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Effects of Catastrophic Anemia in an Intra-Host Model of Malaria

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In this paper, we develop a mathematical model to assess the strength of the effects of catastrophic anemia level on the dynamical transmission of malaria parasite within the body of a host. We first consider a temporal model. The important mathematical features of the model are thoroughly investigated. We found that the model exhibits forward bifurcation. We also consider a spatiotemporal model using reaction–diffusion equations. The model is numerically analyzed to assess the impact of anemia on the dynamical transmission of malaria parasite within the body of a host. Through numerical simulation, we found that malaria can lead to a catastrophic anemia level even if the parasite is nonpersistent within the body of a host. Numerical results also suggest that to reduce or control the anemia level, the strategy should be to accelerate innate cell reproduction rate or should have the ability to clean parasitized red blood cells (PRBCs) with a high mortality rate.

Keywords: Intra-host models; malaria; anemia; bifurcation; stability.

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1. Introduction

Malaria has long been a scourge to humans. The total burden of this disease has been estimated to be 450 million episodes annually and is responsible for 18% of all childhood deaths in sub-Saharan Africa, equivalent to 800 000 deaths each year. According to the World malaria report 2012, there were about 216 million cases of malaria (with an uncertainty range of 149 million to 274 million) and an estimated 655 000 deaths in 2010 (with an uncertainty range from 537 000 to 907 000). Malaria mortality rates have fallen by more than 25% globally since 2000, and by 33% in the WHO African Region. Most deaths occur among children living in Africa where a child dies every minute from malaria [WHO, 2012]. Malaria is caused by a parasite that is passed from one human to another by the bite of infected Anopheles mosquitoes. 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. The symptoms occur in cycles from 48 h to 72 h. On the other hand, the increasing burden of malaria morbidity and mortality over the past years, the potential consequences of blood transfusion in the context of the AIDS epidemic, and the magnitude of the problem, which is imposing an enormous economic load on health services in many areas are some of the reasons behind focusing the attention on one of the major clinical consequences of malaria infection, malarial anaemia [WHO, 2013; Price *et al.*, 2001].

Infection with malaria invariably leads to anaemia [Korenromp *et al.*, 2004; Abdalla *et al.*, 1984; Casals-Pascual & Roberts, 2006]. The groups at risk of developing malarial anaemia include children below the age of five years and pregnant women, especially primigravidae. Prevalence figures of anaemia in the community in malaria-endemic areas of Africa vary between 31% and 90% in children and between 60% and 80% in pregnant women [Crawley, 2004; Brabin *et al.*, 2001]. However, until recently, the molecular mechanisms involved have remained elusive. Severe malarial anaemia is a major complication of malaria infection and is multifactorial resulting from loss of circulating RBCs from parasite replication, as well as immune-mediated mechanisms. Several factors have been suggested to be responsible for its aetiology, including increased destruction of infected and normal red blood cells together with bone marrow suppression. Also, the substantial risk from blood transfusion in areas of high HIV prevalence has led to a review of the criteria for transfusion, and some indicators have been proposed to guide the need for blood transfusion other than just the Hemoglobin (Hb) level [Jakeman *et al.*, 1999; Gravenor & Lloyd, 1998]. There is, however, an urgent need for more high-quality clinical research on the management of severe anaemia (especially in children), which could include setting up clinical and analytical criteria for blood transfusion that are both sensitive and easy to determine.

Over the last five years, malaria parasite ligands have been investigated for their remodeling of erythrocytes and possible roles in the destruction of mature erythrocytes. Because of the complexities involved, the study of severe malarial anemia may need a "systems approach" to yield comprehensive understanding of defects in both erythropoiesis and immunity associated with disease. New and emerging tools such as: (i) mathematical modeling of the dynamics of host control of malarial infection, (ii) *ex vivo* perfusion of human spleen to measure both infected and uninfected erythrocyte retention, and (iii) *in vitro* development of erythroid progenitors to dissect responsiveness to cytokine imbalance or malaria toxins, may be especially useful to develop integrated mechanistic insights and therapies to control this major and fatal disease pathology. Thus, an understanding of the causes of severe malarial anaemia is necessary to develop and implement new therapeutic strategies to tackle this syndrome of malaria. On the other hand, the pathophysiology of malarial anaemia is even more complex than had been proposed, and many questions remain unanswered, e.g. What is the dominant underlying mechanism? Are these mechanisms different in mild/moderate anaemia than in severe anaemia? Is acute malarial anaemia in the nonimmune a different process than that during recurrent, frequent infections in semi-immune individuals? To find effective management and preventive tools, these questions will need to be answered.

Many studies have been conducted using mathematical models for the within-host dynamics of malaria parasites focusing on a number of different issues [Anderson *et al.*, 1989; Hellriegel, 1992; Hetzel & Anderson, 1996; Anderson & May, 1990; Hoshen *et al.*, 2001; Molineaux *et al.*, 2001; Molineaux & Dietz, 2000; Mason *et al.*, 1999]. Most of these studies concentrate on the temporal development of intra-host models of malaria. The key question, as well as difficulty, is how to include spatial effects and quantify the dispersal of RBCs, PRBCs, merozoite and gametocytes. Since spatiotemporal models of the spread of malaria parasites are lacking, it is against this background that we carry out this study. There is seemingly no study modeling the effects of anemia on the transmission dynamics of malaria at least from the mathematical standpoint.

This study aims to assess the strength of the effects of catastrophic anemia level on the dynamical transmission of malaria parasite within the body of a host. We use a mathematical intra-host model of malaria to study the effects of parasite virulence and fitness variation on anemia level. The main interest is to understand the long and short term behaviors of the effects of anemia on the dynamical transmission of malaria parasites within the body of a host and to predict the anemia level.

The rest of the paper is organized as follows. In Sec. 2, we first present a temporal model with some theoretical results (existence and uniqueness of a solution, existence of equilibria, local stability and bifurcation). Later, we extend the temporal model to a spatiotemporal model, which leads to a system of coupled nonlinear reaction–diffusion equations. The model analysis consists of the study of the positivity and boundedness of solutions by using a comparison principle. The proposed model allows us to study the effects of parasite virulence and fitness variation on anemia level. Through numerical simulations, we found that the increase of the diffusion of cells increases the destruction of RBCs which can lead to a catastrophic anemia level of the patient, although the immune response or treatment can sometimes eliminate the infection. We also found that the risk of severe anemia depends on the initial size of the population of RBCs within the body of a host and can occur even if the parasite is not virulent enough to persist. Finally, Sec. 4 is devoted to the discussions and concluding remarks.

2. Temporal Model

In this section, we present a temporal model of the dynamical transmission model of malaria within a host. The interaction of malaria parasites, RBCs, PRBCs, immune response and gametocytes is presented in the model. It is described by a system of five equations in the five variables that represent the density of RBCs x, PRBCs y, free merozoites m, immune response I, and gametocytes g. Red blood cells are recruited from the red bone marrow at a constant rate Λ and die at the natural rate μ_x or are reduced at the rate βxm by contact with free merozoites. The PRBCs may burst at a rate μ_y to release γ merozoites per PRBC. The free merozoites either die at a natural rate μ_m or are absorbed by RBCs at a rate βmx. The release of merozoites and their attack on RBCs trigger an immune response to these (circulating) stages of the parasite. We incorporate specific immune response whose magnitude is proportional to the density of immune cells. The immune cells augment the clearance of merozoites and infected red blood cells from the body. The anti-blood stage immunity is T lymphocyte dependent that is constantly supplied from the thymus. Let a be the rate at which immune cells expand. This rate of expansion encapsulates the positive feedback upon the immune system. We further assume that a regulatory negative feedback force operates to suppress immune population growths at a rate proportional to the square of its density bI^2 [Hetzel & Anderson, 1996]. Also, they are recruited from their resting precursors by contact with PRBCs. Thus, we have a clearance rate of free merozoites, $k_m mI$ due to B-cells and macrophages, clearance rate of PRBCs due to T-cells, $k_y yI$. The rate of change of density

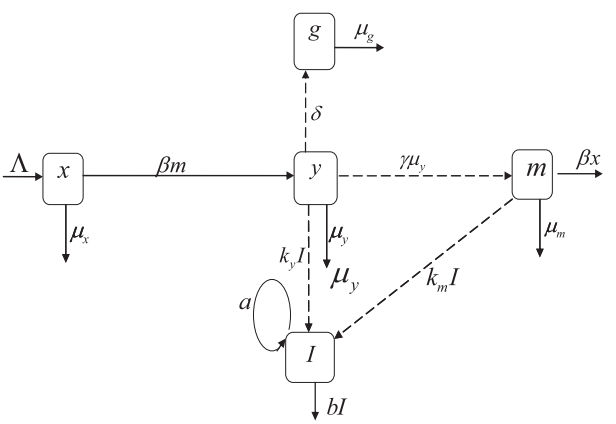


Fig. 1. Structure of the model.

of immune effector cells is described by their proliferation and death rates. They proliferate in response to contact with free merozoites and PRBCs at rates $\rho_m mI$ and $\rho_y yI$, respectively. The gametocytes are produced by PRBCs at a constant rate δ and die at a constant rate μ_g.

