Mathematical analysis of a within-host model of malaria with "allee effect" in immune effectors

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ABSTRACT. In this paper, the dynamic behavior of an intra-host model of malaria with immune effectors is analyzed. Novelty in this work is that the phenomenon called "allee effect " is observed in dynamics of immune effectors which will persist inside a body only if it is greater than a threshold value. Analyzing the model, we show that the model is mathematically well posed and the merozoite-free equilibrium is locally asymptotically stable (LAS) if the basic reproductive ratio of free merozoites is less than unity. When the basic reproductive ratio is greater than one, the endemic equilibrium always exists, is locally asymptotically stable and numerical simulations show that immune effectors play a significant and decisive role in the spread of disease.

RÉSUMÉ. Dans ce travail, nous analysons un modèle intra hôte de paludisme avec "effet allee" dans la réaction des effecteurs du système immunitaire. Le système immunitaire ne persistera dans l'organisme que si sa densité est supérieure à un seuil. Nous démontrons que le système est mathématiquement bien posé et que l'équilibre sans parasites est localement asymptotiquement stable si le taux de reproduction de base est inférieur à 1. Lorsque le taux de reproduction de base est supérieur à 1, l'équilibre endémique existe, est localement asymptotiquement stable et les simulations numériques illustrent le fait que les effecteurs du système immunitaire jouent un rôle significatif et décisif dans la propagation de la maladie.

KEYWORDS : Within-host models; merozoite-free equilibrium; allee effect; Immune effectors.

MOTS-CLÉS : Modèles intra hôtes; Equilibre sans mérozoites; effet allee; effecteurs du système immunitaire.

1. Introduction

Within-hosts models of malaria describe the dynamics of the blood-stage of parasites and their interaction with host-cells, in particular red blood cells (RBC) and immune effectors [1, 2].

In a given human, malaria begins with an inoculum of Plasmodium parasites from the salivary glands of a female Anopheles mosquitoes. These parasites penetrate liver cells, multiply, enter the bloodstream and invade RBCs, where they again multiply and burst the cells, each releasing 8-32 merozoites that invade more RBCs and continue the cycle. Blood stage infection engages a network of interacting cells, cytokines, antibodies and other components of immune system.

Within-host models are used for different purposes : explanation of observations, to predict impact of interventions (antimalarial drugs), estimate hidden states or parameters. The model we analyze here was firstly given by J. J Tewa et al. [3] where mathematical analysis was not completely given. The particularity in this model is the consideration of the "allee effect " phenomenon on the dynamics of the immune effectors. This assumption is very important because it takes into account the organisms in which immune system can weaken at some times, either by the presence of another disease (including AIDS), either due to a bad nutrition [7, 8]. Thus, there is a threshold under which if there are no interventions, the immune effectors will no longer persist. Moreover, if the immune effectors density is greater than this threshold, it converges to his carrying capacity. This new hypothesis on the dynamics of the immune effectors may allow us to evaluate the impact of the immune effectors on the disease progression.

Our paper is organized as follows. In the next Section, we give the formulation of our model. We analyze the model in Section 3. Numerical simulations are given in Section 4, to illustrate the mathematical results and to show the impact of immune effectors on disease. We end this paper with a brief discussion and conclusion.

2. The model formulation

The model we study in this paper is given as follows:

$$\begin{cases} \dot{x} &= \Lambda - \mu_x\, x - \beta\, x\, m = \varphi(x) - \beta x m, \\ \dot{y} &= \beta x m - \mu_y y - \rho_y y I, \\ \dot{m} &= r\mu_y y - \mu_m m - u\beta x m - v\beta y m - \rho_m m I, \\ \dot{I} &= k_y y I + k_m m I + \alpha I(I - M)(K - I), \end{cases} \tag{1}$$

where the variable $x(t)$ denotes the concentration of uninfected red blood cells (RBCs) at time t, $y(t)$ denotes the concentration of parasitized red blood cells (PRBCs) at time t, $m(t)$ denotes the concentration of free merozoites in the blood at time t and $I(t)$ denotes the concentration of immune effectors at time t. The dynamic variable $I(t)$ represents the reaction of the immune system and is assumed to model the non specific and specific immune response. Their magnitude may not be correlated with those of any particular biological factor, but rather represent the overall strength of the immune response. Uninfected blood cells are recruited at a constant rate Λ from the bone marrow. The parameters μ_x, μ_y and μ_m are respectively the death rates of RBCs, PRBCs and free merozoites. The parameter β is the contact rate between uninfected red blood cells and free merozoites. ρ_y and ρ_m denote respectively the immonosensitivities of parasitized of red blood cells and

