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Dynamics of An Intra-Host Model of Malaria with Periodic Antimalarial Treatment

E. Takoutsing[1] *, A. Temgoua[2], D. Yemele[1], S. Bowong[2]
[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

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Abstract: In this paper, we investigate the dynamics of a within-host model of malaria with periodic anti malaria treatment. The aim is to theoretically asses the potential impact of the drug efficiency on the dynamics of infected red blood cells and malaria parasites. We consider a periodic treatment of bang-bang type and use the Floquet theory to provide a theoretical study of the model. The theory is supported by numerical simulations. We found that the eradication is possible under periodic regimens. We also derive a spatio-temporal model, using Diffusion-Reaction equations to describe how the drug duration and efficiency can affect the parasite dispersal and lead to the anemia.

Keywords: Intra-host models; Malaria; Antimalarial treatment; Stability; Anemia

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 African Region (90%), followed by the South-East Asia Region (7%) and the 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 [1, 2].

Malaria is caused by a parasite that is passed from one human to another by the bite of infected Anopheles mosquitoes [1]. 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, and then break open within 48 hour to 72 hour, 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.

Malaria is treated with antimalarial drugs and measures to control symptoms, including medications to control fever, antiseizure medications when needed, fluids, and electrolytes. Common antimalarial drugs only have effect on the asexual forms of the parasite in the blood (blood schizontocidal effect) [2, 3]. 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 [4, 5]. The type of medications that are used to treat malaria depends on the severity of the disease and the likelihood of chloroquine resistance. With proper treatment, symptoms of malaria usually go away quickly, with a cure within two weeks. Without proper treatment, malaria episodes (fever, chills, sweating) can return periodically over a period of years. After repeated exposure, patients will become partially immune and develop milder disease [6, 7]. The malaria parasite, however, has evolved mechanics of resistance to most of these available antimalarials drugs, morbidity and mortality rise as efficiency falls [4, 6]. 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 [4]. Both components of the drug are blood

*Corresponding author. *E-mail address*: sbowong@gmail.com

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schizonticides, and they have complementary pharmacokinetics dissimilar modes of action thus providing synergistic antimalarial activity [6].

The dynamics of malaria parasites 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 [11, 15]. Testing specific hypotheses based on clinical data is often difficult since samples cannot always be taken too frequently from patients, or because detection techniques of the parasite may not be accurate. This justifies the central role played by mathematical models in this area of research. A number of dynamic models have already been developed to describe the population dynamics of HIV-1 following drug treatment and the emergence of drug-resistant mutants [16, 20]. Several mathematical models have been proposed to explain the dynamics of malaria parasites in an infected host with and without treatment by an antimalarial drug [21, 34]. The purpose of this paper is to theoretically and quantitatively assess the impact of a periodic drug treatment in a within-host malaria model. We assume that the drug is of the bang-bang type, that is at each moment during the period of the treatment cycle, the drug is one of two states: either it is active at a fixed efficiency level, or it is inactive. The drug is thus characterized by two parameters: its efficiency level when active, and the duration of the activity. We present the theoretical analysis of the model. More precisely, we show that solutions of the model are ultimately bounded by solutions of a monotone system. We compute the infection-free equilibrium and the Floquet theory to study his global stability. A major role in our analysis is played by the spectral radius of a non-negative matrix (namely of the fundamental matrix solution, evaluated over one cycle, of the linearization at the disease-free equilibrium), which is shown to possess expected monotonicity properties in terms of two parameters that characterize the drug. This spectral radius which also controls the speed of convergence to the disease-free equilibrium is lower when the drug is more potent or when it is active longer. Numerical simulations using a bang-bang type treatment are provided to support theoretical results. 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 and and drug duration and efficiency of the space on the distribution of malaria parasites. We found that depending of the values of the drug efficiency and the treatment duration, the patient can reach the threshold of catastrophic anemia level or the parasites can be cleared from an infection if the drug regiment is sufficiently large. This paper is organized as follows. In Section 2, we first present a 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. 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. Concluding remarks round up the paper in Section 4.

2 Temporal model

2.1 Model construction

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) IRBCs die at an increased rate due to the infection; (iv) IRBCs and free merozoites are killed by immune effectors; (v) free 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 [33]. A density of ≈ 5 million RBCs per μl is maintained in male adults [33]. We model in the first equation the rate of RBCs production as sensitive to changes in the rate of RBCs destruction. Here, the growth of RBCs $x(t)$ in the first equation is replaced by a more realistic 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 a 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 merozoites respectively. It has been reported that up to 500.000 blood cells per μl are

parasitized with *P. falciparum* [35]. The infected cells die at rate μ_y per day and the invasion of RBCs induces a specific immune response.

Common antimalarial drugs only have effect on the asexual forms of the parasite in the blood (blood schizontocidal effect) [4, 6]. 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. Drugs efficiency in this context is the probability that drugs inhibits parasites growth by reducing the rate production of merozoites parasites. 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 $\gamma(1-f(t))\mu_y$. Also, these free parasites suffer a natural death μ_m, are eliminated from circulation by immune cells, that reduced through infecting RBCs and are also reduced by anti malaria drug.

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 [33, 34]. 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 [27, 28, 35]. 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 in [36]. 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. As in Ref. [37, 38] 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 [7, 10]. The gametocytes are produced by PRBCs at rate δ and die at rate μ_g.

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

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

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

2.2 Theoretical analysis

2.2.1 Basic properties

Herein, we study the basic properties of the solutions of model system (1), which are essential in the proofs of stability results. We have the following result.

Theorem 1 *: Model system (1) is a dynamical system on the biologically feasible compact domain:*

$$\Omega=\left\{(x,y,m,I,g)\in\mathbb{R}^5_+,\ x(t)\le K,\ y(t)\le K,\ m(t)\le\frac{\gamma\mu_y K}{\mu_m},\ I(t)\le I_m,\ g(t)\le\frac{\delta K}{\mu_g}\right\}, \tag{2}$$

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

Parameter	Description	Estimated value/range	Source
η	Production rate of RBCs	1 cells/ml/day	Assumed
K	Maximum red blood cell population level	120/day	[35]
β	Contact rate between merozoites and RBCs	16/cell/day	[35]
u	Modification parameter	$0 \leq u \leq 1$	Assumed
$f(t)$	Efficiency of drug	$0 \leq f(t) \leq 1$	Assumed
μ_y	Death rate of PRBCs	0.2/day	[35]
μ_m	Death rate of free merozoites	72/day	[35]
μ_g	Death rate of gametocytes	0.25/day	[26]
γ	Merozoite mean rate produce by PRBCs	16	[35]
D_y	$1/D_y$ half saturation constant of PRBCs	$0.5\ ml$/cell	[39]
D_m	$1/D_m$ half saturation constant of free merozoites	$0.667\ ml$/cell	[39]
ρ_y	Immuno-sensitivity of PRBCs	0.05/cell/day	[40]
ρ_m	Immuno-sensitivity of free merozoites	0.1/cell/day	[39]
k_y	Immune effectors reaction against PRBCs	0.05/cell/day	[39]
k_m	Immune effectors reaction against free merozoites	0.1/cell/day	[39]
a	Increasing rate of immune effectors	0.05/day	[36]
b	Regulation rate of immune effectors	0.01 RBC/ml^{-1}day^{-1}	[35]
δ	Production rate of gametocytes	0.03 ml^{-1} day^{-1}	[26]

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 (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.

