Using Mathematics to Understand Malaria Infection During Erythrocytic Stages

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Abstract

We review the basic intra-host model of malaria, without immunity. The model describes the Erythrocytic stage in a malaria infected human, which involves the interaction between malaria parasites and red blood cells. These two populations interact on a dynamic landscape, in which a population of replicating parasites depletes a population of replenishing red blood cells. This paper shows how concepts from nonlinear dynamics can be used to unravel the underlying dynamical features of the model. The intra-host basic reproductive number R0, crucial to calculations concerning control of the infection is calculated. Using mathematical analysis of stability, conditions necessary for reducing and/or clearing parasites in the host are determined. Numerical simulations are also performed to verify analytic results and illustrate possible behaviour of the model.

Key words: intra-host, malaria, erythrocytic, reproductive number, stability.

1. INTRODUCTION

Four malaria species, *Plasmodium falciparum, P.vivax, P. ovale* and *P. malariae* cause disease in humans. Malaria infection in a human begins with an inoculum of *Plasmodium* parasites from an infectious *Anopheles* mosquito. The parasite, when introduced into the blood stream by a mosquito begins a lifecycle within its definitive host different from that in the vector. About 30 minutes after being introduced into the bloodstream, these parasites enter into the parenchymal cells of the liver [3, 6, 9, 12] which are normally impermeable to drugs. The30 minutes spent in the circulation are too short to evolve the onset of an immune response. Within the parenchyma cells of the liver the parasites now called the pre-erythrocytic schizonts, multiply by schizogony. Once the infected cell fills up with schizonts, it bursts, releasing them to attack fresh liver cells. The liver stage is also called the pre-erythrocytic stage. This cycle is repeated twice in a single infection and eventually the parasites leave the liver cells simultaneously and invade red blood cells in the blood stream. Each individual parasite may produce, in about 6 days, some 40 000 merozoites in the liver of man [3]. These merozoites released into the blood stream infect RBCs (erythrocytes), and undergo sexual reproduction. After about 48-72 hours [4, 7] depending on the *Plasmodium* species the infected erythrocyte bursts releasing daughter parasites that quickly infect fresh erythrocytes. The parasitized red blood cell

(PRBC) that bursts, releases on average 16 merozoites [4]. This cycle also known as the erythrocytic stage maintains infection and generates disease symptoms [6]. Some merozoites, instead of developing asexually, differentiate into sexual forms called gametocytes [4]. Mature gametocytes enclosed within the RBC membrane circulate in the host's blood, available to feeding mosquitoes. Of the four species that infect humans, *P. falciparum* is the most virulent because it attacks both young and old RBCs whereas *P. vivax* or *P. ovale* invasion is restricted to the very youngest circulating RBCs and P. malariae invasion to the very oldest [18]. In 2001, malaria was the eighth highest con-tributor of the global loss of disability-adjusted life years and the second in Africa [26]. In sub-Saharan Africa, malaria is one of the most important infectious diseases, with the severe forms of the disease being the main reason for hospital admissions of people in malaria endemic areas. The burden of malaria disease has been documented in terms of childhood mortality [19], anemia [20], maternal and infant morbidity and mortality [21], neurologic disability [22, 23], and economic and social costs [24, 25]. There has been considerable work on the mathematical modelling of the dynamics of *Plasmodium falciparum* infections [4, 6, 7, 9, 10]. An age-structured mathematical model of malaria parasite life cycle that uses clinical observations to estimate population dynamics of sequestered parasites has been described [6]. A suggestion that a model of within host malaria population dynamics can exhibit unrealistically large growth rates has been made [11] and it was assumed that the error can be avoided by replacing the number of merozoites r , by the value ln(r) + 1. Instead of modeling the intracellular category by a single compartment, Gravenor and Lloyd [5] introduced n categories. One of leading basic models is that of Anderson [2], which attempts to address blood stage asexual cycle of *P. falciparum*, by following the invasion of RBCs by merozoites. Intra-host models deal with all the dynamics that occur inside the body of the host with the pathogen. Intra-host model of malaria describes the dynamics of the blood stages of the parasite and their interaction with host cells, in particular, the red blood cells and the immune effectors [10]. We are going to analyse the basic intra-host model of malaria [2]. In the following section we shall give the formulation and the analysis follows in section 3 where we show that the disease free equilibrium state reduces the system of three non-linear differential equations to a linear differential equation which can easily be solved analytically. The intra-host basic reproductive number is calculated in section 4. In section 5 we analyse the stability of both the disease free and endemic equilibria. We the discuss necessary control measures basing our arguments on the conditions used to attain a stable disease free state. Numerical simulations in section 6 were carried out to determine the general behaviour of the model. A brief discussion rounds up the paper in section 7.

