \\ \dot{P}_j(t) = \beta_j u(t) R_j(t) - (\Gamma_j + \delta_j) P_j(t), \quad j \in \{r, n\}, \\ p_j(t,0) = \delta_j P_j(t), \quad j \in \{r, n\}. \end{cases}$$

Assuming that pair dynamics are fast relative to RBC and parasite dynamics, a quasi-steady-state approximation yields

$$\begin{cases} \dot{R}_r(t) = \Lambda_0 - \theta_r R_r(t) - \beta_r u(t) R_r(t) + \dfrac{\Gamma_r}{\Gamma_r + \delta_r} \beta_r u(t) R_r(t), \\ \dot{R}_n(t) = \theta_r R_r(t) - \theta_n R_n(t) - \beta_n u(t) R_n(t) + \dfrac{\Gamma_n}{\Gamma_n + \delta_n} \beta_n u(t) R_n(t), \\ p_j(t,0) = \dfrac{\delta_j}{\Gamma_j + \delta_j} \beta_j u(t) R_j(t), \quad j \in \{r, n\}, \end{cases}$$

i.e.

$$\begin{cases} \dot{R}_r(t) = \Lambda_0 - \theta_r R_r(t) - \dfrac{\delta_r}{\Gamma_r + \delta_r} \beta_r u(t) R_r(t), \\ \dot{R}_n(t) = \theta_r R_r(t) - \theta_n R_n(t) - \dfrac{\delta_n}{\Gamma_n + \delta_n} \beta_n u(t) R_n(t), \\ p_j(t,0) = \dfrac{\delta_j}{\Gamma_j + \delta_j} \beta_j u(t) R_j(t), \quad j \in \{r, n\}. \end{cases}$$

The above system naturally defines an effective preference coefficient $\beta_j \delta_j / (\Gamma_j + \delta_j)$. This term captures the trade-off between attachment and invasion success and allows preferences for young versus old RBCs to be encoded mechanistically.

For instance, assuming that $\beta_r = \beta_n = \beta$ and

$$\frac{\delta_r}{\Gamma_r + \delta_r} = q\,\chi(q,c), \qquad \frac{\delta_n}{\Gamma_n + \delta_n} = (1-q)\,\chi(q,c), \qquad \text{with } q \in (0,1),$$

the trade-off scenario considered in this study is recovered through (19).

G Existence and characterization of the singular preference strategy

The above result establishes the existence of a singular preference trait, denoted by q^*.

Existence of the singular strategy. *Proof of Theorem 5.1.* Let us set

$$\chi_r(q_1, c) = q_1 \chi(q_1, c), \quad \chi_n(q_1, c) = (1 - q_1)\chi(q_1, c).$$

In what follows, the parameter c is fixed and the prime notation denotes differentiation with respect to the first variable. Thus,

$$\chi_r'(q_1, c) = \partial_{q_1} \chi_r(q_1, c), \qquad \chi_n'(q_1, c) = \partial_{q_1} \chi_n(q_1, c).$$

By (B3), we have

$$f_{q_1}(q_2, c) = \mathcal{R}(q_1, q_2, c) - 1 = \mathcal{R}_{\text{ef}} \cdot \left[\chi_r(q_2, c)\, R_r^*(q_1, c)\, (\Gamma_r + \Gamma_{r\to n}) + \chi_n(q_2, c)\, R_n^*(q_1, c)\, \Gamma_n\right] - 1,$$

and thus

$$S(q_1, c) = \left.\frac{\partial f_{q_1}(q_2, c)}{\partial q_2}\right|_{q_2 = q_1} = \mathcal{R}_{\text{ef}} \cdot \left[\chi_r'(q_1, c)\, R_r^*(q_1, c)\, (\Gamma_r + \Gamma_{r\to n}) + \chi_n'(q_1, c)\, R_n^*(q_1, c)\, \Gamma_n\right].$$