Considerer the first equation of model system (1):

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

Let

$m(t) = -\eta\left(1 - \dfrac{x+y}{K}\right)$, $n(t) = \beta\dfrac{m}{x+y}$, and $\rho(t) = exp(\int_0^t (n(u) + m(u))du)$.

Then, we are going to prove that the product of functions $\rho(t)x(t)$ is constant.

Indeed,

$$\begin{aligned} \frac{d\rho(t)x(t)}{dt} &= x(t)\tfrac{d\rho(t)}{dt} + \rho(t)\tfrac{dx(t)}{dt}, \\ &= (x(t)m(t) + x(t)n(t))\rho(t) + \rho(t)(-x(t)m(t) - x(t)n(t)) = 0, \end{aligned} \tag{3}$$

which 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 $m(t)$ are nonnegative for all $t \geq 0$. To this end, 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 prove now 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. Denote by t_1^m and t_2^m the first real numbers in such a way that $y(t_1^m) = 0$ and $m(t_2^m) = 0$ respectively. From the definitions of t_1^0 and t_0^2, we have $t_1^m > t_1^0$ and $t_2^m > t_2^0$ and

$$y(t) > 0, \forall 0 < t < t_1^m, y(t_1^m) = 0 \quad \text{and} \quad m(t) > 0, \forall 0 < t < t_2^m, m(t_2^m) = 0. \tag{4}$$

Without loss of generality, suppose $t_1^m \leq t_2^m$. Then, from model system (1), one has

$$y'(t_1^m) = \beta m(t_1^m) > 0 \quad \text{and} \quad m'(t_2^m) = \gamma(1 - f(t_2^m))\mu_y y(t_2^m). \tag{5}$$

The above equation implies that there exist two numbers $t_1^{m_1} > t_1^m$ and $t_2^{m_2} > t_2^m$ such that

$$y(t) > 0, \forall 0 < t < t_1^{m_1} \quad \text{and} \quad m(t) > 0, \qquad \forall 0 < t < t_2^{m_2}. \tag{6}$$

Putting the relations (4) and (6) together and use the continuity of $y(t)$ and $m(t)$, we 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 Eq.(5), $y'(t_1^m) > 0$ and $m'(t_2^m) > 0$. Therefore, $t_1^0 = +\infty$ and $t_2^0 = +\infty$. We have show that $y(t)$ and $m(t)$ are always nonnegative, then using a standard comparison theorem we have $I(t) \geq \frac{a}{C_1 a e^{-at} + b} > 0$ 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 (1).

Let $T = x + y$. Then, adding the first two equations in model system (1) yields

$$\frac{dT}{dt} = \eta x \left(1 - \frac{T}{K}\right) - \mu_y y - k_y \frac{Iy}{1 + D_y y}. \tag{7}$$

With this in mind, one can deduce that

$$\frac{dT}{dt} \leq \eta x \left(1 - \frac{T}{K}\right) \leq \eta T \left(1 - \frac{T}{K}\right). \tag{8}$$

Integrating the above differential inequality gives

$$T(t) \leq \frac{K}{1 + C_2 e^{-\eta t} K}, \tag{9}$$

where C_2 is a positive constant. Then, applying Birkhoff's and Rota's theorem on differential inequality [41], as t goes to the infinity, one can deduce that $T(t) \leq K \ \forall t \in \mathbb{R}$ which implies that $x(t) \leq K$ and $y(t) \leq K$ for all $t \geq 0$.

From the third equation of model system (1) and using the fact that $f(t) > 0$ and $y(t) \leq K$, one has

$$\frac{dm}{dt} \leq \gamma \mu_y K - \mu_m m. \tag{10}$$

Solving the above differential inequality yields

$$m(t) \leq \frac{\gamma \mu_y K}{\mu_m}, \tag{11}$$

which prove that the variable $m(t)$ is bounded.

Consider the last equation of model system (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

$$\begin{aligned} I'(t) \leq & \ (\tfrac{\rho_y}{D_y} + \tfrac{\rho_m}{D_m}) I(t) + aI(t) - bI^2(t) \\ \leq & \ AI(t) \left(1 - b\tfrac{I(t)}{A}\right), \end{aligned} \tag{12}$$

where $A = a + \frac{\rho_y}{D_y} + \frac{\rho_m}{D_m}$. A simple integration gives

$$I(t) \leq \frac{A}{AC_3 e^{-At} + b}, \tag{13}$$

where C_3 is a constant. It then follows that as $t \to \infty$,

$$I(t) \leq I_m, \tag{14}$$

where $I_m = \dfrac{A}{b}$.

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

2.2.2 The infection-free equilibrium and its stability

We shall analyze the non-autonomous system (1) for a general drug concentration $f(t)$. For the non-autonomous system (1), the infection-free equilibrium is

$$E_0 = (x_0, 0, 0, I_0, 0), \tag{15}$$

where $x_0 = K$ is the size of healthy RBCs when disease does not present and $I_0 = \dfrac{a}{b}$ is the response of immune effectors in absence of disease.

In the absence of the efficiency of drug, that is, $f(t) = 0$, the reproduction number of model system (1) is

$$\mathcal{R}_0 = \frac{\beta\gamma\mu_y}{(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)}. \tag{16}$$

Suppose now that $\mathcal{R}_0 > 1$, so that a treatment is needed to clear the infection. When the efficiency of drug is constant, that is $f(t) = f$ for all $t \geq 0$, the basic reproduction number of model system (1) denoted by $\mathcal{R}_f$ is

$$\mathcal{R}_f = \frac{\beta\gamma(1-f)\mu_y}{(k_y I_0 + \mu_y)(\mu_m + k_m I_0 + \beta u)}. \tag{17}$$

Obviously, the purpose of the treatment is to clear the infection, hopefully by making the infection-free equilibrium E_0 globally asymptotically stable (GAS) by suitable choosing the drug efficiency f. In term of the basic reproduction number $\mathcal{R}_0$ [12], the existence of a positive endemic equilibrium occurs when $\mathcal{R}_0 > 1$, which will be standing assumption throughout the rest of this paper. Indeed, if $\mathcal{R}_0 < 1$, then the infection-free equilibrium E_0 is locally asymptotically stable (LAS), and hence in this case the infection would always be cleared without treatment [12].

Since the use of treatment is to clear the infection so that the infection-free equilibrium E_0 is GAS, it is useful to modify the model by taking into account the effect of antimalarial drugs. Moreover, in practice, the drug efficiency is not constant through time, and the main purpose of this paper is to investigate the quantitative consequences of this fact. To do so, we consider the drug treatment as a periodic function, we will treat the infection-free equilibrium E_0 as a τ-periodic solution of model system (1). The stability of the infection-free equilibrium E_0 can be studied form the linearized system:

$$\dot{w} = J(t)w, \tag{18}$$

where $w = (x, y, m, I, g)^T$ and

$$J(t) = \begin{pmatrix} -\eta & -\eta & -\beta & 0 & 0 \\ 0 & -\frac{k_y a}{b} - \mu_y & \beta & 0 & 0 \\ 0 & \gamma(1-f(t))\mu_y & -\mu_m - \frac{k_m a}{b} - \beta u & 0 & 0 \\ 0 & \rho_y \frac{a}{b} & \rho_m \frac{a}{b} & -a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{pmatrix}. \tag{19}$$

