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Optimal Control Analysis of Intra-Host Dynamics of Malaria with Immune Response

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Abstract

In this article, a new intra-host model of malaria that describes the dynamics of the blood stages of the parasite and its interaction with red blood cells and immune cells is formulated. The qualitative properties of solutions are established. We then extend the model to incorporate, in addition to immune response, three control variables. The existence result for the optimal control triple, which minimizes malaria infection and costs of implementation, is explicitly proved. Finally, we apply Pontryagin's Maximum Principle to the model in order to determine the necessary conditions for optimal control of the disease.

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1. INTRODUCTION

Intra-hosts models of malaria infection describe the dynamics of the blood-stage parasites and their interaction with host-cells, in particular red blood cells (RBC) and immune cells. In a given human, malaria begins when an infected female Anopheles mosquito injects plasmodial sporozoites into the blood stream during a blood meal. About 30 minutes later, the sporozoites migrate to the liver where they infect the liver cells [27]. They develop into schizonts (a developmental structure that contains merozoites) which rupture and the merozoites are released, then enter the blood stream. These merozoites infect red blood cells (RBCs) and undergo asexual reproduction, which is similar to but quicker and less prolific than that in the liver cells. This occurs

within the parasitophorous vacuole in the RBC [11]. After about 48 hours, the infected RBCs ruptures releasing daughter parasites that quickly invade fresh erythrocytes to renew the cycle [12]. Blood stage infection engages a network of interacting cells, cytokines, antibodies and other components of immune system [1]. When malaria parasites evolve in the host, they can stimulate the activity of immune cells in the host which produce an immune response to fight the infection. Immune response can either prevent the re-invasion of merozoites or increase the death rate of infected red blood cells [30, 32]. Intra-host models are used for different purposes: explanation of observations, prediction the impact of interventions (antimalarial drugs), estimating states or parameters.

The model we analyze here was firstly given by Aminou M. L. et al [1] where stability analysis was presented. In particular, we computed the basic reproduction number R_0 and investigated the existence and the stability of the disease free equilibrium (DFE). We showed that the DFE is locally and asymptotically stable when $R_0 < 1$.

In this paper, We then extend our intra-host model by incorporating three time-dependent control to determine the optimal strategy for controlling the disease. Optimal control theory is used to establish conditions under which the spread of malaria can mitigate**.** The characterization of the optimal control triple is obtained by the application of Pontryagin's maximum principle [25]. The rest of the paper is organized as follows: The next section is devoted to the model formulation, the positivity an boundedness of solutions are established. The optimal control problem is stated in Section 3 and conclusions are summarized in Section 4.

2. MODEL FORMULATION

Our model is developed to describe the dynamics of the blood stage malaria parasites and their interactions with the host cells, particularly red blood cells and immune cells. Our goal is to represent the basic processes of immune response to *Plasmodium falciparum* in the blood [1]. The following notations have been used:

State variables

X = normal red cells

Y = parasitized red cells

m = merozoites

I_4 = interleukin 4 (IL-4)

I_{10} = interleukin 10

I_{12} = interleukin 12

I_γ = interferon γ (IFN-γ)

N = nitric oxide (NO)

A = antibodies (Ab)

M = macrophages

B = B cells

T_0 = precursor Th cells

T_1 = Th1 cells

T_2 = Th2 cells

Parameters

Λ_X, Λ_M …= immigrations rates of X, M …

μ_X, μ_m …= decay rates of X, m …

α_X, α_Y …= maximal growth rates of X, Y

Normal red cells *X* are the susceptibles, entering circulation at rate Λ_X and remove by death at rate μ_X. Normal red cells become parasitized red cells when they are infected by merozoites [2].

Parasitized red cells *Y* may be destroyed either by nitric oxide [30, 33] which production is enhanced by IFN-γ [5] or by antibodies [16] which secretion is promote by IL-4 [8, 15].

Merozoites *m* released following rupture of pre-erythrocytic schizonts enter the blood circulation and infect red cells, k_m additional merozoites are given when parasitized red cells discharge newly formed merozoites into the blood. NO may have antimicrobial activity against blood stage malaria parasite by killing of parasite [10] and parasitized red cells [33].