Substituting R_j^* defined by (15), then the condition $S(q^*, c) = 0$ is equivalent to

$$\frac{\theta_r}{\theta_n + \beta_n(q^*, c)\, u^*(q^*, c)} = -\frac{\chi_r'(q^*, c)\,(\Gamma_r + \Gamma_{r\to n})}{\chi_n'(q^*, c)\,\Gamma_n}, \tag{G1}$$

which rewrites as

$$u^*(q^*, c) = -\frac{1}{\beta_n(q^*, c)}\left(\theta_n + \theta_r \frac{\chi_n'(q^*, c)\,\Gamma_n}{\chi_r'(q^*, c)\,(\Gamma_r + \Gamma_{r\to n})}\right)$$

and is equivalent to (26). Now suppose that q^* is a singular strategy that is the latter equation holds. Then we get $F(q^*) = G(q^*)$, where

$$F(q) := \Lambda_0\, \mathcal{R}_{\text{ef}}\,(\Gamma_r + \Gamma_{r\to n})\left(\chi_r(q, c) - \frac{\chi_r'(q, c)}{\chi_n'(q, c)}\,\chi_n(q, c)\right), G(q) := \theta_r - \frac{\chi_r(q, c)}{\chi_n(q, c)}\left(\theta_n + \theta_r \frac{\chi_n'(q, c)\,\Gamma_n}{\chi_r'(v, c)\,(\Gamma_r + \Gamma_{r\to n})}\right). \tag{G2}$$

Consequently, the candidates for q^* to be a singular strategy is to check whether $F(q^*) = G(q^*)$. By the definition of χ_j in (20), these simplify to:

$$F(q) = \frac{\Lambda_0\, \mathcal{R}_{\text{ef}}\,(\Gamma_r + \Gamma_{r\to n})}{A(q)}\, e^{-c\left(q-\frac{1}{2}\right)^2},$$

$$G(q) = \theta_r - \frac{q\theta_n}{1-q}\left(1 - R \times \frac{A(q)}{B(q)}\right),$$

where

$$A(q) = (1-c) + 3cq - 2cq^2, \qquad B(q) = 1 + cq - 2cq^2.$$

A direct computation gives:

$$F'(q) = \Lambda_0\, \mathcal{R}_{\text{ef}}\,(\Gamma_r + \Gamma_{r\to n}) \cdot c\, \frac{(q-1)\left(4c\left(q-\frac{1}{2}\right)^2 + 2\right)}{A(q)^2}\, e^{-c\left(q-\frac{1}{2}\right)^2}.$$

Since $q - 1 < 0$ for $q \in (0, 1)$ and all other factors are strictly positive, we have $F'(q) < 0$ for all $q \in (0, 1)$ and all $c > 0$: F is strictly decreasing on $(0, 1)$. A direct computation yields:

$$G'(q) = \theta_n \cdot \frac{N(q, c)}{(1-q)^2\, B(q)^2},$$

where

$$N(q, c) = R(1 - c + 6cq(1-q)) - \left(1 + cq - 2cq^2\right)^2,$$

with $R = \dfrac{\theta_r}{\theta_n}\dfrac{\Gamma_n}{\Gamma_r + \Gamma_{r\to n}}$. We write $N(q, c) = R\, N_1(q, c) + N_2(q, c)$, with

$$N_1(q, c) = 1 - c + 6cq(1-q), \qquad N_2(q, c) = -\left(1 + cq - 2cq^2\right)^2 = -B(q)^2 \le 0.$$

The monotony of G is given by the sign of N. If $N_1(q, c) = 0$ then $N(q, c) \le 0$. If $N_1(q, c) \neq 0$, we may introduce the threshold function

$$\widetilde{R}(q, c) = -\frac{N_2(q, c)}{N_1(q, c)} = \frac{\left(1 + cq - 2cq^2\right)^2}{1 - c + 6cq(1-q)} = \frac{B(q)^2}{1 - c + 6cq(1-q)}. \tag{G3}$$

It follows that $N(q, c) > 0 \iff N_1(q, c) > 0$ and $R > \widetilde{R}(q, c)$. Moreover, if $N_1(q, c) < 0$ or if $N_1(q, c) > 0$ and $R < \widetilde{R}(q, c)$ then $N(q, c) < 0$. We distinguish three cases.

