Journal of Applied Analysis and Computation
Volume 9, Number 6, December 2019, 2037–2069
Website:http://jaac.ijournal.cn
DOI:10.11948/20160266

DYNAMICS OF AN INTRA-HOST MODEL OF MALARIA WITH A CONSTANT DRUG EFFICIENCY

E. Takoutsing[1,3], S. Bowong[†,2,3], D. Yemele[1] and A. Temgoua[2]

Abstract In this paper, we investigate the dynamics of an intra-host model of malaria with logistic red blood growth, treatment and immune response. We provide a theoretical study of the model. We derive the basic reproduction number $\mathcal{R}_f$ which determines the extinction and the persistence of malaria within the body of a host. We compute equilibria and study their stability. More precisely, we show that there exists a threshold parameter ζ such that if $\mathcal{R}_f \leq \zeta \leq 1$, the disease-free equilibrium is globally asymptotically stable. However, if $\mathcal{R}_f > 1$, there exist two malaria infection equilibria which are locally asymptotically stable: one malaria infection equilibrium without immune response and one malaria infection equilibrium with immune response. The sensitivity analysis of the model has been performed in order to determine the impact of related parameters on outbreak severity. The theory is supported by numerical simulations. We also derive a spatio-temporal model, using Diffusion-Reaction equations to model parasites dispersal. Finally, we provide numerical simulations for parasites spreading, and test different treatment scenarios.

Keywords Malaria, intra-host models, drug efficiency, stability, sensitivity analysis.

MSC(2010) 34A34, 34D23, 34D40, 92D30.

1. Introduction

Malaria is the most important parasitic disease that human beings still face. The number of malaria deaths globally fell from an estimated 839 000 in 2000 (range: 653 000 - 1.1 million), to 438 000 in 2015 (range: 236 000 - 635 000), a decline of 48%. Most deaths in 2015 were in the WHO African Region (90%), followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%). The malaria mortality rate, which takes into account population growth, is estimated to have decreased by 60% globally between 2000 and 2015. Thus, substantial progress has been made towards the World Health Assembly target of reducing the malaria burden by 75% by 2015 [30].

Malaria is caused by a parasite that is passed from one human to another by

[†]the corresponding author. Email address:sbowong@gmail.com (S. Bowong)
[1]Department of Physics, Faculty of Science, University of Dschang, PO Box 63 Dschang, Cameroon
[2]Department of Mathematics and Computer Science, Faculty of Science, University of Douala, PO Box 24157 Douala, Cameroon
[3]IRD, Sorbonne University, UMMISCO, F-93143, Bondy, France

the bite of infected Anopheles mosquitoes [30]. After infection, the parasites (called sporozoites) travel through the bloodstream to the liver, where they mature and release another form, the merozoites. The parasites enter the bloodstream and infect red blood cells (RBCs). The parasites multiply inside the RBCs, which then break open within 48 h to 72 h, infecting more RBCs. The first symptoms usually occur 10 days to 4 weeks after infection, though they can appear as early as 8 days or as long as one year after infection. On the other hand, common antimalarial drugs only have effect on the asexual forms of the parasite in the blood (blood schizontocidal effect) [29]. There is no effect on the exoerythrocytic liver forms or on the gametocytes. This drug acts against erythrocytic stage of the infection thereby preventing the progression of blood forms of the parasite which is responsible of relapses in malaria infection. The malaria parasite, however, has evolved mechanics of resistance to most of these available antimalarials drugs, morbidity and mortality rise as efficiency falls [25, 29]. In the treatment of malaria, the World Health Organization (WHO) recommends the use of combination therapy due to the rising threat to available drugs and to reduce the intolerable burden of malaria [29]. Both components of the drug are blood schizonticides, and they have complementary pharmacokinetics dissimilar modes of action thus providing synergistic antimalarial activity [14].

Human immune system is composed of two subdivisions, the innate (non-specific) immune system and the adaptive (specific) immune system. The innate immune system is the first line of defense against invading pathogens while the adaptive immune system acts as a second line of defense which also provides protection against re-exposure to the same pathogen. HBV replication itself is not directly cytotoxic to cells, as seen in the large numbers of asymptomatic HBV carriers who have minimal liver injury, despite ongoing intrahepatic replication of the virus. The long-term aim in the treatment of these patients is to prevent the development of cirrhosis and hepatocellular carcinoma [23]. The immune responses to HBV antigens are responsible both for viral clearance during acute infection and for disease pathogenesis. In infected humans, viral clearance follows the development of a vigorous immune response associated with acute, self-limited inflammatory liver disease (acute viral hepatitis). Immune responses involved in viral clearance comprise both humoral and cellular immunity. Major-histocompatibility-complex (MHC) class II-restricted, CD4+ helper T cells contribute to generation of antibodies against viral envelope antigens that clear circulating virus particles. MHC class I-restricted, CD8+ cytotoxic T lymphocytes eliminate infected cells [3, 7, 11].

The dynamics of the malaria parasite are complex due to spontaneous chromosomal mutations. A deep understanding of the disease dynamics would have a significant impact on the effective prevention and control strategies. Mathematical modeling and numerical simulations have the potential, and offer a promising way, to achieve this. Some efforts have been and are still being devoted to the modeling of this disease. Several mathematical models have been proposed to explain the dynamics of malaria parasites within the body of an infected host with and without treatment by an antimalarial drug to gain insight into its transmission dynamics [14, 16, 26, 29]. These mechanistic within-host models that relate blood anti-malarial drug concentrations to the parasite-time profile have the potential to aid anti-malarial drug development.

In this paper, we intend to develop a deterministic intra-host malaria model which incorporates the key epidemiological and biological features of the infection. The main interest in studying the malaria infection is to understand the long and

short term behavior of the dynamics of the infection and to predict whether the infection will die out or will persist within an infected host. The model considered is a generalization of the models in [14,16,26,29]. We use nonlinear bounded Michaelis-Menten-Monod functions to describe how immune cells interact with parasitized red blood cells (PRBCs) and free merozoites. We take into account the fact that the population of merozoites decreases due to the infection with healthy red blood cells as well as the effect of drug therapy. We also replace the traditional mass action with a standard incidence. We present some global or local analysis of the model, namely the existence and stability of the malaria-free, malaria infection without specific immune response, and malaria infection with specific immune response equilibria, in terms of the basic reproduction number $\mathcal{R}_f$. It is shown that if $\mathcal{R}_f > 1$, the mezoroites can infect the host and establish a persistent infection. We also extend the temporal model to a spatio temporal model, which leads to a system of coupled nonlinear reaction-diffusion equations. We use this model to numerically study the influence of the space on the distribution of RBCs, PRBCs, free merozoites, gametocytes and immune effectors. We found that there exists a critical drug efficiency for which parasites can be cleared from an infection.

This paper is organized as follows. In Section 2, we first present the temporal model for the within-host dynamics of malaria infection based on the basic understanding of biological interactions between red blood cells (RBCs), parasitized red blood cells (PRBCs), free merozoites, gametocytes and immune effectors, and some simple assumptions about the immune system. We present the quantitative and qualitative analysis of the model. The sensitivity analysis of the model is carried out to identify the most influential parameters on the model output variables, that is the most robust estimations are required. Numerical simulations are provided to support theoretical results. Afterward, we extend the temporal model to a spatio-temporal model, which leads to a system of coupled nonlinear reaction-diffusion equations in Section 3. We numerically study the model parasites dispersal. Concluding remarks round up the paper in Section 4.

2. Temporal model

2.1. Model formulation

Herein, we present a temporal model of the dynamical transmission of malaria within a host. The interaction of malaria parasites, RBCs, PRBCs, immune effectors and gametocytes is presented in the model. It is described by a system of five ordinary differential equations that represent the density of RBCs x, PRBCs y, free merozoites m, immune effectors I and gametocytes g. The dynamics is governed by the following set of biological assumptions: (i) healthy RBCs are regenerated; (ii) healthy cells transition to an infected state due to the infection by free mezorotes; (iii) PRBCs die at an increased rate due to the infection; (iv) PRBCs and free merozoites are killed by immune effectors; (v) mezoroites are produced by PRBCs; (vi) free mezoroites die at a specified rate; (vii) free mezoroites also disappear due to the interaction with RBCs; (viii) immune effectors are regenerated and (ix) PRBCs and free mezoroites stimulate the proliferation of immune cells.

RBCs emerge from bone marrow into the circulation in uninfected, healthy adults, and they are removed by phagocytosis 120 days later [20]. A density of approximately 5 million RBCs per μl is maintained in male adults [20]. We model

the rate of RBCs production as sensitive to changes in the rate of RBCs destruction. Here, the population of RBCs is assumed to maintain itself logistically so that RBCs recruitment is one in logistic form: $\eta\left(1-\frac{x+y}{K}\right)$ where K is the maximum carrying capacity for RBCs and η is the maximal growth rate.

Successful invasion of RBCs by a parasite depends on direct contact between the two and their population size. We take the contact process itself as random, with contact probabilities proportional to $x(t)$ and $m(t)$, the densities of uninfected susceptible RBCs and free merozoites, respectively. It has been reported that up to $500,000$ blood cells per μl are parasitized with *P. falciparum* [10]. Thus, free merozoites infect RBCs at rate $\frac{\beta xm}{x+y}$ where β describes the rate or probability of successful infection by merozoites. The infected red blood cells die at rate μ_y per day and the invasion of RBCs induces a specific immune response.

We also take into account the treatment effects of antimalarial drugs. We assume that the efficiency of drugs is constant over time, that is $f \in [0,1]$. The drugs efficiency in this context is the probability for which the drugs inhibit parasites growth by reducing the rate production of free merozoites. The production of free merozoites occurs when PRBCs burst. PRBCs burst during death, hence the number of free merozoites produced depends on the death rate of PRBCs. An average of γ merozoites are released per each bursting PRBC. Thus, the production of free merozoites occurs at rate $\gamma(1-f)\mu_y y$. The population of free merozoites decreases due to the infection with RBCs at rate $\frac{\beta uxm}{x+y}$ where $u \in [0,1]$ is a modification parameter. Also, free merozoites suffer from a natural death μ_m and are eliminated from circulation by immune cells.

Immune responses against malaria infections are complex and stages-specific. The malaria parasite induces a specific immune response which can stimulate the release of cytokines and activate the host's monocytes, neutrophils, T-cells and natural killer cells to react to the different stage parasite [10]. It would be reasonable to include various innates. However, for the sake of simplicity and analysis, we only consider the immunity effectors as the capacity of the immune response of the host to infect cells by parasites. Previously, the killing of PRBCs by immune effectors has been modeled by a sample mass-action term depending only on the product of the density of the parasite and the immune cells which is an unbounded bilinear function [2]. Taking into account the fact that cell proliferation can saturate and that there is a handling time in immune responses, the more reasonable bounded Michaelis-Menten-monod function was firstly used by Agur et al. [1]. Though there are no clinical or experimental data to support that the interaction between immune response and malaria parasites satisfies the Michaelis-Menten-monod function. We follow De Boer and Perelson [9], Pilyugin and Antia [22], and Chiyaka et al. [8] to use the functions $k_y\frac{Iy}{1+D_y y}$ and $k_m\frac{Im}{1+D_m m}$ to described the killing of PRBCs $y(t)$ and free merozoites $m(t)$ by the immune effectors $I(t)$ where k_y and k_m are respectively, the rates of successful removal of PRBCs and free merozoites by immune effectors and D_y and D_m are respectively, the constant saturations that simulate immune cells to grow at half of their maximum rate. It is also assumed that the presence of infected cells stimulates the proliferation of immune cells at rates $\rho_y\frac{y}{1+D_y y}$ and $\rho_m\frac{m}{1+D_m m}$ where ρ_y and ρ_m are the proliferation rate of lymphocytes. We point out that the terms $\frac{y}{1+D_y y}$ and $\frac{m}{1+D_m m}$ describe, respectively, how PRBCs

and free merozoites stimulate the activation of immune effectors. The gametocytes are produced by PRBCs at rate δ and die at rate μ_g. They are regarded to describe the humoral and cell-mediated immunity [8].

With these definitions and assumptions, the interaction involving the densities of RBCs, PRBCs, free merozoites, immune effectors and gametocytes is given by the following temporal system:

$$\begin{cases} \dot{x} &= \eta x\left(1-\dfrac{x+y}{K}\right)-\beta\dfrac{xm}{x+y}, \\ \dot{y} &= \beta\dfrac{xm}{x+y}-k_y\dfrac{Iy}{1+D_y y}-\mu_y y, \\ \dot{m} &= \gamma(1-f)\mu_y y-\mu_m m-k_m\dfrac{Im}{1+D_m m}-\beta u\dfrac{xm}{x+y}, \\ \dot{I} &= I\left(\rho_y\frac{y}{1+D_y y}+\rho_m\frac{m}{1+D_m m}\right)+aI-bI^2, \\ \dot{g} &= \delta y-\mu_g g. \end{cases} \tag{2.1}$$

The parameter values used for numerical simulation are given in Table 1.

Table 1. Numerical values for parameters of model system (2.1).

Parameter	Description	Estimated value/range	Source
η	Production rate of RBC	1 cells/ml/day	Assumed
K	Carrying capacity of RBCs	120/day	[2]
β	Contact rate between free merozoites and RBCs	16/cell/day	[2]
u	Modification parameter	$0 \le u \le 1$	Assumed
f	Efficiency of drug	$0 \le f \le 1$	Assumed
μ_y	Death rate of PRBCs	0.2/day	[2]
μ_m	Death rate of free merozoites	72/day	[2]
μ_g	Death rate of gametocytes	0.25/day	[4]
γ	Merozoite mean rate produce by PRBCs	16	[2]
D_y	$1/D_y$ half saturation constant of PRBCs	0.5 ml/cell	[2]
D_m	$1/D_m$ half saturation constant of free merozoites	0.667 ml/cell	[8]
ρ_y	Immunosensitivity of PRBCs	0.05/cell/day	[2]
ρ_m	Immunosensitivity of free merozoites	0.1/cell/day	[2]
k_y	Immune effectors reaction against PRBCs	0.05/cell/day	[2]
k_m	Immune effectors reaction against free merozoites	0.1/cell/day	[2]
a	Increasing rate of immune effectors	0.05/day	[2]
b	Regulation rate of immune effectors	0.01 RBC/ml^{-1}day^{-1}	[2]
δ	Production rate of gametocytes	0.03 ml^{-1} day^{-1}	[4]

2.2. Basic properties

Herein, we study the basic properties of the solutions of model system (2.1), which are essential in the proofs of stability results. We have the following result.