2. FORMULATION OF THE MODEL

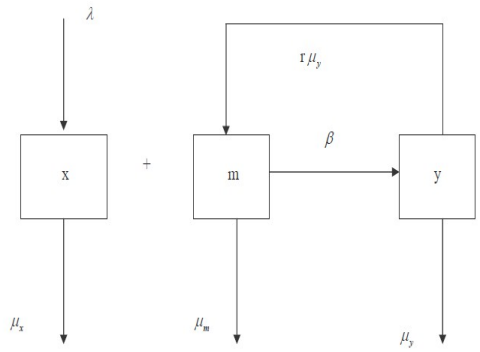

Figure 1*: Schematic illustration of the basic intra-host model of malaria.*

The basic model of parasite dynamics has three populations. The RBCs x , PRBCs y and merozoites m . These quantities denote their concentration in a given volume of blood or tissue. RBCs are recruited at a constant rate, from bone marrow into the

circulation, and have a life expectancy of $\frac{1}{\mu_x}$ days. These cells are infected through contact with merozoites at a rate β and become PRBCs. The PRBCs die at a rate μ_y. Death of a PRBC results in the release of merozoites hence the number of merozoites produced depends on the death rate of the PRBCs. r is the average number of merozoites produced per each bursting PRBCs. Free merozoites are removed from the system through natural death at a rate μ_m or through infecting RBCs. In summary the model variables at any time t and parameters are:

1. Variables
   - $x(t)$ – RBCs,
   - $y(t)$ – PRBCs,
   - $m(t)$ - merozoites.

2. Parameters
   - β - rate of infection,
   - r - average number of merozoites released per each bursting PRBC,
   - λ - supply rate of RBCs from the bone marrow,
   - μ_x - natural death rate of RBCs,
   - μ_y - death rate of PRBCs,
   - μ_m - natural death rate of merozoites,

where λ , β , r , μ_x , μ_y , μ_m are all positive. This model does not take into the effect of the immune system and therefore describes the worst case scenario.

The above assumptions lead to the following system of differential equations

$$\frac{dx(t)}{dt} = \lambda - \mu_x x(t) - \beta x(t)m(t),$$

$$\frac{dy(t)}{dt} = \beta x(t)m(t) - \mu_y y(t), \qquad (1)$$

$$\frac{dm(t)}{dt} = r\mu_y y(t) - \mu_m m(t) - \beta x(t)m(t).$$

3. MODEL ANALYSIS

A steady state or an equilibrium point is a state in which a system is not changing. To find the equilibrium states we set

$$\frac{dx(t)}{dt} = \frac{dy(t)}{dt} = \frac{dm(t)}{dt} = 0,$$

which is equivalent to solving system (2).

$$\lambda - \mu_x x(t) - \beta x(t)m(t) = 0,$$

$$\beta x(t)m(t) - \mu_y y(t) = 0, \qquad (2)$$

$$r\mu_y y(t) - \mu_m m(t) - \beta x(t)m(t) = 0.$$

The two steady states obtained after solving (2) are the disease free equilibrium state denoted by E^0 and the endemic equilibrium state denoted by E^*. E^0 corresponds to the case when there is no infection (infected population) and E^* corresponds to the presence of infection. We first discuss the disease free equilibrium state

$$E^0 = (x^0, y^0, m^0) = \left(\frac{\lambda}{\mu_x}, 0, 0\right).$$

The endemic equilibrium will be discussed later in this section.