The structure of the model is shown in Fig. 1.

All the parameters of the model are assumed to be positive real numbers. With these definitions and assumptions, the interaction involving the densities of parasites, RBCs, PRBCs, immune effector cells and gametocytes is given by the following temporal system:

$$\begin{cases} \dot{x} = \Lambda - \mu_x x - \beta m x, \\ \dot{y} = \beta m x - \mu_y y - k_y I y, \\ \dot{m} = \gamma \mu_y y - \mu_m m - k_m I m - \beta m x, \\ \dot{I} = aI - bI^2 + \rho_m I m + \rho_y I y, \\ \dot{g} = \delta y - \mu_g g. \end{cases} \tag{1}$$

The parameter values of model system (1) used for numerical simulations are given in Table 1.

In Table 1, a^* and b^* stand for the references [Anderson *et al.*, 1989] and [Robert & Boudin, 2002], respectively.

2.1. *Existence and positivity of solutions*

For every nonzero, non-negative initial value, solutions of model system (1) exist for all time $t \geq 0$. Indeed, the local existence of solutions follows from standard arguments since the right-hand side of model system (1) is locally Lipschitz continuous. Global existence follows from *a priori* bounds.

The solutions of model system (1) with positive initial conditions are positive for all $t > 0$. Indeed, the vector field given by the right-hand side of model system (1) points inward on the boundary of $\mathbb{R}^5_+ \backslash \{0\}$. Thus, for example, if $x = 0$, then, $\dot{x} = \Lambda \geq 0$. The same reasoning can be used to show that the other model components (variables) are non-negative.

2.2. *Disease-free equilibrium and its stability*

Model system (1) has a homogeneous disease-free equilibrium, obtained by setting the right-hand sides of equations in model system (1) to zero, given by $Q_0 = \left(\frac{\Lambda}{\mu_x}, 0, 0, \frac{a}{b}, 0\right)$. Linearizing all equations in model system (1) around the disease-free equilibrium Q_0, the Jacobian matrix is

$$J = \begin{bmatrix} -\mu_x & 0 & -\beta x_0 & 0 & 0 \\ 0 & -\mu_y - k_y I_0 & \beta x_0 & 0 & 0 \\ 0 & \gamma \mu_y & -\mu_m - k_m I_0 - \beta x_0 & 0 & 0 \\ 0 & \rho_y I_0 & \rho_m I_0 & -a & 0 \\ 0 & \delta & 0 & 0 & -\mu_g \end{bmatrix},$$

Table 1. Description and estimation of parameters.

Parameter	Description	Estimated Value	Source
Λ	Production rate of RBCs	$1\,\text{RBC ml}^{-1}\,\text{day}^{-1}$	a^*
β	Contact rate between merozoites and RBCs	$0.02\,\text{RBC/ml}^{-1}\,\text{day}^{-1}$	a^*
μ_x	Natural death rate of RBCs	$0.00833\,\text{day}^{-1}$	a^*
μ_y	Death rate of PRBCs	$0.2\,\text{day}^{-1}$	a^*
μ_m	Death rate of merozoites	$72\,\text{day}^{-1}$	a^*
μ_I	Death rate of immune effectors	$0.05\,\text{day}^{-1}$	a^*
μ_g	Death rate of gametocytes	$0.25\,\text{day}^{-1}$	b^*
γ	Merozoites means rate produce by PRBCs	16	a^*
ρ_y	Immunosensitivity of PRBCs	$0.05\,\text{PRBC/ml}^{-1}\,\text{day}^{-1}$	a^*
ρ_m	Immunosensitivity of free merozoites	$0.1\,\text{RBC/ml}^{-1}\,\text{day}^{-1}$	a^*
k_y	Immune effectors reaction against PRBCs	$0.05\,\text{RBC/ml}^{-1}\,\text{day}^{-1}$	a^*
k_m	Immune effectors reaction against free merozoites	$0.1\,\text{RBC/ml}^{-1}\,\text{day}^{-1}$	a^*
a	Increasing rate of immune effectors	$0.05\,\text{day}^{-1}$	a^*
b	Regulation rate of immune effectors	$0.01\,\text{RBC/ml}^{-1}\,\text{day}^{-1}$	a^*
δ	Production rate of gametocytes	$0.03\,\text{ml}^{-1}\,\text{day}^{-1}$	b^*

where $x_0 = \frac{\Lambda}{\mu_x}$ and $I_0 = \frac{a}{b}$. Since $-\mu_x < 0$, $-a < 0$ and $-\mu_g < 0$, the triangular structure of the Jacobian matrix J implies that its stability is associated with the stability of the following submatrix:

$$J_0 = \begin{bmatrix} -\mu_y - k_y I_0 & \beta x_0 \\ \gamma \mu_y & -\mu_m - k_m I_0 - \beta x_0 \end{bmatrix}.$$

The submatrix J_0 is stable if its trace is negative and its determinant is non-negative. Therefore, a sufficient condition for this equilibrium to be stable is given by

$$\frac{\beta x_0 \gamma \mu_y}{(\mu_y + k_y I_0)(\mu_m + k_m I_0 + \beta x_0)} < 1.$$

Model of this type demonstrates clearly an infection threshold. In the presence of a threshold, disease eradication requires the reduction of the infection rate below a critical level where a stable infection-free equilibrium is guaranteed. In epidemiological terminology, the infection threshold may be expressed in terms of the basic reproductive number $\mathcal{R}_0$, the average number of infections produced by a single merozoites in a population of RBCs. From this definition, it is clear that malaria infection cannot spread within a host only if $\mathcal{R}_0 < 1$ [Diekmann *et al.*, 1990; van den Driessche & Watmough, 2002]. It then follows that the basic reproduction number $\mathcal{R}_0 < 1$ is given by

$$\mathcal{R}_0 = \frac{\beta x_0 \gamma \mu_y}{(\mu_y + k_y I_0)(\mu_m + k_m I_0 + \beta x_0)}. \qquad (2)$$

In conclusion, crossing the threshold reduces the basic reproductive number $\mathcal{R}_0$ below unity and the infection is prevented from propagating.

We now perform a sensitivity analysis of the basic reproduction number, $\mathcal{R}_0$. A 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 [Chitnis *et al.*, 2008]. We are thus interested in parameters that significantly affect the basic reproduction number, since they are parameters that should be taken into consideration when considering intervention strategies. If the basic reproduction number is very sensitive to a particular parameter, then a perturbation of the conditions that connect the dynamics to such a parameter may prove to be useful in identifying policies or intervention strategies that reduce epidemic prevalence. Herein, the partial rank correlation coefficients (PRCC) were calculated to estimate the correlation between values of the basic reproduction number and the four model parameters across 1000 random draws from the empirical distribution of $\mathcal{R}_0$ and its associated parameters.

Figure 2 illustrates the PRCCs using $\mathcal{R}_0$ as an output variable. Parameters with positive PRCCs will increase $\mathcal{R}_0$ when they are increased, whereas parameters with negative PRCCs will decrease $\mathcal{R}_0$ when they are increased. The results here suggest that the death rate of PRBCs, the regulation rate of immune effectors, merozoites means rate produced by PRBCs, the production rate of RBCs and the contact rate between merozoites and RBCs may increase the magnitude of $\mathcal{R}_0$ when they are increased, while the immune effectors reaction against PRBCs, the immune effectors reaction against free merozoites, the death rate of merozoites, the natural death