free merozoites. The death of PRBC results in the release of a number of r merozoites. k_y and k_m are respectively immune effectors reaction against PRBCs and immune effectors reaction against free merozoites. Parameters u and v can only take the values 0 or 1, K is the carrying capacity of immune effectors, M is a viability threshold for immune effectors and $K > M$.

3. Mathematical analysis of the model

3.1. Positivity of solutions and dissipativity of the system

We have the following result.

Lemma 3.1. *: The following properties hold.*

1) The nonnegative orthant $\mathbb{R}^4_+$ is positively invariant under the flow induced by the system (1).

2) Let $x^* = \dfrac{\Lambda}{\mu}$. The sets $\Sigma_1 = \left\{(x,y,m,I) \in \mathbb{R}^4_+ \,/\, x \leq x^* + \varepsilon\right\}$, $\Sigma_2 = \{(x,y,m,I) \in \Sigma_1 \,/\, x + y \leq P + x^* + \varepsilon\}$ and $\Sigma_3 = \left\{(x,y,m,I) \in \Sigma_2 / m \leq \dfrac{r\mu_y(P + x^* + \varepsilon) + \varepsilon}{\mu_m}\right\}$ where ε is a very small positive constant and $P \in \mathbb{R}_+$, are positively invariant and absorbing.

Proof : There is no solution of (1) with initial condition $(x(0),\, y(0),\, m(0),\, I(0)) \in \mathbb{R}^4_+$ which goes negative. In fact, for $(x(t),\, y(t),\, m(t),\, I(t)) \in \mathbb{R}^4_+$, $\dot{x} \mid_{x=0} = \Lambda > 0$, $\dot{y} \mid_{y=0} = \beta x m \geq 0$, $\dot{m} \mid_{m=0} = r\mu_y y \geq 0$ and $\dot{I} \mid_{I=0} = 0$, this fact immediately implies that all solutions of the system (1) with initial condition $(x(0),\, y(0),\, m(0),\, I(0)) \in \mathbb{R}^4_+$ stays in the first quadrant. □

Remark 1. *: This first part of the lemma ensures the positivity of trajectories. Since the function φ is continuous and decreasing on $\mathbb{R}_+$, let $m_\varphi = \max\limits_{x \geq 0} \varphi(x)$. Thus, for $\varepsilon > 0$, a real P exists such that $\mu_y P > m_\varphi + \varepsilon$.*

Now, let us prove the second part of the lemma which means that the solution of the system is bounded for $t \geq 0$.

Proof : Consider the following vectorial function $X : \mathbb{R}^4_+ \longrightarrow \mathbb{R}^4$ defined by

$$X(x,y,m,I) = \begin{pmatrix} \Lambda - \mu_x x - \beta x m \\ \beta x m - \mu_y y - \rho_y y I \\ r\mu_y y - \mu_m m - u\beta x m - v\beta y m - \rho_m m I \\ k_y y I + k_m m I + \alpha I(I - M)(K - I) \end{pmatrix}.$$

For the function $H_1(x,y,m,I) = x - x^* - \varepsilon$, we have $\langle \nabla H_1 | X \rangle \leq \varphi(x^* + \varepsilon) \leq 0$, where $\langle \cdot | \cdot \rangle$ is the usual scalar product in $\mathbb{R}^4$. Then Σ_1 is invariant. Otherwise, we have $\dot{x} \leq \Lambda - \mu_x x$. This immediately implies that $0 \leq x(t) \leq h(t) \to x^*$ as $t \to +\infty$ where h is the solution of the equation $h'(t) = \Lambda - \mu_x h(t)$ and $h(0) = x(0) > 0$. Henceforth, $\forall \varepsilon > 0, \exists\, T_1 > 0 \,/\, x(t) \leq x^* + \varepsilon \;\forall t > T_1$. Then Σ_1 is absorbing.