The disease free equilibrium state E^0 reduces the system of three nonlinear differential equations (1) to a linear differential equation

$$\frac{dx(t)}{dt} = \lambda - \mu_x x(t), \qquad (3)$$

which can be solved analytically. The analytic solution of equation (3) is given by solving

$$\int \frac{dx}{\lambda - \mu_x x} = \int dt$$

From which we obtain

$$x = \frac{1}{\mu_x}(\lambda - De^{-\mu_x t}), \qquad (4)$$

Where D is a constant of integration. The equilibrium point is found by solving $\frac{dx}{dt} = 0$. As $t \to \infty$, in equation (4), $x \to \frac{\lambda}{\mu_x}$ which is the disease free equilibrium point.

For the disease free population

a) If $\lambda \gg \mu_x$ then the susceptible (x) either increase or decrease to the fixed point depending on the initial value x_0 as shown in Figure 2 and the fixed point is always greater than one.
b) If $\mu_x \gg \lambda$ then the fixed point is always a fraction since the death rate exceeds the supply rate. RBCs exponentially decrease to the fixed point and this is shown in Figure 3.

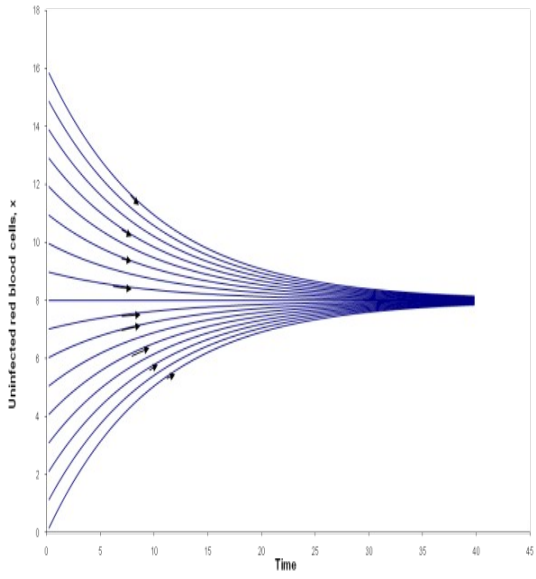

Figure 2: *Graphs of uninfected red blood cells, x against time with different initial values of x where λ = 0.8 and $\mu_x = 0.1$. All the graphs come to the equilibrium point $x = \frac{\lambda}{\mu_x} = \frac{0.8}{0.1} = 8$ irregardless of the initial value.*

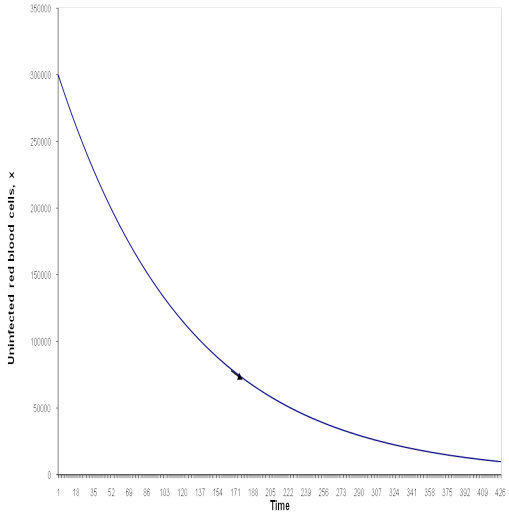

Figure 3*: A graph of uninfected red blood cells, x against time with the initial value of $x = 300000$, $\mu_x = 0.8$ and $\lambda = 0.1$. The fixed point is $\frac{0.1}{0.8} = \frac{1}{8}$.*

4. INTRA-HOST BASIC REPRODUCTIVE NUMBER

Generally the basic reproductive number, is defined as the average number of secondary cases produced by a typical infected (assumed infectious) individual during his/her entire life as infectious (infectious period) when introduced in a population of susceptible individuals [16]. It is implicitly assumed that the infected outsider is in the host population for the entire infectious period and mixes with the host population in exactly the same way that a population native would mix.

The *intra-host* basic reproductive number (R_0) of the malaria parasite is the number of secondary parasitised red blood cells (PRBC) produced per primary PRBC in a non-immune human individual at the onset of infection [10]. It is a key parameter of asexual parasitaemia, crucial to calculations concerning its control by any mechanism, natural or artificial.