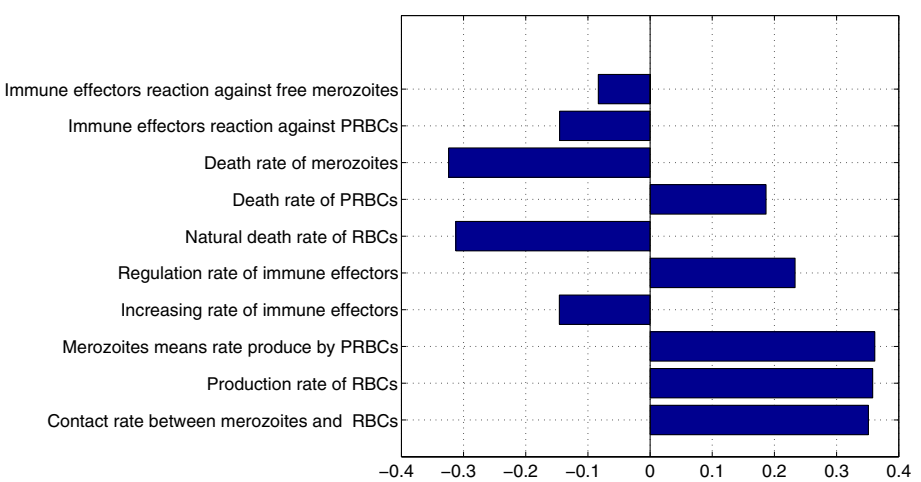
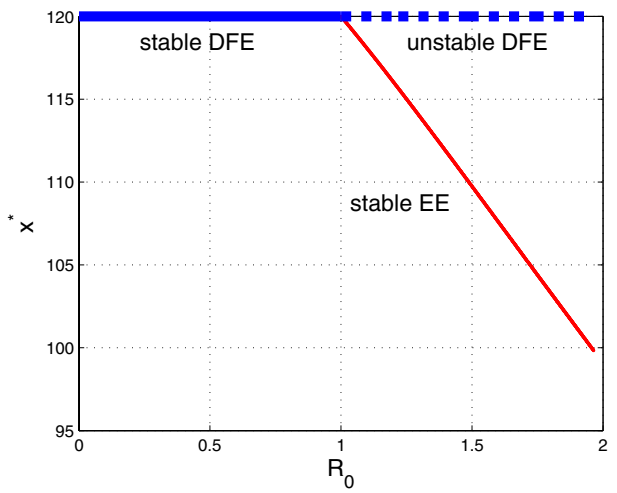
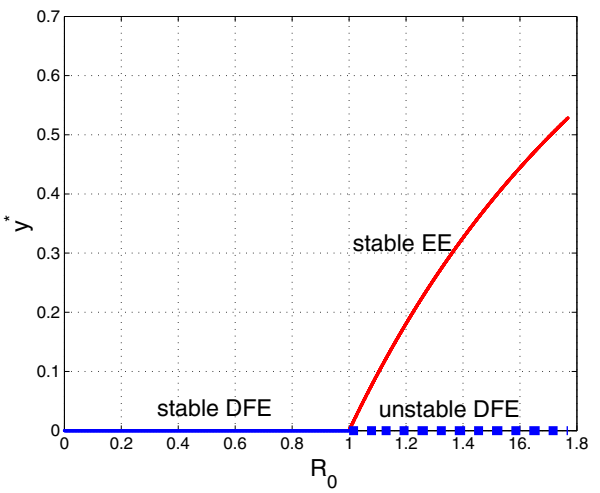


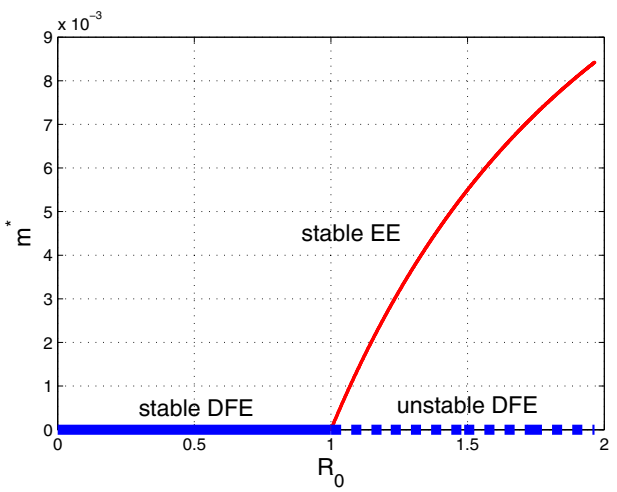
Fig. 2. Partial rank correlation coefficients (PRCC) showing the effects of parameter variation on the basic reproduction number, $\mathcal{R}_0$ using the parameters in Table 1.



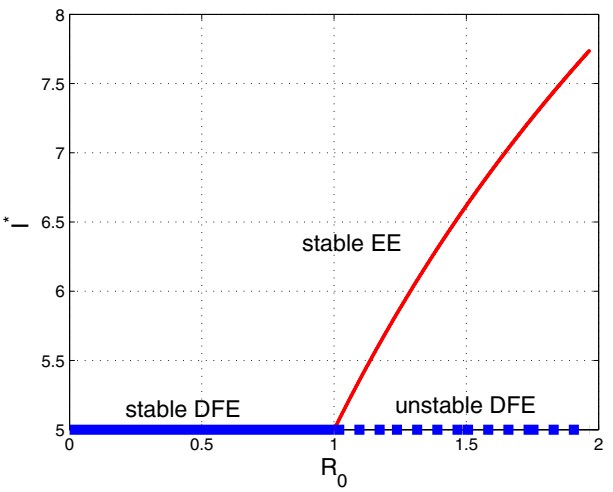
(a)



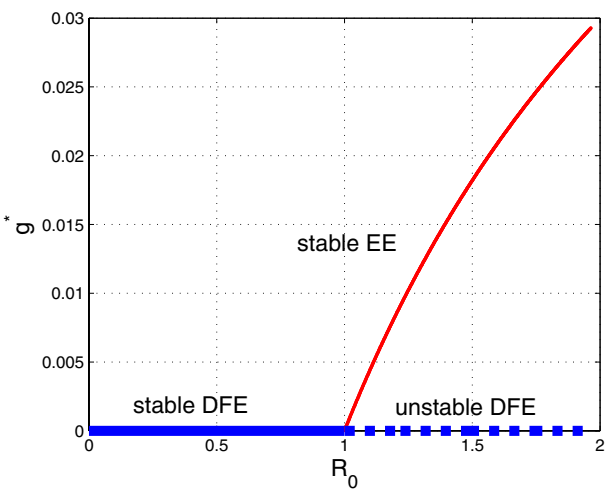
(b)



(c)



(d)



(e)

Fig. 3. Bifurcation diagram of model system (1). (a) x^*, (b) y^*, (c) m^*, (d) I^* and (e) g^*. The notations DFE and EE stand for disease-free equilibrium and endemic equilibrium, respectively.

rate of RBCs and the increasing rate of immune effectors have a negative influence on the magnitude of $\mathcal{R}_0$. Thus, we can practically control malaria within a host through increasing the immune effectors reaction against PRBCs, the immune effectors reaction against free merozoites, the death rate of merozoites, the natural death rate of RBCs and the increasing rate of immune effectors.

2.3. *Endemic equilibria and bifurcation*

Let $Q^* = (x^*, y^*, m^*, I^*, g^*)$ be a homogeneous endemic equilibrium of model system (1) with x^*, y^*, m^*, I^* and g^* satisfying the following equations:

$$\begin{cases} \Lambda - \mu_x x^* - \beta m^* x^* = 0, \\ \beta m^* x^* - \mu_y y^* - k_y I^* y^* = 0, \\ \gamma\mu_y y^* - \mu_m m^* - k_m I^* m^* - \beta m^* x^* = 0, \\ \rho_m I^* m^* + \rho_y I^* y^* + aI^* - bI^{*^2} = 0, \\ \delta y^* - \mu_g g^* = 0. \end{cases} \tag{3}$$

Using the first, second, third and fifth equations in (3), one yields

$$\begin{aligned} x^* &= \frac{\Lambda}{\mu_x + \beta m^*}, \quad y^* = \frac{\beta m^* \Lambda}{(\mu_x + \beta m^*)(k_y I^* + \mu_y)}, \quad g^* = \frac{\delta y^*}{\mu_g} \quad \text{and} \\ m^* &= \frac{-k_m\mu_x k_y (I^*)^2 - (\mu_m\mu_x k_y + k_m\mu_x\mu_y + \beta\Lambda k_y) I^* + \gamma\mu_y\beta\Lambda - \mu_m\mu_x\mu_y - \beta\Lambda\mu_y}{\beta(\mu_y + k_y I^*)(\mu_m + k_m I^*)}. \end{aligned} \tag{4}$$

Substituting (4) in the fourth equation of (3), it can be shown that the nonzero equilibria of model system (1) satisfy the following four order equation in terms of I^*:

$$a_4 (I^*)^4 + a_3 (I^*)^3 + a_2 (I^*)^2 + a_1 I^* + a_0 = 0, \tag{5}$$

where

$$\begin{cases} a_4 = b\beta k_m k_y^2, \\ a_3 = 2b\beta k_m\mu_y k_y - a\beta k_m k_y^2 + \rho_m k_m\mu_x k_y^2 + b\beta\mu_m k_y^2 - b\beta k_m k_y\gamma\mu_y - \rho_y k_m^2\mu_x k_y, \\ a_2 = k_y^2\rho_m\mu_m\mu_x + k_y^2\rho_m\beta\Lambda - k_y^2 a\beta\mu_m - 2k_y\rho_y\mu_m\mu_x k_m + 2k_y\rho_m k_m\mu_x\mu_y \\ \qquad - k_y\rho_m k_m\mu_x\gamma\mu_y - k_y\rho_y\beta\Lambda k_m + k_y a\beta\gamma\mu_y k_m + 2k_y b\beta\mu_y\mu_m - 2k_y a\beta\mu_y k_m \\ \qquad - k_y b\beta\gamma\mu_y\mu_m - \rho_y k_m^2\mu_x\mu_y + b\beta\mu_y^2 k_m - b\beta\gamma\mu_y^2 k_m, \\ a_1 = -2k_y a\beta\mu_y\mu_m - k_y\rho_y\beta\Lambda\mu_m - 2k_y\rho_m\gamma\mu_y\beta\Lambda - k_y\rho_m\mu_m\mu_x\gamma\mu_y + 2k_y\rho_m\beta\Lambda\mu_y \\ \qquad - k_y\rho_y\mu_m^2\mu_x + k_y a\beta\gamma\mu_y\mu_m + 2k_y\rho_m\mu_m\mu_x\mu_y + \rho_y\gamma\mu_y\beta\Lambda k_m + a\beta\gamma\mu_y^2 k_m - a\beta\mu_y^2 k_m \\ \qquad - b\beta\gamma\mu_y^2\mu_m + \rho_m k_m\mu_x\mu_y^2 - 2\rho_y\mu_m\mu_x\mu_y k_m - \rho_y\beta\Lambda\mu_y k_m + b\beta\mu_y^2\mu_m - \rho_m k_m\mu_x\mu_y^2\gamma, \\ a_0 = \mu_y(\mu_y\rho_m\beta\Lambda - \mu_y a\beta\mu_m + \mu_y\rho_m\mu_m\mu_x + \mu_y\rho_m\gamma^2\beta\Lambda - \mu_y\rho_m\mu_m\mu_x\gamma + \mu_y a\beta\gamma\mu_m \\ \qquad - 2\mu_y\rho_m\gamma\beta\Lambda - \rho_y\mu_m^2\mu_x + \rho_y\gamma\beta\Lambda\mu_m - \rho_y\beta\Lambda\mu_m). \end{cases}$$

Finding the analytical solutions of Eq. (5) is a difficult task. To solve this equation, we proceed with numerical simulations.

The associated bifurcation diagram using the parameters of Table 1 is depicted in Fig. 3. From this figure, it clearly appears that the disease-free equilibrium is stable if $\mathcal{R}_0 < 1$, while if $\mathcal{R}_0 > 1$, the disease-free equilibrium is unstable and there exists a unique endemic equilibrium which is stable. Thus, model system (1) exhibits a forward bifurcation.

3. Spatiotemporal Model

We now extend model system (1) taking into account the spatial component in the modeling. Indeed, after the infection, the parasites travel through the bloodstream to the liver, where they mature and release other merozoites. The release of merozoites and their attack on RBCs triggers an immune response and immune effectors move to parasites in order to neutralize them. Also,

instead of replicating, the merozoites in these cells develop into gametocytes, that circulate in the bloodstream. In this section, we consider the movement of RBCs, PRBCs, free merozoites, immune response and gametocytes within the body of a host. We assume that all red blood cells and parasites diffuse randomly in two finite-dimensional domains.

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

$$\begin{cases} \dfrac{\partial x}{\partial t}(t,w) = \Lambda - \mu_x x - \beta m x + \varepsilon_x \Delta x, \\ \dfrac{\partial y}{\partial t}(t,w) = \beta m x - \mu_y y - k_y I y + \varepsilon_y \Delta y, \\ \dfrac{\partial m}{\partial t}(t,w) = \gamma \mu_y y - \mu_m m - k_m I m \\ \qquad\qquad - \beta m x + \varepsilon_m \Delta m, \\ \dfrac{\partial I}{\partial t}(t,w) = aI - bI^2 + \rho_m I m + \rho_y I y + \varepsilon_I \Delta I, \\ \dfrac{\partial g}{\partial t}(t,w) = \delta y - \mu_g g + \varepsilon_g \Delta g, \end{cases} \tag{6}$$

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

3.1. *Model basic properties*

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

$$\begin{aligned} \frac{\partial x}{\partial \nu}(t,w) &= \frac{\partial y}{\partial \nu}(t,w) = \frac{\partial m}{\partial \nu}(t,w) \\ &= \frac{\partial I}{\partial \nu}(t,w) = \frac{\partial g}{\partial \nu}(t,w) \\ &= 0, \quad (t,w) \in \mathbb{R} \times \partial\Omega, \\ x(0,w) &= x_0(w), \quad y(0,w) = y_0(w), \\ m(0,w) &= m_0(w), \quad I(0,w) = I_0(w) \quad \text{and} \\ g(0,w) &= g_0(w), \quad w \in \Omega \subset \mathbb{R}^2, \end{aligned} \tag{7}$$

where Ω 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 Ω. In the sequel, we will denote by $\overline{\Omega}$ the closure of Ω.

For model system (6), 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 (6) 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 Ω. Now, let

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

It is obvious that $(0,0,0,0,0)$ is a lower solution of model system (6). Moreover, we have

$$\begin{gathered} \overline{x_0} \geq 0, \quad \overline{y_0} \geq 0, \quad \overline{m_0} \geq 0, \\ \overline{I_0} \geq 0 \quad \text{and} \quad \overline{g_0} \geq 0. \end{gathered}$$

Thus, by the maximum principle, one can conclude that

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

This implies that any solution of model system (6) with positive initial condition will remain positive.

Now, we will prove that the solutions of model system (1) admit also upper limits. Without loss of generality, we assume that $\varepsilon_x = \varepsilon_y = \varepsilon_1$. Then, from model system (6), one has

$$\frac{\partial z}{\partial t} \leq \Lambda - \mu z + \varepsilon_1 \Delta z,$$

where $\mu = \min(\mu_x, \mu_y)$.

Consider the following equation:

$$\frac{\partial \overline{z}}{\partial t} = \Lambda - \mu \overline{z} + \varepsilon_1 \Delta \overline{z}.$$

Solving the above equation gives

$$\overline{z}(t) = \frac{\Lambda}{\mu} + \left(\overline{z}(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t},$$

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

$$\begin{aligned} z(t,w) &\leq \overline{z}(t) \\ &= \frac{\Lambda}{\mu} + \left(\overline{x_0} + \overline{y_0} - \frac{\Lambda}{\mu}\right) e^{-\mu t} \\ &\leq \overline{x_0} + \overline{y_0}, \quad \forall (t,w) \in \mathbb{R}^+ \times \Omega. \end{aligned} \tag{8}$$

Using the same reasoning, one can establish that

$$\begin{aligned} m(t,w) &\leq \frac{\gamma \mu_m (\overline{x_0} + \overline{y_0})}{\mu_m} \\ &\quad + \left(\overline{m_0} - \frac{\gamma \mu_m (\overline{x_0} + \overline{y_0})}{\mu_m}\right) e^{-\mu_m t}. \end{aligned} \tag{9}$$

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

Note that the inequality (9) suggests that the density of merozoites cannot blow up but remains

