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Modelling the Erythrocytic Stage of Malaria Infection: the Role of Gametocytes

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Abstract

An intra-host mathematical model that describes the transmission dynamics of malaria parasite (i.e., merozoites and gametocytes) and its interaction with red blood cells is proposed. Local asymptotic stability of the disease free equilibrium is investigated and the basic reproduction number is calculated. We deduce that malaria disease can be effectively controlled and possibly eradicated if antimalarial drugs that attack and destroy the sexual forms of the malaria parasites (i.e., gametocytes) before they are ingested by a feeding Anopheles mosquito is administered to an infected human. Numerical simulations are carried out and these illustrate some dynamical behaviours of the model.

Key words: malariaintra-host model, basic reproduction number, local asymptotic stability, numerical simulations.
AMS Subject Classification: 34D05, 34D23, 93D23, 92B05

1.0 Introduction

Malaria is an ancient disease with an enormous health and socio-economic burden. The disease is mostly present in Sub-Saharan African and South East Asia. The disease is a major public health problem in Nigeria where it accounts for more cases and deaths than any other country in the world, with an estimated 100 million malaria cases with over 300,000 deaths per year. Malaria is a mosquito-borne infectious disease of humans and other animals, and it is potentially deadly if not properly treated [1,2]. The disease is caused by the *Plasmodium* parasite, and till date, no effective malaria vaccine has been successfully developed, and many of the existing anti-malaria drugs are losing effectiveness due to the evolution of drug resistant malaria parasite. Thus, interdisciplinary approach involving not only medial and biological experts, but also mathematical approach is very essential. Human malaria is caused by four *Plasmodium* parasite species, i.e., *P, falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and the disease is transmitted by the bite of an *Anopheles* mosquito [3].Globally, the virulence of *P. falciparum* makes it responsible for a majority of all chronic malaria cases, and is thus the main contributor to malaria morbidity and mortality [4–6].

The malaria parasite exhibit a complex life cycle within their *Anopheles* mosquito host which enables them to be transmitted between their human hosts. The cycle begins when malaria sporozoites (parasite) from the salivary glands of a *Anopheles*mosquito are injected into their vertebrate hosts when it takes a blood meal from humans [7,8]. Most of the sporozoites are carried by the host circulatory system to the liver where they invade the hepatocytes (liver cells), and replicate asexually into tens of thousands of rounded haploids forms [9,10]. These rounded forms eventually develop into schizont which contains thousands of merozoites and are released into the host blood stream where they quickly invade the host red blood cells.Within the infected red blood cells, the merozoites continue to replicate asexually producing thousands of daughter merozoites until the infected erythrocyte ruptures releasing the merozoites into the blood stream, which in turn quickly invade new red blood cells [11] re-initiating another rounds of blood-stage replicative cycle.

The erythrocytic stage of malaria resulting in the destruction of red blood cells and production of daughter merozoites is responsible for the recurrent fever and other symptoms associated with malaria that can last for months if not properly treated [12,13].However, a few of these parasites differentiates into sexual forms called gametocytes through a process called gametocytogenesis. Gametocytes are large and they fill up the red blood cells circulating in the blood streams waiting for a feeding *Anopheles* mosquito to ingest them. When a mosquito bites an infected human, it ingests the gametocytes, and within the midgut of the mosquito, the gametocytes develop into gametes, i.e., the male and form of the parasite. And after several developmental stages, tiny elongated sporozoites are produced. The sporozoites drift to the salivary glands of the mosquito where they are readily injected into the subcutaneous tissue and blood stream of the next available human and/or non-human mammalian host, thus completing their life cycle [14–20].

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The use of host-vector models to study the dynamics of malaria dates back to the work of Ross (1911)(as cited in[21]) who explained the relationship between the number of mosquito and the morbidity of malaria disease. More recently, the authors in [22] developed a mathematical model for malaria transmission recommended that an increase in the treatment rate of individuals' decreases the number of infected mosquitoes which directly lowers the incidence rate of malaria. Using a delayed Ross-Macdonald malaria model in [23], it was proposed that prolonging the incubating period in either humans or mosquito (through medicine or control measures) could reduce the prevalence of malaria infection. In [24], the authors formulated a model for malaria in human numerically deduced that treatment of the partially immune humans assists in reducing the severity of the disease and that transmission blocking vaccines would be effective in a partially immune population. In[25] a malaria model is developed to show how vaccination and personal protection can suppress the transmission rates of the parasites from human to mosquito and vice-versa. Other researchers in [26] derived a deterministic model for the spread of malaria and using optimal control theory, they derived conditions under which the disease can be optimally eradicated.