To find the intra-host basic reproductive number, we follow the method of the next generation approach [17]. Following this method we deduce that the matrices F and the inverse of V denoted as V^{-1}, are found to be

$$F = \begin{pmatrix} 0 & \beta\frac{\lambda}{\mu_x} \\ 0 & 0 \end{pmatrix},$$

and

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu_y} & 0 \\ \frac{r}{\mu_m + \beta\frac{\lambda}{\mu_x}} & \frac{1}{\mu_m + \beta\frac{\lambda}{\mu_x}} \end{pmatrix}.$$

The product FV^{-1} is called the next generation matrix [17]. The dominant eigenvalue of the next generation matrix gives the reproductive number. For the model system (1), the intra-host basic reproductive number is

$$R_0 = \frac{r\beta\lambda}{\mu_m\mu_x + \beta\lambda}. \qquad (5)$$

To bring the infection (parasitaemia) under control we seek conditions on the parameters of the transmission process that will guarantee the existence of a stable disease free equilibrium state.

5. STABILITY ANALYSIS

5.1. Stability of the disease free state

To determine the local stability of a steady state, we study the eigenvalues of the Jacobian matrix evaluated at that steady state. We denote the Jacobian matrix of model system (1) evaluated at the disease free equilibrium point by J_{E^0} .

$$J_{E^0} = \begin{pmatrix} -\mu_x & 0 & -\beta\frac{\lambda}{\mu_x} \\ 0 & -\mu_y & \beta\frac{\lambda}{\mu_x} \\ 0 & r\mu_y & -\mu_m - \beta\frac{\lambda}{\mu_x} \end{pmatrix}. \quad (6)$$

The eigenvalues z , of J_{E^0} are obtained by solving the following characteristic equation

$$(-\mu_x - \lambda)\left(z^2 + \left(\mu_y + \mu_m + \beta\frac{\lambda}{\mu_x}\right)z + \mu_y\left(\mu_m + \beta\frac{\lambda}{\mu_x}\right) - r\mu_y\beta\frac{\lambda}{\mu_x}\right) = 0. \qquad (7)$$

For the disease free equilibrium state to be stable the roots of equation (7) which correspond to the eigenvalues of J_{E^0} should all be negative. Clearly one of the roots of equation (7), $z = -\mu_x$ is negative. Using the *Routh-Hurwitz* stability criterion (see Appendix) the roots of the remaining quadratic equation of (7) are negative if

$$\mu_y\left(\mu_m + \beta\frac{\lambda}{\mu_x}\right) - r\mu_y\beta\frac{\lambda}{\mu_x} > 0. \qquad (8)$$

The inequality in (8) reduces to $R_0 < 1$. Therefore the disease free equilibrium is locally stable if $R_0 < 1$, otherwise it is unstable.

Theorem 1 *If* $R_0 < 1$ *, then the disease free equilibrium state is globally stable i.e.* $\lim_{t\to\infty}(x(t), y(t), m(t)) \to \left(\frac{\lambda}{\mu_x}, 0, 0\right)$.

Proof *We first rewrite the infected and infecting compartments* $y(t), m(t)$ *respectively as*

$$y(t) = \int_{-\infty}^{t} \beta x(s) m(s) e^{-\mu_y (t-s)} ds,$$
$$m(t) = \int_{-\infty}^{t} r\mu_y y e^{-(\mu_m + \beta x(s))(t-s)} ds. \quad (10)$$

Using substitution $u = t - s$ *,taking* $\limsup$ *of both sides of the equation for* $y(t)$ *and apply the fact that* $\limsup \int f \leq \int \limsup f$ *(see [27]) we have*

$$\limsup_{t\to\infty} y(t) = \limsup_{t\to\infty} \int_0^{\infty} \beta x(t-u) m(t-u) e^{-\mu_y u} du$$
$$\leq \int_0^{\infty} \limsup_{t\to\infty} \beta x(t-u) \times m(t-u) e^{-\mu_y u} du$$

$$\leq \limsup_{t\to\infty} \beta x(t) \limsup_{t\to\infty} m(t) \times \int_0^{\infty} e^{-\mu_y u} du$$

$$\leq \frac{\beta\lambda}{\mu_m \mu_x} \limsup_{t\to\infty} m(t).$$

Similarly for the second equation of (9) we get

$$\limsup_{t\to\infty} m(t) \leq \frac{r\mu_y}{\mu_m + \beta\frac{\lambda}{\mu_x}} \limsup_{t\to\infty} y(t).$$