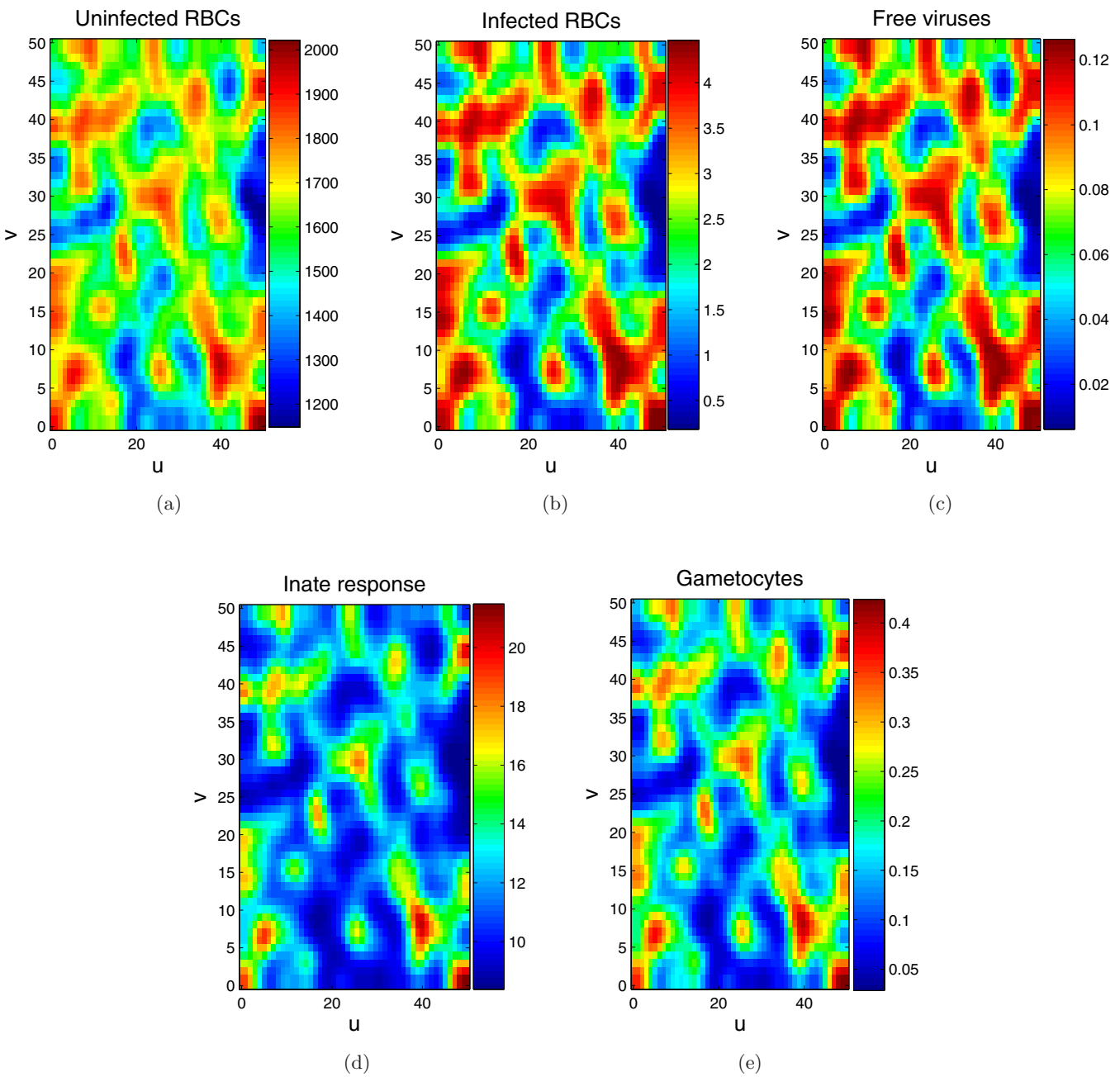


Fig. 4. Spatiotemporal evolution of model system (6) after 20 days when $\beta = 0.02$ (so that $\mathcal{R}_0 = 0.2 < 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.1$.

finite for any merozoites virulence and fitness. However, the most important issue is to determine at what level of merozoites virulence and fitness, the patient will achieve a catastrophic threshold of anemia that the immune system could withstand.

3.2. *General dynamics*

Herein, we numerically investigate the general dynamics of model system (6).

The spatiotemporal evolution of model system (6) for different values of the diffusion parameters and the contact rate between merozoites and RBCs after 20 days is depicted in Figs. 4–6. Without loss of generality, we assume that the diffusion parameters of RBCs, PRBCs, malaria parasites, immune response and gametocytes are the same, that is $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_g = \varepsilon_I$. The boundary conditions are of Neumann type, i.e. the flow at the edge is zero. We assume that

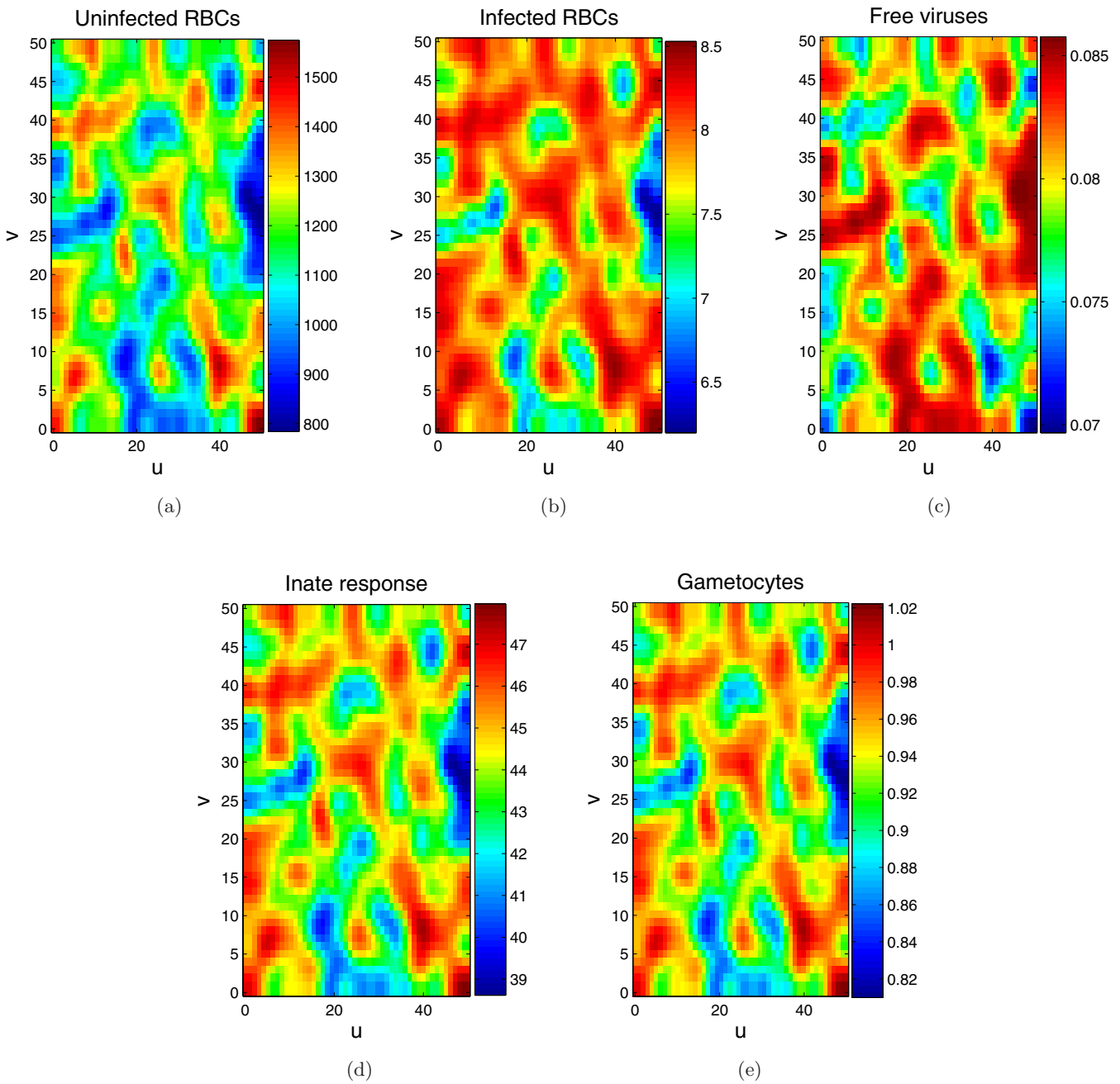


Fig. 5. Spatiotemporal evolution of model system (6) after 20 days when $\beta = 0.2$ (so that $\mathcal{R}_0 = 1.7 > 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.1$.