Together with nitric oxide and antibodies, we model four cytokines known to play a key role during malaria infection: pro-inflammatory Th1-cytokines IFN-γ and IL-12 on the one hand, and anti-inflammatory Th2-cytokines IL-4 and IL-10 on the other hand.

IFN-γ is produced by Th1 cells. Its production is enhanced by IL-12 [6, 35, 36].

IL-4 is produced by Th2 cells [26]. Its production is increased by NO [4, 29].

IL-10 is produced by Th2 cells and some APC's. The production of IL-10 has been found to be particularly induced by IL-12 [35, 36].

IL-12 is produced by Th1 cells [34] and APC's. Its production is enhanced by IFN-γ [7].

NO is produced by various cells including macrophages. Its production is triggered by IFN-γ and inhibited by IL-4 [5, 13].

Antibodies are produced by plasma cells which derive from B cells. Production of Ab is enhanced by IL-4 [8, 19, 20].

The most notable cells that are involved in the immune regulation during malaria blood stage infection are macrophages, B cells and helper T cells.

Macrophages population coming at the site of infection at rate Λ_M [6].

B cells population accumulate at the site of infection at rate Λ_B [6]. When activated by Th2-cytokines such as IL-4, B cells may proliferate and differentiate into either B memory cells or plasma cells [6, 8].

Th cells arrive at the site of infection as precursor cells (denote by Th_0) at rate Λ_0. In response to antigen in lymphoid tissues, Th_0 differentiates [19, 31, 32] into either Th_1 cells witch differentiation is enhanced by IL-12 [17, 21] or Th_2 cells witch differentiation is enhanced by IL-4 [28].

From the description above, we have the following system of differential equations:

$$\frac{d\dot{X}}{dt} = \Lambda_X - \alpha_X X(t)m(t) - \mu_X X(t)$$

$$\frac{dY}{dt} = \alpha_X X(t)m(t) - (\alpha_Y N(t) + \beta_Y A(t) + \mu_Y)Y(t)$$

$$\frac{dm}{dt} = k_m \mu_Y Y(t) - (\alpha_m N(t) + \mu_m)m(t)$$

$$\frac{d\dot{I}_\gamma}{dt} = \alpha_\gamma T_1(t)I_{12}(t) - \mu_\gamma I_\gamma(t)$$

$$\frac{dI_4}{dt} = \alpha_4 T_2(t)N(t) - \mu_4 I_4(t)$$

$$\frac{dI_{10}}{dt} = \alpha_{10} T_2(t)I_{12}(t) - \mu_{10} I_{10}(t)$$

$$\frac{dI_{12}}{dt} = \alpha_{12}T_1(t)I_\gamma(t) - \mu_{12}I_{12}(t) \qquad (1)$$

$$\frac{dN}{dt} = \alpha_N M(t)I_\gamma(t) - \mu_N N(t)$$

$$\frac{dA}{dt} = \alpha_A B(t)I_4(t) - \mu_A A(t)$$

$$\frac{dM}{dt} = \Lambda_M - \mu_M M(t)$$

$$\frac{dB}{dt} = \Lambda_B + \alpha_B B(t)I_4(t) - \mu_B B(t)$$

$$\frac{dT_0}{dt} = \Lambda_0 - \alpha_1 T_0(t)I_{12}(t) - \alpha_2 T_0(t)I_4(t) - \mu_0 T_0(t)$$

$$\frac{dT_1}{dt} = \alpha_1 T_0(t)I_{12}(t) - \mu_1 T_1(t)$$

$$\frac{dT_2}{dt} = \alpha_2 T_0(t)I_4(t) - \mu_2 T_2(t)$$

2.1. Positivity of solutions

Lemma : Solutions of system (1) with positive initial conditions $X(0)$, $Y(0)$, $m(0)$, $I_\gamma(0)$ $I_4(0)$, $I_{10}(0)$, $I_{12}(0)$, $N(0)$, $A(0)$, $M(0)$, $B(0)$, $T_0(0)$, $T_1(0)$, $T_2(0)$ remain positive for all time $t > 0$

Proof : The first equation of system (1) gives rise to $\frac{dX}{dt} + (\alpha_X m(t) + \mu_X)X \geq 0$

which on integration yields $\frac{d}{dt}\left(X(t)\exp(\int_0^t \alpha_X m(s)ds + \mu_X t) \right) \geq 0$

implying that $X(t) \geq X(0)\exp(-\int_0^t \alpha_X m(s)ds - \mu_X t)$ then $X(t) > 0$, $\forall\ t > 0$