Within-host models have also played a significant role in modeling *in vivo* situation within an infected human host, i.e., the interaction of malaria parasite with red blood cells, and sometimes with immune cells. The basic within host model to show that to reduce parasitaemia within the blood, it is effective to find mechanism that assist in reducing the average number of merozoites produced and increasing the death rates of merozoites. Others [28] proposed an intra-host model for the erythrocytic stage of malaria, and deduced that infection can be eradicated within the host if the drug efficacy level exceeds a certain threshold value. Tewa et al [29] provided a complete mathematical analysis of a general within-host model and demonstrated mathematically that the immune response increase with time when the parasites persists. Mason et al [30] presented a mathematical of the within-host dynamics of a mixed-species malaria infection in a human, suggested that an existing *P. malariae* infection can reduce the peak parasitaemia of a subsequent *P. falciparum* super-infection.

Several research workshave been done on the modelling of malaria infection human population, as well as within host models that describe the interaction between the malaria parasite and the red blood cells. However, to the best of our knowledge, only very few authors [28] have considered the transmission dynamics of *P. falciparum* in the presence of host red blood cells and immune response. In particular, gametocyte is often not included in most existing models.

2.0 Model Formulation

Our model is an extension of the earlier work bythe authors in [28], and we have made the following modifications: (1) we include a separate compartment for the sexual forms of the malaria parasites (gametocytes), (2) we use an exponentially decaying function to model the activity of the immune cells and antibodies, instead of a saturating function. The model consist of six compartments: uninfected red blood cells R, infected red blood cells I, merozoites M, Immune cells T, AntibodiesB, and GametocytesG(see Table 1).

*Uninfected red blood cells (RBCs),*R(t)

The red blood cells population is generated at a constant rateλ_R from the bone marrows. Production of RBCs is further stimulated by the presence of infected RBCs at a rate$0 \le \alpha < 1$. The concentration of RBCs is reduced by natural death (at a rate μ_R), infection of erythrocytes by merozoites (at a rate β), and bursting of infected red blood cells by immune cells (at a rateω). Antibodies hinders the inversion of RBCs by free merozoites and this process is described by the exponential function $f(B, c_v) = e^{-c_v B(t)}$, where c_v is the efficacy of malaria specific antibodies to hinder free merozoites from invading RBCs. As the level of antibodies diminishes ($B \to 0$), the function $f(B, c_v) \to 1$, implying an increase in the rate of infection of RBCs by malaria merozoites. On the other hand, as the level of antibodies rises ($B \to \infty$) the function $f(B, c_v) \to 0$, implying a decrease in the rate of infection of RBCs by malaria parasites. Infected RBCs are destroyed by immune cells at an average rate ω. Putting all these information together gives the equation describing the dynamics of uninfected RBCs.

$$\frac{dR(t)}{dt} = \lambda_R + \alpha R(t) - \beta R(t)M(t)e^{-c_v B(t)} - \omega R(t)M(t)T(t) - \mu_R R(t). \quad (1)$$

Infected red blood cells (IRBCs), I(t)

Infected red blood cells population are generated by infection of RBCs by free merozoites. This population is diminished through natural death (at a rate μ_I), and the destruction of infected red cells by immune cells. The immuno-sensitivity of infected erythrocytes is modelled by κ_I. Thus we have

$$\frac{dI(t)}{dt} = \beta R(t)M(t)e^{-c_v B(t)} - \kappa_I T(t)I(t) - \mu_I I(t). \quad (2)$$

Merozoites, M(t)

Malaria merozoites are generated as a result of the rupturing of infected RBCs, releasing on the average r daughter merozoites per rupture. Out of these released merozoites, a fraction $0 \le g < 1$ develops into asexual forms called gametocytes, which can be transmitted from humans to the *Anopheles* mosquito. In this case, the exponential function$f(T, c_1) = e^{-c_1 T(t)}$ models the suppression of the production rate of daughter merozoites, where c_1 is a measure of the efficacy of immune cells in suppressing merozoites multiplication. As the production of immune cells diminishes ($T \to 0$), the function $f(T, c_1) \to 1$ implying that a decrease in the population of immune cells will result in an increase in the

growth rate of malaria parasite. Conversely, as the density of immune cells increases($T \to \infty$) the function $f(T, c_1) \to 0$ indicating that as the population of immune cells increases, the rate of parasite production is reduced. The merozoites population is reduced through natural death (at a rate μ_M), destruction of merozoites by immune cells (where κ_M is the immune-sensitivity), and infection of red blood cells by merozoites at a rate β. This gives

$$\frac{d}{d}(\mathbb{t}) = r\mu_I I(t)(1-g)e^{-c_1 T(\mathbb{t})} - \kappa_M T(t)M(t) - \beta\ (t)M(t)e^{-c_0 B(\mathbb{t})} - \mu_M M(t). \quad (3)$$