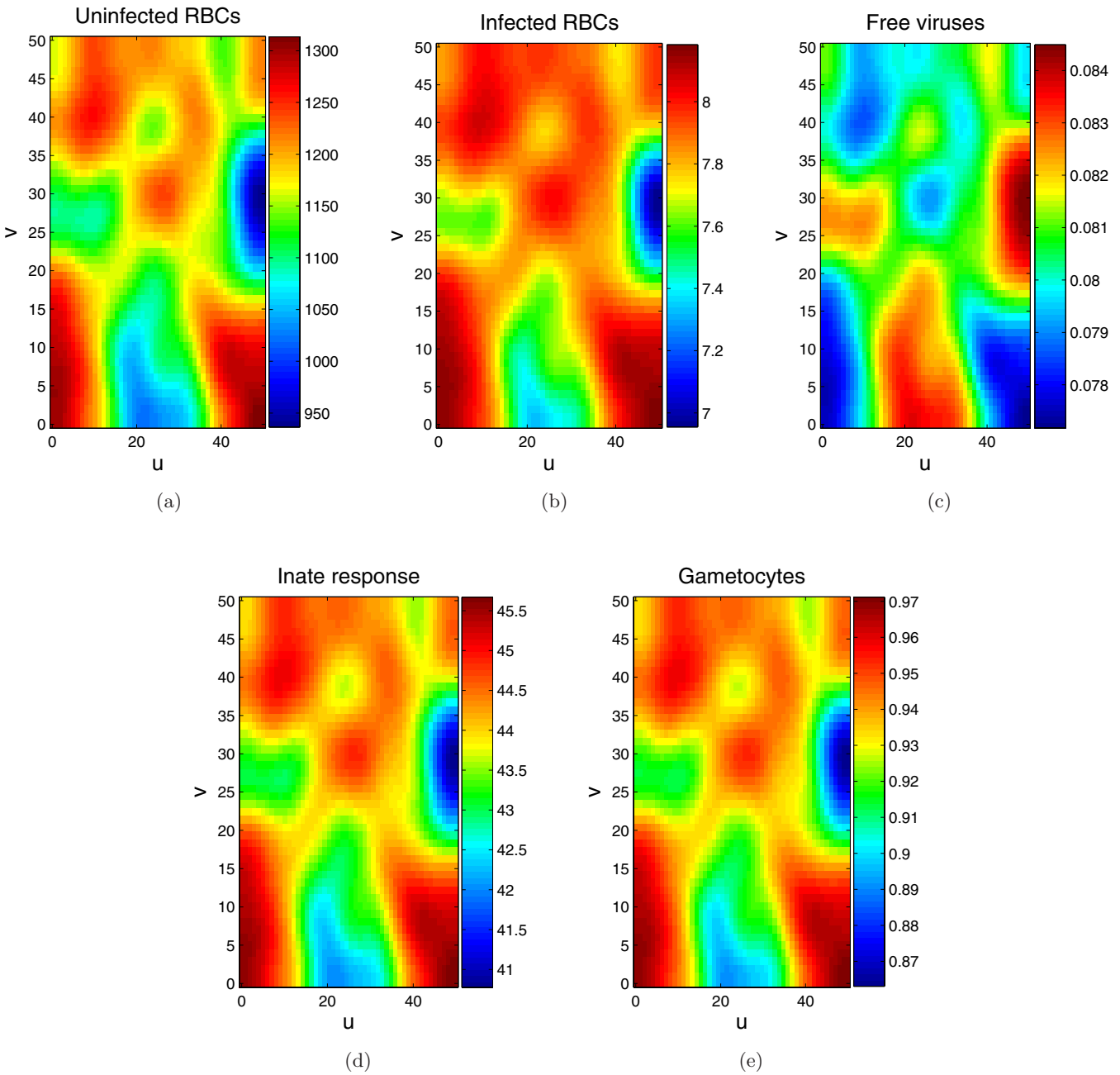


Fig. 6. Spatiotemporal evolution of model system (6) after 20 days when $\beta = 0.2$ (so that $\mathcal{R}_0 = 1.7 > 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.5$.

initially, the densities of RBCs, PRBCs, free merozoites, immune response, and gametocytes are randomly distributed between 0 and 4000 in cylinders and outside the cylinders, their densities are zero. All these cylinders are contained in $\Omega = [0, 50] \times [0, 50] \times [0, 50] \times [0, 50] \times [0, 50]$ field in which the problem is studied.

Figure 4 shows the spatial repartition of RBCs, PRBCs, malaria parasites, immune response and gametocytes after 20 days when $\beta = 0.02$ (so that $\mathcal{R}_0 = 0.2 < 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.1$. This corresponds to the case where the host does not suffer from malaria. It illustrates that the number of parasites within the body of the host is not sufficient to provoke an infection.

Figure 5 gives the results of numerical simulations of RBCs, PRBCs, malaria parasites, immune response and gametocytes after 20 days when $\beta = 0.2$ (so that $\mathcal{R}_0 = 1.7 > 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.1$. This corresponds to the case where

the host suffers from malaria. As expected, there are more PRBCs, less RBCs, parasites and more immune effectors and gametocytes within the body of the host than in Fig. 4. Indeed, when a host suffers from malaria, the number of RBCs decreases and the number of PRBCs increases due to the infection. As a consequence, the number of free merozoites will decrease because more free merozoites will enter PRBCs. Also, since the body is attacked, this will stimulate the immune response that will increase when the number of PRBCs increases.

Now, we investigate the role of the diffusion parameters on the dynamical transmission of malaria parasites within the body of a host. Figure 6 presents the spatiotemporal evolution of model system (1) when $\beta = 0.2$ (so that $\mathcal{R}_0 = 1.7 > 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 0.5$. In comparison to Fig. 5, when the diffusion parameters increase, the number of RBCs, PRBCs, immune effectors and gametocytes decrease. Indeed, an increase of the diffusion parameters will increase the contact rates between RBCs and free merozoites. This will lead to the destruction of RBCs which result in a decrease of the number of free merozoites because they enter RBCs. This result suggests that as the diffusion parameters increase, more RBCs become infected and malaria disease can lead to a catastrophic anemia level of the patient.

3.3. *Effects of anemia*

Anemia (hemoglobin level $< 11\,\mathrm{g/dL}$) remains one of the most intractable public health problems in malaria-endemic countries of Africa. It affects more than half of all pregnant women and children less than five years old, and has serious consequences since severe anemia (hemoglobin level $< 5\,\mathrm{g/dL}$) is

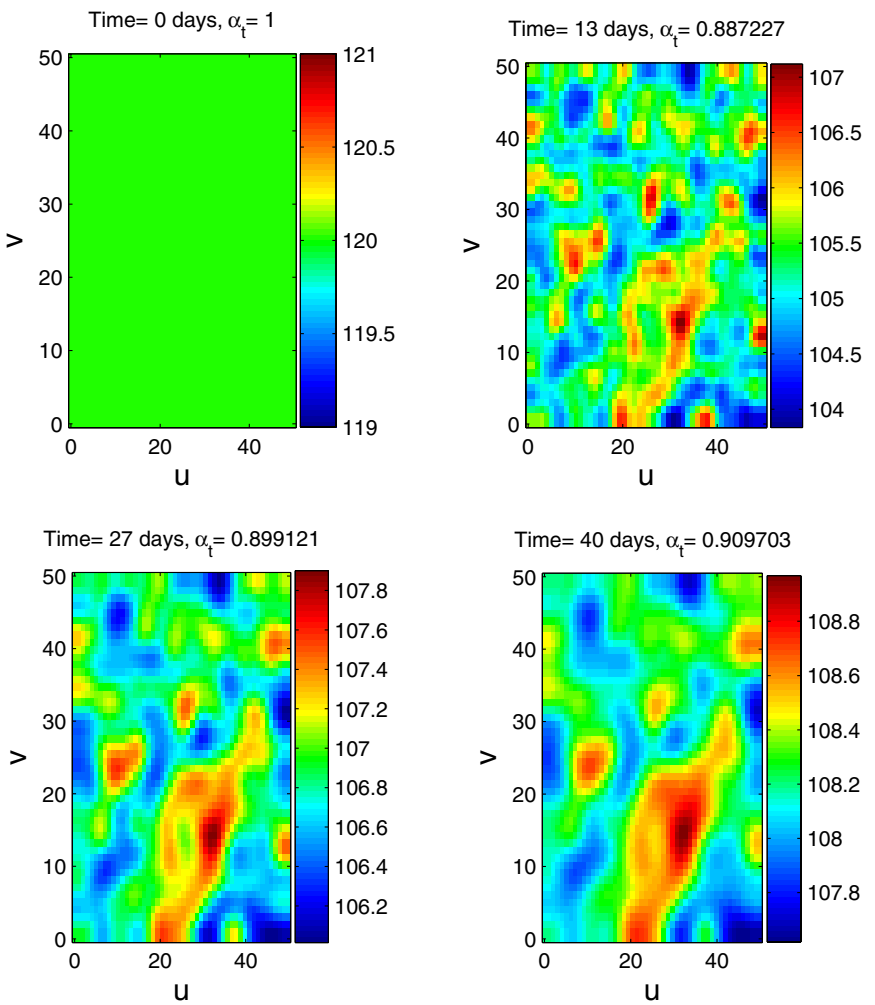


Fig. 7. Spatiotemporal evolution of RBCs when $\beta = 0.08$ (so that $\mathcal{R}_0 = 0.8315 < 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$.

associated with an increased risk of death [Brabin *et al.*, 2001], while iron deficiency and anemia may impair cognitive and motor development, growth, immune function, and physical work capacity [Crawley, 2004]. The aim of this section is to evaluate the effects of some model parameters on the time at which a patient reaches the threshold of catastrophic anemia. This will be done using numerical simulations.

Mathematically, the anemia level α_t can be defined as

$$\alpha_t = \frac{\int_\Omega x(t,w)dw}{\int_\Omega x(t_0,w)dw}. \quad (10)$$

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

$$T_{\text{anemia}} = \min(120 \text{ days},\ \inf(t, \alpha_t < 75\%)), \quad (11)$$

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

For the 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 time t is equal to or less than 75% of the initial RBCs.

Figure 7 presents the spatiotemporal evolution of RBCs within a host when $\beta = 0.08$ (so that $\mathcal{R}_0 = 0.8315 < 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$. This figure shows that with the chosen parameter values and initial conditions, after 20 days, the patient will not reach the threshold of catastrophic anemia level.