Σ_2 is a subset of Σ_1 which is positively invariant. For the function $H_2(x,y,m,I) = x + y - P - x^* - \varepsilon$, we have $\langle \nabla H_2 | X \rangle \leq \varphi(x) - \mu_y(P + x^* + \varepsilon - x) - \varepsilon \leq \varphi(x) - m_\varphi - \mu_y(x^* + \varepsilon - x) - \varepsilon \leq 0$; then Σ_2 is positively invariant. To show that Σ_2 is absorbing set, let us set $N(t) = x(t) + y(t)$. We have $\dot{N}(t) \leq \mu_y(P + x) - \varepsilon - \mu_y N$. Thus, $\forall t \geq T_1$, $\dot{N}(t) \leq \mu_y(P + x^* + \varepsilon) - \varepsilon - \mu_y N$.

This implies that $N(t) \leq P+x^*+\varepsilon-\frac{\varepsilon}{\mu_y}+\Big(N(0)-(P+x^*+\varepsilon-\frac{\varepsilon}{\mu_y})\Big)\,e^{-\mu_y t}$. Hence, $\lim\limits_{t\to+\infty} N(t) \leq P+x^*+\varepsilon-\frac{\varepsilon}{\mu_y}$. Then, there exists $T_2>0$ such that $N(t)\leq P+x^*+\varepsilon$. Thus, Σ_2 is absorbing.

Σ_3 is positively invariant. consider the function $H_3(x,y,m,I)=m-\dfrac{r\mu_y(P+x^*+\varepsilon)+\varepsilon}{\mu_m}$. We have $\langle\nabla H_3|X\rangle \leq r\mu_y(y-P-x^*-\varepsilon)-\varepsilon\leq 0$. Then Σ_3 is positively invariant. To show that Σ_3 is absorbing, from Eq.1, we have $\dot{m}\leq r\mu_y y-\mu_y m$. Then, $\forall\, t>T_2$, we have $\dot{m}\leq r\mu_y(P+X^*+\varepsilon)-\mu_y m$. This implies that $\forall t>T_2$, we have $\lim\limits_{t\to+\infty} m(t)\leq \dfrac{r\mu_y(P+x^*+\varepsilon)}{\mu_m}$. There exists $T_3>T_2$ such that for $t>T_3$, $m(t)\leq \dfrac{r\mu_y(P+x^*+\varepsilon)+\varepsilon}{\mu_m}$. Then Σ_3 is absorbing. This end the proof. □

For the system (1), let us give the equilibria without merozoites.

Lemma 3.2. *In absence of disease, the system $\dot{I}=\alpha I(I-M)(K-I)$ has three equilibria $I=0$, $I=M$ and $I=K$. Only the equilibrium $I=K>0$ is locally asymptotically stable. Moreover, equilibrium $I=0$ is stable.*

Proof : It is evident that the equilibria of the system $\dot{I}=\alpha I(I-M)(K-I)$ are 0, M and K. Note that $M<K$ and the equilibrium M is unstable since the real $\alpha M(K-M)>0$ is the eigenvalue. Moreover, equilibrium K is locally asymptotically stable since the eigenvalue is $\alpha K(M-K)<0$. The eigenvalue of the equilibrium $I=0$ is $-\alpha MK$ and then, 0 is locally stable. □

Theorem 3.3. *: For System (1), there exists a sufficiently large $I_{max}>0$ such that the compact set $\hat{\Gamma}=\{(x,y,m,I)\in\Sigma_3:\ M<I\leq I_{max}\}$ is a weak attractor.*

For the proof of this theorem, we need the following lemma which assumes that the concentration of immune effectors in an organism must be limited.

Lemma 3.4. *: Let us consider the function*
$\Phi(y,m,I)=k_y yI+k_m mI+\alpha I(I-M)(K-I)$. *There exists a constant $L=\max\{k_y,k_m\}$ such that $\mid\Phi(y,m,I)-\Phi(y',m',I)\mid\leq LI\parallel(|y-y'|,|m-m'|)\parallel_1$.*

In a healthy human, some homeostasis is maintained with a speed of convergence for large concentration of immune effectors. Then, the following lemma holds.