It can be shown, using similar method, that the remaining states variables $Y(t)$, $m(t)$, $I_\gamma(t)$,

$I_4(t)$, $I_{10}(t)$, $I_{12}(t)$, $N(t)$, $A(t)$, $M(t)$, $B(t)$, $T_0(t)$, $T_1(t)$, $T_2(t)$ are positives for all time $t > 0$

2.2. Invariant region

Consider $\Omega = \Omega_1 \cup \Omega_2$, where

$$\Omega_1 = \left\{0 \le X \le \tfrac{\Lambda_X}{\mu_X},\ 0 \le Y,\ 0 \le m,\ 0 \le I_\lambda,\ 0 \le I_4,\ 0 \le I_{10},\ 0 \le I_{12},\ 0 \le N,\ 0 \le A\right\}$$

$$\Omega_2 = \left\{0 \le M \le \tfrac{\Lambda_M}{\mu_M},\ 0 \le B \le \tfrac{\Lambda_B}{\mu_B},\ 0 \le T_0 \le \tfrac{\Lambda_0}{\mu_0},\ 0 \le T_1,\ 0 \le T_2\right\}$$

Theorem 2.2 : The region Ω is positively invariant for the system (1)

Proof : One of the tools to be used in the proof that the solutions of the system (1) stays

bounded is the classical Gronwall's inequality which states that if $Y(t):\ [0,T] \to R$ satisfies the differential inequality $\dfrac{dY(t)}{dt} \le a(t)Y(t) + b(t)$ with ***a*** and ***b*** continuous , then

$$Y(t) \le Y(0)\exp\left(\int_0^t a(s)ds\right) + \int_0^t b(s)\exp\left(\int_s^t a(r)dr\right)ds$$

The first equation of system (1) gives rise to $\dfrac{dX}{dt} \le \Lambda_X - \mu_X X$

From Gronwall's inequality, it follows that $X(t) \le X(0)e^{-\mu_X t} + \dfrac{\Lambda_X}{\mu_X}(1 - e^{-\mu_X t})$,

implying that $\lim\limits_{t \to +\infty} X(t) \le \dfrac{\Lambda_X}{\mu_X}$. Particularly, $X(t) \le \dfrac{\Lambda_X}{\mu_X}$ if $X(0) \le \dfrac{\Lambda_X}{\mu_X}$

From the second equation of system (1), we have $\dfrac{dY}{dt} \le \alpha_X X(t)m(t) - \mu_Y Y(t)$

Which yields

$Y(t) \le Y(0)e^{-\mu_Y t} + \alpha_X e^{-\mu_Y t}\int_0^t X(s)m(s)e^{\mu_Y s}ds \le Y(0)e^{-\mu_Y t} + \frac{\alpha_X \Lambda_X}{\mu_X \mu_Y}\|m\|_\infty (1-e^{-\mu_Y t})$ Thus

$Y(t) \le Y(0) + \frac{\alpha_X \Lambda_X}{\mu_X \mu_Y}\|m\|_\infty$

Following the same reasoning, we will deduce that the remaining states variables are bounded and all solutions of (1) starting in Ω approach, enter or stay in Ω. Thus Ω is an attracting positively invariant for the system (1).

3. ANALYSIS OF THE OPTIMAL CONTROL MODEL

3.1. Optimal control model

In this section, we incorporate in the system (1) three time-dependent controls functions u_1, u_2 and u_3. The control u_1 represent the use of personal protection measures such as the use of insecticide-treated nets, application of repellents or insecticides to skin and the use of windows and doors screens to prevent mosquito's bites both during the day and at night. These measures protect the normal red blood cells, preventing their infection *i.e.* keeping them from turning into parasitized red blood cells. The control u_2 simulates the effect of the nitric oxide or antibodies which destroy parasitized red blood cells, preventing them from releasing new merozoites in the blood circulation. The control u_3 represents the efficiency of drug therapy in killing the merozoites in the blood. With these modifications, the system (1) can be reformulated as:

$$\frac{d\dot{X}}{dt} = \Lambda_X - (1-u_1)\alpha_X X(t)m(t) - \mu_X X(t)$$

$$\frac{dY}{dt} = (1-u_1)\alpha_X X(t)m(t) - (\alpha_Y N(t) + \beta_Y A(t) + \mu_Y + u_2)Y(t)$$

$$\frac{dm}{dt} = (1-u_3)k_m \mu_Y Y(t) - (\alpha_m N(t) + \mu_m)m(t)$$

$$\frac{d\dot{I}_\gamma}{dt} = \alpha_\gamma T_1(t)I_{12}(t) - \mu_\gamma I_\gamma(t)$$

$$\frac{dI_4}{dt} = \alpha_4 T_2(t)N(t) - \mu_4 I_4(t)$$

$$\frac{dI_{10}}{dt} = \alpha_{10} T_2(t)I_{12}(t) - \mu_{10} I_{10}(t)$$

$$\frac{dI_{12}}{dt} = \alpha_{12} T_1(t)I_\gamma(t) - \mu_{12} I_{12}(t) \qquad (2)$$

$$\frac{dN}{dt} = \alpha_N M(t) I_\gamma(t) - \mu_N N(t)$$

$$\frac{dA}{dt} = \alpha_A B(t) I_4(t) - \mu_A A(t)$$

$$\frac{dM}{dt} = \Lambda_M - \mu_M M(t)$$

$$\frac{dB}{dt} = \Lambda_B + \alpha_B B(t) I_4(t) - \mu_B B(t)$$

$$\frac{dT_0}{dt} = \Lambda_0 - \alpha_1 T_0(t) I_{12}(t) - \alpha_2 T_0(t) I_4(t) - \mu_0 T_0(t)$$

$$\frac{dT_1}{dt} = \alpha_1 T_0(t) I_{12}(t) - \mu_1 T_1(t)$$

$$\frac{dT_2}{dt} = \alpha_2 T_0(t) I_4(t) - \mu_2 T_2(t)$$

3.2. Objective function

We use an approach similar to the one in Barret and Hoel [3] which consists in applying the Pontryagin's maximum principle [25] to determine the conditions under which eradication of the disease can be achieved in finite time. The use is to minimize the following objective or cost functional by increasing the number of normal red blood cells, decreasing the number of parasitized red blood cells and merozoites and minimizing the costs of implementing the control strategies $u_i(t)$ (i = 1,2,3). Denote $u(t) = (u_1(t), u_2(t), u_3(t))$

$$J(u) = \int_0^T (A_1 X(t) + A_2 Y(t) + A_3 m(t) + \frac{1}{2}\sum_{i=1}^{3} B_i u_i^2(t))dt \qquad (3)$$

where A_i and B_i (i=1,2,3) are positive weight constants. The expected final time for the control implementation is represented by T. The objective functional (3) includes the cost control function for personal protection $\frac{1}{2}B_1 u_1^2(t)$, the cost control function for application of prophylaxis (destroying the parasitized red blood cells) $\frac{1}{2}B_2 u_2^2(t)$ and the cost of treating infectious humans which represents the cost control function of drug therapy $\frac{1}{2}B_3 u_3^2(t)$. In this work, as in other studies [18, 22], the cost control functions take a quadratic form.

Our target is to find an optimal triple control $u^* = (u_1^*, u_2^*, u_3^*)$ such that

$$J(u^*) = \min\{J(u_1,u_2,u_3)/u = (u_1,u_2,u_3) \in U\} \quad (4)$$

where $U = \{u(t) = (u_1(t),u_2(t),u_3(t)),\ 0 \le u_i(t) \le 1,\ t \in [0,T],\ \textit{Lebesgue measurable}\}$ is the control set

3.3. Existence of an optimal control

Theorem 3.3: Given the objective functional (3), defined on the control set U, and subject to the system (2) with non-negative initial conditions at $t = 0$, there exists an optimal control $u^* = (u_1^*,u_2^*,u_3^*)$ such that

$J(u^*) = \min\{J(u_1,u_2,u_3)/u = (u_1,u_2,u_3) \in U\}$

Proof:

The proof of theorem 3.3 is based in satisfying following properties, using a result by Fleming and Rishel in [9] and by Lukes in [14] :

(i) The set of controls and corresponding state variables is non-empty

(ii) The control set U is convex and closed

(iii) The state system is bounded by a linear function in the state and controls variables

(iv) The integrand of the objective functional is convex on U

(v) There exists constants $c_1, c_2 > 0$ and $\beta > 1$ such that integrand of the objective functional is bounded below by $c_1(\sum u_i^2)^{\frac{\beta}{2}} - c_2$

(i) We use a result by Lukes in [14] to give the existence of solutions of system (2) corresponding to the every admissible control set U. We note that all the solutions are bounded.