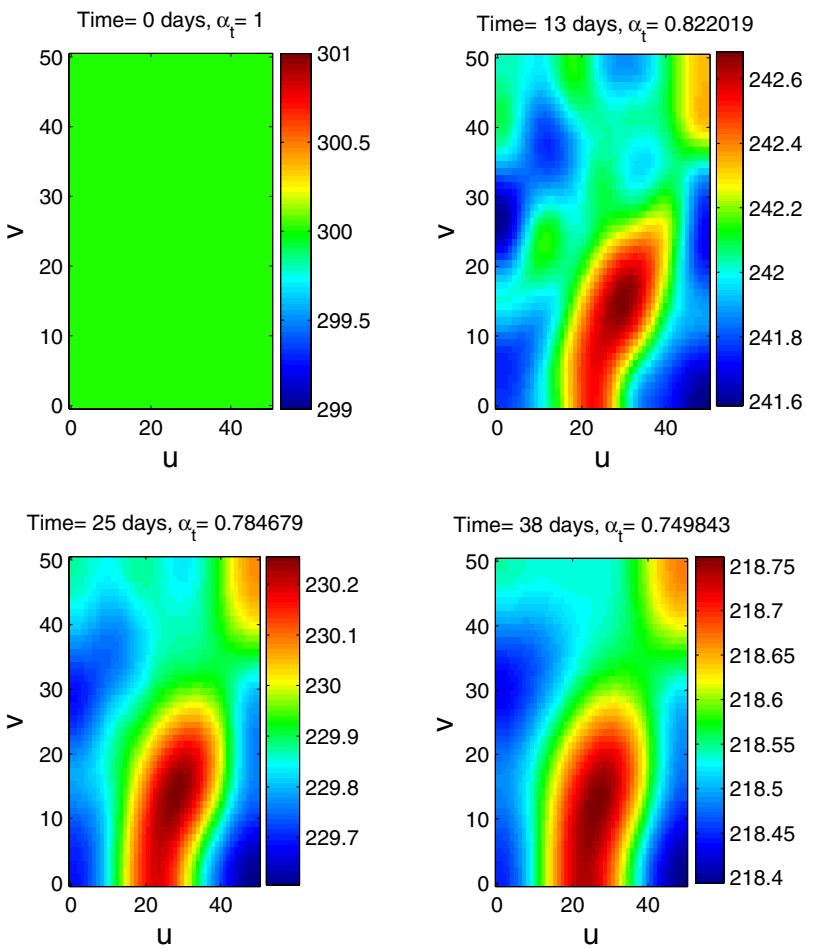


Fig. 8. Spatiotemporal evolution of RBCs when $\beta = 0.08$ (so that $\mathcal{R}_0 = 0.8315 < 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$.

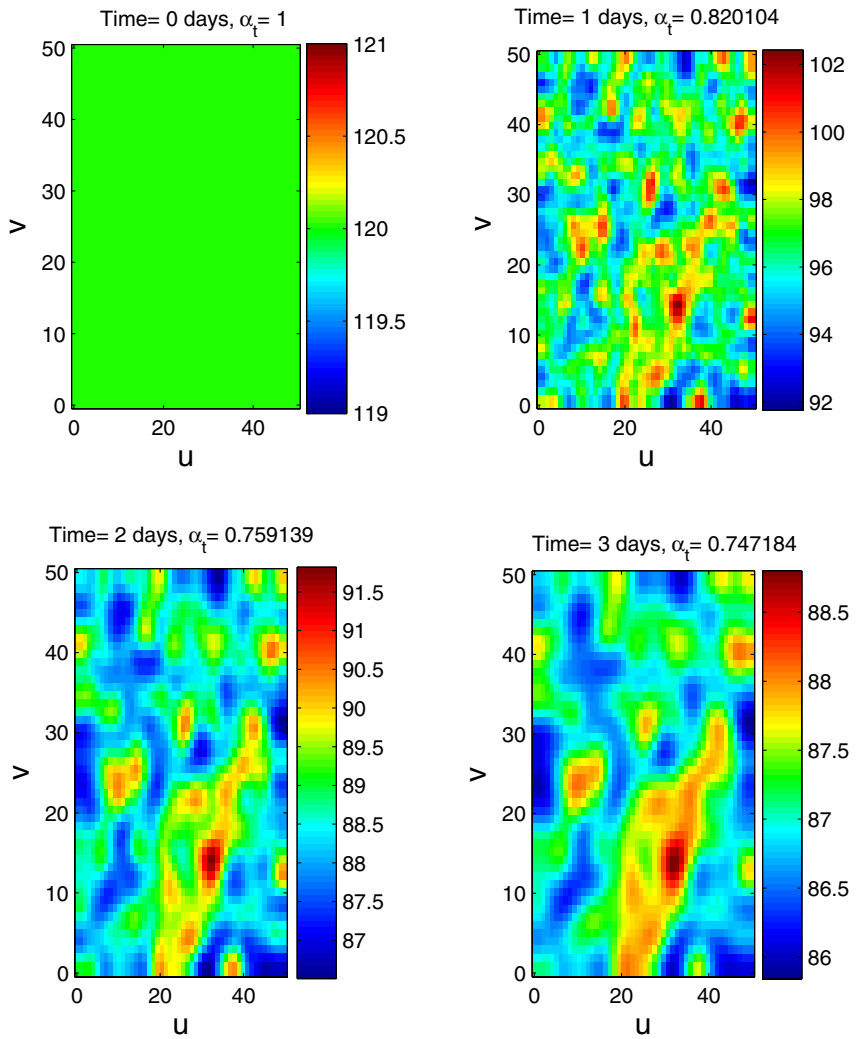


Fig. 9. Spatiotemporal evolution of RBCs when $\beta = 0.16$ (so that $\mathcal{R}_0 = 1.48 > 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$.

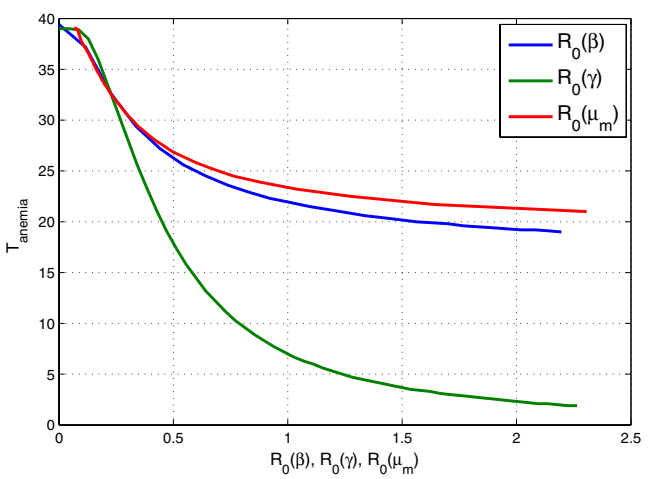


Fig. 10. Anemia time T_{anemia} as a function of $\mathcal{R}_0(\beta)$, $\mathcal{R}_0(\gamma)$ and $\mathcal{R}_0(\mu_m)$ when $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$.

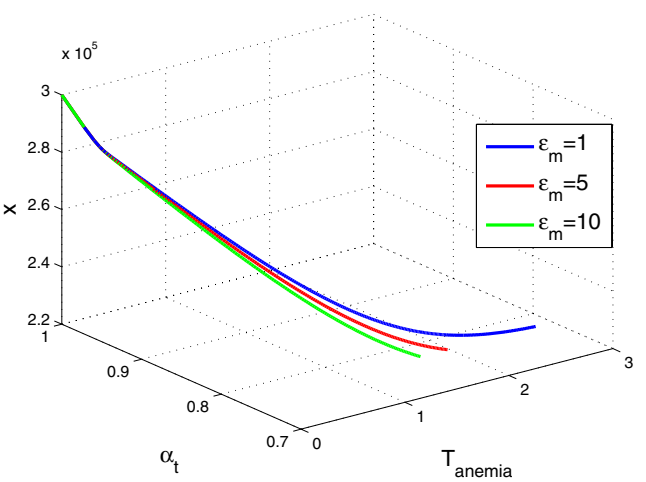
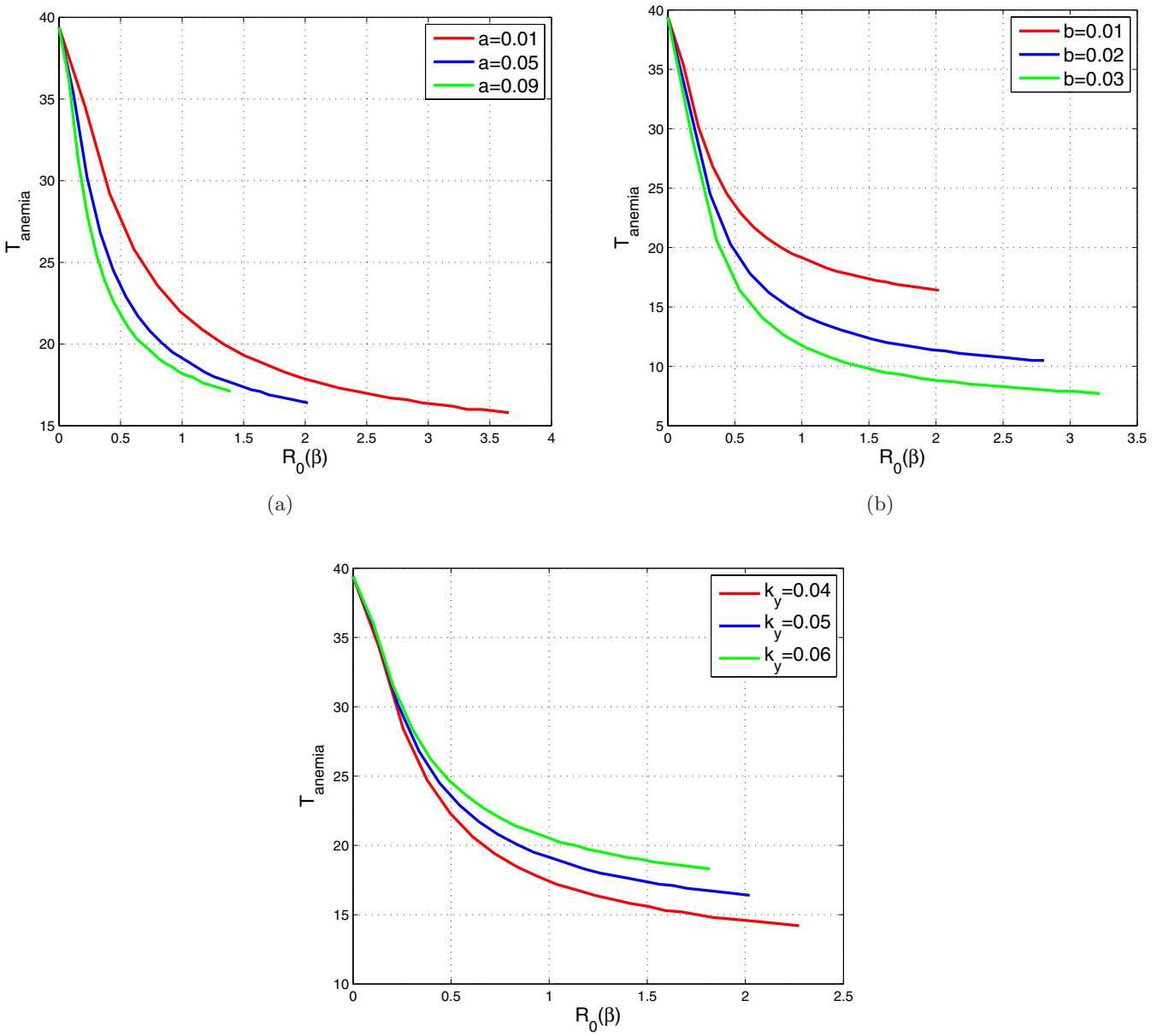