Lemma 3.5. *: There exists a positive constant $I_0=\dfrac{(K+M)+\sqrt{(K-M)^2+4}}{2}$ such that for $I\geq I_0$, $\Phi(0,0,I)\leq-\alpha I$.*

Lemma 3.6. *: Let us consider the system (1). Setting $\hat{\Gamma}_+=\{(x,y,m,I)\in\Sigma_3:\ I>I_{max}\}$. If there exists a trajectory $(x(t),y(t),m(t),I(t))$ of (1) in $\hat{\Gamma}_+$, then for $\varepsilon>0$, $\exists T>0$, $\forall\, t>0$, $\ t>T\Rightarrow y(t)+m(t)<\varepsilon$.*

Proof of theorem 3.3 : Let us show that there exists a sufficiently large I_{max} such that $\hat{\Gamma}$ is a weak attractor. Let us assume that there exists a trajectory $(x(t),y(t),m(t),I(t))$ of (1) in $\hat{\Gamma}_+$. Using lemma 3.6, $\forall\,\varepsilon>0$, $\exists\, T_\varepsilon>0$, $\forall\, t>0$, $\ t>T_\varepsilon\Rightarrow y(t)+m(t)<\varepsilon$. Since Σ_3 is an absorbing set, there exists $T_{\varepsilon,3}>0$ such that $\forall t>T_{\varepsilon,3}$, $(x(t),y(t),m(t),I(t))\in\Sigma_3$. Since $\dot{I}\leq\mid\Phi(y,m,I)-\Phi(0,0,I)\mid+\Phi(0,0,I)$, using lemma 3.4 and lemma 3.5, there exists two constants L and I_0 such that
$I>I_0\Rightarrow\dot{I}\leq LI(y(t)+m(t))-\alpha I$. Hence, for $I>I_0$ and $t>T_\varepsilon$, we have

$\dot{I} \leq LI\varepsilon - \alpha I \leq (L\varepsilon - \alpha)I + L\varepsilon$. Choosing ε such that $\frac{\alpha}{L} > \varepsilon$, this implies that $t > T_\varepsilon \Rightarrow I(t) \leq \frac{L\varepsilon}{\alpha - L\varepsilon}$. Thus, with ε sufficiently small such that $\frac{L\varepsilon}{\alpha - L\varepsilon} < I_{max}$, there is a contradiction with our initial supposition. □

Theorem 3.7. *: All the trajectories of system (1) are forward bounded.*

Proof : Since $\hat{\Gamma}$ is a weak attractor, we have from the Bhatia-Szego theorem [4] that the first positive prolongation $D^+(\hat{\Gamma})$ of $\hat{\Gamma}$ is a compact forward absorbing set and all trajectories which begin in $\hat{\Gamma}_+$ (complementary of $\hat{\Gamma}$) go in $\Omega = D^+(\hat{\Gamma})$. □

3.2. Basic reproductive ratio and equilibria

The basic reproductive ratio of the merozoites, which describes the average number of newly free merozoites generated from one free merozoite at the beginning of the infectious process, is obtained at the merozoite-free equilibrium. The merozoite-free equilibrium is obtained when $m = 0$ in equations at equilibrium. Thus, when $m = 0$, we obtain $P_0 = (x^*, 0, 0, 0)$, $P_1 = (x^*, 0, 0, M)$ and $P_2 = (x^*, 0, 0, K)$. Note that, P_0 is not biologically realistic. P_1 is always unstable since $M(K - M) > 0$ is an eigenvalue of jacobian matrix at P_1. Hence, the merozoite free equilibrium is P_2. Using the notations in van den Driessche and Watmough (2002) [6] for the System (1), the matrices F and V for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = \begin{pmatrix} 0 & \beta x^* \\ r\mu_y & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \mu_y + \rho_y K & 0 \\ 0 & \mu_m + u\beta x^* + \rho_m K \end{pmatrix}.$$

Thus, the basic reproductive ratio is given by

$$\mathcal{R}_0 = \frac{\beta x^* r \mu_y}{(\mu_y + \rho_y K)(\mu_m + u\beta x^* + \rho_m K)}. \tag{2}$$

Thus, using theorem 2 of (Van den Driessche and Watmough 2002), we have established the following result.