- **Case $c < 1$.** Since $N_1(q, c) \ge 1 - c > 0$ for all $q \in (0, 1)$, the threshold function $\widetilde{R}$ is well-defined. The boundary values are:

  $$\widetilde{R}(0, c) = \frac{1}{1-c}, \qquad \widetilde{R}(1, c) = 1 - c.$$

  A direct computation gives

  $$\partial_q \widetilde{R}(q, c) = \frac{2c(1 + cq - 2cq^2)P(q, c)}{N_1(q, c)^2} = \frac{2cB(q)P(q, c)}{N_1(q, c)^2}$$

where

$$P(q,c) = 12cq^3 - 18cq^2 + (7c+2)q - (c+2) = (q-1)\left(12cq^2 - 6cq + c + 2\right).$$

For $q \in (0,1)$, we have $q - 1 < 0$. In addition, $12cq^2 - 6cq + c + 2 > 0$, since its discriminant is

$$\Delta = -12c(c+8) < 0$$

hence $P(q,c) < 0$. The roots of the polynomial function B are

$$q_B^-(c) = \frac{1 - \sqrt{1 + \frac{8}{c}}}{4} < 0, \qquad q_B^+(c) = \frac{1 + \sqrt{1 + \frac{8}{c}}}{4}. \tag{G4}$$

Since $c < 1$ then $q_B^+(c) > 1$ and $B(q) > 0$ for each $q \in [0,1]$ and since $N_1(q,c) > 0$ we obtain

$$\partial_q \widetilde{R}(q,c) < 0$$

so $\widetilde{R}$ is strictly decreasing on $[0,1]$, with

$$\max_{q\in[0,1]} \widetilde{R}(q,c) = \frac{1}{1-c}, \qquad \min_{q\in[0,1]} \widetilde{R}(q,c) = 1 - c.$$

Therefore, there are three subcases.

– Suppose that $R < 1 - c$. Since $\widetilde{R}$ is strictly decreasing on $[0,1]$ then we have

$$R < \widetilde{R}(q,c) \qquad \text{for every } q \in (0,1).$$

Hence, $G'(q) < 0$ for all $q \in (0,1)$, so that G is strictly decreasing and

$$G(q) < G(0) = \theta_r, \qquad \forall q \in (0,1).$$

By definition of G, it comes

$$1 - \frac{RA(q)}{B(q)} > 0, \quad \forall q \in (0,1)$$

and $u^*(q,c) < 0$ by using (26) which is absurd. Consequently, no biologically admissible candidate singular strategy exists in this case.

– Suppose that $1 - c < R < \dfrac{1}{1-c}$. Since $\widetilde{R}$ is strictly decreasing on $(0,1)$, there exists a unique $q_c \in (0,1)$ such that

$$R = \widetilde{R}(q_c, c).$$

Moreover,

$$G'(q) < 0 \quad \text{for } q \in (0, q_c), \qquad G'(q) > 0 \quad \text{for } q \in (q_c, 1).$$

Thus, G is strictly decreasing on $(0, q_c)$ and strictly increasing on $(q_c, 1)$. Also, since $R > 1 - c$ we have

$$\lim_{q\to 1^-} G(q) = +\infty$$

and there exists a unique $\bar{q} \in (q_c, 1)$ such that $G(\bar{q}) = \theta_r$ (because $G(0) = \theta_r$). It follows that

$$G(q) < \theta_r \qquad \text{for every } q \in (0, \bar{q}).$$

The same argument that for the previous case shows that $u^*(q,c) < 0$ for every $q \in (0,\bar{q})$, hence a singular strategy necessarily satisfies $q^* \in (\bar{q}, 1)$. On $(\bar{q}, 1)$, the function G is strictly increasing, whereas F is strictly decreasing. Therefore, $H = G - F$ is strictly increasing on $(\bar{q}, 1)$ and admits at most one zero. Furthermore,

$$H(\bar{q}) = G(\bar{q}) - F(\bar{q}), \quad \text{and} \quad \lim_{q\to 1^-} H(q) = +\infty.$$

Thus, the equation $F(q) = G(q)$ admits exactly one candidate in $(\bar{q}, 1)$ if and only if $F(\bar{q}) > G(\bar{q}) = \theta_r$. Under this condition there exists at most one singular strategy.