Theorem 2.1. *Model system (2.1) is a dynamical system on the biologically feasible compact domain:*

$$\Omega=\left\{(x,y,m,I,g)\in\mathbb{R}^5_+,\ x(t)\le K,\ y(t)\le K,\ m(t)\le\frac{\gamma(1-f)\mu_y K}{\mu_m},\ I(t)\le I_m,\ g(t)\le\frac{\delta K}{\mu_g}\right\}, \tag{2.2}$$

where $I_m=\dfrac{1}{b}\left(a+\dfrac{\rho_y}{D_y}+\dfrac{\rho_m}{D_m}\right)$.

Proof. The proof is provided in two steps.

Step 1: We show that the solution $(x(t), y(t), m(t), I(t), g(t))$ of model system (2.1) corresponding to initial conditions such that $x(0) > 0$, $y(0) > 0$, $m(0) > 0$, $I(0) > 0$ and $g(0) > 0$ are nonnegative.

Consider the first equation of model system (2.1):

$$\frac{dx}{dt} = \eta x\left(1 - \frac{x+y}{K}\right) - \beta\frac{xm}{x+y}.$$

Let $m(t) = -\eta\left(1 - \frac{x+y}{K}\right)$, $n(t) = \beta\frac{m}{x+y}$ and $\rho(t) = exp(\int_0^t (n(u) + m(u))du)$. Then, the time derivative of $\rho(t)x(t)$ satisfies

$$\begin{aligned}\frac{d(\rho(t)x(t))}{dt} &= x(t)\tfrac{d\rho(t)}{dt} + \rho(t)\tfrac{dx(t)}{dt},\\ &= (x(t)m(t) + x(t)n(t))\rho(t) + \rho(t)(-x(t)m(t) - x(t)n(t)),\\ &= 0.\end{aligned} \tag{2.3}$$

This implies that $\rho(t)x(t) = \rho(0)x(0)$. Since $\rho(t) > 0$, one can deduce that $x(t) \geq 0$ for all $t \in \mathbb{R}_+$.

Similarly, it can be shown that the variable $I(t)$ remains nonnegative for all $t > 0$.

Now, let us show that the variables $y(t)$ and $m(t)$ remain nonnegative for all $t \geq 0$. Let $y(t) > 0$, $m(t) > 0$, then by a continuity argument of the functions $y(t)$ and $m(t)$, they are two positive real numbers $t_1^0 > 0$ and $t_2^0 > 0$ in such a way that $y(t) > 0$ for all $0 < t < t_0^1$ and $m(t) > 0$ for all $0 < t < t_2^0$. We shall now prove that $t_1^0 = +\infty$ and $t_2^0 = \infty$.

Assume the contradiction that $t_1^0 < \infty$ and $t_2^0 < \infty$, then $y(t)$ and $m(t)$ will vanish each for at least once. Let t_1^m and t_2^m be the first real numbers such that $y(t_1^m) = 0$ and $m(t_2^m) = 0$, respectively. From the definitions of t_1^0 and t_0^2, one has $t_1^m > t_1^0$ and $t_2^m > t_2^0$ and

$$y(t) > 0,\ \forall 0 < t < t_1^m,\ y(t_1^m) = 0 \text{ and } m(t) > 0,\ \forall 0 < t < t_2^m,\ m(t_2^m) = 0. \tag{2.4}$$

Without loss of generality, suppose $t_1^m \leq t_2^m$. Then, from model system (2.1), one has

$$y'(t_1^m) = \beta m(t_1^m) > 0 \quad \text{and} \quad m'(t_2^m) = \gamma(1-f)\mu_y y(t_2^m). \tag{2.5}$$

The above equation implies the existence of two numbers $t_1^{m_1} > t_1^m$ and $t_2^{m_2} > t_2^m$ such that

$$y(t) > 0, \qquad \forall 0 < t < t_1^{m_1} \quad \text{and} \quad m(t) > 0, \qquad \forall 0 < t < t_2^{m_2}. \tag{2.6}$$

Putting the relations (2.4) and (2.6) together and use the continuity of $y(t)$ and $m(t)$, one can conclude that t_1^m and t_2^m are extrema (more precisely, a minima) of $y(t)$ and $m(t)$, respectively. Moreover, since $y(t)$ and $m(t)$ are differentiable functions on $\mathbb{R}$, one has $y'(t_m^1) = 0$ and $m'(t_m^2) = 0$. This is a contradiction since from (2.5), $y'(t_1^m) > 0$ and $m'(t_2^m) > 0$. Therefore, $t_1^0 = +\infty$ and $t_2^0 = +\infty$.

Since $y(t)$ and $m(t)$ are always non negative, using a standard comparison theorem, one has

$$I(t) \geq \frac{a}{C_1 a e^{-at} + b} > 0,$$

where C_1 is a positive constant. Therefore, $I(t)$ is always positive. Similarly, it can be shown that the variable $g(t)$ remains nonnegative for all $t > 0$.

Step 2: Now, we prove the boundedness of the trajectories of model system (2.1).

Let $T = x + y$, then from the first and second equations in model system (2.1), one has

$$\begin{aligned}\dot{T}(t) &= \eta x\left(1-\tfrac{T}{K}\right) - \mu_y y - k_y \tfrac{Iy}{1+D_y y},\\ &\leq \eta x\left(1-\tfrac{T}{K}\right),\\ &\leq \eta T\left(1-\tfrac{T}{K}\right).\end{aligned}$$

Integrating the above differential inequality gives

$$T(t) \leq \frac{KT(0)e^{\eta t}}{K + T(0)(e^{\eta t}-1)},$$

where $T(0)$ is the initial condition of $T(t)$. Applying Birkhoff's and Rota's theorem on differential inequality [5], as t goes to the infinity, one can deduce that $T(t) \leq K$, $\forall t \in \mathbb{R}_+$. This implies that $x(t) \leq K$ and $y(t) \leq K$ for all $t \in \mathbb{R}_+$.

From the third and fifth equations of model system (2.1), using the fact that $y(t) \leq K$, one has

$$\dot{m} \leq \gamma(1-f)\mu_y K - \mu_m m \qquad \text{and} \qquad \dot{g} \leq \delta K - \mu_g g.$$

Solving the above differential inequalities yields

$$m(t) \leq \frac{\gamma(1-f)\mu_y K}{\mu_m}(1-e^{-\mu_m t}) + m(0)e^{-\mu_m t} \text{ and } g(t) \leq \frac{\delta K}{\mu_g}(1-e^{-mu_g t}) + g(0)e^{-\mu_g t},$$

where $m(0)$ and $g(0)$ are the initial conditions of $m(t)$ and $g(t)$, respectively. Thus, as $t \to \infty$, one can deduce that

$$m(t) \leq \frac{\gamma(1-f)\mu_y K}{\mu_m} \qquad \text{and} \qquad g(t) \leq \frac{\delta K}{\mu_g}.$$

Finally, consider the last equation of model system (2.1). Using the fact that $\frac{y(t)}{1+D_y y(t)} \leq \frac{1}{D_y}$ and $\frac{m(t)}{1+D_m m(t)} \leq \frac{1}{D_m}$, one has

$$I'(t) \leq AI(t)\left(1-\tfrac{I(t)}{I_m}\right),$$

where $A = a + \frac{\rho_y}{D_y} + \frac{\rho_m}{D_m}$ and $I_m = \dfrac{1}{b}\left(a + \dfrac{\rho_y}{D_y} + \dfrac{\rho_m}{D_m}\right)$. A simple integration gives

$$I(t) \leq \frac{I_m I(0)e^{At}}{I_m + I(0)(e^{At}-1)}.$$

It then follows that as $t \to \infty$, $I(t) \leq I_m$.

Combining Step 1 and Step 2, Theorem 1 follows from the classical theory of dynamical systems. This concludes the proof. □

2.3. The disease free equilibrium (DFE) and its stability

The DFE state represents a condition where there is no infection or where the infection can be always be eradicated. Model system (2.1) has four disease-free equilibria, obtained by setting the right-hand sides of equations in the model to zero with $m = 0$, given by

$$E_0 = \left(K, 0, 0, \frac{a}{b}, 0\right), \quad E_0^1 = (0, 0, 0, 0, 0), \quad E_0^2 = \left(0, 0, 0, \frac{a}{b}, 0\right) \quad \text{and} \quad E_0^3 = (K, 0, 0, 0, 0). \tag{2.7}$$

The equilibria E_0^1, E_0^2 and E_0^3 are always unstable.

Indeed, the Jacobian matrix of model system (2.1) at E_0^1 is

$$J(E_0^1) = \begin{pmatrix} \eta & 0 & 0 & 0 & 0 \\ 0 & -\mu_y & 0 & 0 & 0 \\ 0 & \gamma(1-f)\mu_y & -\mu_m & 0 & 0 \\ 0 & 0 & 0 & a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{pmatrix}.$$

Since, $\eta > 0$ is an eigenvalue of $J(E_0^1)$, it follows that E_0^1 is an unstable equilibrium for model system (2.1).

At E_0^2, the Jacobian of model system (2.1) is

$$J(E_0^2) = \begin{pmatrix} \eta & 0 & 0 & 0 & 0 \\ 0 & -k_y\frac{a}{b} - \mu_y & 0 & 0 & 0 \\ 0 & \gamma(1-f)\mu_y & -\mu_m - k_m\frac{a}{b} & 0 & 0 \\ 0 & \rho_y\frac{a}{b} & \rho_m\frac{a}{b} & -a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{pmatrix},$$

which implies that E_0^2 is also unstable because $\eta > 0$ is an eigenvalue of $J(E_0^2)$.

Also, the Jacobian matrix of model system (2.1) at E_0^3 is

$$J(E_0^3) = \begin{pmatrix} -\eta & -\eta & -\beta & 0 & 0 \\ 0 & -\mu_y & \beta & 0 & 0 \\ 0 & \gamma(1-f)\mu_y & -\mu_m - \beta u & 0 & 0 \\ 0 & 0 & 0 & a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{pmatrix}.$$

It then follows that $a > 0$ is an eigenvalue which implies that the equilibrium E_0^3 is unstable.

Then, the realistic disease-free equilibrium is $E_0 = \left(K, 0, 0, \frac{a}{b}, 0\right)$.

2.3.1. Basic reproduction number

The Jacobian matrix of model system (2.1) at E_0 is

$$J(E_0) = \begin{pmatrix} -\eta & -\eta & -\beta & 0 & 0 \\ 0 & -\frac{k_y a}{b} - \mu_y & \beta & 0 & 0 \\ 0 & \gamma(1-f)\mu_y & -\mu_m - \frac{k_m a}{b} - \beta u & 0 & 0 \\ 0 & \rho_y \frac{a}{b} & \rho_m \frac{a}{b} & -a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{pmatrix}.$$

Since $-\eta < 0$, $-\mu_g < 0$ and $-a < 0$ are the eigenvalues of $J(E_0)$, the stability of the Jacobian matrix $J(E_0)$ is associated to the stability of the following sub-matrix:

$$J_0 = \begin{pmatrix} -\frac{k_y a}{b} - \mu_y & \beta \\ \gamma(1-f)\mu_y & -\mu_m - \frac{k_m a}{b} - \beta u \end{pmatrix}.$$

A sufficient condition for J_0 to be stable is

$$\frac{\beta\gamma(1-f)\mu_y}{(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)} < 1,$$

where $I_0 = a/b$. Thus, the basic reproduction number of model system (2.1) is

$$\mathcal{R}_f = \frac{\beta\gamma(1-f)\mu_y}{(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)}. \tag{2.8}$$

The basic reproductive number $\mathcal{R}_f$ of the malaria parasite is defined as the number of secondary PRBCs produced by a free merozoite in a completely RBCs at the onset of infection. If $\mathcal{R}_f \leq 1$, then on average a free merozoite produces less than one new PRBCs and the infection cannot grow. However, if $\mathcal{R}_f > 1$, then on average a free merozoite produces more than one new PRBC and infection is maintained.

For a better control on the disease, the global asymptotic stability (GAS) of the DFE is needed. Actually, enlarging the basin of attraction of E_0 to be a part or the entire Ω for the model under consideration is a more challenging task involving relatively new result.

2.3.2. Global stability of the disease free equilibrium

Herein, we focus on the global stability of the disease-free equilibrium E_0 of model system (2.1). To do so, we use the result of Kamgang and Sallet [15].