Theorem 3.8. *: The merozoite-free equilibrium P_2 of the System (1) is locally asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

We analyze now the existence of equilibria of the model (1). For all possible parameter values, the system (1) has a merozoite-free equilibrium $P_2 = (\frac{\Lambda}{\mu_x}, 0, 0, K)$. To seek endemic equilibrium, we look for $(\bar{x}, \bar{y}, \bar{m}, \bar{I})$ such that all of the right-hand sides of (1) are zero. Let

$$\Lambda - \mu_x \bar{x} - \beta \bar{x} \bar{m} = 0, \tag{3}$$

$$\beta \bar{x} \bar{m} - \mu_y \bar{y} - \rho_y \bar{y} \bar{I} = 0, \tag{4}$$

$$r\mu_y \bar{y} - \mu_m \bar{m} - u\beta \bar{x} \bar{m} - v\beta \bar{y} \bar{m} - \rho_m \bar{m} \bar{I} = 0, \tag{5}$$

$$k_y \bar{y} \bar{I} + k_m \bar{m} \bar{I} + \alpha \bar{I}(\bar{I} - M)(K - \bar{I}) = 0. \tag{6}$$

By (3) to (5), we have

$$\bar{m} = \frac{r\mu_y \beta \Lambda - (\mu_m \mu_x + u\beta\Lambda + \rho_m \mu_x \bar{I})(\mu_y + \rho_y \bar{I})}{v\beta^2 \Lambda + \beta(\mu_m + \rho_m \bar{I})(\mu_y + \rho_y \bar{I})}, \quad \bar{x} = \frac{\Lambda}{\mu_x + \beta \bar{m}}, \quad \bar{y} = \frac{\beta \bar{m} \bar{x}}{\mu_y + \rho_y \bar{I}}. \tag{7}$$

Since $\bar{x}$, $\bar{y}$, $\bar{m}$ and $\bar{I}$ are positives, the following equation must be satisfy:

$$-\rho_m\rho_y\mu_x\bar{I}^2-(\mu_m\mu_x\rho_y+u\beta\Lambda\rho_y+\rho_m\mu_x\mu_y)\bar{I}+r\mu_y\beta\Lambda-\mu_m\mu_x\mu_y-u\beta\Lambda\mu_y>0 \quad (8)$$

The discriminant of (8) is given by

$$delta=(\mu_m\mu_x\rho_y+u\beta\Lambda\rho_y-\rho_m\mu_x\mu_y)^2+4\rho_m\rho_y\mu_x r\mu_y\beta\Lambda>0.$$

Using the Descartes'rules sign, Eq.(8) has a positive roots if

$$r\mu_y\beta\Lambda-\mu_m\mu_x\mu_y-u\beta\Lambda\mu_y>0. \quad (9)$$

So, if the above condition is verified and $I\in[0,I_2]$, with $I_2=\dfrac{-(\mu_m\mu_x\rho_y+u\beta\Lambda\rho_y+\rho_m\mu_x\mu_y)+\sqrt{delta}}{\rho_m\rho_y\mu_x}$, then the model can have an endemic equilibrium.

Substituting (7), into (6), gives the following equation

$$a_0+a_1\bar{I}+a_2\bar{I}^2+a_3\bar{I}^3+a_4\bar{I}^4+a_5\bar{I}^5+a_6\bar{I}^6=0, \quad (10)$$

where the coefficients a_0, a_1, a_2, a_3, a_4, a_5 and a_6 are obtained after computations on Maple. Let us show now that the above equation has at least one solution $I^*\in[0,I_2]$. The following lemma holds.

Lemma 3.9. *If $I_2\leq K$, then $\mathcal{R}_0<1$.*

Proof : We suppose that $I_2\leq K$. Then,

$$I_2-K=\frac{-(\mu_m\rho_y+u\beta\rho_y x^*+\rho_m\mu_y)+\sqrt{(\mu_m\rho_y+u\beta\rho_y x^*-\rho_m\mu_y)^2+4\rho_m\rho_y r\mu_y\beta x^*}-K\rho_m\rho_y}{\rho_m\rho_y} \quad (11)$$

and the following equivalence also holds

$I_2-K\leq 0 \quad\Leftrightarrow\quad 4r\beta x^*\mu_y\leq 2(\mu_y+K\rho_y)(\mu_m+u\beta x^*+\rho_m K)+2\mu_y(\mu_m+u\beta x^*)-K^2\rho_m\rho_y.$
Therefore, $I_2-K\leq 0\Rightarrow\quad \mathcal{R}_0<1$.