(ii) Given that the control set $U = [0,1]^3$, U is convex and closed by definition

(iii) Let $x = (X, Y, m, I_\gamma, I_4, I_{10}, I_{12}, N, A, M, B, T_0, T_1, T_2)$

and $f(t,x,u)$ the right-hand side of system (2) given by

$$f(t,x,u)=\begin{pmatrix}\Lambda_X-(1-u_1)\alpha_X X(t)m(t)-\mu_X X(t)\\(1-u_1)\alpha_X X(t)m(t)-(\alpha_Y N(t)+\beta_Y A(t)+\mu_Y+u_2)Y(t)\\(1-u_3)k_m\mu_Y Y(t)-(\alpha_m N(t)+\mu_m)m(t)\\\alpha_\gamma T_1(t)I_{12}(t)-\mu_\gamma I_\gamma(t)\\\alpha_4 T_2(t)N(t)-\mu_4 I_4(t)\\\alpha_{10}T_2(t)I_{12}(t)-\mu_{10}I_{10}(t)\\\alpha_{12}T_1(t)I_\gamma(t)-\mu_{12}I_{12}(t)\\\alpha_N M(t)I_\gamma(t)-\mu_N N(t)\\\alpha_A B(t)I_4(t)-\mu_A A(t)\\\Lambda_M-\mu_M M(t)\\\Lambda_B+\alpha_B B(t)I_4(t)-\mu_B B(t)\\\Lambda_0-\alpha_1 T_0(t)I_{12}(t)-\alpha_2 T_0(t)I_4(t)-\mu_0 T_0(t)\\\alpha_1 T_0(t)I_{12}(t)-\mu_1 T_1(t)\\\alpha_2 T_0 I_4(t)-\mu_2 T_2(t)\end{pmatrix} \tag{5}$$

It is clear from (5) that $f(t,x,u)=g(t,x)+h(t,x)u$, where

$$g(t,x)=\begin{pmatrix}\Lambda_X-\alpha_X X(t)m(t)-\mu_X X(t)\\\alpha_X X(t)m(t)-(\alpha_Y N(t)+\beta_Y A(t)+\mu_Y)Y(t)\\k_m\mu_Y Y(t)-(\alpha_m N(t)+\mu_m)m(t)\\\alpha_\gamma T_1(t)I_{12}(t)-\mu_\gamma I_\gamma(t)\\\alpha_4 T_2(t)N(t)-\mu_4 I_4(t)\\\alpha_{10}T_2(t)I_{12}(t)-\mu_{10}I_{10}(t)\\\alpha_{12}T_1(t)I_\gamma(t)-\mu_{12}I_{12}(t)\\\alpha_N M(t)I_\gamma(t)-\mu_N N(t)\\\alpha_A B(t)I_4(t)-\mu_A A(t)\\\Lambda_M-\mu_M M(t)\\\Lambda_B+\alpha_B B(t)I_4(t)-\mu_B B(t)\\\Lambda_0-\alpha_1 T_0(t)I_{12}(t)-\alpha_2 T_0(t)I_4(t)-\mu_0 T_0(t)\\\alpha_1 T_0(t)I_{12}(t)-\mu_1 T_1(t)\\\alpha_2 T_0 I_4(t)-\mu_2 T_2(t)\end{pmatrix}$$

and

$$h(t,x)=\begin{pmatrix} \alpha_X X(t)m(t) & 0 & 0 \\ -\alpha_X x(t)m(t) & -Y(t) & 0 \\ 0 & 0 & -k_m\mu_Y Y(t) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Hence,

$\|f(t,x,u)\| \le \|g(t,x)\| + \|h(t,x)\|\|u\| \le a_1 + a_2\|u\|$ where a_1 and a_2 are positive constants.