Following Kamgang and Sallet [15], model system (2.1) can be written in the following pseudo-triangular form:

$$\begin{cases} \dot{w_1} = A_1(w)(w_1 - w_1^*) + A_{12}(w)w_2, \\ \dot{w_2} = A_2(w)w_2, \end{cases} \tag{2.9}$$

where $w_1 = (x, I)^T$ denotes the non infected classes (i.e. RBCs and immune effectors), $w_2 = (y, m, g)^T$ represents the infected classes (i.e. PRBCs, merozoites and

gametocytes), $w = (w_1, w_2)^T$, $w_1^* = (K, I_0)$ is the non zero components of the disease-free equilibrium,

$$A_1(w) = \begin{pmatrix} \frac{\eta x}{x-K}(1 - \frac{x+y}{K}) & 0 \\ 0 & \frac{aI-bI^2}{I-\frac{a}{b}} \end{pmatrix}, \quad A_{12}(w) = \begin{pmatrix} 0 & \beta\frac{x}{x+y} \\ \rho_y \frac{I}{1+D_y y} & \rho_m \frac{I}{1+D_m m} \end{pmatrix} \quad \text{and}$$

$$A_2(w) = \begin{pmatrix} -\mu_y - k_y \frac{I}{1+D_y y} & \beta\frac{x}{x+y} & 0 \\ \gamma(1-f)\mu_y & -\mu_m - k_m \frac{I}{1+D_m m} - \beta u \frac{x}{x+y} & 0 \\ \delta & 0 & -\mu_g \end{pmatrix}.$$

One of the eigen values is $-\mu_g < 0$, thus the stability of the matrix $A_2(w)$ is reduced to the study of the stability of 2x2 matrix given by

$$\hat{A}_2(w) = \begin{pmatrix} -\mu_y - k_y \frac{I}{1+D_y y} & \beta\frac{x}{x+y} \\ \gamma(1-f)\mu_y & -\mu_m - k_m \frac{I}{1+D_m m} - \beta u \frac{x}{x+y} \end{pmatrix}. \tag{2.10}$$

The conditions $H_1 - H_5$ below must be met to guarantee the global asymptotic stability (GAS) of the DFE E_0.

- H_1 : Model system (2.9) is defined on a positive invariant set $\mathcal{D}$ of Ω. The system is dissipative on $\mathcal{D}$.
- H_2 : The sub-system $\dot{w_1} = A_1(w_1, 0)(w_1 - w_1^*)$ is globally asymptotically stable at the equilibrium w_1^* on the canonical projection of $\mathcal{D}$ on $\mathbb{R}^2_+$.
- H_3 : The matrix $\hat{A}_2(w)$ is Metzler and irreducible for any given $w \in \mathcal{D}$ (A metzler matrix is a matrix with off-diagonal entries nonnegative).
- H_4 : There is an upper-bound matrix $\bar{A}_2$ for $\mathcal{M} = \{\hat{A}_2(w),\ w \in \mathcal{D}\}$ with the property that either $\bar{A}_2 \notin \mathcal{M}$ or, if $\bar{A}_2 \in \mathcal{M}$ (i.e, $\bar{A}_2 = \max_{\mathcal{D}} \mathcal{M}$), then for any $\bar{w} \in \mathcal{D}$ in such a way that $\bar{A}_2 = \hat{A}_2(\bar{w}), \bar{w} \in \mathcal{D} \times \{0\}$(i.e., the points where the maximum is realized are contained in the disease-free sub-manifold).
- H_5 : $\alpha(\bar{A}_2) \leq 0$ where $\alpha(\bar{A}_2)$ denotes the largest real part of the eigenvalues of $\bar{A}_2$.

The result of Kamgang-Sallet approach [15] uses the algebraic structure of model system (2.9), namely the fact that $A_1(w)$ and $\hat{A}_2(w)$ are Metzler matrices. The matrices $A_1(w)$ and $\hat{A}_2(w)$ are Metzler. Since the matrix $\hat{A}_2(w)$ should to be irreducible, we will reduce the domain to

$$\mathcal{D} = \{(w_1, w_2) \in \Omega, \quad w_1 \neq 0\}. \tag{2.11}$$

Then, the set $\mathcal{D}$ is positively invariant because only the initial point of any trajectory can have $w_1 = 0$ (see Theorem 2.1). Indeed, from the first and fourth equations of model system (2.1), one has $x' > 0$ and $I' > 0$ whenever $x(0) \neq 0$ and $I(0) \neq 0$. Thus,

$$\hat{A}_2(w) \quad \text{is Metzler and irreductible for all} \quad w \in \mathcal{D}. \tag{2.12}$$

The sub-system:

$$\dot{w}_1 = A_1(w_1, 0)(w_1 - w_1^*),$$

can be expressed as

$$\begin{cases} \dot{x} = \eta x \left(1 - \dfrac{x}{K}\right), \\ \\ \dot{I} = aI - bI^2. \end{cases} \tag{2.13}$$

Resolving the above equations and taking the limit of solutions when t go to the infinity yields

$$\lim_{t\to\infty} x(t) = K \qquad \text{and} \qquad \lim_{t\to\infty} I(t) = \frac{a}{b}. \tag{2.14}$$

Therefore, the reduced model system (2.13) is globally asymptotically stable at the equilibrium $x_1^* = (K, \frac{a}{b})$, on the sub-domain $\{w \in \mathcal{D}, \quad w_2 = 0\}$. Then, hypothesis H_2 is satisfied.

The theorem of Kamgang and Sallet (see [15], Theorem 4.3) gives the GAS of the DFE of a dissipative system of the form (2.9) which satisfies (2.12) and (2.14) provided there exists a matrix $\hat{A}_2(w)$ with the following additional properties:

$$\begin{cases} \hat{A}_2(w) \leq \bar{A}_2, \quad w \in \mathcal{D}, \\ \text{if} \quad \hat{A}_2(\bar{w}) = \bar{A}_2 \quad \text{for some} \quad \bar{w} = (\bar{w}_1, \bar{w}_2)^T \in \mathcal{D} \quad \text{then} \quad \bar{w}_2 = 0, \\ \alpha(\bar{A}_2) \leq 0. \end{cases} \tag{2.15}$$

Using the fact that $\frac{x}{x+y} \leq 1$, the upper bound of $\hat{A}_2(w)$ is

$$\bar{A}_2 = \begin{pmatrix} -\mu_y & \beta \\ \gamma(1-f)\mu_y & -\mu_m \end{pmatrix}. \tag{2.16}$$

The equality $\hat{A}_2(w) = \overline{A_2}$ does not hold in $\mathcal{D}$. Indeed, $\hat{A}_2(w) = \overline{A_2}$ implies that $y = I = 0$ and $u = 0$. However, $I > 0$ in $\mathcal{D}$ which implies that $\hat{A}_2(w) \neq \overline{A_2}$, $\forall w \in \mathcal{D}$. Therefore, the first and second conditions in (2.15) hold. $\bar{A}_2$ is a Metzler matrix which satisfies the stability condition of Kamgang and Sallet [15]. Moreover, the trace of matrix $\bar{A}_2$ is $-(\mu_y + \mu_m) < 0$ and the determinant is $\mu_y\mu_m - \gamma(1-f)\mu_y\beta$. Thus, $\bar{A}_2$ is stable if

$$\mu_y\mu_m - \gamma(1-f)\mu_y\beta \geq 0,$$

that is,

$$\mathcal{R}_f \leq \zeta, \tag{2.17}$$

where

$$\zeta = \frac{\mu_y\mu_m}{(\mu_y + k_yI_0)(\mu_m + k_mI_0 + \beta u)} < 1. \tag{2.18}$$

We can now apply Theorem 4.3 in Kamgang and Sallet [15] and conclude that under condition (2.17), the disease-free equilibrium $(x_1^0, 0)$ is GAS in $\mathcal{D}$. From Eq. (2.11) for the points of $\mathcal{D}$ where $x_1 = 0$, and from Eq. (2.17) the disease-free equilibrium is GAS on Ω.

We have established the following result.

Theorem 2.2. *: The disease-free equilibrium E_0 of model system (2.1) is globally asymptotically stable on Ω if $\mathcal{R}_f \leq \zeta < 1$.*

Remark 2.1. : When $\zeta \leq \mathcal{R}_f < 1$, model system (2.1) can exhibit the phenomenon of backward bifurcation where the locally asymptotically stable DFE co-exists with a locally asymptotically stable endemic equilibrium. However, numerical results tend to support that E_0 is GAS in $\mathbb{R}^5_+$.

Figure 1 shows the GAS of the disease-free equilibrium E_0 using various initial conditions when $\beta = 10$ and $f = 0.6$ (so that $\zeta = 0.4295$, $\mathcal{R}_f = 0.3818 < \zeta$). All other parameter values are given in Table 1. This figure illustrates that the trajectories of model system (2.1) converge to the disease-free equilibrium. This means that the infection disappears within the body of a host when $\mathcal{R}_f \leq \zeta$ and the disease is controllable within the host (see Theorem 2).

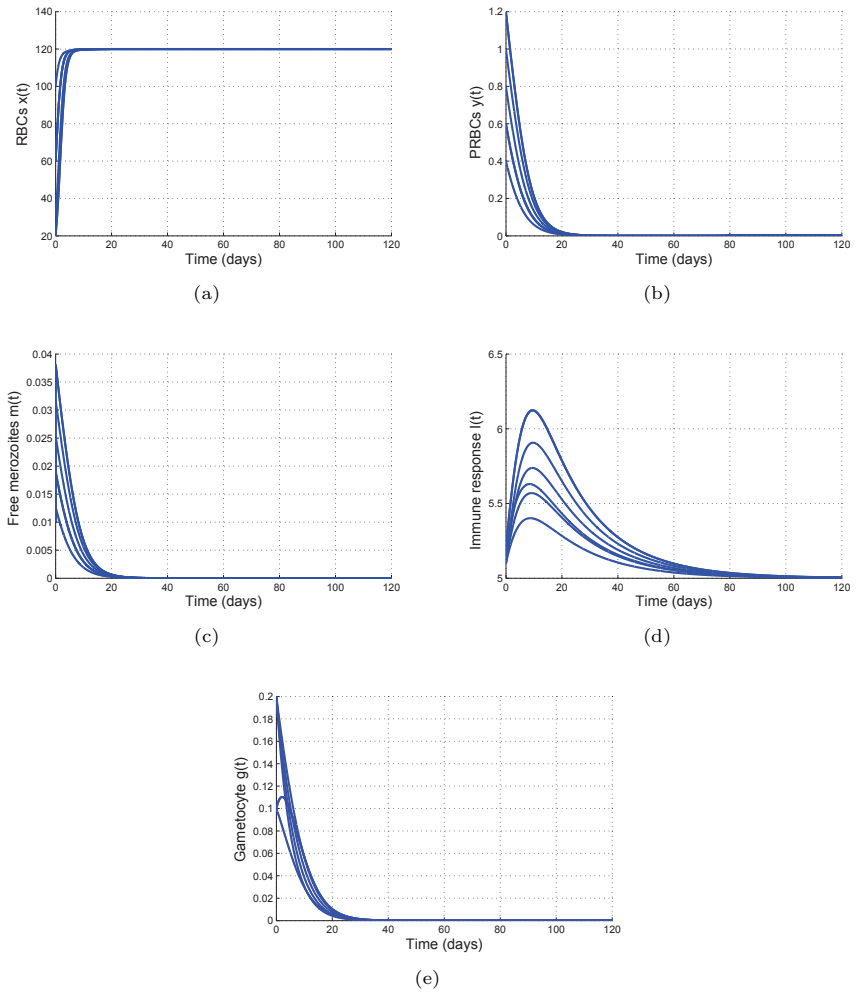


Figure 1. Time plot of densities of (a) RBCs $x(t)$, (b) PRBCs $y(t)$, (c) free merozoites $m(t)$, (d) immune effectors $I(t)$ and (e) gametocytes $g(t)$ using various initial conditions when $\beta = 10$ and $f = 0.6$ (so that $\zeta = 0.4295$, $\mathcal{R}_f = 0.3818 < \zeta$). All other parameter values are given in Table 1.

Now, we investigate the effect of the malaria treatments on the dynamics of model system (2.1). A key parametrization to the model is the basic reproduction number $\mathcal{R}_f$ that measure the number of secondary infections generated by a single free merozoite in an environment where the drug is used as a control strategy. The primary focus of drug therapy is the possibility of clearing free merozoites. Thus, if $\mathcal{R}_f \leq \zeta$, then free merozoites are cleared.

Suppose that at time $t = 0$, the drug is applied to an infected host. The basic reproduction number of model system (2.1) in the absence of treatment (i.e. $f = 0$) is

$$\mathcal{R}_0 = \frac{\beta\gamma\mu_y}{(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)}. \tag{2.19}$$

With this in mind, one has

$$\mathcal{R}_f = \mathcal{R}_0(1 - f). \tag{2.20}$$

Observe that $\mathcal{R}_f \leq \mathcal{R}_0$. Equality is only achieved when $f = 0$, i.e., when there is no treatment. Note that the constraint $\mathcal{R}_f \leq \zeta$ defines implicitly a critical treatment efficacy $f > f_c$ that must be achieved for the clearance of the parasites:

$$f_c = 1 - \frac{\mu_y\mu_m}{\mathcal{R}_0(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)}. \tag{2.21}$$

Thus, the malaria parasites can be eradicated within the host of an infected individual if $f > f_c$. Treating an infected host at the critical level f_c does not instantly lead to parasite clearance. The immunity level within the host requires time to build up and at the critical level it may take some time before the required herd immunity is achieved. Thus, from a public health perspective, f_c acts as a lower bound on what should be achieved, with higher levels of treatment leading to a more rapid elimination of malaria parasites. For a better control of the disease and avoid the case when $\zeta \leq \mathcal{R}_f < 1$, the threshold parameter ζ should be large as possible, that is very close to the unity. We stress that the case when $\zeta \leq \mathcal{R}_f < 1$ corresponds to the case when model system (2.1) may exhibit the phenomenon of backward bifurcation where the locally asymptotically stable DFE co-exists with a locally asymptotically stable endemic equilibrium. To do so, we perform the sensitivity analysis of the threshold parameter ζ.

Sensitivity analysis is used to determine the relative importance of model parameters to malaria parasite transmission and its prevalence. We perform the analysis by calculating the sensitivity indices of the threshold parameter ζ. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually errors in data collection and estimated values. We are thus interested in parameters that significantly affect the threshold parameter ζ since these are the parameters that should be taken into consideration when considering an intervention strategy. Since the threshold parameter ζ is a differentiable function of the parameters, the sensitivity index may alternatively be defined using partial derivatives. For instance, the computation of the sensitivity index of ζ with respect to u using the parameter values in the Table 1 is given by

$$\prod_u^{\zeta} = \left(\frac{\partial\zeta}{\partial u}\right)\left(\frac{u}{\zeta}\right) = -\frac{\beta u}{(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)} < 0. \tag{2.22}$$

This shows that ζ is an decreasing function of u and the parameter u does not have an influence on the threshold parameter ζ. We tabulate the indices of the

remaining parameters in Table 2. From Table 2, parameters whose sensitivity indices have negative signs decrease the value of ζ as their values increase, while those with positive signs increase the value of ζ as they increase. On can observe that the parameters μ_y, b and μ_m are the most influential parameters of the threshold parameter ζ. Thus, when these parameters increase, the threshold parameter ζ will also increase and can approach the unity which is better for the control of the infection within an infected host.