– Suppose that $R \geq \dfrac{1}{1-c}$. Since $\widetilde{R}$ is strictly decreasing on $[0,1]$ and

$$\max_{q\in[0,1]} \widetilde{R}(q,c) = \widetilde{R}(0,c) = \frac{1}{1-c},$$

we have $R > \widetilde{R}(q,c)$ for every $q \in (0,1)$. Hence, $G'(q) > 0$ for every $q \in (0,1)$, and G is strictly increasing. In particular $G(q) > \theta_r$ for every $q \in (0,1)$. Moreover $H = G - F$ is strictly increasing and the equation $F(q) = G(q)$ admits at most one solution in $(0,1)$. Since

$$H(0) = \theta_r - F(0), \quad \text{and} \quad \lim_{q\to 1^-} H(q) = +\infty,$$

the function H admits a unique zero if and only if $F(0) > \theta_r$. Under this condition there exists at most one singular strategy.

- **Case $c = 1$.** In this case,

$$A(q) = q(3-2q), \qquad B(q) = (1-q)(1+2q).$$

The function F is strictly decreasing on $(0,1)$ and satisfies $\lim_{q\to 0^+} F(q) = +\infty$. Moreover, the threshold function becomes

$$\widetilde{R}(q,1) = \frac{(1-q)(1+2q)^2}{6q}$$

that is a strictly decreasing function on $q \in (0,1)$ and satisfies

$$\lim_{q\to 0^+} \widetilde{R}(q,1) = +\infty, \qquad \lim_{q\to 1^-} \widetilde{R}(q,1) = 0.$$

Therefore, for every $R > 0$, there exists a unique $q_c \in (0,1)$ such that $R = \widetilde{R}(q_c,1)$.

Furthermore,

$$G'(q) < 0 \quad \forall q \in (0,q_c), \qquad G'(q) > 0 \quad \forall q \in (q_c,1)$$

hence G is strictly decreasing on $(0,q_c)$ and increasing on $(q_c,1)$ with

$$\lim_{q\to 1^-} G(q) = +\infty.$$

Since $G(0) = \theta_r$, there exists a unique point $\bar{q} \in (q_c,1)$ such that $G(\bar{q}) = \theta_r$. Consequently $G(q) < \theta_r$ for every $q \in (0,\bar{q})$. The same arguments than before shows that any biologically admissible singular strategy q^* must belong to $(\bar{q},1)$.

On the interval $(\bar{q},1)$, G is strictly increasing, whereas F is strictly decreasing. Hence, $H = G - F$ is strictly increasing and admits at most one zero. Moreover,

$$H(\bar{q}) = \theta_r - F(\bar{q}), \qquad \lim_{q\to 1^-} H(q) = +\infty.$$

It follows that the function H admits a unique zero on $(\bar{q},1)$ if and only if $F(\bar{q}) > \theta_r$. Under this condition there exists at most one singular strategy.

- **Case $c > 1$.** In this case, the functions A and B may vanish on $(0,1)$. The roots of A are

$$q_A^-(c) = \frac{3-\sqrt{1+\frac{8}{c}}}{4}, \qquad q_A^+(c) = \frac{3+\sqrt{1+\frac{8}{c}}}{4}.$$

Since $c > 1$, we have $q_A^-(c) \in (0,1)$ and $q_A^+(c) > 1$. Moreover, since A is a concave quadratic polynomial, it follows that

$$A(q) > 0 \quad \Longleftrightarrow \quad q \in \left(q_A^-(c),1\right).$$

The roots of B are given in (G4). Since $c > 1$, we have $q_B^+(c) \in (0,1)$. Also, by the previous concavity argument it comes

$$B(q) > 0 \quad \Longleftrightarrow \quad q \in \left(0,q_B^+(c)\right).$$

Therefore we define the following interval

$$I_c = (q_{\min}(c), q_{\max}(c)),$$

where

$$q_{\min}(c) = q_A^-(c), \qquad q_{\max}(c) = q_B^+(c).$$

On this interval, $A(q)$ and $B(q)$ are positive, so F and G are well defined on I_c. Also, since $(1-q)^2 B(q)^2 > 0$ for every $q \in I_c$, then the sign of $G'(q)$ is the sign of $N(q,c)$. The roots of the function N_1 are given by

$$q_{N_1}^-(c) = \frac{1}{2} - \frac{1}{6}\sqrt{3\left(1+\frac{2}{c}\right)}, \qquad q_{N_1}^+(c) = \frac{1}{2} + \frac{1}{6}\sqrt{3\left(1+\frac{2}{c}\right)}.$$