It is well know that the stability properties of the origin of $J(t)$ the linearized system (18) (and generally the local stability of the infection-free equilibrium E_0 for model system (1)) are determined by the Floquet multipliers of $J(t)$. The block-triangular structure of $J(t)$ implies that these are

$$\lambda_1 = -\eta, \quad \lambda_2 = -\mu_g, \quad \lambda_3 = -a, \quad \lambda_4 \qquad \text{and} \qquad \lambda_5,$$

where λ_4 and λ_5 are the Floquet multipliers of the τ-periodic system:

$$\dot{\tilde{w}} = \begin{pmatrix} -\frac{k_y a}{b} - \mu_y & \beta \\ \gamma(1-f(t))\mu_y & -\mu_m - \frac{k_m a}{b} - \beta u \end{pmatrix} \tilde{w}, \tag{20}$$

where $\tilde{w} = (y, m)^T$. The Floquet multipliers λ_4 and λ_5 are the eigenvalues of $W(\tau)$ where $W(t)$ is the principal fundamental solution to system (20). Since $\lambda_1 = -\eta$, $\lambda_2 = -\mu_g$ and $\lambda_3 = -a$ are all negatives, so we focus our attention on λ_4 and λ_5.

Since the matrix in (20) is quasi positive, $W(t)$ has non negative entries for all $t \geq 0$. Therefore, by the Perron-Frobenius Theorem, the spectral radius of $W(\tau)$ is an eigenvalue (the eigenvalue with maximal modulus is positive). Let $\rho(W(\tau))$ be the spectral radius and λ_5 the dominant Floquet multiplier of the matrix (20), that is $\lambda_5 = \rho(W(\tau))$. In fact, by a beautiful argument due to d'Onofrio [17], it turns out that the same conditions imply the much stronger result of global asymptotic stability of E_0 for model system (1). Now, using the result of d'Onofrio [17], we have the following result.

Theorem 2 *: Let the Floquet multipliers of system (20) be contained inside the open unit disk in the complex plane. The infection-free equilibrium E_0 is GAS for model system (1), hence the infection is cleared.*

Indeed, if $\rho(W(\tau)) > 1$, then E_0 is unstable. If $\rho(W(\tau)) < 1$, then by Theorem 2, E_0 is GAS. We note that the spectral radius $\rho(W(\tau))$ is really a measure treatment effectiveness when $\rho(W(\tau)) < 1$. The smaller it is, the faster the convergence to E_0 will be. This result shows how relevant and important it is to determine the Floquet multipliers of model system (20). Unfortunately, for general functions $f(t)$, this is a notoriously difficult task. Therefore, we will consider the simpler case where $f(t)$ is a piecewise constant, bearing in mind that piecewise constant functions are often good approximations to continuous function.

Now, let us investigate the effect of including periodic antimalarial drug of bang-bang type.

2.2.3 Drug efficiency of the bang-bang type

Herein, we consider model system (1) with $f(t)$ a function of time with range in the interval $[0, 1]$ and represent the time-varying drug efficiency. When $f(t)$ is close to zero, the drug has almost no effect, while if they is near 1, the merozoites replication is almost completely inhibited. The real shape of that function is determined by the pharmacokinetics that describe what happens to a drug after the moment of intake and before starting to be active at the infection site [4, 6].

Moreover, we assume the efficiency functions to be of the bang-bang type, i.e., at any time during treatment, the drug either active or inactive. It is clear that is just an approximation of the real shape determined by pharmacokinetics. The bang-bang type is not perfectly to model the real drug efficacy function, but some insight can be gained on how the phase shift affects the effectiveness of the treatment. The following assumption regarding the shape of the graph of the τ-periodic function $f(t)$ is illustrated in Fig. 1:

$$f(t) = \begin{cases} f, & t \in [0, p], \\ 0, & t \in [p, \tau], \end{cases} \tag{21}$$

where $p \in (0, \tau)$ is the time duration which the drug is supposed to be active with efficiency $f \in [0, 1]$. During the remaining part the treatment period drug is assumed to be totally inefficient. Clearly, this is not a good way to approximate, but some key properties are to be learned from this case.

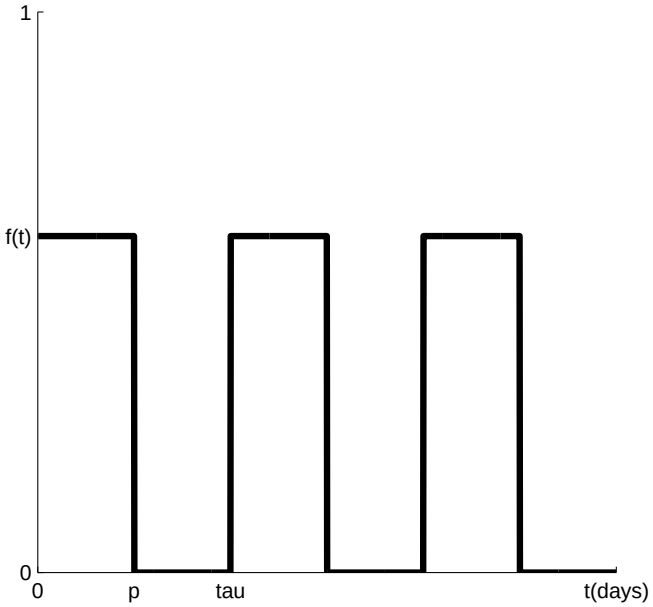

Figure 1: Periodic drug efficacy $f(t)$ of the bang-bang type.

There are two possible parameters that can vary Eq.(21), namely f and p. The aim of this section is to investigate their effect on the Floquet multipliers of model system (20) with (21). As in Ref. [19], the Floquet multipliers are the eigenvalues of the following matrix:

$$\Phi(f,p) = EXP[(\tau - p)A(0)]EXP[pA(f)], \tag{22}$$

where

$$A(f) = \begin{pmatrix} -\frac{k_y a}{b} - \mu_y & \beta \\ \gamma(1-f(t))\mu_y & -\mu_m - \frac{k_m a}{b} - \beta u \end{pmatrix}. \tag{23}$$

Since $A(f)$ and $A(0)$ are quasi-positive matrices their matrix exponentials are non-negative matrices. Thus, $\Phi(f,p)$ is a nonnegative matrix and by Perron-Frobenius Theorem (see [15]); its spectral radius $\rho(\Phi(f,p))$ is an eigenvalue of $\Phi(f,p)$. Thus, the Floquet multipliers of system (20) with (21) are contained in the interior of the unit disk of the complex plane if and only is $\rho(\Phi(f,p)) < 1$. This guarantees that the infection is cleared (globally) by Theorem 2.

The following result reveals that $\rho(\Phi(f,p))$ has the expected monotonicity properties: it decreases with f (efficient treatment) and with p (effective longer).