Fig. 11. 3D graph showing the evolution of RBCs as a function of α_t and anemia time T_{anemia} when $\beta = 0.8$ (so that $\mathcal{R}_0 = 1.63$) and $\varepsilon_x = \varepsilon_y = \varepsilon_I = \varepsilon_g = 1$ for different values of ε_m.

Now, we suppose that RBCs, PRBCs, free merozoites, immune response and gametocytes within the body of a host are initially at the disease-free equilibrium with 300 RBCs distributed uniformly at each point.

Figure 8 presents the spatiotemporal evolution of RBCs within the body of a host when $\beta = 0.08$ (so that $\mathcal{R}_0 = 0.8315 < 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$. From this figure, it is evident that in spite of the fact that the basic reproduction number is less than unity, the host can suffer from severe anemia after 38 days. In this case, anemia results from other factors such as malnutrition, coinfection with HIV/AIDS, heavy alcohol drinking and so on. In comparison with Fig. 7, one can also see that when $\mathcal{R}_0 \leq 1$, the catastrophic anemia level may also depend on the initial size of RBCs within the body of the host. Thus, when the basic reproduction number is less than unity, a huge initial size of RBCs will lead to a catastrophic anemia level within the body of a host, although the host does not suffer from malaria.

Figure 9 presents the spatiotemporal evolution of RBCs within the body of a host when $\beta = 0.16$



(a)

(b)

(c)

Fig. 12. Anemia time T_{anemia} as a function of $\mathcal{R}_0(\beta)$ for three different values of (a) a, (b) b and (c) k_y.

(so that $\mathcal{R}_0 = 1.48 > 1$) and $\varepsilon_x = \varepsilon_y = \varepsilon_m = \varepsilon_I = \varepsilon_g = 1$. It illustrates that the population of RBCs reaches the threshold $\alpha_t = 0.749163$ after three days of the infection and the host will suffer from anemia.

Figure 10 shows the time at which a patient's anemia level becomes catastrophic T_{anemia} as a function of the basic reproduction number $\mathcal{R}_0$. It illustrates that when the basic reproduction number $\mathcal{R}_0$ increases due to the variation of the transmission rate β, the production of parasites γ and the parasite mortality μ_m, the anemia time T_{anemia} decreases. Thus, as $\mathcal{R}_0$ increases due to the variation of β, γ and μ_m, the anemia time becomes small and the patient will quickly suffer from anemia. Note that anemia can occur in a patient before 120 days which corresponds to the RBCs periodic recycling duration. This figure also shows that the increase of γ induces the decrease of T_{anemia} more quickly than the increase of β and μ_m. Thus, the increase of the production of merozoites may quickly result in a catastrophic anemia level. This suggests that a drug that can stop the multiplication of parasites inside the RBCs can be the best strategy to fight against the disease in areas where malaria is endemic. This will prevent the occurrence of anemia.

Figure 11 gives a 3D graph showing the evolution of RBCs as a function of α_t and T_{anemia} when $\beta = 0.16$ (so that $\mathcal{R}_0 = 1.48 > 1$) for three different values of the diffusion parameter of free merozoites ε_m. This figures clearly shows that the malaria infection can cause anemia after three days if it is not quickly treated. This suggests that the best strategy for the disease control is to reduce the transmission rate β and the treatment must be done during a time shorter than the critical anemia time T_{anemia}. However, in malaria endemic areas where the bites of mosquitoes per human range to 150–200 per year, it is difficult to control the transmission rate β. One issue is to reduce the bites of mosquitoes by using for example bednet as malaria therapy prophylaxis. This result also suggests that the treatment of malaria should start as soon as the disease is declared in a patient in order to avoid the loss of a huge number of RBCs.

Figure 12 presents the anemia time as a function of the basic reproduction number when the transmission rate of the infection varies. Figure 12(a) gives T_{anemia} as a function of $\mathcal{R}(\beta)$ for three different values of the increasing rate of immune effectors. It shows that as a increases, T_{anemia} also increases. This suggests that we can practically control anemia within a host by increasing the immune effectors. The anemia time T_{anemia} as a function of $\mathcal{R}(\beta)$ for three different values of b is depicted in Fig. 12(b). It shows that as b increases, T_{anemia} decreases. Figure 12(c) presents T_{anemia} as a function of $\mathcal{R}(\beta)$ for three different values of k_y. It is evident that T_{anemia} increases with k_y. This is an expected result, since the role of the immune effectors is to fight malaria within the body of a host. Thus, to reduce or control the anemia level, one strategy should be to accelerate innate cell reproduction rate.

4. Discussions and Concluding Remarks

A mathematical model for the interactions between RBCs, PRBCs, malaria parasites, immune response and gametocytes is presented as a system of partial differential equations. We use this spatiotemporal model to study effects of the catastrophic anemia level on the dynamical transmission of malaria parasite within the body of a host. The effect of anemia on the actual malaria dynamics within a patient is two-fold: it is a major cause of mortality and morbidity in patients, especially children and pregnant women, living in malarial endemic areas and it can improve the understanding of malarial anemia that may help in the design of appropriate management strategies.

A qualitative analysis of the model has been presented. The epidemic threshold parameter which determines the outcome of the disease is computed and used to assess the dynamics of the disease within a host. The disease-free and endemic equilibria are obtained and their stabilities are investigated depending on the system parameters. Using numerical simulations, we found that the model exhibits a forward bifurcation, that is the disease-free equilibrium is stable when the basic reproduction number is less than unity and when the basic reproduction number is greater than unity, the disease-free equilibrium is unstable and there exists a unique endemic equilibrium which is stable.

Through numerical simulations, we found that in the presence of immune response, malaria infection may impact the anemia. The risk of severe anemia can occur even if the parasite is not virulent enough to persist with the basic reproduction number less than unity. Although the control strategy of the outbreak is determined by the basic

reproduction number $\mathcal{R}_0$, the infection can have harmful consequences on the patient. The selected treatment strategy should be effective over a short period whose duration is strictly less than T_{anemia}. Usually the treatment starts several days after the infection, while the patient has already lost a huge amount of RBCs. Thus, for a more effective control of the anemia level, one needs to stimulate rapidly the activation of the immune response in order to produce a sufficient number of innate immune cells to clear PRBCs and to increase the mortality rate of merozoites by activating innate immune cells. It will be important to involve health programs as diverse as malaria, nutrition, reproductive and child health, HIV/AIDS, helminth control, and laboratory and blood transfusion services. There needs to be communication and collaboration with other disciplines, particularly environmental health and agriculture [Allen, 2003]. Research institutions, nongovernmental organizations and the media have important roles to play. Politically, it is essential that ministers of health and finance need to understand that anemia control is cost-effective and yields substantial health benefits.

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