Theorem 3.10. *If $\mathcal{R}_0\geq 1$, then condition (9) is verified, there exists at least one solution of equation (10) in $[K,I_2]$ and therefore at least one endemic equilibrium for the system.*

Proof : Let us suppose that $\mathcal{R}_0\geq 1$ and consider the function f define by

$$\begin{array}{rccl} f: & [0,\ I_2] & \longrightarrow & \mathbb{R} \\ & I & \longmapsto & f(I)=a_0+a_1I+a_2I^2+a_3I^3+a_4I^4+a_5I^5+a_6I^6. \end{array} \quad (12)$$

- For $\bar{I}=K$, we have $\bar{m}=\xi\big[\mathcal{R}_0-1\big]$, $\bar{x}=\dfrac{\Lambda}{\mu_x+\beta\bar{m}}$, $\bar{y}=\dfrac{\beta\bar{m}\bar{x}}{\mu_y+\rho_y K}$,
  where $\xi=\dfrac{\mu_x(\mu_m+u\beta x^*+\rho_m K)}{v\beta^2\mu_x x^*+\beta(\mu_m+\rho_m K)(\mu_y+\rho_y K)}$. So, if $\mathcal{R}_0\geq 1$, then
  $$f(K)=k_m\xi(\mathcal{R}_0-1)+\frac{k_y\beta\xi\mu_x x^*(\mathcal{R}_0-1)}{(\mu_y+\rho_y K)\big[\mu_x+\beta\xi(\mathcal{R}_0-1)\big]}\geq 0.$$
- For $\bar{I}=I_2$, we have $\bar{m}=0$, $\bar{x}=x^*$, $\bar{y}=0$. Then,
  $$f(I_2)=\alpha(I_2-M)(K-I_2)\leq 0 \quad \text{since} \quad I_2>K>M.$$

□

4. Numerical simulations

In this section, we use numerical simulations to illustrate the results. The parameters values are taken as $\Lambda = 1\,RBC.\,ml^{-1}.day^{-1}$; $\beta = 0.1\,(RBC/ml)^{-1}.day^{-1}$; $\mu_x = 0.00833day^{-1}$; $\mu_y = 0.2day^{-1}$; $\mu_m = 72day^{-1}$; $r = 16$; $\rho_y = 0.05\,(PRBC/ml)^{-1}\,day^{-1}$; $\rho_m = 0.1\,(RBCs/ml)^{-1}\,day^{-1}$; $k_y = 0,05\,(RBCs/ml)^{-1}\,day^{-1}$; $k_m = 0.1\,(RBCs/ml)^{-1}\,day^{-1}$; $\alpha = 0.2$; $M = 1000$; $K = 2000$; $u = v = 1$; these datas are based on [5] in the following simulations except as noted in the figures.

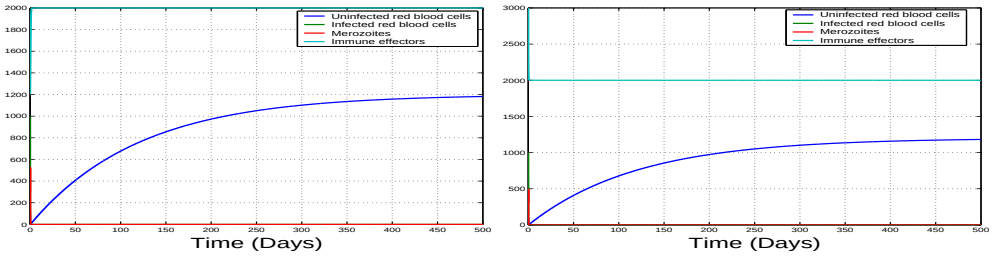

Figure 1: The trajectories of model for $\mathcal{R}_0 = 0.9896$, $\beta = 0.17$, $\Lambda = 10$, $\mu_y = 0.3$ and $r = 480$, with initial condition $x(0) = 100$, $y(0) = 1000$, $m(0) = 300$. At left, we have $I(0) = 1200 < K$ and at right $I(0) = 3000 > K$.