Theorem 3 *: Let f, $f' \in [0,1]$ and p, $p' \in [0,\tau]$. Then, the map $(f,p) \to \rho(\Phi(e,p))$ is continuous,*

$$f < f' \quad p \neq 0 \Rightarrow \rho(\Phi(f',p)) < \rho(\Phi(f,p)), \tag{24}$$

and

$$p < p' \quad p \neq 0 \Rightarrow \rho(\Phi(f',p)) < \rho(\Phi(f,p)). \tag{25}$$

Moreover,

$$\rho(\Phi(e,0)) = \rho(\Phi(0,\tau)) = \rho(EXP[\tau A(0)]) > 1, \quad \textit{for all } f \in [0,1] \textit{ and all } p \in [0,\tau] \textit{ (no treatment)} \tag{26}$$

and

$$\rho(\Phi(1,\tau)) = \rho(EXP[\tau A(1)]) = \textit{ max}\,\{EXP[-(\tfrac{k_y a}{b} + \mu_y)\tau], EXP[-(\mu_m + \tfrac{k_m a}{b} + \beta u)\tau]\} < 1 \quad \textit{(constant, 100\%effective treatment).} \tag{27}$$

We numerically evaluate the effect of the drug efficiency f and the time duration of active drug p on the dominant Floquet multiplier when the treatment is of bang-bang type.

Fig. 2 presents the spectral radius of $\rho(\Phi(f,p))$ as a function of the drug efficiency f and the time duration of active drug p. All other parameter values are as in Table 1. Remind that $\rho(\Phi(f,p))$ (provided it is less than 1) is a measure of how fast the solution of model system (1) associated with a treatment of type (21) approaches the DFE E_0. It clearly appears that when the treatment is periodic of the bang-bang type, the infection can be cleared within the body of a host. It also illustrates that when the treatment is more efficient, or lasts longer, then the infection is cleared more quickly.

We now numerically investigate the effect of the treatment of bang-bang efficiency on the dynamics of model system (28). For computer runs, we set the initial densities of RBCs, PRBCs, free merozoites, immune cells and gametocytes at 10,10, 0,5 and 1 respectively. The drug dosing interval is equal to 1 day ($\tau = 1$ day). However, our main thrust is on the overall effect the drug efficiency have on the basic reproduction number, which is the basis for an infection to persist or be eradicated.

The results of numerical simulations without drug therapy (red line) and with drug therapy (blue line) when $f = 0.8$ and $p = 0.8$ (so that $\rho(\Phi(f,p)) < 1$) are depicted in Fig. 3. All other parameter values are as in Table 1. From the red curves, one can observe that the densities of RBCs, PRBCs, free merozoites, immune response, and gametocytes increase and reach a steady endemic state E^* since $\mathcal{R}_0 > 1$. Hence, the infection-free equilibrium is unstable and the disease persists within the body of a host. This means that the only effect of innate immune response is not able to fight against the infection. Hence, the drug is now administrated. From the blue curves, one can see that the the densities of RBCs, PRBCs, free merozoites, immune response, and gametocytes decrease to reach the infection-free equilibrium. This implies that the disease is controlled, since the dosage is sufficiently large. Thus, if the treatment is periodic of the bang-bang type, the parasite can be eradicated. One can also observe that the infection is cleared more rapidly when the treatment is more effective or it lasts longer.

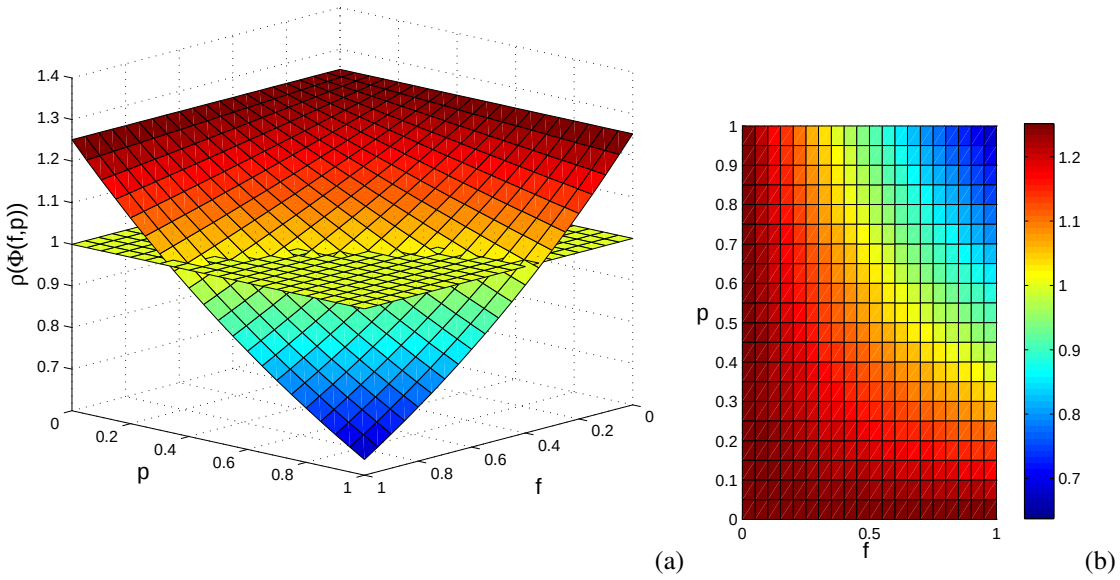

Figure 2: Spectral radius $\rho(\Phi(f,p))$ as a function of the drug efficiency f and treatment duration p when the treatment is of bang-bang type. The horizontal surface corresponds to $\rho = 1$. All other parameter values are as in Table 1.

3 The spatio-temporal model

In this section, we extend model system (1) taking into account the spatial component in the mathematical modeling. 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 [31, 42]. 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:

$$\begin{cases} \dfrac{\partial x}{\partial t}(t,w) &= \eta x\left(1-\dfrac{x+y}{K}\right)-\beta\dfrac{xm}{x+y}+\varepsilon_x\Delta x,\\ \dfrac{\partial y}{\partial t}(t,w) &= \beta\dfrac{xm}{x+y}-k_y\dfrac{Iy}{1+D_y y}-\mu_y y+\varepsilon_y\Delta y,\\ \dfrac{\partial m}{\partial t}(t,w) &= \gamma(1-f(t))\mu_y y-\mu_m m-k_m\dfrac{Im}{1+D_m m}-\beta u\dfrac{xm}{x+y}+\varepsilon_m\Delta m,\\ \dfrac{\partial I}{\partial t}(t,w) &= I\left(\rho_y\dfrac{y}{1+D_y y}+\rho_m\dfrac{m}{1+D_m m}\right)+aI-bI^2+\varepsilon_I\Delta I,\\ \dfrac{\partial g}{\partial t}(t,w) &= \delta y-\mu_g g+\varepsilon_g\Delta g, \end{cases} \tag{28}$$

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.