(iv) The integrand of the objective functional is the Lagrangian of the form:

$$L(t,x,u) = A_1X(t) + A_2Y(t) + A_3m(t) + \frac{1}{2}\sum_{i=1}^{3} B_i u_i^2(t) = g_1(t,x) + h_1(t,u)$$

It suffices to show that $h_1(t,u) = \frac{1}{2}\sum_{i=1}^{3} B_i u_i^2(t)$ is convex on the control variable $u \in U$.

Since $h(t,u)$ is a finite linear combination with positive coefficients of the function $q_i(u) = \frac{1}{2}u_i^2$, it is more convenient to show that the function $q(u) = \frac{1}{2}u^2$ is convex.

To do this, let $u, v : [0,T] \to [0,1]$ and $\lambda \in [0,1]$. Then,

$$q(\lambda u + (1-\lambda)v) - (\lambda q(u) + (1-\lambda)q(v)) = \frac{1}{2}(\lambda u + (1-\lambda)v)^2 - \frac{1}{2}(\lambda u^2 + (1-\lambda)v^2)$$

$$= \frac{1}{2}(\lambda^2 - \lambda)(u^2 - 2uv + v^2) = \frac{1}{2}\lambda(\lambda - 1)(u - v)^2 \leq 0$$

(v) $$L(t,x,u) = A_1 X(t) + A_2 Y(t) + A_3 m(t) + \frac{1}{2}\sum_{i=1}^{3} B_i u_i^2(t) \geq \frac{1}{2}\sum_{i=1}^{3} B_i u_i^2 \geq c_1 \left(\sum_{i=1}^{3} u_i^2 \right)^{\frac{\beta}{2}} - c_2$$

where $c_1 = \frac{1}{2}\min\{B_1, B_2, B_3\}$, $\beta = 2$ and $c_2 > 0$

3.4 Characterisation of an optimal control

In a attempt to obtain necessary conditions for the optimal control of malaria governed by the system (2), the use is made of the Pontryagin's Maximum Principle [25] which converts the state system (2), with the objective functional (3) and (4) into a problem of minimizing point wise, with respect to the controls u_1, u_2 and u_3, a Hamiltonian H given by the following:

$$H = A_1 X(t) + A_2 Y(t) + A_3 m(t) + \frac{1}{2}\left(B_1 u_1^2(t) + B_2 u_2^2(t) + B_3 u_3^2(t)\right)$$

$$+ \lambda_X [\, \Lambda_X - (1-u_1)\alpha_X X(t) m(t) - \mu_X X(t) \,]$$

$$+ \lambda_Y [\, (1-u_1)\alpha_X X(t) m(t) - (\alpha_Y N(t) + \beta_Y A(t) + \mu_Y + u_2) Y(t) \,]$$

$$+ \lambda_m [\, (1-u_3) k_m \mu_Y Y(t) - (\alpha_m N(t) + \mu_m) m(t) \,]$$

$$+ \lambda_{I_\gamma} [\, \alpha_\gamma T_1(t) I_{12}(t) - \mu_\gamma I_\gamma(t) \,]$$

$$+ \lambda_{I_4} [\, \alpha_4 T_2(t) N(t) - \mu_4 I_4(t) \,]$$

$$+ \lambda_{I_{10}} [\, \alpha_{10} T_2(t) I_{12}(t) - \mu_{10} I_{10}(t) \,]$$

$$+ \lambda_{I_{12}}[\alpha_{12}T_1(t)I_\gamma(t) - \mu_{12}I_{12}(t)]$$

$$+ \lambda_N[\alpha_N M(t)I_\gamma(t) - \mu_N N(t)]$$

$$+ \lambda_A[\alpha_A B(t)I_4(t) - \mu_A A(t)]$$

$$+ \lambda_M[\Lambda_M - \mu_M M(t)]$$

$$+ \lambda_B[\Lambda_B + \alpha_B B(t)I_4(t) - \mu_B B(t)]$$

$$+ \lambda_{T_0}[\Lambda_0 - \alpha_1 T_0(t)I_{12}(t) - \alpha_2 T_0(t)I_4(t) - \mu_0 T_0(t)]$$

$$+ \lambda_{T_1}[\alpha_1 T_0(t)I_{12}(t) - \mu_1 T_1(t)]$$

$$+ \lambda_{T_2}[\alpha_2 T_0(t)I_4(t) - \mu_2 T_2(\mathrm{t})] \qquad (6)$$

where λ_X, λ_Y, λ_m, λ_{I_γ}, λ_{I_4}, $\lambda_{I_{10}}$, $\lambda_{I_{12}}$, λ_N, λ_A, λ_M, λ_B, λ_{T_0}, λ_{T_1}, λ_{T_2} are the adjoint variables or co-state variables. The following result gives the necessary conditions for the optimal control.