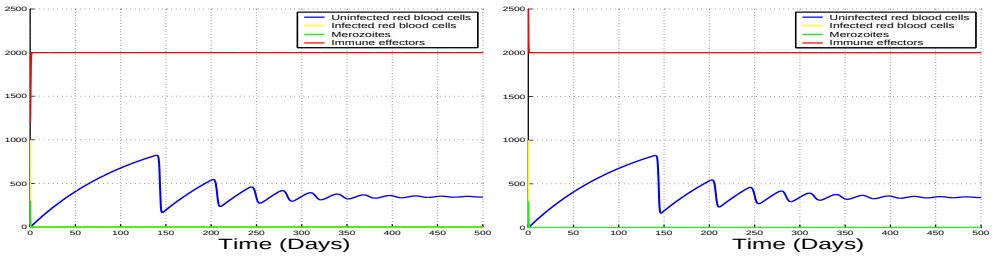

Figure 2: The trajectories of model when $\beta = 0.5$, $\Lambda = 10$, $\mu_y = 0.3$ and $r = 480$, $\mathcal{R}_0 = 1.2449 > 1$ which converge to an endemic equilibrium.

Fig.1 represents the trajectory plot of our model when $\mathcal{R}_0 < 1$. From this figure, one can see that the trajectory converges to the merozoite free equilibrium when the initial conditions are $I(0) = 1200$ and $I(0) = 3000$. This means that the disease disappears from the host population. In figure 2, we have $\mathcal{R}_0 > 1$ with initial conditions $I(0) > M$ and the merozoite free equilibrium is unstable. The trajectory converges to the endemic equilibrium. We have $m(500) = 0.04$ and $y(500) = 0.068$. Thus, the disease persists in the host population. Fig.3 evaluate the impact of immune response in our model. Then, we consider the model without immune effectors, with immune effectors reaction only against free merozoites ($k_y = \rho_y = 0$), with immune effectors reaction only against infected blood cells ($k_m = \rho_m = 0$), with immune effectors reaction against both free merozoites and infected red blood cells. At left, we have the temporal changes in total density of red blood cells for the host $(x(t) + y(t))$ and at right, the temporal changes in the proportion of parasitized cells $\left(\frac{y(t)}{x(t)+y(t)}\right)$ for the host. We observe that immune effectors have an important impact on merozoites population. So, it is very difficult to eradicate the parasites in the host when the immune effectors reaction is only against free

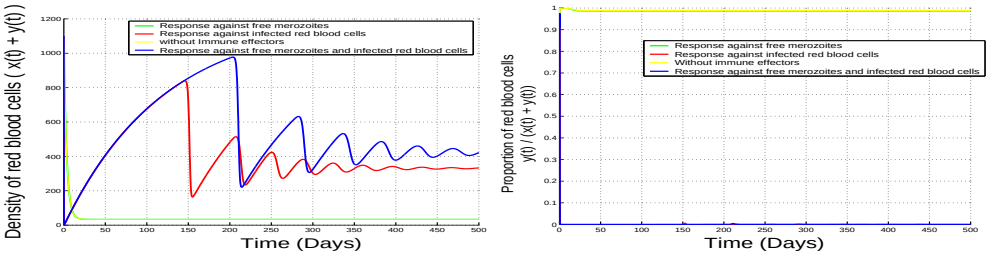

Figure 3: Impact of immune effectors in evolution of red blood cells density and prevalence.

merozoites. The principal reason is that merozoites have very short lifetime in the blood. It is important to observe that the immune effectors reaction only against parasitized red blood cells can eradicate the parasites.

5. Conclusion

In this paper, we have analyzed a within-host model of malaria in which dynamic of immune effectors has a phenomenon of allee effect. Mathematical analysis shows that the model is well posed and there exists a merozoite free equilibrium which is LAS when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$. The model has at least one endemic equilibrium when $\mathcal{R}_0 \geq 1$. Numerical simulations illustrate the fact that immune effectors have an important role in eradication of merozoites inside body. The immune response against merozoites is more difficult to observe than immune response against parasitized red blood cells. Thus, it is important to manufacture new drugs which can strengthen immune effectors to react against both merozoites and infected red blood cells, or which can strengthen immune effectors to react only against infected red blood cells.

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