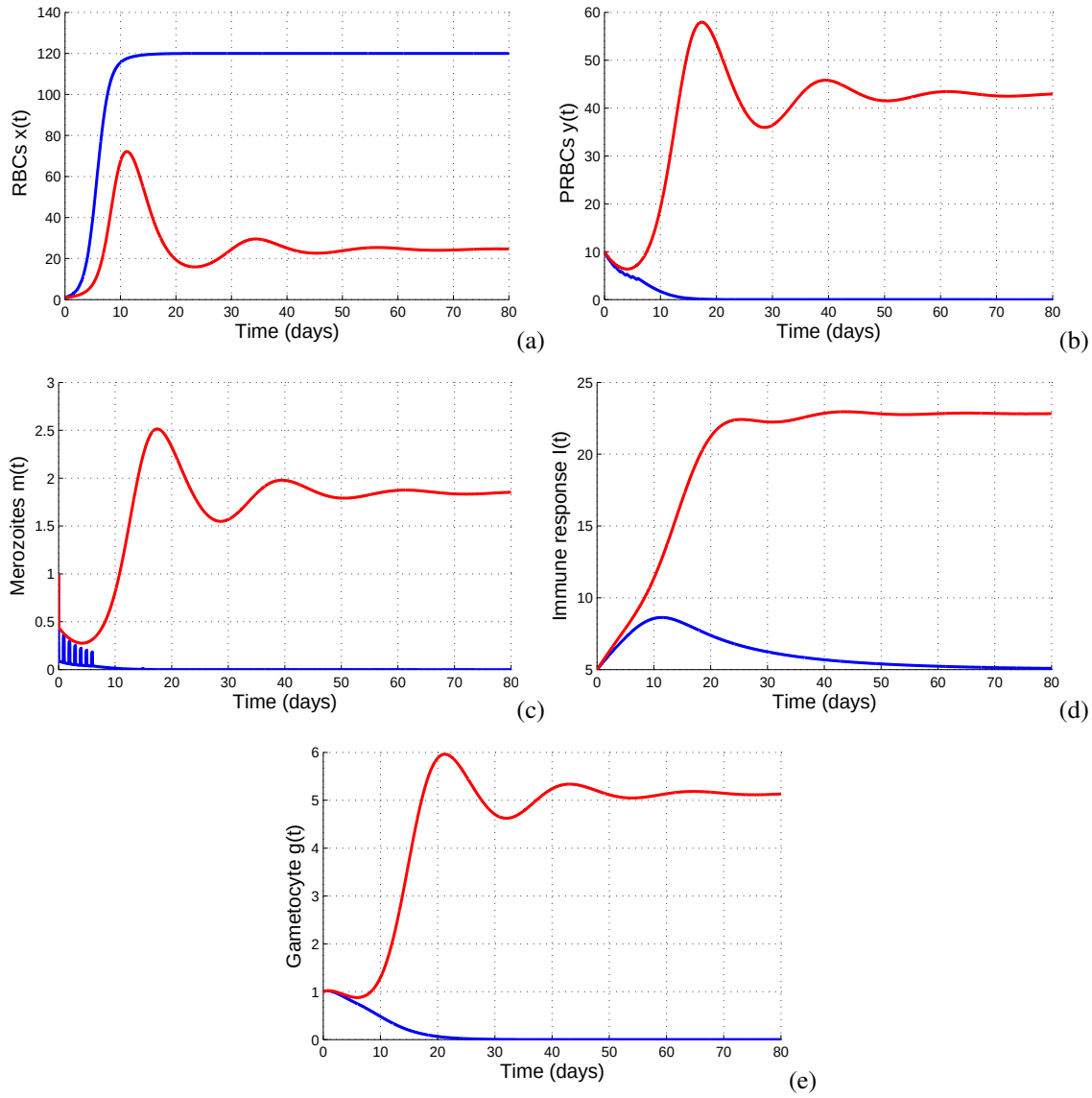

Figure 3: Time plot of densities of (a) RBCs $x(t)$, (b) PRBCs $y(t)$, (c) free merozoites $m(t)$, (d) immune effectors $I(t)$ and (e) gametocytes $g(t)$ without treatment (red line) and with treatment (blue line) when $f = 0.8$ and $p = 0.8$ (so that $\rho(\Phi(f,p)) < 1$) (blue line). All other parameter values are in Table 1.

To avoid a migration of populations, we consider the following Neumann boundary conditions:

$$\begin{aligned} &\frac{\partial x}{\partial \nu}(t,w) = \frac{\partial y}{\partial \nu}(t,w) = \frac{\partial m}{\partial \nu}(t,w) = \frac{\partial I}{\partial \nu}(t,w) = \frac{\partial g}{\partial \nu}(t,w) = 0, \qquad (t,w) \in \mathbb{R}_+ \times \partial\Gamma, \\ &x(0,w) = x_0(w), \qquad y(0,w) = y_0(w), \qquad m(0,w) = m_0(w), \quad I(0,w) = I_0(w) \\ &\text{and } g(0,w) = g_0(w), \ \ w \in \Gamma \subset \mathbb{R}^2, \end{aligned} \tag{29}$$

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 (28), 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 (28) 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

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

It is obvious that $(0,0,0,0,0)$ is a lower solution of model system (28). 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

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

This implies that any solution of model system (28) with positive initial condition will remain positive.

Now, we will prove that the solutions of model system (28) admit also upper limits. Without loss of generality, we assume that $\varepsilon_x = \varepsilon_y = \varepsilon_1$. Then, from model system (28), 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

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

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

$$T(t,w) \quad \leq \quad \overline{T}(t) = \frac{K\overline{T}(0)}{\overline{T}(0) + (K - \overline{T}(0))e^{-\eta t}}. \tag{30}$$

Applying Birkhoff's and Rota's Theorem on differential inequality [41], 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

$$m(t,w) \leq \frac{\gamma \mu_y K}{\mu_m}. \tag{31}$$

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

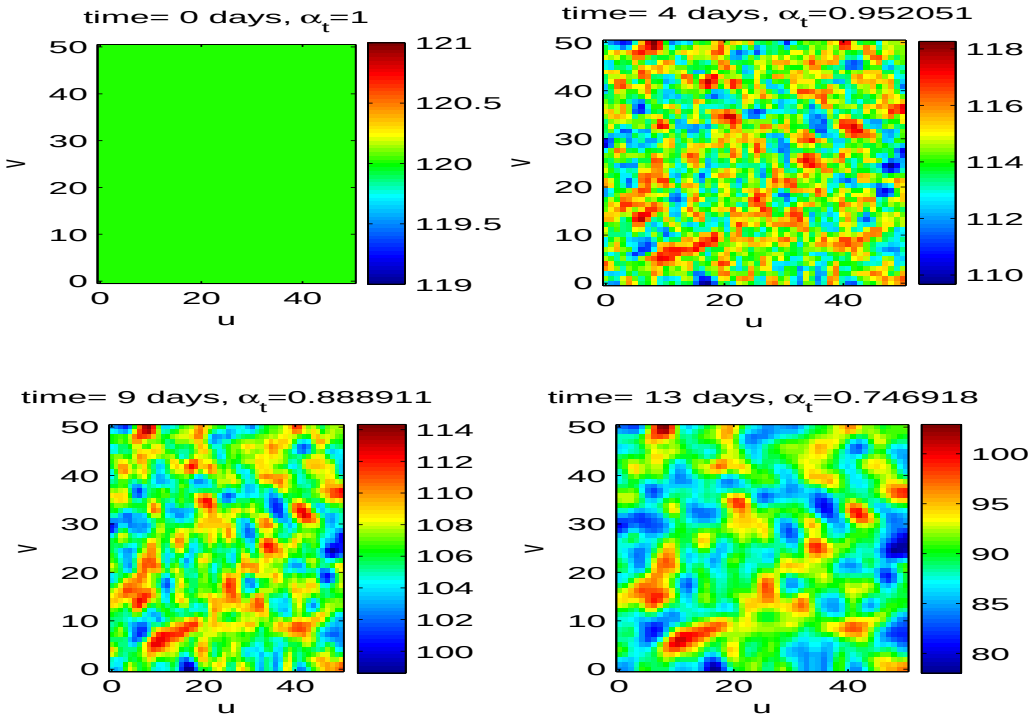

Figure 4: Spatiotemporal evolution of RBCs when $\tau = 1$, $p = 0.3$, and $e = 0.3$.