*Immune cells,*T(t)

Immune cells are produced at a constant rate$h$. The recruitment of immune cells is further stimulated by the presence of infected red blood cells and merozoites. The population is reduced through natural death (at a rate μ_T). It is assumed that all different immune cells are lumped together as one (for simplicity). The parameter k_0 is the population of infected erythrocytes needed such that the growth rate of immune cells is $\rho_I/2$ in the absence of merozoites, and $k_1$is the population of merozoites needed such that the growth rate if immune cells is $\rho_M/2$ in the absence of infected erythrocytes. Thus we have,

$$\frac{d}{d}(\mathbb{t}) = h + \left(\rho_I \frac{I(\mathbb{t})}{k_0 + I(\mathbb{t})} + \rho_M \frac{M(\mathbb{t})}{k_1 + M(\mathbb{t})}\right) T(t) - \mu_T T(t). \quad (4)$$

Antibodies, B(t)

Antibodies are generated as immune cells secretion which is stimulated by the presence of merozoites, and the population is decreased through decay of antibodies (at a rate μ_B). The upper bound for the rate of increase is assumed to be η, and is the population of merozoites needed such that antibodies reach half of their maximum value. This gives

$$\frac{d}{d}(\mathbb{t}) = \eta\ (t)\left(\frac{M(\mathbb{t})}{k_1 + M(\mathbb{t})}\right) T(t) - \mu_B B(t). \quad (5)$$

*Gametocytes,*G(t)

This population is generated as a fraction of the released daughter merozoites that develops into sexual forms instead of their asexual counterparts. The population is assumed to diminished through natural deaths (at a rate μ_G). The function $f(T, c_1) = 1/(1 + c_1 T(t))$ models the ability of immune cells to suppress the maturation of merozoites to gametocytes. As the population of immune cells diminishes ($T \to 0$), the function $f(T, c_1) \to 1$ implying that a decrease in the population of immune cells will result in an increase in the growth rate of malaria parasites. On the other hand, an increase in immune cells population ($T \to \infty$) the function $f(T, c_1) \to 0$ indicating that as the number of immune cells increases, the rate of parasite production is reduced. This gives the dynamics of gametocytes population

$$\frac{d}{d}(\mathbb{t}) = g\ \mu_I I(t)e^{-c_1 T(\mathbb{t})} - \mu_G G(t). \quad (6)$$

Table 1: Symbols and description of sub-population

State Variables	Description
R	Uninfected red blood cells (RBC)
I	Infected red blood cells
M	Merozoites
T	Immune cells
B	Antibodies
G	Gametocytes

Putting together the above assumptions in Equations (1) – (6), we arrive at the system of ordinary differential equations:

$$\begin{aligned}
\frac{d}{d}(t) &= \lambda_R + \alpha\ (t) - \beta\ (t)M(t)e^{-c_0 B(\mathbb{t})} - \omega\ (t)M(t)T(t) - \mu_R R(t)\\
\frac{d}{d}(t) &= \beta\ (t)M(t)e^{-c_0 B(\mathbb{t})} - \kappa_I T(t)I(t) - \mu_I I(t)\\
\frac{d}{d}(\mathbb{t}) &= r\mu_I I(t)(1-g)e^{-c_1 T(\mathbb{t})} - \kappa_M T(t)M(t) - \beta\ (t)M(t)e^{-c_0 B(\mathbb{t})} - \mu_M M(t) \quad (7)\\
\frac{d}{d}(t) &= h + \left(\rho_I \frac{I(t)}{k_0 + I(t)} + \rho_M \frac{M(t)}{k_1 + M(t)}\right) T(t) - \mu_T T(t)\\
\frac{d}{d}(t) &= \eta\ (t)\left(\frac{M(t)}{k_1 + M(t)}\right) T(t) - \mu_B B(t)\\
\frac{d}{d}(t) &= r\ \mu_I I(t)e^{-c_1 T(\mathbb{t})} - \mu_G G(t)
\end{aligned}$$

The model (7) possesses two equilibrium states, the diseases free equilibrium (DFE)

$$E_0 = (R^*, I^*, M^*, T^*, B^*, G^*) = \left(\frac{A_R}{\mu_R}, 0, 0, \frac{h}{\mu_T}, 0, 0\right),$$

as well as the endemic equilibrium point (EEP)

$\mathcal{E}_0 = (R^{**}, I^{**}, M^{**}, T^{**}, B^{**}, G^{**})$.