Table 2. Sensitivity indices for ζ.

Parameter	Index	Parameter	Index
μ_y	0.552	β	-0.042
k_y	-0.555	μ_m	0.048
k_m	-0.006	u	-0.042
a	-0.562	b	0.562

Now, we numerically investigate the effect of drug efficiency on the dynamics of model system (2.1). The time evolution of the trajectories of model system (2.1) using various initial conditions when $\beta = 16$, $f_c = 0.7188$ and $f = 0.8$ (so that $\zeta = 0.4227$, $\mathcal{R}_0 = 1.5030 > 1$, $\mathcal{R}_f = 0.3006 < \zeta$ and $f > f_c$) is depicted in Fig. 2. All other parameters values are given in Table 1. It is evident that with the chosen parameters, if $f > f_c$ the merozoites are cleared within the body of an infected host due to the effect of drug.

2.4. Infection endemic equilibria and their stabilities

2.4.1. Infection equilibrium without immune response and its stability

Let $\overline{E} = (\overline{x}, \overline{y}, \overline{m}, \overline{I}, \overline{g})$ be any endemic equilibrium of model system (2.1) with $\overline{x} \neq 0$, $\overline{y} \neq 0$, $\overline{m} \neq 0$, $\overline{I} = 0$ and $\overline{g} \neq 0$. Then, $\overline{x}$, $\overline{y}$, $\overline{m}$, $\overline{I}$ and $\overline{g}$ satisfy the following system of equations:

$$\begin{cases} \eta\overline{x}\left(1 - \dfrac{\overline{T}}{K}\right) - \beta\dfrac{\overline{x}\overline{m}}{\overline{T}} = 0, \\ \beta\dfrac{\overline{x}\overline{m}}{\overline{T}} - \mu_y\overline{y} = 0, \\ \gamma(1-f)\mu_y\overline{y} - \mu_m\overline{m} - k_m\overline{m}V - \beta u\dfrac{\overline{x}\overline{m}}{\overline{T}} = 0, \\ \delta\overline{y} - \mu_g\overline{g} = 0, \end{cases} \tag{2.23}$$

where $\overline{T} = \overline{x} + \overline{y}$.

It would be pointed out that the basic reproduction number of model system (2.1) without immune response is

$$\tilde{\mathcal{R}_0} = \frac{\beta\gamma(1-f)}{\mu_m + \beta u}, \tag{2.24}$$

is the basic reproduction number of model system (2.1) without immune response.

From the first equation of (2.23), one has

$$\overline{m} = \frac{\eta}{\beta}\overline{T}\left(1 - \frac{\bar{T}}{K}\right). \tag{2.25}$$

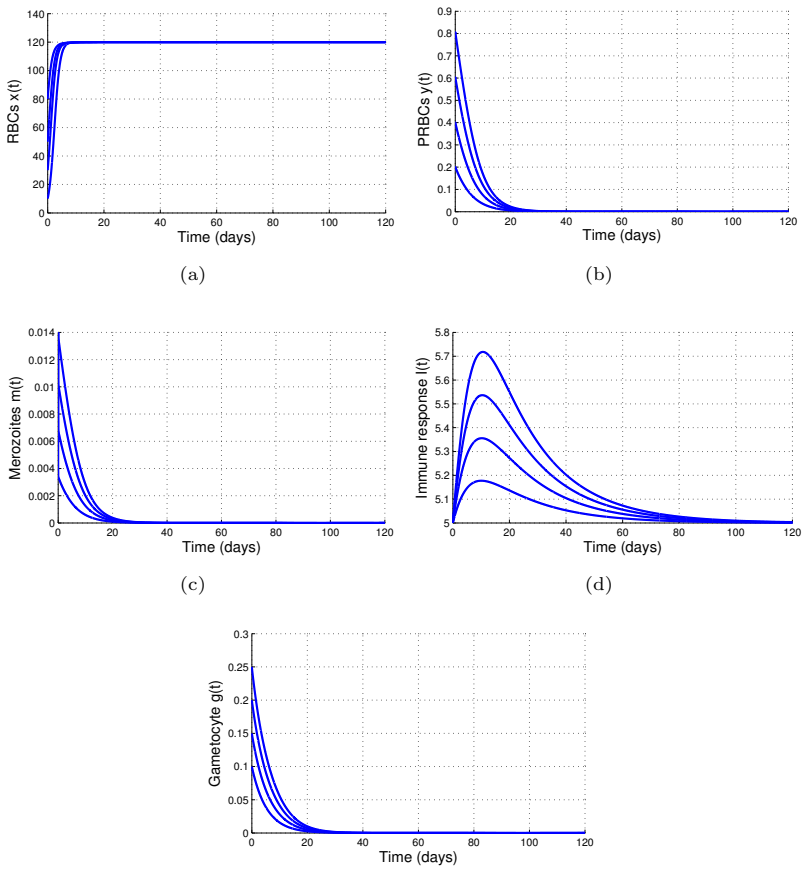


Figure 2. Time plot of densities of (a) RBCs $x(t)$, (b) PRBCs $y(t)$, (c) free merozoites $m(t)$, (d) immune effectors $I(t)$ and (e) gametocytes $g(t)$ using various initial conditions when $\beta = 16$, $f_c = 0.7188$ and $f = 0.8$ (so that $\zeta = 0.4227$, $\mathcal{R}_0 = 1.5030 > 1$, $\mathcal{R}_f = 0.3006 < \zeta$ and $f > f_c$). All other parameter values are given in Table 1.

Plugging the above expression of $\overline{m}$ in the second equation of (2.23) gives

$$\overline{y} = \frac{\eta}{\mu_y}\overline{x}\left(1 - \frac{\overline{T}}{K}\right). \tag{2.26}$$

Replacing the expressions of $\overline{y}$ and $\overline{m}$ given in Eqs. (2.25) and (2.26) in the third equation of (2.23) yields

$$[\beta[\gamma(1-f)-u]-\mu_m]\overline{x} = \mu_m\overline{y}. \tag{2.27}$$

Combining Eqs. (2.26) and (2.27) gives

$$\overline{T} = \frac{K(\mu_y\mu_m + \mu_m\eta + \mu_y\beta u)(1-\tau_0)}{\mu_m\eta}, \tag{2.28}$$

where

$$\tau_0 = \frac{\beta\gamma\mu_y(1-f)}{\mu_m\eta + \mu_y(\mu_m + \beta u)}. \tag{2.29}$$

Then, using Eqs. (2.25), (2.26) and (2.27), one has

$$\begin{cases} \overline{x} &= \dfrac{K(\mu_y\mu_m + \mu_m\eta + \mu_y\beta u)(1-\tau_0)}{\eta\beta(\gamma(1-f)-u)}, \\ \overline{y} &= \dfrac{K(\beta u+\mu_m)(\mu_y\mu_m + \mu_m\eta + \mu_y\beta u)(\tilde{\mathcal{R}}_0-1)(1-\tau_0)}{\mu_m\beta\eta[(1-f)\gamma+u]}, \\ \overline{m} &= \dfrac{K(\beta u+\mu_m)(\mu_y\mu_m + \mu_m\eta + \mu_y\beta u)(\tilde{\mathcal{R}}_0-1)(1-\tau_0)}{\beta\eta\mu_m^2}, \\ \overline{g} &= \dfrac{K\delta(\beta u+\mu_m)(\mu_y\mu_m + \mu_m\eta + \mu_y\beta u)(\tilde{\mathcal{R}}_0-1)(1-\tau_0)}{\mu_g\mu_m\beta\eta[(1-f)\gamma+u]}, \end{cases} \tag{2.30}$$

which can be rewritten in terms of $\tilde{\mathcal{R}}_0$ as

$$\begin{cases} \overline{x} &= \dfrac{K\left(\mu_m\eta - \mu_y(\mu_m+\beta u)(\tilde{\mathcal{R}}_0-1)\right)}{\eta\left(\mu_m\tilde{\mathcal{R}}_0 + \beta u(\tilde{\mathcal{R}}_0-1)\right)}, \\ \overline{y} &= \dfrac{K(\mu_m+\beta u)\left(\mu_m\eta - \mu_y(\mu_m+\beta u)(\tilde{\mathcal{R}}_0-1)\right)(\tilde{\mathcal{R}}_0-1)}{\eta\mu_m\left(\mu_m\tilde{\mathcal{R}}_0 + \beta u(\tilde{\mathcal{R}}_0-1)\right)}, \\ \overline{m} &= \dfrac{K\mu_y(\mu_m+\beta u)\left(\mu_m\eta - \mu_y(\mu_m+\beta u)(\tilde{\mathbb{R}_0}-1)\right)(\tilde{\mathcal{R}}_0-1)}{\beta\,\eta\,{\mu_m}^2}, \\ \overline{g} &= \dfrac{K\delta(\mu_m+\beta u)\left(\mu_m\eta - \mu_y(\mu_m+\beta u)(\tilde{\mathbb{R}_0}-1)\right)(\tilde{\mathcal{R}}_0-1)}{\eta\mu_m\mu_g\left(\mu_m\tilde{\mathcal{R}}_0 + \beta u(\tilde{\mathcal{R}}_0-1)\right)}. \end{cases} \tag{2.31}$$

Note that $\tau_0 < \tilde{\mathcal{R}}_0$. Thus if $\tau_0 < 1$ and $\tilde{\mathcal{R}}_0 > 1$, then $\overline{x} > 0$, $\overline{y} > 0$, $\overline{m} > 0$ and $\overline{g} > 0$.

We have proved the following result.

Lemma 2.1. *: Model system (2.1) has one endemic equilibrium without immune effectors* $\overline{E} = (\overline{x}, \overline{y}, \overline{m}, 0, \overline{g})$ *where* $\overline{x}$ *,*$\overline{y}$*,* $\overline{m}$ *and* $\overline{g}$ *are defined as in Eq.(2.31) whenever* $\tau_0 < 1$ *and* $\tilde{\mathbb{R}}_0 > 1$*.*

Now, we investigate the stability of the endemic equilibrium $\overline{E}$. The Jacobian matrix of model system (2.1) at $\overline{E}$ is

$$J(\overline{E}) = \begin{pmatrix} \frac{2\,\mu_y(\beta\,u+\mu_m)\left(\tilde{\mathcal{R}}_0-1\right)-\eta\,\mu_m}{\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0} & \frac{2\,\mu_y(\beta\,u+\mu_m)\left(\tilde{\mathcal{R}}_0-1\right)-\eta\,\mu_m}{\beta\,u\left(\tilde{\mathcal{R}}_0-1\right)+\mu_m\tilde{\mathcal{R}}_0} & \frac{\mu_2}{f\gamma-\gamma+u} & 0 \\ \frac{\mu_y(\tilde{\mathcal{R}}_0-1)^2(\beta\,u+\mu_m)^2}{\mu_m(\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0)} & -\frac{2\left(\tilde{\mathcal{R}}_0-1\right)u\beta+\left(2\tilde{\mathcal{R}}_0-1\right)\mu_m}{\mu_m(\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0)} & -\frac{\mu_m}{f\gamma-\gamma+u} & 0 \\ \frac{u\mu_y(\tilde{\mathcal{R}}_0-1)^2(\beta\,u+\mu_m)^2}{\mu_m(\beta\,u(\tilde{R}_0-1)+\mu_m\tilde{\mathcal{R}}_0)} & -\frac{\mu_y\left(\beta\,f^2\gamma^2-2\,\beta\,f\gamma^2+\beta\,\gamma^2-\beta\,u^2-u\mu_2\right)}{\beta\,(f\gamma-\gamma+u)} & -\frac{\mu_m\gamma\,(f-1)}{f\gamma-\gamma+u} & 0 \\ 0 & \delta & 0 & -\mu_g \end{pmatrix}.$$

The eigenvalues of the jacobian matrix $J(\overline{E})$ are $-\mu_g$ and the eigenvalues of the

sub-matrix

$$J_0(\overline{E}) = \begin{pmatrix} \frac{2\,\mu_y(\beta\,u+\mu_m)\left(\tilde{\mathcal{R}}_0-1\right)-\eta\,\mu_m}{\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0} & \frac{2\,\mu_y(\beta\,u+\mu_m)\left(\tilde{\mathcal{R}}_0-1\right)-\eta\,\mu_m}{\beta\,u\left(\tilde{\mathcal{R}}_0-1\right)+\mu_m\tilde{\mathcal{R}}_0} & \frac{\mu_2}{f\gamma-\gamma+u} \\ \frac{\mu_y(\tilde{\mathcal{R}}_0-1)^2(\beta\,u+\mu_m)^2}{\mu_m(\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0)} & -\frac{2\left(\tilde{\mathcal{R}}_0-1\right)u\beta+\left(2\tilde{\mathcal{R}}_0-1\right)\mu_m}{\mu_m(\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0)} & -\frac{\mu_m}{f\gamma-\gamma+u} \\ \frac{u\mu_y(\tilde{\mathcal{R}}_0-1)^2(\beta\,u+\mu_m)^2}{\mu_m(\beta\,u(\tilde{\mathcal{R}}_0-1)+\mu_m\tilde{\mathcal{R}}_0)} & -\frac{\mu_y\left(\beta\,f^2\gamma^2-2\,\beta\,f\gamma^2+\beta\,\gamma^2-\beta\,u^2-u\mu_2\right)}{\beta\,(f\gamma-\gamma+u)} & -\frac{\mu_m\gamma\,(f-1)}{f\gamma-\gamma+u} \end{pmatrix}.$$