3.2 The complexity of nutrition and anemia

In regions where malaria is endemic, malaria is commonly considered to be a principal cause of severe anemia, which in turn is a major cause of morbidity and mortality. Counterfeit (fake) and substandard antimalarial drugs may contain no active ingredients, less than the required amount of active ingredients, or ingredients not described on the package label. These medicines may have too little or too much of the active ingredients and may not be absorbed properly by the body. If they are taken to treat an illness like malaria, they may be incompletely effective and can lead to severe anemia [31, 42]. A counterfeit or substandard treatment can prolong illness and increase the risk of severe disease or death. If substandard medicines are widely used, they can also select for drug-resistant parasites.

We now focus on the effect of that counterfeit drug on the malaria dynamic and how it can lead to severe anemia. As in [31], the anemia level α_t can be mathematically defined as

$$\alpha_t = \frac{x(t)}{x(t_0)}. \tag{32}$$

A patient has a catastrophic anemia level if $\alpha_t < 75\%$ which corresponds to a hemoglobin level$< 11g/dL$[42]. Then, mathematically, the minimum anemia time T_{anemia} at which the patient reaches the threshold of catastrophic anemia can be estimated as

$$T_{\text{anemia}} = \min(120 \text{ days}, \ \inf(t, \alpha_t < 75\%)), \tag{33}$$

where 120 days correspond to RBCs periodic recycling duration and t the time for which $\alpha_t < 75$. Obviously, T_{anemia} depends on the mosquitoes' chrematistics such as efficiency, virulence, and fitness.

For numerical simulation, we assume that RBCs, PRBCs, free merozoites, immune response, and gametocytes within the body of a host are initially at the disease free-equilibrium with 120 RBCs distributed uniformly at each point. Simulations have been stopped when the number of RBCs at the time t is equal to or less than 75% of the initial RBCs.

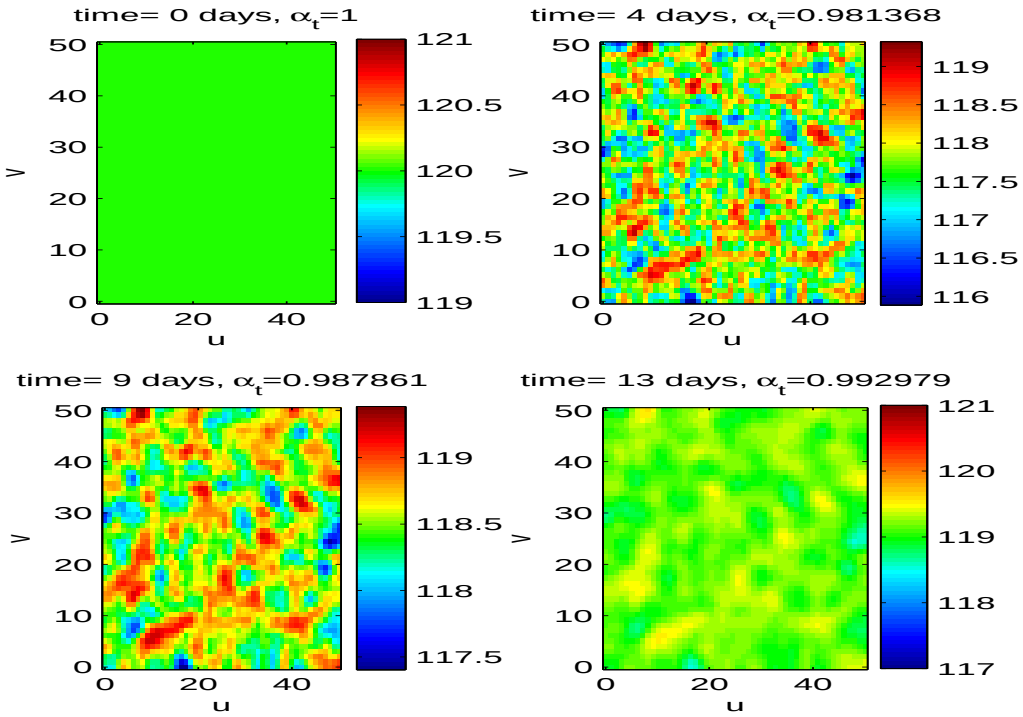

Figure 5: Spatiotemporal evolution of RBCs when $\tau = 1$, $p = 0.7$, and $e = 0.8$.

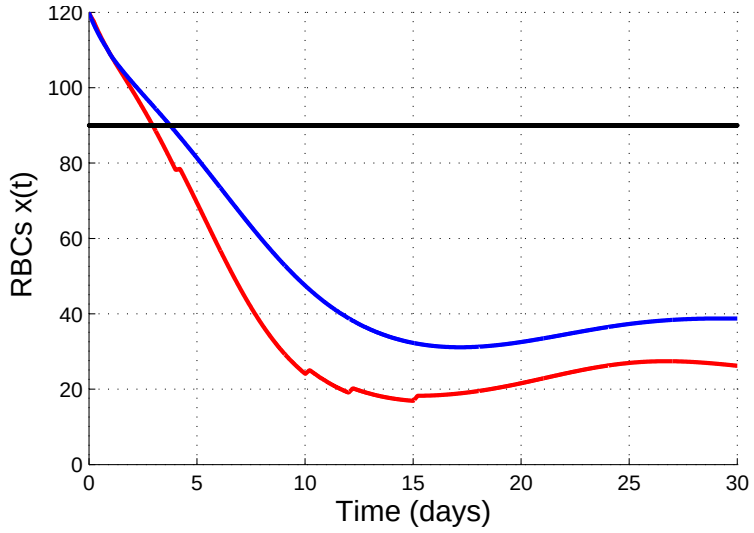

Figure 6: Simulation over the first 30 days of drug treatment.

Fig. 4 presents the spatiotemporal evolution of RBCs when $e = 0.3$ and $p = 0.3$ (so that $\rho(\Phi(f,p)) > 1$). It illustrates that with the chosen parameter values and initial conditions after 13 days, the patient will reach the threshold of catastrophic anemia level.

Fig. 5 presents the spatiotemporal evolution of RBCs when $e = 0.8$ and $p = 0.7$ (so that $\rho(\Phi(f,p)) < 1$). One can see that with the chosen parameter values and initial conditions, after 13 days, the patient will not reach the threshold

of catastrophic anemia level, and the system come back to the infection-free equilibrium. Thus, if the drug regiment is sufficiently large, the malaria infection can be treated within the body of a host.

A counterfeit medication or a counterfeit drug is a medication or pharmaceutical product which is produced and sold with the intent to deceptively represent its origin, authenticity or effectiveness. A counterfeit drug may contain inappropriate quantities of active ingredients, or none, may be improperly processed within the body (e.g., absorption by the body), may contain ingredients that are not on the label (which may or may not be harmful), or may be supplied with inaccurate or fake packaging and labeling. Medicines which are deliberately mislabeled to deceive consumers including mislabeled but otherwise genuine generic drugs are counterfeit.

The use of diluents in illegal drugs reduces the potency of the drugs and makes it hard for users to determine the appropriate dosage level. Those diluents have strong effect on the efficiency of drug, by changing the initial drug concentration and the time of drug effect. The drug is thus characterized by two parameters: its efficiency level when active, and the duration of the activity. Then, the indeed of this section is to determine witch parameters lead at the first level to a catastrophic anemia level.