3.0 Local Asymptotic Stability of the DFE

In this section, we investigate the local stability of the disease free equilibrium by studying the linearized form of model (7) at the disease free equilibrium $\mathcal{E}_0$. The Jacobian matrix corresponding to the system (7) and evaluated at the disease-free equilibrium $\mathcal{E}_0$ is given below as:

$$J_{\mathcal{E}_0} = \begin{vmatrix} -\mu_R - \lambda & \sigma & -\frac{\beta\lambda_R}{\mu_R} - \frac{\omega h\lambda_R}{\mu_R\mu_T} & 0 & 0 & 0 \\ 0 & -\mu_T - \frac{h\kappa_I}{\mu_T} - \lambda & -\frac{\beta\lambda_R}{\mu_R} & 0 & 0 & 0 \\ 0 & -\tau(1-g)\mu_I e^{-c_1 h/\mu_T} & -\frac{\beta\lambda_R}{\mu_R} - \frac{h\kappa_M}{\mu_T} - \mu_M - \lambda & 0 & 0 & 0 \\ 0 & \frac{h\rho_I}{K_0\mu_T} & \frac{h\rho_M}{K_1\mu_T} & -\mu_T - \lambda & 0 & 0 \\ 0 & 0 & \frac{\eta h}{K_1\mu_T} & 0 & -\mu_B - \lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & -d - \lambda \end{vmatrix} \quad (8)$$

The characteristic equation corresponding to the Jacobian matrix (8) is given as

$$(-d-\lambda_1)(-\mu_R-\lambda_2)(-\mu_T-\lambda_3)(-\mu_B-\lambda_4)\left[\frac{\tau\lambda_R(1-g)\mu_I e^{-c_1 h/\mu_T}}{\mu_R} + \left(\frac{h\kappa_I}{\mu_T} - \mu_I - \lambda_5\right)\left(-\frac{\beta\lambda_R}{\mu_R} - \frac{h\kappa_M}{\mu_T} - \lambda_6\right)\right] = 0. \quad (9)$$

It is obvious from Equation (9) that the roots: $\lambda_1, \lambda_2, \lambda_3$ and λ_4 are all negative and real. By the Routh-Hurwitz Criterion, λ_5 and λ_6 are also negative and real if and only if

$\frac{\tau\lambda_R(1-g)\mu_I e^{-c_1 h/\mu_T}}{\mu_R} > 0 \Leftrightarrow 1-g > 0 \Leftrightarrow g < 1.$

Thus the disease free equilibrium of the model is locally asymptotically stable (LAS) if and only if $g < 1$. The epidemiological implication of this is that the spread of malaria can be significantly reduced if the density of gametocytes in the blood stream of an infected human isless than unity. In this case, we recommend malaria therapy that not only target the malaria merozoites, but also rapidly destroy the gametocytes before they are ingested by feeding *Anopheles* mosquitos[31–32].

In order to examine the local asymptotic stability of the DFE in terms of the basic reproduction number, we employ the next generator approach [33–34]. The matrices F and Vcontains new infection terms, and transfer terms respectively:

$$F = \begin{bmatrix} 0 & \beta\frac{\lambda_R}{\mu_R} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \qquad V = \begin{bmatrix} \mu_I + \kappa_I\frac{h}{\mu_T} & 0 & 0 \\ -\tau(1-g)\mu_I e^{-c_1 h/\mu_T}\mu_M + \kappa_M\frac{h}{\mu_T} + \beta\frac{\lambda_R}{\mu_R} & 0 & \\ -\tau\ \mu_I e^{-c_1 h/\mu_T} & 0 & G \end{bmatrix},$$

Thus

$$\mathrm{R}_0 = \frac{\tau\lambda_R(1-g)\mu_I\mu_T^2 e^{-c_1 h/\mu_T}}{(h\kappa_I+\mu_I\mu_T)(h\kappa_M\mu_R+\beta\lambda_R\mu_T+\mu_R\mu_M\mu_T)}, \quad (10)$$

where R_0 is obtained from $\rho(FV^{-1})$, withρbeing the spectral radius of the matrix FV^{-1}. The next result in Lemma 1 follows from Theorem 2 in [34].