The characteristic equation of $J_0(\overline{E})$ is

$$P(\lambda) = \Lambda^3 + a_1\Lambda^2 + a_2\Lambda + a_3, \tag{2.32}$$

where

$$a_1 = \frac{\mu_m((\mu_m+\beta u)\tilde{\mathcal{R}}_0+\eta+\mu_y)}{\beta\,u\left(\tilde{\mathcal{R}}_0-1\right)+\mu_m\tilde{\mathcal{R}}_0} > 0,$$

$$a_2 = \mu_y((f\gamma-\gamma+u)^2\,(2\,f\gamma\,\mu_y-2\,\gamma\,\mu_y-u\mu_m+2\,u\mu_y)\,\beta^2+\mu_y\mu_m\,(f\gamma-\gamma+u)^2$$
$$\times\,(2\,\mu_y-\mu_m+\eta)\,\beta+\gamma\,{\mu_2}^3\,(1-f)\,(\mu_y+\eta))/\beta(\gamma(1-f)-u)^2\mu_m > 0,$$

$$a_3 = \frac{\mu_y(\mu_m+\beta u)(\tilde{\mathcal{R}}_0-1)(\mu_m\eta-\mu_y(\mu_m+\beta u)(\tilde{\mathcal{R}}_0-1))}{\beta\,u\left(\tilde{\mathcal{R}}_0-1\right)+\mu_m\tilde{\mathcal{R}}_0} > 0.$$

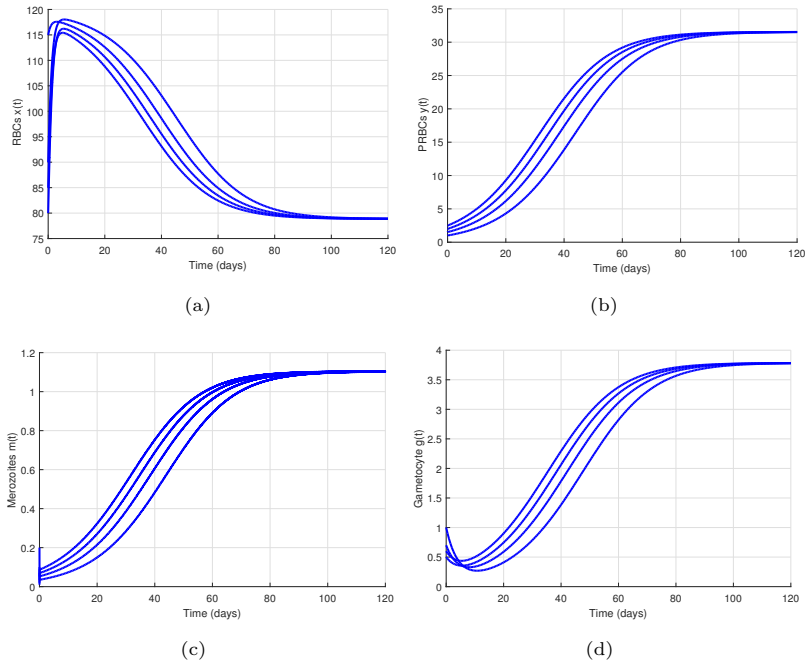
Then, using the Routh-Hurwitz stability criterion, the steady state associated with the characteristic equation (2.32) is stable due to the fact that a_1, a_2 and a_3 are non negative and $a_1a_2 - a_3 > 0$. Hence, $\bar{E}$ is locally asymptotically stable.

Figure 3 shows the local stability of the endemic equilibrium without immunity response. Using various initial conditions when $\beta = 0.8$ and $f = 0.2$ (so that $\tau_0 = 0.2362 < 1$ and $\tilde{\mathcal{R}}_0 = 1.3913 > 1$) all other parameters values are given in Table 1. From this figure, the trajectories of model system 2.1 in absence of immunity response converge to the endemic equilibrium. This means that the disease persists in an infected host which supports result of Lemma 1.

2.4.2. Endemic equilibrium with immune response and its stability

When $\mathcal{R}_f > 1$, the DFE is unstable and model system (2.1) can have an endemic equilibrium point. Let $E^* = (x^*, y^*, m^*, I^*, g^*)$ be any endemic equilibrium of model system (2.1) with $m^* \neq 0$ and $I^* \neq 0$. The explicit form of the endemic equilibrium corresponding to an infection is quite cumbersome because of the complexity of the model, we have managed to obtain some relationships that can be used to determine the existence of an endemic equilibrium. To this end, let

$$U = \frac{I^*}{1+D_y y^*} > 0 \quad \text{and} \quad V = \frac{I^*}{1+D_m m^*} > 0. \tag{2.33}$$



(a) (b) (c) (d)

Figure 3. Time plot of densities of (a) RBCs $x(t)$, (b) PRBCs $y(t)$, (c) free merozoites $m(t)$, (d) gametocytes $g(t)$ using various initial conditions when $\beta = 8$ and $f = 0.2$ (so that $\tau_0 = 0.2362 < 1$, $\tilde{\mathcal{R}}_0 = 1.3913 > 1$). All other parameter values are given in Table 1.

Then, the components of x^*, y^*, m^*, I^* and g^* of E^* satisfy the following system of equations:

$$\begin{cases} \eta x^* \left(1 - \dfrac{x^* + y^*}{K}\right) - \beta \dfrac{x^* m^*}{x^* + y^*} = 0, \\ \beta \dfrac{x^* m^*}{x^* + y^*} - k_y y^* U - \mu_y y^* = 0, \\ \gamma(1-f)\mu_y y^* - \mu_m m^* - k_m m^* V - \beta u \dfrac{x^* m^*}{x^* + y^*} = 0, \\ \rho_y U y^* + m\rho_m V + aI^* - b(I^*)^2 = 0, \\ \delta y^* - \mu_g g^* = 0. \end{cases} \tag{2.34}$$

From the first, second and third equations of (2.34), one has

$$\begin{aligned} x^* &= \frac{K[A_1 + U(Vk_m + \beta u + \mu_m)k_y + \eta(Vk_m + \mu_m)](Uk_y + \mu_y)}{\beta\eta(((1-f)\gamma - u)\mu_y - Uuk_y)}, \\ y^* &= \frac{B_1}{[(1-f)\gamma - u]\mu_y - Uuk_y} \qquad \text{and} \qquad m^* = \frac{B_1}{(Vk_m + \mu_m)}, \end{aligned} \tag{2.35}$$

where

$$A_1 = [[(-1+f]\,\gamma + u)\,\beta + Vk_m + \mu_m]\,\mu_y \qquad \text{and}$$
$$B_1 = -K\frac{(A + U\beta\, uk_y + (Vk_m + \mu_m)(Uk_y + \eta))(A + U(Vk_m + \beta\, u + \mu_m k_y))}{\beta\eta(Vkm + \mu_m)}. \tag{2.36}$$

With in this mind, from the fourth and fifth equations of (2.34), one has

$$I^* = \frac{a + \sqrt{4b\rho_m m^* + 4b\rho_y y^* + a^2}}{2b} \qquad \text{and} \qquad g^* = \frac{\delta y^*}{\mu_g}. \tag{2.37}$$

From Eq. (2.33), one has that

$$U = \frac{I^*}{1 + D_y y^*} \qquad \text{and} \qquad V = \frac{I^*}{1 + D_m m^*}. \tag{2.38}$$

Now, plugging Eq. (2.37) into Eq. (2.38) gives

$$U = UF(U,V) \quad \text{and} \quad V = VG(U,V), \tag{2.39}$$

where

$$F(U,V) = \frac{\left(a + \sqrt{4\,bm^*\rho_m + 4\,by^*\rho_y + a^2}\right)(Uuk_y + f\gamma\,\mu_y - \gamma\,\mu_y + u\mu_y)}{2Ub\,(Uuk_y + f\gamma\,\mu_y - \gamma\,\mu_y + u\mu_y + B_1 D_y)}$$
$$G(U,V) = \frac{\left(a + \sqrt{4\,bm^*\rho_m + 4\,by^*\rho_y + a^2}\right)(Vk_m + \mu_m)}{2Vb\,(B_1 D_m + Vk_m + \mu_m)}, \tag{2.40}$$

with x^* and y^* defined as in Eq. (2.35). Since we are looking for an endemic equilibrium E^* such that $U \neq 0$ and $V \neq 0$, Eq. (2.39) can be simplified as

$$F(U,V) = 1 \quad \text{and} \quad G(U,V) = 1. \tag{2.41}$$

From Eqs. (2.40) and (2.41), the interior endemic equilibrium E^* corresponds to the intersection point (U,V) of the two curves $F(U,V) = 1$ and $G(U,V) = 1$ with $U > 0$ and $V > 0$. Equations in (2.41) is very difficult to solve analytically due to the high nonlinearity of F and G. Nonetheless, we can numerically plot these two curves and examine how the intersection point(s) change with model parameters. We choose $\beta = 16$, $u = 0.5$ and $f = 0.2$ (so that $\mathcal{R}_f = 1.1307 > 1$). All other parameter values are as in Table 1.

Figure 4 illustrates the existence of an interior equilibrium E^* when the basic reproduction number is great than the unity. From this figure, the surfaces of $F(U,V)$ and $G(U,V)$ are plotted and the curves $F(U,V) = 1$ and $G(U,V) = 1$ are shown as intersections of the surfaces with the plane of unity (see Figs. 4 (a) and (b)). Figure 4(c) illustrates that there is a unique point (U,V) at which $F(U,V) = G(U,V) = 1$.

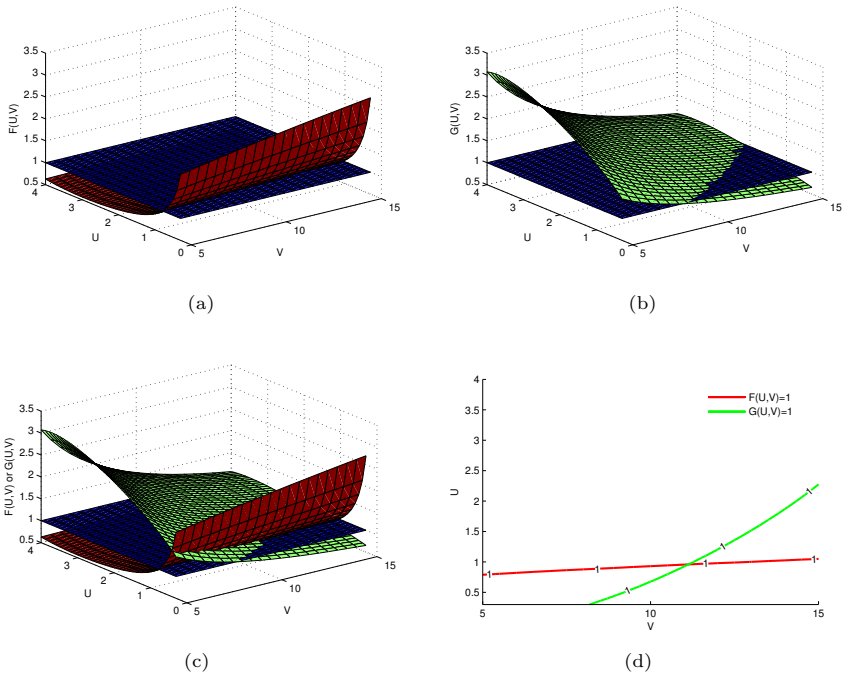


Figure 4. In (a) and (b) we see that there is a curve in the (U, V) which plane along with $F(U, V) = 1$ and $G(U, V) = 1$, respectively. (c) illustrates that there is a unique point at which $F(U, V) = G(U, V) = 1$. This point determines an endemic equilibrium E^*. (d) shows the contour curves $F(U, V) = 1$ and $G(U, V) = 1$, and there is a unique intersection point. We choose $\beta = 16$, $u = 0.5$ and $f = 0.2$ (so that $\mathcal{R}_f = 1.1307 > 1$). All other parameter values are as in Table 1.

Proposition 2.1. *: The unique endemic equilibrium E^* of the model (2.1) guaranteed numerically is locally asymptotically stable for $\mathcal{R}_f > 1$ but close to* 1.

The proof of the Proposition 2.1 is given in Appendix.

Figure 5 shows the result of numerical simulations of model system (2.1) using various initial conditions when $\beta = 16$ and $f = 0.2$ (so that $\mathcal{R}_f = 1.12024 > 1$). All other parameters values are given in Table 1. It clearly appears that the trajectories of model system (2.1) converge to the unique endemic equilibrium point. This means that the disease persists in an infected host which supports result of Proposition 2.1.

2.5. Sensitivity analysis

The asymptotic dynamics of model system (2.1) are completely determined by the threshold quantity $\mathbb{R}_f$, which determines the prevalence of the disease. Since model system (2.1) is a deterministic model, the only uncertainty is generated by the input variation and parameters. We present parameter-related global sensitivity analysis of each malaria model (2.1) output variable to all parameters as a whole. Parameter estimates can be uncertain because of many reasons including natural variations, error in measurements, or a lack of measuring techniques. The sensitivity analysis identifies critical model parameters and quantifies the impact of each input parameter on the value of an output in the presence of the other input parameters.