Fig. 6 illustrates what happen when the patient takes a counterfeit drug. The blue curve illustrate the case when the drug concentration $f = 0.2$, and the time of drug effect $p = 0.8$ (from Fig. 2 we have $\rho(\Phi(f,p)) > 1$). The red curve is the concentration of RBCs for the drug concentration $f = 0.8$ and the time of drug effect $p = 0.2$. The horizontal black line define the anemia level reached when the concentration of RBCs decrease bellow 75% of the initial concentration. The comparison of the blue and red curves shown that, the counterfeit drug with fake time drug effect ($f = 0.8$ and $p = 0.2$) reach more quickly a catastrophic anemia. Then, we predict that to control the viral load, increasing the time of drug effect is more effective than increasing the doses.

4 Conclusion

In this paper, we investigate the dynamics behaviors of a within host model of malaria with a periodic drug treatment. 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, 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. More precisely, we shown that the dynamic behaviors is determined by its dominant Floquet multiplier $\rho(\Phi(f,p))$, that is, if $\rho(\Phi(f,p)) < 1$, then the infection-free equilibrium is globally asymptotically stable, and if $\rho(\Phi(f,p)) > 1$, then the infection is uniformly persistent. Numerical simulations are carried out to support theoretical analysis. We have extended the temporal model to a spatio-temporal model using Diffusion-Reaction equations to describe how the drug duration and efficiency can affect the parasite dispersal and lead to the anemia. We have numerically assessed the importance of the spatial distribution of RBCs, PRBCs, merozoites, gametocytes, and immune effectors within a host. We found that depending of the values of the drug efficiency f and the treatment duration p, the patient can reach the threshold of catastrophic anemia level or the parasites can be cleared from an infection if the drug regiment is sufficiently large. Thus, it will be interesting to focus on the dynamics of malaria infection when a counterfeit drug medication is taken. Efforts to discover an develop new antimalarial drugs have increased dramatically in recent years, both as result of the recognition of the global importance of fighting malaria, and the public-private partnership strategy to discover, develop and deliver news drugs. Increased funding from the public sector and philanthropic agencies has fuelled strong academic engagement in drug discovery, and increased partnerships with pharmaceutical companies mean that sets of complementary expertise are becoming available to drive and sustain the development of news drugs for diseases of low commercial return. Yet at the same time malaria mortality is on the increase due in large part of the increasing ineffectiveness of drugs, and the current lack of affordable alternatives. Current enthusiasm for combining scientific innovation with expertise in the drug discovery and development process offers hope that a concreted effort can allow us to gain the upper hand in treating this disease.

References

[1] World Malaria Report. Tech. Rep, World Health Organisation. 2015.

[2] WHO, Tech. rep. Malaria, 2015.

[3] K. Haldar, S.M. Murphy, D.A. Milner and T.E. Taylor. Malaria: mechanisms of erythrocytic infection and pathological correlates of severe disease. *Annual Review of Pathology: Mechanisms of Disease*, 2(2007): 217-249.

[4] N. White. Antimalarial drug resistance and combination chemotherapy. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 354(1999): 739-749.
[5] I.A. Clark, J.L. Virelizier, E.A. Carswell and P.R. Wood. Possible importance of macrophage-derived mediators in acute malaria. *Infect. Immun.*, 32(1981): 1058-1066.
[6] J.A. Simpson, E.R. Watkins, R.N. Price, L. Aarons, D.E. Kyle and N.J. White. Mefloquine pharmacokinetic-pharmacodynamic models: implications for dosing and resistance. *Antimicrobial agents and chemotherapy*, 44(12)(2000): 3414-3424.
[7] M.F. Good, H. Xu, M. Wykes and C.R. Engwerda. Development and regulation of cell-mediated immune responses to the blood stages of malaria: Implications for vaccine research, *Annual Review of Immunology*, 23(2005): 69-99.
[8] K. Kirk. Membrane transport in the malaria-infected erythrocyte. *Physiology Review*, 81(2001): 495-537.
[9] D. Kwiatkowski. Malaria toxins and the regulation of parasite density. *Parasitology Today*, 11(1995): 206-212.
[10] K. Artvanis-tsakonas, J.E. Tongren and E.M. Riley. The war between the malaria parasite and the immune system: Immunity, immunoregulation and immunopathology. *Clin. Exp. Immunol.*, 133(2003): 145-152.
[11] R.M. Anderson and R.M. May. Infectious disease of humans, dynamical and control. *Oxford: Oxford University Press*, 1992.
[12] J.A.P. Heesterbeek. Mathematical epidemiology of infectious diseases: model building, analysis and interpretation. *International Journal of Epidemiology*, 30(1)(2001): 186.
[13] V. Capasso. Mathematical structures of epidemic systems, Lecture notes in biomathematics. Berlin, Springer, 1993.
[14] H.W. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42(2000): 599-653.
[15] H.R. Thieme. Mathematics in Population Biology, Princeton, Series Theoretical Computational Biology, Princeton University Press, Princeton, NJ, 2003.
[16] L. Rong, Z. Feng and A.S. Perelson. Emergence of hiv-1 drug resistance during antiretroviral treatment. *Bulletin of Mathematical Biology*, 69(6)(2007): 2027-2060.
[17] A. Onofrio. Periodically varying antiviral therapies: conditions for global stability of the virus free state. *Applied Mathematics and Computation*, 168(2)(2005): 945-953.
[18] J. Rob and A.P. De Boer. Towards a general function describing t cell proliferation. *Journal of Theoretical Biology*, 1995: 175.
[19] P.D. Leenheer. Within-Host Virus Models with Periodic Antiviral Therapy. *Bulletin of Mathematical Biology*, 71(2009): 189-210.
[20] B.J. Song, J. Lou and Q.Z. Wen. Modelling two different therapy strategies for drug T-20 on HIV-1 patients. *Applied Mathematics and Mechanics*, 32(4)(2011): 419-436.
[21] F.E. McKenzie and W.H. Bossert. The Dynamics of Plasmodium falciparum Blood-stage Infection. *Journal of Theoretical Biology*, 188(1)(1997): 127-140.
[22] Z. Dong and J.A. Cui. Dynamical model of vivax malaria intermittence attack in vivo. *International Journal of Biomathematics*, 2(2009): 507-524.
[23] B. Kamangira, P. Nyamugure and G.A. Magombedze. Theoretical mathematical assessment of the effectiveness of coartemether in the treatment of Plasmodium falciparum malaria infection. *Mathematical Biosciences*, 256(2014): 28-41.
[24] L. Molineaux, H.H. Diebner, M. Eichner, W.E. Collins, G.M. Jeffery and K. Dietz. Plasmodium falciparum parasitaemia described by a new mathematical model. *Parasitology*, 122(04)(2001): 379-391.
[25] M.B. Hoshen, R. Heinrich, W.D. Stein and H. Ginsburg. Mathematical modelling of the within-host dynamics of Plasmodium falciparum, *Parasitology*, 121(03)(2000): 227-235.
[26] F.E. McKenzie and W.H. Bossert. The Optimal Production of Gametocytes by Plasmodium falciparum. *Journal of Theoretical Biology*, 193(3)(1998): 419-428.
[27] P. Adda, J.L. Dimi, A. Iggidr, J.C. Kamgang, G. Sallet and J.J Tewa. General models of host-parasite systems: Global analysis. *Discrete Continuous Dynamical Systems Series B*, 8(2007): 1-17.
[28] A. Iggidr, J.C. Kamgang, G. Sallet and J.J Tewa. Global analysis of new malaria intra host models with a competitive exclusion principle. *SIAM Journal of Applied Mathematics*, 67(2006): 260-278.
[29] J.L. Mitchell and T.W. Carr. Oscillations in an intra-host model of plasmodium falciparum malaria due to cross-reactive immune response. *Bulletin of Mathematical Biology*, 72(2010): 590-610.
[30] Y. Li, S. Ruan and D. Xiao. The within-host dynamics of malaria infection with immune response. *Mathematical Biosciences and Engineering*, 8(4)(2011): 999-1018.
[31] E. Takoutsing, S. Bowong, D. Yemele and J. Kurths. Effects of Catastrophic Anemia in an Intra-Host Model of