Substituting (10) into (9) we get

$$\limsup_{t\to\infty} y(t) \leq \frac{\beta\lambda}{\mu_m\mu_x} \times \frac{r\mu_y}{\mu_m + \beta\frac{\lambda}{\mu_x}} \limsup_{t-}$$
$$= R_0 \limsup_{t\to\infty} y(t).$$

Thus if $R_0 < 1$ *, we have a strict inequality (and contradiction)* $\limsup_{t\to\infty} y(t) < \limsup_{t\to\infty} y(t)$*, unless* $\limsup_{t\to\infty} y(t) = 0$.

We conclude therefore, that the disease free equilibrium state is a global attractor when $R_0 < 1$.

5.2. The endemic equilibrium and its stability

When $R_0 > 1$, the condition for the stability of the disease free equilibrium state is violated, and besides the disease free state the model system (1) has an endemic equilibrium state. The endemic equilibrium will be denoted by $E^* = (x^*, y^*, m^*)$. The endemic equilibrium state is given as

$$E^* = \begin{cases} x^* = \dfrac{\mu_m}{\beta(r-1)}, \\ y^* = \dfrac{\beta(r-1)\lambda - \mu_m\mu_x}{\beta(r-1)\mu_y}, \\ m^* = \dfrac{\beta(r-1)\lambda - \mu_m\mu_x}{\beta\mu_m}. \end{cases}$$

To determine the local stability of the endemic equilibrium, we evaluate the Jacobian matrix of the model system (1) at E^*. The matrix takes the following form

$$J_{E^*} = \begin{pmatrix} -a_1 & 0 & -\beta x^* \\ \beta m^* & -\mu_y & \beta x^* \\ -\beta m^* & r\mu_y & -a_2 \end{pmatrix}.$$

Where

$a_1 = \mu_x + \beta x^*$ and $a_2 = \mu_m + \beta x^*$.

The characteristic equation associated with J_{E^*} is given by

$$z^3 + B_2 z^2 + B_1 z + B_0 = 0, \quad (12)$$

where

$$B_2 = a_1 + a_2 + \mu_y.$$
$$B_1 = a_1 a_2 + \mu_y(a_1 + a_2) - \beta x^* (\beta m^* + r\mu_y).$$
$$B_0 = \mu_y \mu_m \beta m^*.$$

Using the *Routh-Hurwitz* criterion, the endemic equilibrium is stable if $B_2 B_1 - B_0 > 0$. Using Mathematica, the inequality $B_2 B_1 - B_0 > 0$ is found to be true. Hence we conclude that for the model

system (1), when $R_0 > 1$ the endemic equilibrium is locally asymptotically stable.

5.3. Implications for control

The intra-host basic reproductive number of malaria R_0 is a key parameter of asexual parasitaemia, crucial to calculations concerning its control by any mechanism, natural or artificial. The condition that gives a stable disease free equilibrium is $R_0 < 1$. To reduce the parasitaemia, we seek for parameters in the expression of R_0 which achieve this. We deduce the following from the expression of R_0: (a) A decrease in the infection rate β reduces the intra-host reproduction number. (b) A decrease in the average number of merozoites and (c) increasing the death rate of merozoites reduces R_0.

Natural or artificial mechanisms that can help in either reducing the infection rate, or reducing the number of merozoites produced or increasing the death rate of merozoites are beneficial to the host in reducing the infection. These mechanisms are either boosting the immune system or malaria prophylactic drugs.

6. NUMERICAL SIMULATIONS

In this section we analyse the model system (1) numerically. Programming language in C^{++} was used to simulate the results in this section. The numerical values of parameters used are shown in Table (1). All numerical values of the parameters are estimated.