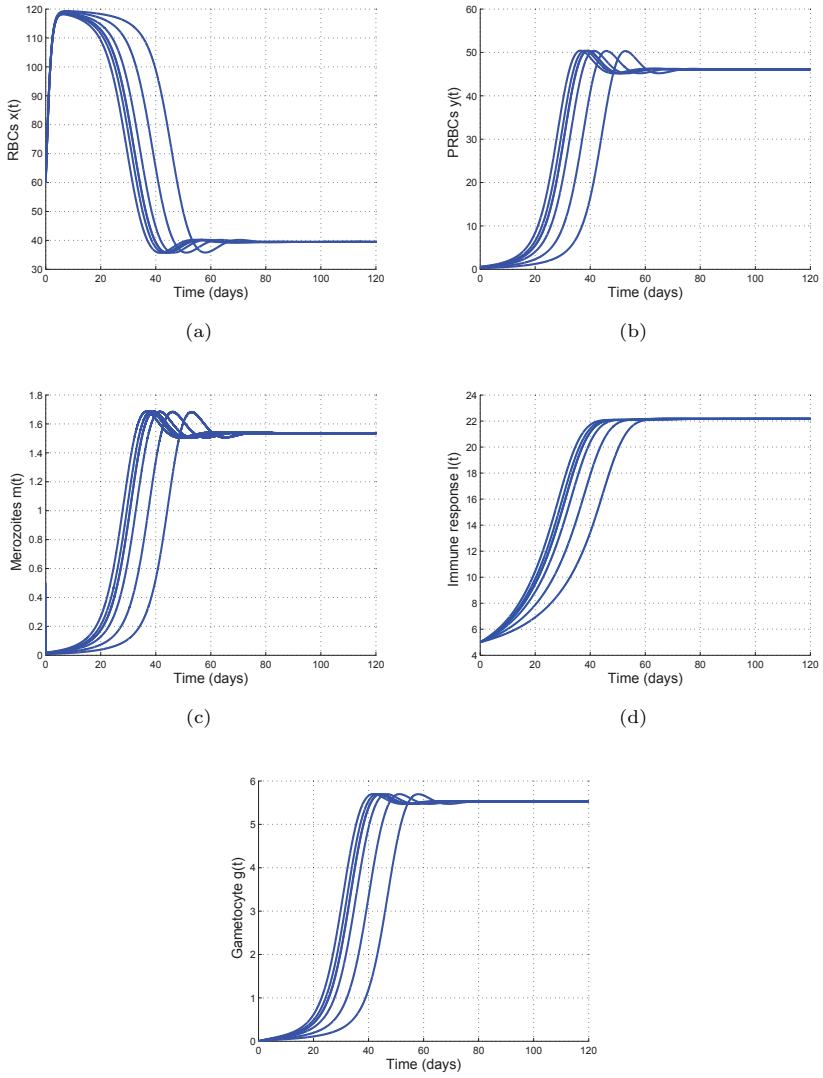


Figure 5. Time plot of densities of (a) RBCs $x(t)$, (b) PRBCs $y(t)$, (c) free merozoites $m(t)$, (d) immune effectors $I(t)$ and (e) gametocytes $g(t)$ using various initial conditions when $\beta = 16$ and $f = 0.2$ (so that $\mathcal{R}_f = 1.12024 > 1$). All other parameter values are given in Table 1.

This analysis has the advantage that the entire parameter is explored, but this design is extremely time consuming and hence impractical for complex transmission models that contain a multiple of parameters.

A sensitivity analysis carried out by estimating the partial rank correlation coefficients (PRCC) for each input parameter and each outcome variable, can identify which parameters are important in contributing to the variability outcomes [24]. Then, we point out interesting insights that emerge from a comparison of the terms that appear in $\mathbb{R}_f$. Examination of $\mathbb{R}_f$ indicates that β, γ, k_y, k_m, μ_y, μ_m, f, and u

are potentially influential terms. The relative importance of the input variables can be directly evaluated by comparing the values of the PRCC. The sign of the PRCC indicates the qualitative relationship between each input variable and each output variables. The magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the outcome variable. Using Latin hypercube sampling, 500 samples from a uniform distribution of the parameter ranges of model were taken. PRCCs were calculated following the procedures described in [17]. PRCC falls between -1 and +1, with an absolute value of PRCC close to 1 indicating that the parameter has a strong impact on the model output.

These PRCC were used to identify the key input variables that contributed to the prediction imprecision; the PRCC results are presented in Fig. 6. Figures 6(a)-(e) show PRCC values for uninfected RBCs $x(t)$, PRBCs $y(t)$, free merozoites $m(t)$, immune effectors $I(t)$ and gametocytes $g(t)$. This analysis identifies several mechanisms that regulate malaria infection outcome. The most significant (PRCC values above 0.5 or below -0.5) sensitivity parameter are γ, k_y, μ_y and f. The sensitivity analysis shows that the drug efficiency f is negatively correlated with PBRCs $y(t)$, free merozoites $m(t)$ and immune effectors $I(t)$, while RBCs $x(t)$ is positively correlated with drug efficiency. This suggests that these parameters need to be estimated with precision in order to accurate the dynamics of malaria infection.

3. The spatio-temporal model

In this section, we extend model system (2.1) taking into account the spatial component in the modeling [26]. Following the invasion of a blood vessel, sporozoites travel with the blood flow to the liver, where they are arrested and moved on the endothelium, before passing through liver-resident macrophages and invade hepatocytes. Now, we consider that movement of RBCs, PRBCs, free merozoites, immune effectors and gametocytes within the body of a host. We assume that all cells diffuse randomly in an isotropy two-dimensional domains.

According to the above explanations, we derive the following spatiotemporal model:

$$\begin{cases} \dfrac{\partial x}{\partial t}(t,w) &= \eta x\left(1-\dfrac{x+y}{K}\right)-\beta\dfrac{xm}{x+y}+\varepsilon_x\Delta x,\\ \dfrac{\partial y}{\partial t}(t,w) &= \beta\dfrac{xm}{x+y}-k_y\dfrac{Iy}{1+D_y y}-\mu_y y+\varepsilon_y\Delta y,\\ \dfrac{\partial m}{\partial t}(t,w) &= \gamma(1-f)\mu_y y-\mu_m m-k_m\dfrac{Im}{1+D_m m}-\beta u\dfrac{xm}{x+y}+\varepsilon_m\Delta m,\\ \dfrac{\partial I}{\partial t}(t,w) &= I\left(\rho_y\dfrac{y}{1+D_y y}+\rho_m\dfrac{m}{1+D_m m}\right)+aI-bI^2+\varepsilon_I\Delta I,\\ \dfrac{\partial g}{\partial t}(t,w) &= \delta y-\mu_g g+\varepsilon_g\Delta g, \end{cases} \tag{3.1}$$

where ε_x, ε_y, ε_m, ε_I and ε_g are respectively, the diffusion parameters of RBCs, PRBCs, free merozoites, immune effectors and gametocytes, $w=(u,v)\in\mathbb{R}^2_+$ is the space and $\Delta=\dfrac{\partial^2}{\partial u^2}+\dfrac{\partial^2}{\partial v^2}$ the Laplacian operator.

To avoid a migration of populations, we consider the following Neumann bound-

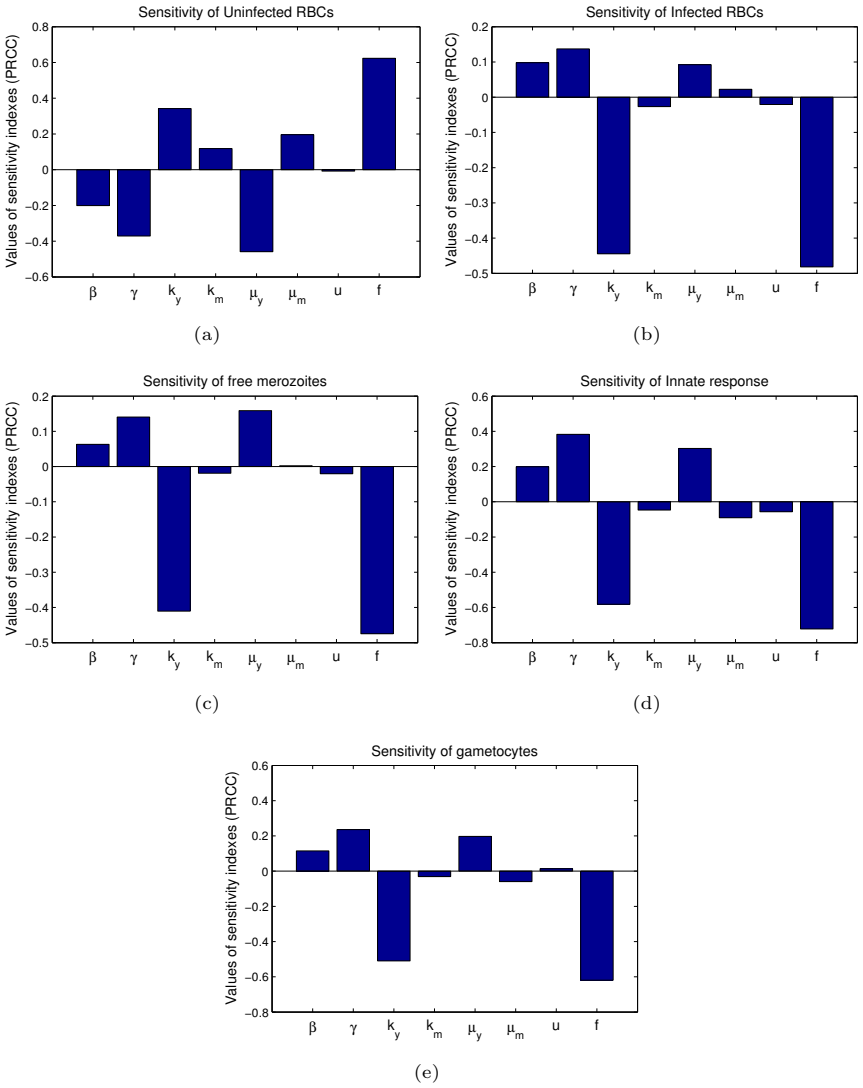


Figure 6. Values of sensitivity indexes (PRCC) of uninfected RBCs, PRBCs, free merozoites, immune effectors and gametocytes.

ary conditions:

$$\begin{aligned}
&\frac{\partial x}{\partial \nu}(t,w) = \frac{\partial y}{\partial \nu}(t,w) = \frac{\partial m}{\partial \nu}(t,w) = \frac{\partial I}{\partial \nu}(t,w) = \frac{\partial g}{\partial \nu}(t,w) = 0, \qquad (t,w) \in \mathbb{R}_+ \times \partial\Gamma,\\
&x(0,w) = x_0(w), \qquad y(0,w) = y_0(w), \qquad m(0,w) = m_0(w), \;\; I(0,w) = I_0(w)\\
&\text{and } g(0,w) = g_0(w), \;\; w \in \Gamma \subset \mathbb{R}^2,
\end{aligned} \tag{3.2}$$

where Γ is a bounded domain and the initial conditions x_0, y_0, m_0, I_0 and g_0 are non-negative and bounded functions defined in Γ. In the sequel, we will denote by

$\overline{\Gamma}$ the closure of Γ.

3.1. Model basic properties

For model system (3.1), all solutions with non-negative initial functions are ultimately bounded. Indeed, let $(x(t,w), y(t,w), m(t,w), I(t,w), g(t,w))$ be the solution of model system (3.1) such that $x(0,w) = x_0(w)$, $y(0,w) = y_0(w)$, $m(0,w) = m_0(w)$, $I(0,w) = I_0(w)$, and $g(0,w) = g_0(w)$ are non-negative and bounded functions defined in Γ. Now, let

$$z(t,w) = x(t,w) + y(t,w), \quad \overline{x}_0 = \max_{\overline{\Gamma}} x_0(w), \quad \underline{x}_0 = \min_{\overline{\Gamma}} x_0(w), \quad \overline{y}_0 = \max_{\overline{\Gamma}} y_0(w),$$
$$\underline{y}_0 = \min_{\overline{\Gamma}} y_0(w), \quad \overline{m}_0 = \max_{\overline{\Gamma}} m_0(w), \quad \underline{m}_0 = \min_{\overline{\Gamma}} m_0(w), \quad \overline{I}_0 = \max_{\overline{\Gamma}} I_0(w),$$
$$\underline{I}_0 = \min_{\overline{\Gamma}} I_0(w), \quad \overline{g}_0 = \max_{\overline{\Gamma}} g_0(w) \text{ and } \underline{g}_0 = \min_{\overline{\Gamma}} g_0(w).$$

It is obvious that $(0,0,0,0,0)$ is a lower solution of model system (3.1). Moreover, we have

$$\overline{x_0} \geq 0, \qquad \overline{y_0} \geq 0, \qquad \overline{m_0} \geq 0, \qquad \overline{I_0} \geq 0, \qquad \text{and} \qquad \overline{g_0} \geq 0.$$

Thus, by the maximum principle, one can conclude that

$$x(t,w) \geq 0, \quad y(t,w) \geq 0, \quad m(t,w) \geq 0, \quad I(t,w) \geq 0 \text{ and } g(t,w) \geq 0.$$

This implies that any solution of model system (3.1) with positive initial condition will remain positive.

Now, we will prove that the solutions of model system (3.1) admit also upper limits. Without loss of generality, we assume that $\varepsilon_x = \varepsilon_y = \varepsilon_I$. Then, from model system (3.1), one has

$$\frac{\partial T}{\partial t} = \eta x \left(1 - \frac{T}{K}\right) - \mu_y y - k_y \frac{Iy}{1 + D_y y} + \varepsilon_1 T.$$

From the above equation, one can deduce that

$$\frac{\partial T}{\partial t} \leq \eta x \left(1 - \frac{T}{K}\right) + \varepsilon_1 T \leq \eta T(1 - \frac{T}{K}) + \varepsilon_1 T.$$

Consider the following equation:

$$\frac{\partial \overline{T}}{\partial t} = \eta \overline{T} \left(1 - \frac{\bar{T}}{K}\right) + \varepsilon_1 \overline{T}.$$

Solving the above equation gives

$$\overline{T}(t) = \frac{K\overline{T}(0)}{\overline{T}(0) + (K - \overline{T}(0))e^{-\eta t}}$$

where $\overline{T}(0) = \overline{x_0} + \overline{y_0}$. Now, using the maximum principle, one has

$$T(t,w) \leq \overline{T}(t) = \frac{K\overline{T}(0)}{\overline{T}(0) + (K - \overline{T}(0))e^{-\eta t}}. \tag{3.3}$$

Applying Birkhoff's and Rota's theorem on differential inequality , as t goes to the infinity, one can deduce that $T(t,w) \leq K$, $\forall t \in \mathbb{R}_+$ which implies that $x(t,w) \leq K$ and $y(t,w) \leq K$ for all $t \in \mathbb{R}_+$.