Malaria. *International Journal of Bifurcation and Chaos*, 24(07)(2014): 1450105.
[32] L. Malaguarnera and S. Musumeci. The immune response to Plasmodium falciparum malaria. *The Lancet infectious diseases*, 2(8)(2002): 472-478.
[33] P.G. McQueen and F.E. McKenzie. Age-structured red blood cell susceptibility and the dynamics of malaria infections. *Proceedings of the National Academy of Sciences of the United States of America*, 101(24)(2004): 9161-9166.
[34] H.H. Diebner, M. Eichner, L. Molineaux, W.E. Collins, G.M. Jeffery and K. Dietz. Modelling the transition of asexual blood stages of Plasmodium falciparum to gametocytes. *Journal of Theoretical Biology*, 202(2)(2000): 113-127.
[35] R.M. Anderson, R.M. May and S. Gupta. Non-linear phenomena in host-parasite interactions. *Parasitology*, 99(S1)(1989): S59-S79.
[36] Z. Agur, D. Abiri and 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 National Academy of Sciences*, 86(23)(1989): 9626-9630.
[37] R.J. De Boer and A.S. Perelson. Towards a general function describing T cell proliferation. *Journal of Theoretical Biology*, 175(4)(1995): 567-576.
[38] S.S. Pilyugin and R. Antia. Modeling immune responses with handling time. *Bulletin of Mathematical Biology*, 62(5)(2000): 869-890.
[39] C. Chiyaka, W. Garira and S. Dube. Modelling immune response and drug therapy in human malaria infection. *Computational and Mathematical Methods in Medicine*, (2008): 143-163.
[40] J. Tumwiine, J.Y.T. Mugisha and L.S. Luboobi. On global stability of the intra-host dynamics of malaria and the immune system. *Journal of Mathematical Analysis and Applications*, 341(2008): 855-869.
[41] G.C.R. Garrett Birkhoff. Ordinary differential equations. Wiley, 1989.
[42] G.N. Jakeman, A. Saul, W.L. Hogarth and W.E. Collins. Anaemia of acute malaria infections in non immune patients primarily results from destruction of uninfected erythrocytes. *Parasitology*, 119(1999): 127-133.
[43] A. Berman and R. Plemmons. Nonnegative Matrices in the Mathematical Sciences, SIAM, Philadelphia, 1994.

Appendix: Proof of Proposition 3

Proof. Herein, we prove that $\rho(\Phi(f,p))$ decreases with f (efficient treatment) and with p (effective longer). To do this, we use the result of Patrick De Leenheer [19]:

1. If A is quasi-positive and $A < B$ but $A \neq B$, then $0 \leq EXP[tA] \leq EXP[tB]$ but $EXP[tA] \neq EXP[tB]$ for all $t > 0$.

   To see this, let $\alpha > 0$ be such that $C = A + \alpha I \geq 0$. Then, setting $D = B + \alpha I$, one has that $0 \leq C \leq D$ but $C \neq D$. With this in mind, it follows that $EXP[tC] \leq EXP[tD]$, but $EXP[tC] \neq EXP[tD]$ for all $t > 0$. It follows that $EXP[tA] \leq EXP[tB]$ but $EXP[tA] \neq EXP[tB]$ for all $t > 0$.

2. For all $t > 0$, $EXP[tA(f)] > 0$ if $f \neq 1$, while $EXP[tA(f)] \geq 0$ (but not> 0) if $f = 1$.

3. If $A > 0$ and $B \geq 0$ has no zero row or zero column, then $AB > 0$ and $BA > 0$. This is true in particular when $B = EXP[tC]$ for $t \geq 0$ and C is a quasi-positive matrix because of Fact 1 and the fact that matrix exponentials are invertible.

4. If $0 < A \leq B$ but $B \neq A$, then $\rho(A) \rho(B)$, see Corollary 1.5 in Chap. 2 in Berman and Plemmons [43].

Continuity of the map $(f,p) \to \rho(\Phi(f,p))$ follows from the definition (22) of ρ and the fact that the spectral radius of any matrix is continuous in terms of its entries.

Let $0 \leq f < f' < 1$ and $p \neq 0$. Then

$$A(f') \leq A(f) \text{ and } A(f') \neq A(f)$$

$\Rightarrow 0 < EXP[pA(f')] \leq EXP[pA(f)]$ and $EXP[pA(f')] \neq EXP[pA(f)]$

by Fact 1 and 2

$\Rightarrow 0 < EXP[(\tau - p)A(0)]EXP[pA(f')] \leq [(\tau - p)A(0)]EXP[pA(f)]$

and $\quad EXP[(\tau - p)A(0)]EXP[pA(f')] \leq [(\tau - p)A(0)]EXP[pA(f)]$

by Fact 1 and 3 and invertibility of matrix exponentials

$\Rightarrow 0 < Phi(f', p) \leq \Phi(f, p)$ and $\Phi(f', p) \neq \Phi(f, p)$

$\Rightarrow \rho(\Phi(f', p) < \rho(\Phi(f, p))$ by Fact 4.

This result remains valid if $f' = 1$ because $\rho(\phi(f, p))$ is continuous. This establishes (24).
Let $0 \leq p < p' < \tau$ and $f \neq 0$. Then

$A(f) \leq A(0) and A(f) \neq A(0)$
$\Rightarrow 0 \leq EXP[(p' - p)A(f)] \leq EXP[(p' - p)A(0)]$

and $EXP[(p' - p)A(e)] \neq EXP[(p' - p)A(0)]$ by Fact 1

and invertibility of exponentials

$\Rightarrow 0 < EXP[(\tau - p')A(0)]EXP[(p' - p)A(f)]EXP[pA(f)]$

$\leq EXP[(\tau - p')A(0)]EXP[(p' - p)A(0)]EXP[pA(f)]$ and

$EXP[(\tau - p')A(0)]EXP[(p' - p)A(f)]EXP[pA(e)]$

$\neq EXP[(\tau - p']A(0)]EXP[(p' - p)A(0)]EXP[pA(f)]$

by Fact 2 and invertibility of exponentials

$\Rightarrow 0 < \Phi(f, p') \leq \Phi(e, p)$ and $\Phi(f, p') \neq \Phi(f, p)$

$\Rightarrow \rho(\Phi(e, p') < \rho(\Phi(e, p))$ by Fact 4.

This remains valid if $p' = \tau$ because $\rho(\Phi(e, p))$ is continuous. This establishes (25).

Finally, it follows from the standing assumption, that the determinant of $A(0)$ is negative. Thus, $A(0)$ has a positive eigenvalue which implies (26). Also, (27) is immediate from (23). This concludes the proof. ■