Theorem 3.4: Given an optimal control triple $u^* = (u_1^*, u_2^*, u_3^*)$ that minimizes objective functional (3) over the control set U subject to the system (2), then there exist adjoint variables λ_X, λ_Y, λ_m, λ_{I_γ}, λ_{I_4}, $\lambda_{I_{10}}$, $\lambda_{I_{12}}$, λ_N, λ_A, λ_M, λ_B, λ_{T_0}, λ_{T_1}, λ_{T_2} satisfying:

$$\frac{d\dot{\lambda}_X}{dt} = (1-u_1)\alpha_X m(t)(\lambda_X - \lambda_Y) + \mu_X \lambda_X - A_1$$

$$\frac{d\lambda_Y}{dt} = \lambda_Y(\alpha_Y N(t) + \beta_Y A(t) + \mu_Y + u_2) - \lambda_m(1-u_3)k_m\mu_Y - A_2$$

$$\frac{d\lambda_m}{dt} = (1-u_1)\alpha_X X(t)(\lambda_X - \lambda_Y) + \lambda_m(\alpha_m N(t) + \mu_m) - A_3$$

$$\frac{d\dot{\lambda}_{I_\gamma}}{dt} = -\lambda_{I_{12}}\alpha_{12}T_1(t) - \lambda_N\alpha_N M(t) + \mu_\gamma\lambda_{I_\gamma}$$

$$\frac{d\lambda_{I_4}}{dt} = -(\lambda_A\alpha_A + \lambda_B\alpha_B)B(t) + \alpha_2 T_0(t)(\lambda_{T_0} - \lambda_{T_2}) + \mu_4\lambda_{I_4}$$

$$\frac{d\lambda_{I_{10}}}{dt} = \mu_{10}\lambda_{I_{10}}$$

$$\frac{d\lambda_{I_{12}}}{dt} = -\lambda_{I_\gamma}\alpha_\gamma T_1(t) - \lambda_{I_{10}}\alpha_{10}T_2(t) + \alpha_1 T_0(t)(\lambda_{T_0} - \lambda_{T_1}) + \mu_{12}\lambda_{I_{12}} \quad (7)$$

$$\frac{d\dot{\lambda}_N}{dt} = \lambda_Y\alpha_Y Y(t) + \lambda_m\alpha_m m(t) - \lambda_{I_4}\alpha_4 T_2(t) + \mu_N\lambda_N$$

$$\frac{d\lambda_A}{dt} = \lambda_Y\beta_Y Y(t) + \mu_A\lambda_A$$

$$\frac{d\lambda_M}{dt} = -\lambda_N\alpha_N I_\gamma(t) + \mu_M\lambda_M$$

$$\frac{d\lambda_B}{dt} = -(\lambda_A\alpha_A + \lambda_B\alpha_B)I_4(t) + \mu_B\lambda_B$$

$$\frac{d\lambda_{T_0}}{dt} = \alpha_1 I_{12}(t)(\lambda_{T_0} - \lambda_{T_1}) + \alpha_2 I_4(t)(\lambda_{T_0} - \lambda_{T_2}) + \mu_0\lambda_{T_0}$$

$$\frac{d\lambda_{T_1}}{dt} = -\lambda_{I_\gamma}\alpha_\gamma I_{12}(t) - \lambda_{I_{12}}\alpha_{12}I_\gamma(t) + \mu_1\lambda_{T_1}$$

$$\frac{d\lambda_{T_2}}{dt} = -\lambda_{I_4}\alpha_4 N(t) - \lambda_{I_{10}}\alpha_{10}I_{12}(t) + \mu_2\lambda_{T_2}$$

with transversality conditions:

$$\lambda_X(T) = 0,\ \lambda_Y(T) = 0,\ \lambda_m(T) = 0,\ \lambda_{I_\gamma}(T) = 0,\ \lambda_{I_4}(T) = 0,\ \lambda_{I_{10}}(T) = 0,\ \lambda_{I_{12}}(T) = 0,$$
$$\lambda_N(T) = 0,\ \lambda_A(T) = 0,\ \lambda_M(T) = 0,\ \lambda_B(T) = 0,\ \lambda_{T_0}(T) = 0,\ \lambda_{T_1}(T) = 0,\ \lambda_{T_2}(T) = 0 \quad (8)$$

and

$$u_1^*(t) = \min\left\{\max\left\{0,\ \frac{\alpha_X X(t)m(t)(\lambda_Y - \lambda_X)}{B_1}\right\},\ 1\right\}$$

$$u_2^*(t) = \min\left\{\max\left\{0,\ \frac{\lambda_Y Y(t)}{B_2}\right\},\ 1\right\} \tag{9}$$

$$u_3^*(t) = \min\left\{\max\left\{0,\ \frac{\lambda_m k_m \mu_Y Y(t)}{B_3}\right\},\ 1\right\}$$

Proof:

The adjoint equations (7) are obtained by taking partial derivates of the Hamiltonian H given by (6) with respect to the associated state variables, so that

$$\frac{d\lambda_X}{dt} = -\frac{\partial H}{\partial X}, \qquad \frac{d\lambda_Y}{dt} = -\frac{\partial H}{\partial Y}, \qquad \frac{d\lambda_m}{dt} = -\frac{\partial H}{\partial m}, \qquad \frac{d\lambda_{I_\gamma}}{dt} = -\frac{\partial H}{\partial I_\gamma}$$

$$\frac{d\lambda_{I_4}}{dt} = -\frac{\partial H}{\partial I_4}, \qquad \frac{d\lambda_{I_{10}}}{dt} = -\frac{\partial H}{\partial I_{10}}, \qquad \frac{d\lambda_{I_{12}}}{dt} = -\frac{\partial H}{\partial I_{12}}, \qquad \frac{d\lambda_N}{dt} = -\frac{\partial H}{\partial N},$$

$$\frac{d\lambda_A}{dt} = -\frac{\partial H}{\partial A}, \qquad \frac{d\lambda_M}{dt} = -\frac{\partial H}{\partial M}, \qquad \frac{d\lambda_B}{dt} = -\frac{\partial H}{\partial B}, \qquad \frac{d\lambda_{T_0}}{dt} = -\frac{\partial H}{\partial T_0},$$

$$\frac{d\lambda_{T_1}}{dt} = -\frac{\partial H}{\partial T_1}, \qquad \frac{d\lambda_{T_2}}{dt} = -\frac{\partial H}{\partial T_2}$$

with transversality or terminal conditions (8). Moreover, the optimal control characterization given by (9) is determined by solving the following partial differential equations:

$$\frac{\partial H}{\partial u_1} = 0 \quad for \quad u_1^*, \qquad \frac{\partial H}{\partial u_2} = 0 \quad for \quad u_2^*, \qquad \frac{\partial H}{\partial u_3} = 0 \quad for \quad u_3^*$$

By standard control arguments involving bounds on the control, then

$$u_i^* = \begin{cases} 0 & if \quad v_i^* \le 0 \\ v_i^* & if \quad 0 \le v_i^* \le 1 \\ 1 & if \quad v_i^* \ge 1 \end{cases}$$

for $i = 1, 2, 3$ and where

$$v_1^* = \frac{\alpha_X X(t) m(t)(\lambda_Y - \lambda_X)}{B_1}, \qquad v_2^* = \frac{\lambda_Y Y(t)}{B_2}, \qquad v_3^* = \frac{\lambda_m k_m \mu_Y Y(t)}{B_3}$$

This completes the proof.

4. CONCLUSION

In this paper, we formulated an intra-host model of malaria infection and analyzed the qualitative properties of the solutions. The effective eradication or control of malaria may be too costly because it means that for constant controls, one needs to keep prophylaxis and treating for infinite time. Therefore, we considered time dependent controls as a way out, to ensure the eradication of the disease in a finite time, and in a situation where eradication is impossible or of less benefit compared with the cost of intervention, we also derived and analyzed the necessary conditions for optimal control of the disease.

However this conclusion must be taken with caution: The theoretical results obtained here were not observed from numerical simulation because of uncertainties around the parameter values.

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