Consequently we get

$$N_1(q,c) > 0 \quad \Longleftrightarrow \quad q \in (q_{N_1}^-(c), q_{N_1}^+(c)).$$

Moreover, one may check the following inequalities:

$$q_{N_1}^-(c) < q_{\min}(c) < q_{\max}(c) < q_{N1}^+(c).$$

On one hand it implies that for every $q \in (0, q_{\min}(c))$ we have $A(q) < 0$ and $B(q) > 0$ whence $1 - R\dfrac{A(q)}{B(q)} > 0$ and $G(q) < \theta_r$ for every $q \in (0, q_{\min}(c))$. Similarly on the interval $(q_{\max}(c), 1)$ we have $A(q) > 0$ and $B(q) < 0$ when $G(q) < \theta_r$ for every $q \in (q_{\max}(c), 1)$. It follows that any singular strategy candidate q^* must belong to the interval I_c.

On the other hand we see that $I_c \subsetneq (q_{N_1}^-(c), q_{N_1}^+(c))$, which implies $N_1(q,c) > 0$ for all $q \in I_c$. Thus, the threshold function $\widetilde{R}(q,c)$ is well-defined and strictly positive on the entire domain I_c (since $B(q) > 0$ for every $q \in I_c$). To determine the behavior of G, we study the variations of $\widetilde{R}(q,c)$ on I_c. There are two subcases.

- Supose that $R \geq \widetilde{R}(q_{\min}(c), c)$. Since $\widetilde{R}$ is strictly decreasing, we have $R > \widetilde{R}(q,c)$ for all $q \in I_c$. This implies $N(q,c) > 0$, and consequently $G'(q) > 0$ on the whole interval I_c. Thus, G is strictly increasing on I_c. Since F is strictly decreasing on I_c, then the function $H = G - F$ is strictly increasing on I_c with

  $$\lim_{q \to (q_{\min}(c))^+} H(q) = -\infty \quad \text{and} \quad \lim_{q \to (q_{\max}(c))^-} H(q) = +\infty.$$

  Hence the equation $F(q) = G(q)$ admits a unique solution q^* in I_c and there is at most one singular strategy.
- Suppose that $R \leq \widetilde{R}(q_{\min}(c), c)$. Using the facts that $\widetilde{R}(q_B^+(c), c) = 0$ and $R > 0$, then by the intermediate value theorem, there exists a unique critical point $q_c \in I_c$ such that $R = \widetilde{R}(q_c, c)$. For $q \in (q_{\min}(c), q_c)$, we have $R < \widetilde{R}(q,c)$ so $G'(q) < 0$, and for $q \in (q_c, q_{\max}(c))$, we have $R > \widetilde{R}(q,c)$ so $G'(q) > 0$. On one hand since $A(q_{\min}(c)) = 0$ then

  $$G(q_{\min}(c)) = \theta_r - \frac{q_{\min}(c)}{1 - q_{\min}(c)}\theta_n < \theta_r.$$

  On the other hand, since $B(q_{\max}(c)) = 0$, then

  $$\lim_{q \to (q_{\max}(c))^-} \frac{A(q)}{B(q)} = +\infty,$$

  which yields

  $$\lim_{q \to (q_{\max}(c))^-} G(q) = +\infty.$$

  Consequently there exists a unique point $\bar{q} \in (q_c, q_{\max}(c)) \subset I_c$ such that $G(\bar{q}) = \theta_r$. It follows that $G(q) < \theta_r$ for every $q \in (q_{\min}(c), \bar{q})$ and necessarily any singular strategy candidate q^* must belong to the interval $(\bar{q}, q_{\max}(c))$. Finally, on this interval the function $H = G - F$ is strictly increasing and admits at most one zero. Moreover

  $$H(\bar{q}) = \theta_r - F(\bar{q}), \qquad \lim_{q \to (q_{\max}(c))^-} H(q) = +\infty.$$

  It follows that the function H admits a unique zero on $(\bar{q}, q_{\max}(c))$ if and only if $F(\bar{q}) > \theta_r$. Under this condition there exists at most one singular strategy.