Lemma 1:*The disease free equilibrium (DFE) of the model (7) is locally asymptotically stable if* $\mathrm{R}_0 < 1$ *and unstable if*$\mathrm{R}_0 > 1$.

The threshold quantity R_0 is the basic reproduction number for the malaria model in (7). In epidemiological terms, Lemma 1 implies that malaria can be eliminated from the community (when $\mathrm{R}_0 < 1$) if the initial sizes of the subpopulations of the model are in the basin of attraction of the DFE $\mathcal{E}_0$. It was established from Lemma 1 that if the disease free equilibrium exists, then it is locally asymptotically stable if and only if $\mathrm{R}_0 < 1$. Clearly, from (10), we observe thatR_0 is a positive quantity only when $g < 1$ confirming our earlier result that the disease free equilibrium is locally asymptotically stable if and only if $g < 1$

4.0 Numerical Simulation

In order to investigate the dynamics of the model over time, we integrate the system of equations using the fourth order Runge–Kutta methods in MATLAB programming language. For the computer simulations, we set the initial population of the RBCs, infected RBCs, merozoites, immune cells, antibodies at 500, 5, 50, 30, and 0 respectively (Chiyaka et al., 2008[b]). The initial density of gametocytes is set at 0. After an infective bite by the *Anopheles* mosquito, a period of time, i.e., the 'incubation period' elapses before the initial symptoms begin to manifest. The incubation period of malaria resulting from *P. falciparum* is 7 days [35];hence for our numerical simulations, we male use of a time span of 10 days.The gametocytes, g

take values between 0 and 1, i.e., $0 \leq g < 1$, since only a fraction of the merozoites eventually differentiates into gametocytes. The values of the other fixed parameters are shown in Table 2.

Table 2: Parameter information and reference for the model

Parameter	Description	Value	Units	Reference
λ_R	Rate of production of RBCs from bone marrow	41664	$c\,\mu l^{-1}d^{-1}$	[36]
α	Rate of recruitment of RBC due to infection	0.009	$c\,d^{-1}$	[28]
β	Rate of infection	0.08	$M\,\mu l^{-1}d^{-1}$	[28]
c_0	Efficiency of antibodies	0.6	μl	[28]
ω	Rate at which RBCs are destroyed	$1.2\,x\,10^{-5}$	$c\,d^{-1}$	[28]
μ_R	Death rate of RBCs	0.8	d^{-1}	[28]
κ_I	Immuno-sensitivity of infected RBCs	0.9	$c\,\mu l\,d^{-1}$	[28]
μ_I	Death rate of infected RBCs	1.0	d^{-1}	[28]
r	Number of merozoites released per each bursting infected RBCs	16	$m\,\mu l^{-1}$	[28]
g	Fraction of merozoites differenting into gametocytes	0.02	μl^{-1}	[28]
c_1	Rate at which parasite production is suppressed	0.85	$c\,\mu l$	[28]
κ_M	Immuno-sensitivity of merozoites	0.3	$m\,\mu l\,d^{-1}$	[28]
μ_M	Death rate of merozoites	3.0	d^{-1}	[28]
h	Production rate of immune cells	30	$c\,\mu l\,d^{-1}$	[28]
ρ_I	Immuno-genecity of infected RBCs	0.05	d^{-1}	[28]
k_0	Stimulation constant for immune cells due to presence of infected RBCs	2000	$c\,\mu l^{-1}$	[28]
ρ_M	Immuno-genecity of merozoites	0.05	d^{-1}	[28]
k_1	Stimulation constant for immune cells due to presence of merozoites	1500	$m\,\mu l^{-1}$	[28]
μ_T	Death rate of immune cells	1.53	d^{-1}	[28]
η	Maximum rate of antibodies increase	0.6	μl^{-1}	[28]
μ_B	Waning rate of antibodies	0.4	d^{-1}	[28]
μ_G	Death rate of gametocytes	3.5	d^{-1}	[28]

The graphs in Figure 1 show the behaviour of the model system (7). We observe that the populations of infected RBCs, merozoites and gametocytes reach a steady disease free state for the chosen fixed parameter values and with non-varying. The density of red blood cells and immune cells maintain steady state solution which is expected for a healthy uninfected human.