Using the same reasoning, one can establish that

$$m(t,w) \leq \frac{\gamma(1-f)\mu_y K}{\mu_m}. \tag{3.4}$$

We can use the same reasoning to prove that $I(t,w)$ and $g(t,w)$ are ultimately bounded.

3.2. Numerical simulations

We now provide several simulations, resulting from the spatio-temporal models (3.1). We assume that the diffusion paramaters of RBCs, PRBCs, malaria parasites, immune effectors and gametocytes are the same that $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.5$. The boundary conditions are of Neumann type, i.e. the flow at the edge is zero. Initially, the densities or RBCs, PBRCs, free merozoites, immune effectors and gametocytes are randomly distributed in space $w = (u,v) \in \mathbb{R}^2_+$ and outside the space, their densities are zero.

We first consider the spatio-temporal model system (3.1) in the absence of any antimalarial treatment, that is $f = 0$ (so that $\mathcal{R}_f = R_0 = 1.5030 > 1$) using the parameter values given in Table 1. Using these parameter values, the movement paths of $x(t)$, $y(t)$, $m(t)$, $I(t)$ and $g(t)$ after 10 days are presented in Fig. 7. It clearly appears that PRBcs, free merozoites and gametocytes increase and reach a steady endemic state since $\mathcal{R}_f > 1$. This figure also shows that the only effect of the immune response is not sufficient to vanish the populations of PRBCs and free merozoites when $\mathcal{R}_f > 1$. Indeed, the populations of uninfected RBCs, PRBCs, free merozoites, immune effectors and gametocytes reach a steady endemic state since $\mathcal{R}_f > 1$.

Figure 8 shows the spatial repartition of the spatio-temporal model system (3.1) after 10 days with insufficient drug efficiency when $f = 0.15$ and $f_c = 0.7188$ (so that $\mathcal{R}_f = 1.4134$ and $f < f_c$). All other parameter values as in Table 1. It illustrates that the population tends the endemic equilibrium point. This means that the drug efficiency is completely ineffective when $f < f_c$.

Figure 9 shows the behavior of the spatio-temporal model system (3.1) after 10 days with a sufficient drug efficiency when $f = 0.8$ and $f_c = 0.7188$ (so that $\mathcal{R}_0 = 1.4134$, $\mathcal{R}_f = 0.3006$ and $f > f_c$). All other parameter values as in Table 1. From this figure, the parasites are eliminated due to the effect of drugs. This implies that the infection can be eradicated if the drug efficiency is greater than the critical drug efficiency (i.e. $f > f_c$).

4. Concluding remarks

In this paper, we have proposed and analyzed a deterministic model for the dynamical transmission of malaria within the body of a host. We have first considered a temporal compartmental approach and then include the spatial component that leads to a system of coupled diffusion-reaction-like equations to model parasite dispersal. The temporal model considered takes into account the standard incidence,

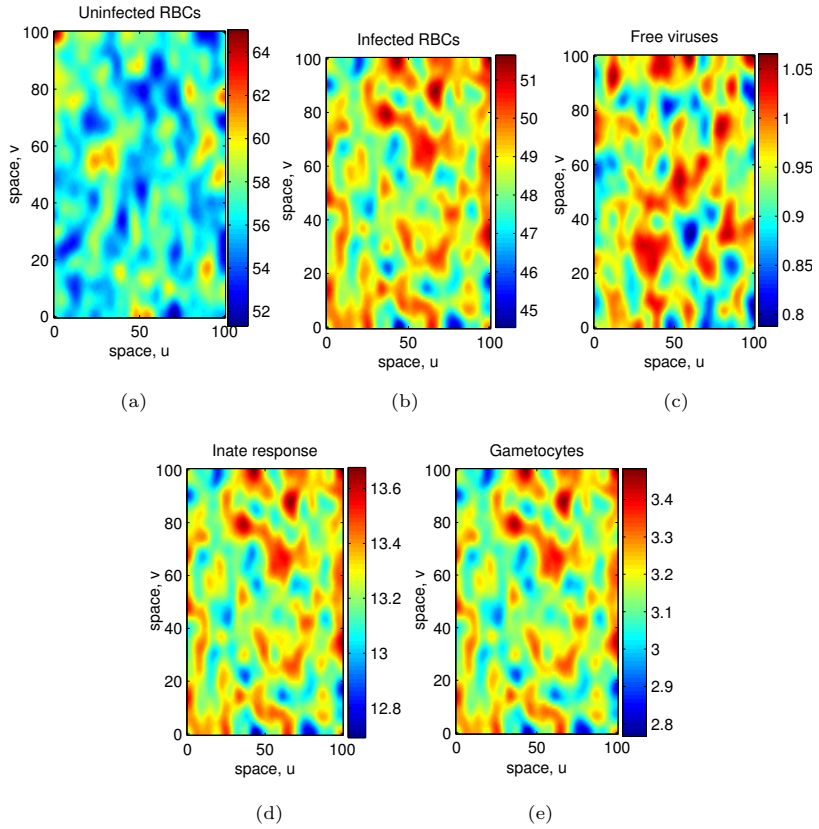


Figure 7. Spatio-temporal evolution of model system (3.1) after 10 days without any treatment, that is $f = 0$ (so that $\mathcal{R}_f = \mathcal{R}_0 = 1.5030$ and $f_c = 0.7188$) All other parameter values as in Table 1.

the immune response and the treatment with antimalarial drugs. We used Michaelis-Menten-Monod functions to describe how immune cells interact with PRBCs and free merozoites. A qualitative analysis of the temporal model has been presented. The epidemic threshold parameter $\mathcal{R}_f$ which determines the outcome of the disease is computed and used to assess the dynamics of the disease within a host. The malaria disease-free equilibrium is obtained and its stability is investigated depending on the system parameters. More precisely, we shown that depending of the values of the parameters, there exists a threshold parameter ζ close to 1 such that the malaria free equilibrium is GAS if $\mathcal{R}_f < \zeta < 1$. However, we also shown that if $\mathcal{R}_f > 1$, the model has two endemic equilibria: one endemic equilibrium without immune response which is stable under certain condition and one endemic equilibrium point with immune response whose existence has been proved through numerical simulation which is locally asymptotically stable when $\mathcal{R}_f$ close to 1. We performed the sensitivity analysis of the threshold parameter ζ. We found that the threshold parameter ζ increase with the death rates of PRBCs and free merozoites and the increasing rate of immune effectors. Thus, if the increasing rate of immune effectors is sufficiently large the malaria parasites can be cleared within the body of an infected host. This result is expected. The sensitivity analysis of the mod-

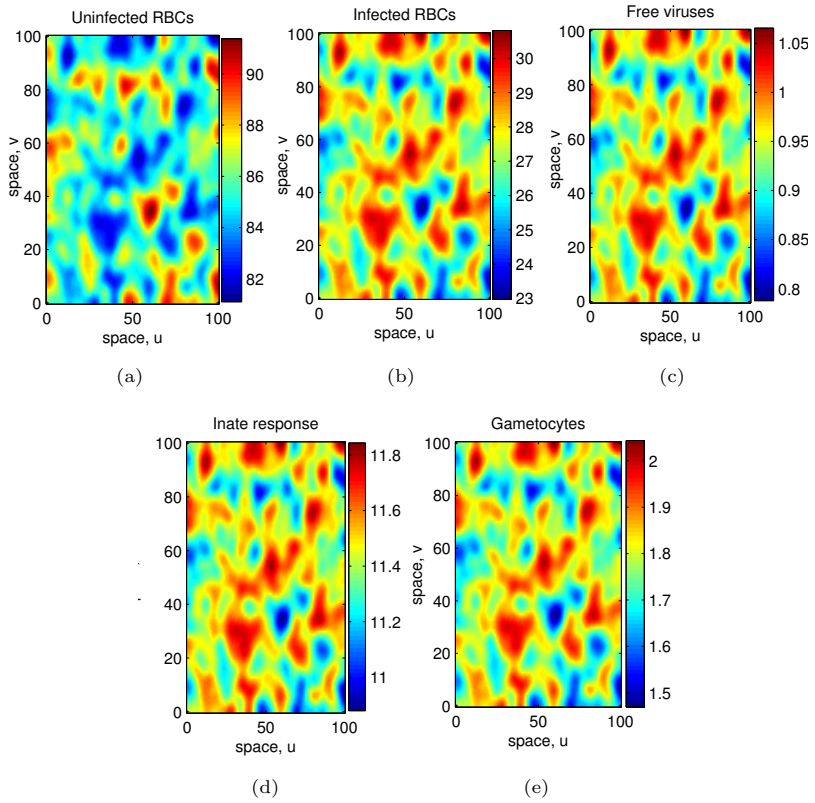


Figure 8. Spatio-temporal evolution of model system (3.1) after 10 days with insufficient drug efficiency when $f = 0.20$ and $f_c = 0.7188$ (so that $\mathcal{R}_f = 1.2024$ and $f < f_c$). All other parameter values as in Table 1.

el has been investigated to assess the impact of changes in parameter values on the values of output model variables. We found that the model variables are most sensitive to merozoites mean rate produce by PRBCs γ, immune effectors reaction against PRBCs k_y, the death rate of PRBCs and the drug efficiency f. Numerical simulations have been presented to support theoretical results.

We have extended the temporal model to a spatio-temporal model using Diffusion-Reaction equations. We have numerically assessed the importance of the spatial distribution of RBCs, PRBCs, merozoites, gametocytes and immune effectors within a host. We found that there exists parasites can be cleared from an infection if the efficiency of drug f is great than the critical drug efficiency f_c, that is $f > f_c$. This implies that drugs with a critical efficiency of drug f_c are required to treat the infection within a host.

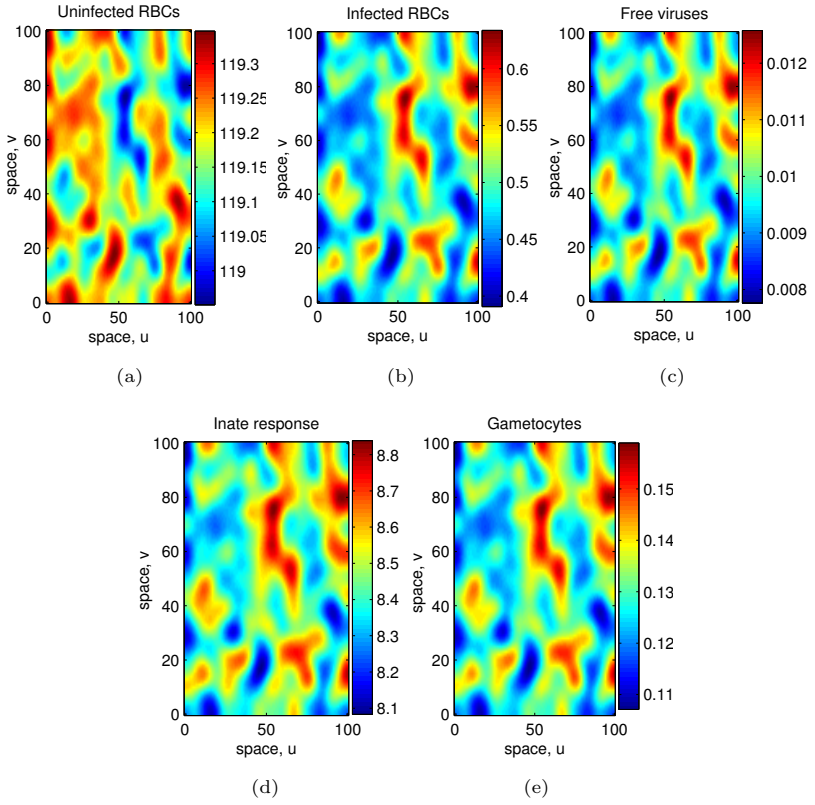


Figure 9. Spatio-temporal evolution of model system (3.1) after 10 days with a sufficient drug efficiency when $f = 0.8$ and $f_c = 0.7188$ (so that $\mathcal{R}_0 = 1.4134$, $\mathcal{R}_f = 0.3006$ and $f > f_c$). All other parameter values as in Table 1.

5. Appendix: Proof of Proposition 2.1

Herein, we prove that the unique endemic equilibrium with immune response E^* is locally asymptotically stable whenever $\mathcal{R}_0 > 1$. To do this, we use the following theorem of Castillo-Chavez and Song [6].

Theorem 5.1 (C. Castillo-Chavez, B. Song, 2004)**.** *Consider the following general system of ordinary differential equations with a parameter ϕ:*

$$\frac{dz}{dt} = f(z,\phi), \qquad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \qquad \text{and} \qquad f \in C^2(\mathbb{R}^n, \mathbb{R}), \tag{5.1}$$

where 0 is an equilibrium point of the system (that is, $f(0,\phi) \equiv 0$ for all ϕ) and assume

1. *$A = D_z f(0,0) = \left(\dfrac{\partial f_i}{\partial z_j}(0,0)\right)$ is the linearization matrix of system (5.1) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*
2. *Matrix A has a right eigenvector u and a left eigenvector v (each corresponding to the zero eigenvalue).*

Let f_k be the k^{th} component of f and

$$a_1 = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial z_i \partial z_j}(0,0),$$
$$b_1 = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial z_i \partial \phi}(0,0),$$

then, the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b.

1. *$a_1 > 0$, $b_1 > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*
2. *$a_1 < 0$, $b_1 < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;*
3. *$a_1 > 0$, $b_1 < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;*
4. *$a_1 < 0$, $b_1 > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a_1 > 0$ and $b_1 > 0$, then a backward bifurcation occurs at $\phi = 0$.