■

Nature of the singular strategy. We compute the coefficients S_{ij} introduced in (25) in order to determine the nature of the singular strategy q^*.

To check for the ESS potential property of the potential singularity characterized by (G2), we compute:

$$\begin{aligned}
S_{22} =& \chi_r''(q^*,c)\mathcal{R}_0^r \frac{R_r^*(q^*,c)}{\bar{R}_r} + \chi_n''(q^*,c)\mathcal{R}_0^n \frac{R_n^*(q^*,c)}{\bar{R}_n} + \chi_r''(q^*,c)\mathcal{R}_0^{r\to n} \frac{R_r^*(q^*,c)}{\bar{R}_r} \\
=& \chi_r''(q^*,c)\left(\mathcal{R}_0^r + \mathcal{R}_0^{r\to n}\right) \frac{R_r^*(q^*,c)}{\bar{R}_r} + \chi_n''(q^*,c)\mathcal{R}_0^n \frac{R_n^*(q^*,c)}{\bar{R}_n}, \\
=& \frac{\theta_r}{\theta_r + \beta\chi_r(q^*,c)u^*}\left(\chi_r''(q^*,c)\left(\mathcal{R}_0^r + \mathcal{R}_0^{r\to n}\right) + \chi_n''(q^*,c)\mathcal{R}_0^n \frac{\theta_n}{\theta_n + \beta\chi_n(q^*,c)u^*}\right).
\end{aligned}$$

and from (G1) we obtain:

$$\frac{\theta_n}{\theta_n + \beta\chi_n(q^*,c)u^*} = -\frac{\chi_r'(q^*,c)\left(\mathcal{R}_0^{r\to n} + \mathcal{R}_0^r\right)}{\chi_n'(q^*,c)\mathcal{R}_0^n},$$

that is

$$S_{22} = \frac{\theta_r\left(\mathcal{R}_0^r + \mathcal{R}_0^{r\to n}\right)}{\theta_r + \beta\chi_r(q^*,c)u^*}\left(\chi_r''(q^*,c) - \chi_n''(q^*,c)\frac{\chi_r'(q^*,c)}{\chi_n'(q^*,c)}\right).$$

The prefactor

$$\frac{\theta_r\left(\mathcal{R}_0^r + \mathcal{R}_0^{r\to n}\right)}{\theta_r + \beta\chi_r(q^*,c)u^*},$$

is strictly positive on $(0,1)$, so the sign of the curvature is the sign of

$$E(q^*) = \chi_r''(q^*,c) - \chi_n''(q^*,c)\frac{\chi_r'(q^*,c)}{\chi_n'(q^*,c)}. \tag{G5}$$

The equation (G5) becomes

$$E(q^*) = \frac{c\left(4c(q^*)^2 - 4cq^* + c + 2\right)}{c\left(2(q^*)^2 - 3q^* + 1\right) - 1} e^{-c(q^* - \frac{1}{2})^2} = \frac{c\left(c(2q^* - 1)^2 + 2\right)}{c\left(2(q^*)^2 - 3q^* + 1\right) - 1} e^{-c(q^* - \frac{1}{2})^2}.$$

Since $c(2q^* - 1)^2 + 2 > 0$, for all $q^* \in (0,1)$ and $c > 0$, the function E is of the sign of

$$f(q^*) = c\left(2(q^*)^2 - 3q^* + 1\right) - 1 = -A(q^*).$$

We easily find that

$$f(q^*) < 0 \iff q^* \in \left(\max(0, q_{\min}(c)), 1\right),$$

with

$$q_{\min}(c) = \frac{1}{4}\left(3 - \sqrt{1 + \frac{8}{c}}\right).$$

Therefore, the singular strategy q^* is an ESS iff $q^* \in (\max(0, q_{\min}(c)), 1)$. This completes the proof of Theorem 5.1.