Figure 2 shows the behaviour of the model system (7) where the rate of elimination of red blood cells due to the effect of, ω varying from 0.0 to 0.1 in steps of 0.02. The graph shows that as ω increases, there is a corresponding decrease in the population of RBCs, infected RBCs and gametocytes. A decrease in the population of red blood cells yields a corresponding decrease in the number of infected red blood cells and gametocytes, which makes the population of immune cells and antibodies stimulated to decrease as well.

The graphs in Figure 3 illustrate the behaviour of the model system (4) as the fraction of the merozoites that becomes gametocytes, g is gradually increased from 0.0 to 0.2 in steps of 0.04. The graphs indicate that the dynamics of the system remains unchanged as the number of gametocytes is increased. This behaviour is expected since gametocytes are not coupled with other sub-population, i.e., they do not affect the dynamics of the other compartments, but they are only responsible for the transmission of the malaria parasite from an infected human host to a susceptible *Anopheles* mosquito vector.

The graphs in Figure 4 show an increase in the death rate of merozoites μ_M from 0.0 to 5 in steps of 0.9. This corresponds to a decrease in the number of gametocytes since there will be fewer merozoites available to differentiate or mature into gametocytes. A decrease in the density of infected red blood cells us also observed since, as the death rate merozoites is increased, there will be fewer parasite invading uninfected red blood cells.

Figure 5 shows the behaviour of the model system (7) as the death rate of immune cells μ_T is varied from 0.0 to 3.5 in steps of 0.6while keeping all other parameters constant. Obviously the population of infected RBCs, malaria merozoites, and gametocytes increases.

In Figure 6, the rate of deterioration of antibodies μ_B is increased from 0.0 to 2.3 in steps of 0.4. Antibodies act to block red blood cells from being invaded by malaria parasite, and when they are reduced, the graphs show that the population of infected red blood cells, merozoites and gametocytes increases.

The plots in Figure 7 show the death rate of gametocytes μ_G being increased from 0.0 to 5.3 in steps of 0.9.Similar to Figure 3, we again observe that the overall dynamics of the model system (7) is not affected by this increase, since the gametocytes are not coupled with the other compartments.

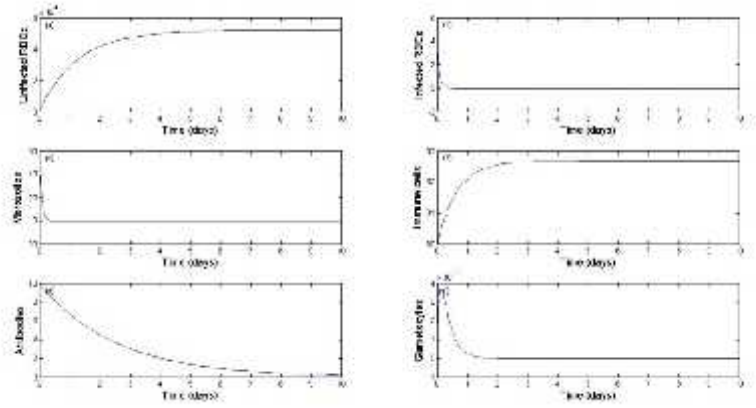

Figure 1: Graphs that show the behaviour of the malaria model with immune response only. The dynamics of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes

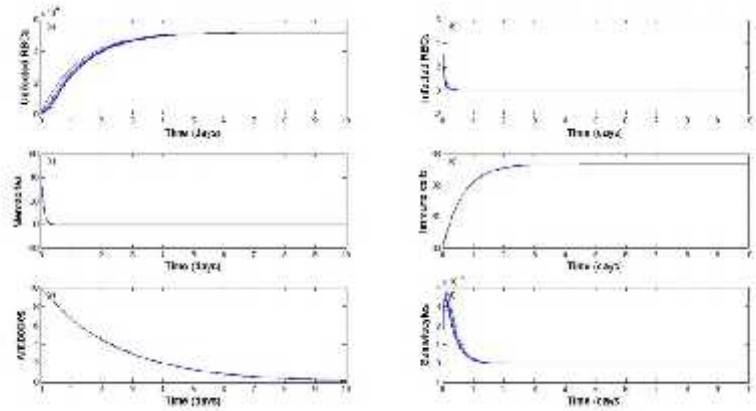

Figure 2: Graphs that show the behaviour of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes. They are obtained by varying the bursting rate ω of infected RBCs from 0.0 to 0.1 in steps of 0.02, while keeping all other parameters constant.