Table 1*: Table showing numerical values of parameters used in the simulations.*

Parameter	Symbol	Value
Supply rate of RBCs	λ	**10**
Rate of infection	β	**1.0**
Death rate of RBCs	μ_x	**0.02**
Death rate of PRBCs	μ_y	**0.24**
Death rate of merozoites	μ_m	**0.8**
Merozoites released per each bursting PRBC	r	**16**

Figure (4) shows the long time behaviour of model system (1). As time increases the populations do not change, this means that the endemic equilibrium is attained. Figure (5) shows the phase plane portrait of the Y the fraction of PRBCs against X, the fraction of RBCs. $Y = \frac{y}{x_T}$ and $X = \frac{x}{x_T}$, where $x_T = x + y$ is the total population of red blood cells (RBCs + PRBCs). The graph shows that starting with different initial conditions the system goes to the endemic equilibrium since the parameters used give $R_0 > 1$.

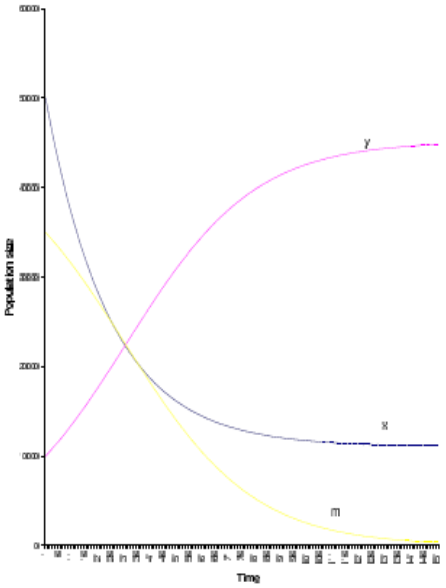

Figure 4*: Graphs of population sizes, uninfected red blood cells x, infected red blood cells y, and merozoites m, with initial values $x_0 = 50000$, $y_0 = 10000$, $m_0 = 35000$.*

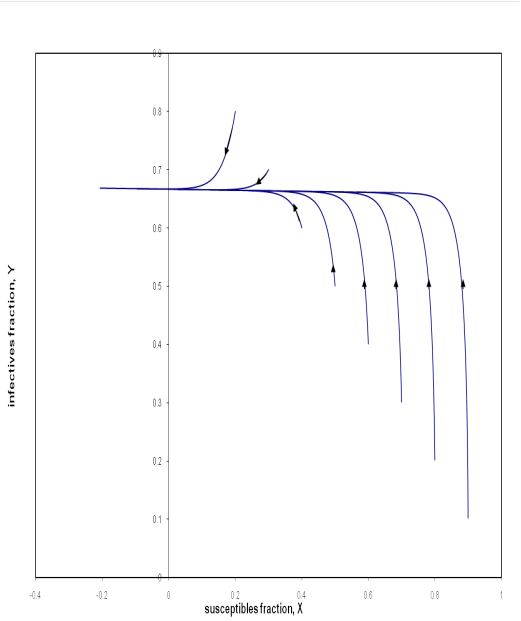

Figure 5: *Phase plane portrait of the fraction of PRBCs* Y *against fraction of RBCs* X .

6.1. Bifurcation analysis

Behaviour of systems of differential equations depend on parameters. The qualitative structure of the flow can change as parameters are varied. There can be creation or destruction of fixed points or their stability might change. These qualitative changes in the dynamics of a system are called bifurcations and the parameter values at which they change are called bifurcation points. In general we can define a bifurcation point as a set of parameter values at which an equilibrium point of a given system appears and/or disappears or changes stability.

In epidemiology, bifurcation phenomena are associated with threshold parameters, the most common of which is the basic reproductive number, R_0. Figure (6) shows the bifurcation diagram of system (1). The graph was obtained by varying r, the average number of merozoites. The graph shows that there is an exchange of stability between disease-free and endemic equilibria when $R_0 = 1$. The bold lines show stability and dashed lines show instability. This graph shows that when $R_0 < 1$ the disease free state is stable and when $R_0 > 1$, it becomes unstable while the endemic equilibrium becomes stable.