In order to apply Castillo-chavez and Song theorem [6], the following simplification and change of variables are first of all made.

Let $x_1 = x$, $x_2 = y$, $x_3 = m$, $x_4 = I$ and $x_5 = g$. Further, by using the vector notation $x = (x_1, x_2, x_3, x_4, x_5)^T$, model system (2.1) can be written in the form $x' = F(x)$, with $F = (F_1, F_2, F_3, F_4)^T$ and $T = x_1 + x_2$, as follows:

$$\begin{cases} \dot{x}_1 = F_1 = \eta x_1 \left(1 - \dfrac{T}{K}\right) - \beta \dfrac{x_1 x_3}{T}, \\ \dot{x}_2 = F_2 = \beta \dfrac{x_1 x_3}{T} - \mu_y x_2 - k_y \dfrac{x_2 x_4}{1 + D_y x_2}, \\ \dot{x}_3 = F_3 = \gamma(1-f)\mu_y x_2 - \mu_m x_3 - k_m \dfrac{x_3 x_4}{1 + D_y x_3} - \beta u \dfrac{x_1 x_3}{T}, \\ \dot{x}_4 = F_4 = x_4 \left(\rho_y \dfrac{x_2}{1 + D_y x_2} + \rho_m \dfrac{x_3}{1 + D_m x_3}\right) + a x_4 - b x_4^2, \\ x_5' = F_5 = \delta x_2 - \mu_g x_5. \end{cases} \tag{5.2}$$

System (5.2) has a DFE given by $E_0 = (x_1^0, 0, 0, x_4^0, 0)$ where $x_1^0 = K$ and $x_4^0 = \frac{a}{b}$. Consider now the case when $\mathbb{R}_f = 1$. Suppose, further, that $\gamma = \gamma^*$ is chosen as a bifurcation parameter, with γ standing for Φ in the Theorem 4.1 of Castillo-Chavez and Song [6]. Solving for γ from $R_f = 1$ gives

$$\gamma = \gamma^* = \frac{(k_y x_4^0 + \mu_y)(\mu_m + k_m x_4^0 + \beta u)}{\beta(1-f)\mu_y}. \tag{5.3}$$

The Jacobian matrix of the temporal model system (5.2 around the disease free-equilibrium when $\gamma = \gamma^*$ is

$$J(E_0) = \begin{pmatrix} -\eta & -\eta & -\beta & 0 & 0 \\ 0 & -\frac{k_y a}{b} - \mu_y & \beta & 0 & 0 \\ 0 & \gamma^*(1-f)\mu_y & -\mu_m - \frac{k_m a}{b} - \beta u & 0 & 0 \\ 0 & \rho_y \frac{a}{b} & \rho_m \frac{a}{b} & -a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{pmatrix}. \tag{5.4}$$

It can be easily seen that the Jacobian $J(E_0)$ of system (5.2) at the DFE E_0, with $\gamma = \gamma^*$, named J_{γ^*} has zero as a simple eigenvalue (with all other eigenvalues having negative real parts). Hence, the Center Manifold theory can be used to analyze the dynamics of system (5.2). In particular, the theorem in Castillo-Chavez and Song [6] will be used to show that when $\mathbb{R}_0 > 1$, the unique endemic equilibrium of system 2.1 (as show numerically in Fig. 4) is locally asymptotically stable for $\mathbb{R}_0$ near 1 under certain condition.

In order to apply Castillo-Chavez and Song theorem [6], we need to compute:

- **Eigenvectors of J_{γ^*}**
  For the case when $R_f = 1$, it can be shown that the Jacobian of system (5.2) has a right eigenvector (corresponding to the zero eigenvalue), given by $w = (w_1, w_2, w_3, w_4, w_5)^T$, where,

$$\begin{cases} w_1 = -\dfrac{\eta + k_y x_4^0 + \mu_y}{\eta} w_2, \\ w_2 = w_2 > 0, \\ w_3 = \dfrac{k_y x_4^0 + \mu_y}{\beta} w_2, \\ w_4 = \dfrac{x_4^0}{a}\left(\rho_y + \dfrac{\rho_m(k_y x_4^0 + \mu_y)}{\beta}\right) w_2, \\ w_5 = \dfrac{\delta}{\mu_g} w_2. \end{cases} \tag{5.5}$$

  Similarly, the components of the left eigenvector (corresponding to the zero eigenvalue) denoted by $v = (v_1, v_2, v_3, v_4, v_5)^T$ are given by

$$\begin{cases} v_1 = 0, \\ v_2 = v_2 > 0, \\ v_3 = \dfrac{k_y x_4^0 + \mu_y}{\gamma \mu_y (1-f)} v_2, \\ v_4 = 0, \\ v_5 = 0. \end{cases}$$

- **Computation of b_1**

It can be shown that the associated non-vanishing second partial derivatives of F at E_0 are:

$$\frac{\partial^2 F_3}{\partial x_2 \partial \gamma}(E_0) = \gamma(1-f)\mu_y.$$

Then, once can deduce that

$$\begin{aligned} b_1 &= \sum_{i,k=1}^{5} v_k w_i \frac{\partial^2 F_k}{\partial x_i \partial \gamma}(E_0), \\ &= v_3 w_2 \frac{\partial^2 F_k}{\partial x_2 \partial \gamma}(E_0), \\ &= k_y \frac{a}{b} + \mu_y > 0. \end{aligned}$$

- **Computation of a_1**
  For model system (5.2), the associated non-vanishing second partial derivatives of F at E_0 are

$$\begin{aligned} &\frac{\partial^2 F_2}{\partial^2 x_2^2}(E_0) = 2k_y D_y x_4^0, \quad \frac{\partial^2 F_2}{\partial x_2 \partial x_3}(E_0) = \frac{-\beta}{K}, \quad \frac{\partial^2 F_2}{\partial x_2 \partial x_4}(E_0) = -k_y, \\ &\frac{\partial^2 F_3}{\partial x_2 \partial x_3}(E_0) = \frac{\beta u}{K}, \quad \frac{\partial^2 F_2}{\partial^2 x_3^2}(E_0) = 2k_m D_m x_4^0, \quad \frac{\partial^2 F_3}{\partial x_3 \partial x_4}(E_0) = -k_m. \end{aligned}$$

Therefore,

$$\begin{aligned} a_1 &= \sum_{i,j,k=1}^{5} v_k w_i w_j \frac{\partial^2 F_k}{\partial x_i \partial x_j}(E_0), \\ &= v_2 \left[w_2^2 \frac{\partial^2 F_2}{\partial^2 x_2^2}(E_0) + 2w_2 w_2 \frac{\partial^2 F_2}{\partial x_2 \partial x_3}(E_0) + 2w_2 w_4 \frac{\partial^2 F_2}{\partial x_2 \partial x_4} \right] \\ &\quad + v_3 \left[w_3^2 \frac{\partial^2 F_2}{\partial^2 x_3^2}(E_0) + 2w_2 w_3 \frac{\partial^2 F_2}{\partial x_2 \partial x_3}(E_0) + 2w_3 w_4 \frac{\partial^2 F_2}{\partial x_3 \partial x_4}(E_0) \right], \\ &= -2v_2 w_2^2 \left[\frac{(\mu_y + k_y x_4^0)(\mu_m + k_m x_4^0)}{K(\mu_m + k_m x_4^0 + \beta u)} + \frac{k_y x_4^0}{a}(\rho_y - D_y a) \right] \\ &\quad -2v_2 w_2^2 \left[\frac{k_m x_4^0 (\mu_m - a D_m)(\mu_y + k_y x_4^4)^3}{\gamma \mu_y (1-f)\beta^2 a} + \frac{k_m \rho_y x_4^0 (\mu_y + k_y x_4^0)^2}{a\gamma\mu_y(1-f)\beta} \right. \\ &\quad \left. + \frac{k_y \rho_y x_4^0 (\mu_y + k_y x_4^0)}{a\beta} \right] < 0. \end{aligned}$$

Thus, since $a_1 < 0$, the endemic equilibrium E^* is locally asymptotically stable with the basic reproduction number near to 1. This concludes the proof. □

Acknowledgements. The authors are grateful to the anonymous referees for their useful suggestions which improve the contents of this article.

References

[1] Z. Agur, D. Abiri, L. H. Van der Ploeg, *Ordered appearance of antigenic variants of African trypanosomes explained in a mathematical model based on a*

stochastic switch process and immune-selection against putative switch intermediates, Proceedings of the Nat. Acad. of Sci., 1989, 86(23), 9626–9630.

[2] R. M. Anderson, R. M. May, S. Gupta, *Non-linear phenomena in host parasite interactions,* Parasitology, 1989, 99(S1), S59–S79.

[3] A. Bertoletti, A. J. Gehring, *The immune response during hepatitis B virus infection,* J. of Gen. Virol., 2006, 1439–1449.

[4] C. Boudin, V. Robert, *Plasmodium falciparum: epidemiometrie de la transmission homme-moustique et de l'infection chez le vecteur,* Bull Soc Pathol Exot, 2003, 96(4), 335–340.

[5] G. Birkhoff, G. Rota, *Ordinary differential equations*, Wiley, 1989, 4th ed.

[6] C. Castillo-Chavez, B. Song, *Dynamical models of tuberculosis and their applications,* Math. biosc. and engineering, 2004, 1(2), 361–404.

[7] F. V. Chisari, M. Isogawa, S. F. Wieland, *Pathogenesis of hepatitis B virus infection,* Pathologie Biologie, 2010, 58(4), 258–266.

[8] C. Chiyaka, W. Garira, S. Dube, *Modelling immune response and drug therapy in human malaria infection,* Comput. and Math. Methods in Medicine, 2008, 9(2), 143–163.

[9] R. J. De Boer, A. S. Perelson, *Towards a general function describing T cell proliferation,* J of theo. biology, 1995, 175(4), 567–576.

[10] H. Diebner, M. Eichner, L. Molineaux, W. E. Collins, G. M. Jeffery, K. Dietz, *Modelling the transition of asexual blood stages of Plasmodium falciparum to gametocytes,* J. of Theo. Biology, 2000, 202(2), 113–127.

[11] C. F. Huang, S. S. Lin, Y. C. Ho, F. L. Chen, C. C. Yang, *The immune response induced by hepatitis B virus principal antigens,* Cell Mol Immunol, 2006, 97–106.

[12] J. A. P. Heesterbeek, *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation,*John Wiley & Sons,2000, Vol. 5.

[13] M. B. Hoshen, R. Heinrich, W. D. Stein, H. Ginsburg, *Mathematical modelling of the within-host dynamics of Plasmodium falciparum,* Parasitology, 2000, 121(03), 227–235.

[14] B. Kamangira, P. Nyamugure, G. Magombedze, *A theoretical mathematical assessment of the effectiveness of coartemether in the treatment of Plasmodium falciparum malaria infection,* Math. biosci., 2014, 256, 28–41.

[15] J. C. Kamgang, G. Sallet, *Computation of threshold conditions for epidemiological models and global stability of the disease-free equilibrium (DFE)*, Mathematical biosciences, 2008, 213(1), 1–12.

[16] L. Malaguarnera, S. Musumeci, *The immune response to Plasmodium falciparum malaria,* The Lancet infectious diseases, 2002, 2(8), 472–478.

[17] S. Marino, I. B. Hogue, C. J. Ray, D. E. Kirschner, *A methodology for performing global uncertainty and sensitivity analysis in systems biology,*. J. of theo. biology, 2008, 254(1), 178–196.

[18] F. E. McKenzie, W. H. Bossert, *The Dynamics of Plasmodium falciparumBlood-stage Infection,* J. of Theo. Biology, 1997, 188(1), 127–140.

[19] F. E. McKenzie, W. H. Bossert, *The Optimal Production of Gametocytes by Plasmodium falciparum,* Journal of Theoretical Biology, 1998, 193(3), 419–428.

[20] P. G. McQueen, F. E. McKenzie, *Age-structured red blood cell susceptibility and the dynamics of malaria infections.* Proceedings of the Nat. Acad. of Sci. of USA, 2004, 24, 9161–9166.

[21] L. Molineaux, H. H. Diebner,M. Eichner, W. E Collins, G. M. Jeffery, K. Dietz, *Plasmodium falciparum parasitaemia described by a new mathematical model,* Parasitology, 2001, 122(04), 379–391.

[22] S. S. Pilyugin, R. Antia, *Modeling immune responses with handling time*, Bulletin of mathematical biology, 2000, 62(5), 869–890.

[23] C. Pramoolsinsup, *Management of viral hepatitis B*, Journal of gastroenterology and hepatology, 2002, 17, S125–S145.

[24] M. A. Sanchez, S. M. Blower, *Uncertainty and sensitivity analysis of the basic reproductive rate: tuberculosis as an example,* American Journal of Epidemiology, 1997, 145(12), 1127–1137.

[25] J. A. Simpson, E. R. Watkins, R. N. Price, L. Aarons, D. E. Kyle, N. J. White, *Mefloquine pharmacokinetic-pharmacodynamic models: implications for dosing and resistance,* Antimicrobial agents and chemotherapy, 2000, 44(12), 3414–3424.

[26] E. Takoutsing, S. Bowong, D. Yemele, J. Kurths, *Effects of Catastrophic Anemia in an Intra-Host Model of Malaria* Internat. J. of Bifur. Chaos, 2014, 24, 1450105.

[27] P. Van den Driessche, J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. biosc., 2002, 180(1), 29–48.

[28] L. Wang, Z. Teng, T. Zhang, *Threshold dynamics of a malaria transmission model in periodic environment,* Communicat. in Nonl. Sci. and Numerical Simulation, 2013, 18(5), 1288–1303.

[29] N. White, *Antimalarial drug resistance and combination chemotherapy,* Philosophical Transactions of the Royal Society of London B: Biol. Sci., 1999, 739–749.

[30] World Health Organisation, *World Malaria Report,* 2015, http://www.who.int/malaria/world-malariareport- 2015/en/.