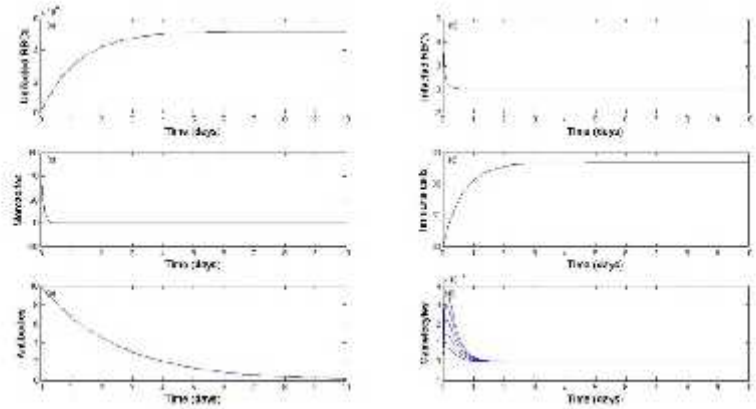

Figure 3: Graphs that show the behaviour of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes. They are obtained by varying the fraction of merozoites g differentiating into gametocytes from 0.0 to 0.2 in steps of 0.04, while keeping all other parameters constant.

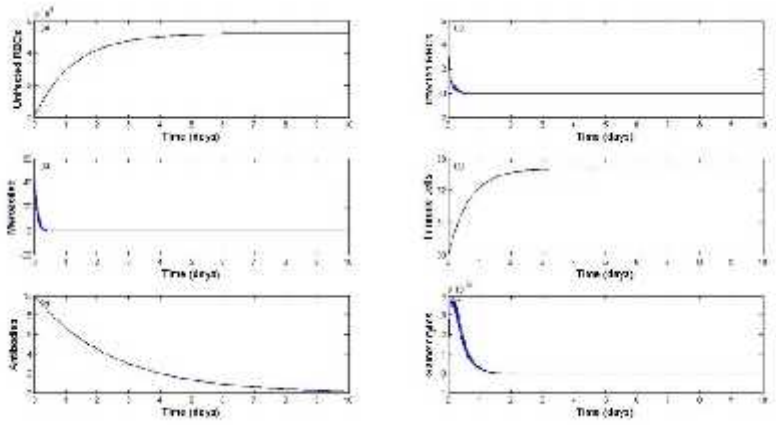

Figure 4: Graphs that show the behaviour of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes. They are obtained by varying the death rate of merozoites μ_M from 0.0 to 5 in steps of 0.9, while keeping all other parameters constant.

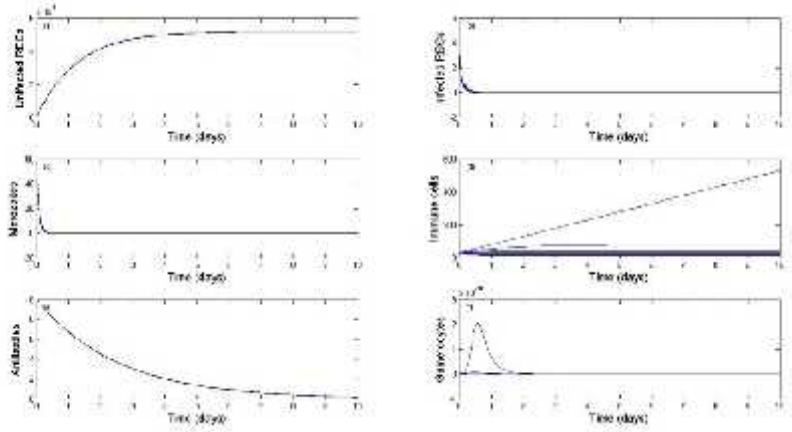

Figure 5: Graphs that show the behaviour of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes. They are obtained by varying the death rate of immune cells μ_T from 0.0 to 3.5 in steps of 0.6, while keeping all other parameters constant.