7. DISCUSSION

An intra-host basic model of malaria is analysed. Analysis yielded a generalisation of the intra-host basic reproductive number from which control strategies are deduced. Our results show that to reduce parasitaemia it is effective to find mechanisms that assist

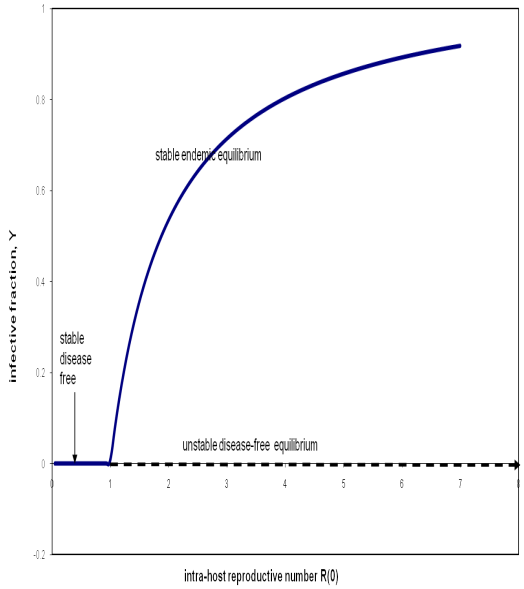

Figure 6*: The bifurcation diagram for the model system (1).*

in reducing the infection rate, reducing average number of merozoites produced and increasing the death rate merozoites.

The model considered in this paper serves to determine the most likely effects of malaria when one first encounters the parasite. Since one of the commonest symptoms of malaria is headache, most unsuspecting victims continue taking analgisic until too late. If the dynamics of the parasite are worked out, then the way the disease presents at various points in life of plasmodium could be

worked out from the model. This may pinpoint certain indicators which people might not have taken note previously and assist in identifying the disease earlier to have early treatment. One might attempt to diagnose the parasite toxins in the urine using kits before the onset of the currently brown symptoms which take place when the disease is at an advanced stage.

Reliable clinical data for estimating the total parasite load for *P. falciparum* is difficult to obtain. The reason being that in most developing countries like Zimbabwe health practitioners are advised to start malaria treatment as soon as they suspect that a person is infected with the malaria parasite. Malaria is treatable and thus normally a curable disease and its control mostly depend on effective diagnosis and efficacious drugs. Therefore, the cornerstone of global malaria control strategy is early diagnosis and treatment. This strategy is however being hampered by the resistance of *P. falciparum* to the easily accessible drugs.

Malaria effects vary according to the species of the parasite that causes them. *P. falciparum* being especially dangerous and most common in Zimbabwe, affects people by either weakening their resistance to other diseases, or to stunt, their mental and physical development and to shorten their lives. Its effects on agriculture, industry, the economy and social aspect maybe severe. There is no aspect of life which is not affected, either directly or indirectly by this disease in this country.

We have considered in this paper the dynamics of the interaction between the RBCs and the malaria parasite within the human body in the absence of the immune system. The immune system is our primary defense against pathogenic organisms and cells that have become malignantly transformed. Without it the parasite continues to invade fresh erythrocytes and multiplying within these cells. During its life within the cell, the parasite damages the host-cell and eventually destroys it. Thousands, and sometimes millions, of malarial parasites may be produced in the blood. An intra-host model that takes into account the immune response and drug therapy will be considered elsewhere.

8. APPENDIX

Let $P(\tau) = \tau^n + a_1\tau^{n-1} + a_2\tau^{n-2} + \cdots + a_{n-1}\tau + a_n$ be a polynomial with real coefficients. Let L_n be an n-dimensional square matrix whose coefficients $a_{l,m}$ are given by $a_{l,m} = a_{2l-m}$ for $0 < 2l - m \leq n, a_{l,m} = 1$ for $2l = m$ and $a_{l,m} = 0$ for $2l < m$ or $2l > m + n$. Let D_i be the ith principle sub-determinant of L_n for $1 \leq i \leq n$. We state the *Routh-Hurwitz* criterion.

Theorem 2 *All solutions of the algebraic equation* $P(\tau) = 0$ *have negative real parts if and only if* D_i *are positive for all* $1 \leq i \leq n$.

We remark that $D_i > 0$ for $1 \leq i \leq n$ if and only if $D_i > 0$ for $1 \leq i \leq n-1$ and $a_n > 0$, because $D_n = D_{n-1}a_n$. For example if $n = 3$, then the conditions $a_1 > 0$, $a_3 > 0$, $a_1a_2 - a_3$, should be satisfied.

Acknowledgements

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