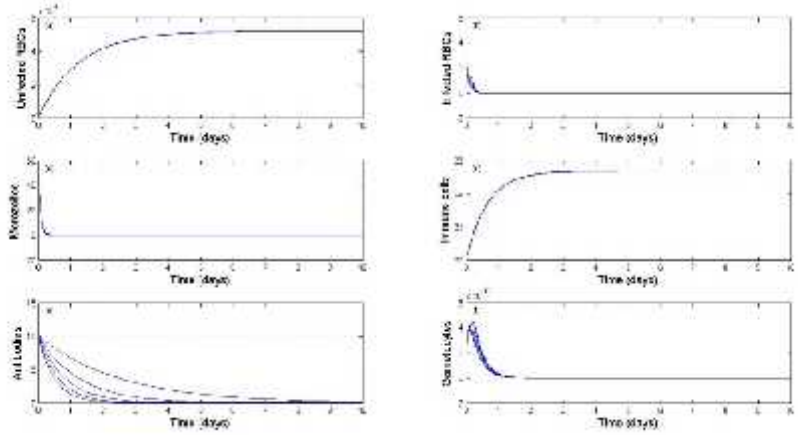

Figure 6: Graphs that show the behaviour of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes. They are obtained by varying the deterioration rate of antibodiesμ_B from 0.0 to 2.3 in steps of 0.4, while keeping all other parameters constant.

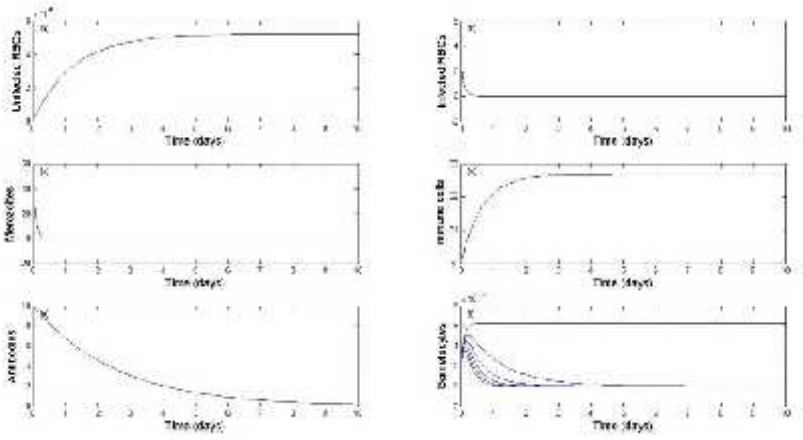

Figure 7: Graphs that show the behaviour of (a) uninfected RBCs, (b) infected RBCs, (c) merozoites, (d) immune cells, (e) antibodies, (f) gametocytes. They are obtained by varying the death rate of gametocytes μ_G from 0.0 to 5.3 in steps of 0.9, while keeping all other parameters constant.

5.0 Discussion

A deterministic system of nonlinear differential equations was developed to model human immune response to malaria resulting from *Plasmodium falciparum* infection. From our mathematical analysis, we obtained a general form of the intra-host basic reproduction number, from which effective control strategies that help in assessing interventions are deduced. Our results indicate that the density of gametocytes in the blood stream of an infected human do not alter the dynamics of the system, since gametocytes do not contribute to manifestation of malaria symptoms, but they only are responsible for the transmission of the parasites from humans to mosquitoes.

The result indicate that the most effective natural way to clear malaria parasites from within an infected human is for the host immune system to prevent the parasite from replicating within the infected red blood cells. As a result, it is more effective to raise the death rate of infected erythrocytes by immune cells than killing freely circulating merozoites. This is because an infected red blood cell produces an average of 16 daughter merozoites, and so killing one infected erythrocyte corresponds to killing 16 merozoites. Consequently, antimalarial drugs that target infected red blood cells should be developed and encouraged for treating malaria infection. We observed that to curtail the spread of malaria within a population, the density of the gametocytes (i.e., the transmissible form of the parasite from humans to mosquito) must be kept at a minimum or if possible none of the gametocytes should be allowed to survive.More effective antimalarial drugs targeting and destroying *Plasmodium falciparum* gametocytes should be developed and encouraged for treating malaria infection.We recommend that destroying malaria gametocytes. This will prevent the transmission of the parasite from an infected human to a susceptible mosquito, leading to an eradication of the parasite from the community.

It is observed with malaria infection is even more severe and potentially deadly if not quickly and properly treated in the case of individuals with previously infected with pathogens that destroys or compromise their immune system. This is the case for individuals who are infected with *Mycobacterial tuberculosis* (the pathogen responsible for tuberculosis disease) which kills the macrophages or *human immunodeficiency virus* (the pathogen that causes acquired immunodeficiency syndrome) which kills the $CD4^+$ T cells. Such infection compromises the host immune system and makes them very vulnerable to severe complications resulting from minor *Plasmodium falciparum* infection which would have been easily repelled and cleared by the host immune system.

6.0 References

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