

Optimal control of malaria chemotherapy

Gesham Magombedze^a, Christinah Chiyaka^b, Zindoga Mukandavire^b

^aComputational Biology Group
Institute of Infectious Diseases and Molecular Medicine
University of Cape Town
Obs, Anzio Rd, 7925, Cape Town, South Africa
gmagombedze@gmail.com; gesham.magombedze@uct.ac.za

^bEmerging Pathogens Institute, University of Florida
Gainesville, FL 32610, USA
chrischiyaka@gmail.com; zmukandavire@gmail.com

Received: 30 August 2010 / **Revised:** 15 September 2011 / **Published online:** 7 December 2011

Abstract. We present an intra-host mathematical model of malaria that describes the interaction of the immune system with the blood stage malaria merozoites. The model is modified by incorporating the effects of malaria drugs that target blood stage parasites. The optimal control represents a percentage effect of the chemotherapy of chloroquine in combination with chlorpheniramine on the reproduction of merozoites in erythrocytes. First we maximise the benefit based on the immune cells, and minimise the systemic cost based on the percentage of chemotherapies given and the population of merozoites. An objective functional to minimise merozoite reproduction and treatment systemic costs is then built. The existence and uniqueness results for the optimal control are established. The optimality system is derived and the Runge–Kutta fourth order scheme is used to numerically simulate different therapy efforts. Our results indicate that highly toxic drugs with the compensation of high infection suppression have the potential of yielding better treatment results than less toxic drugs with less infection suppression potential or high toxic drugs with less infection suppression potential. In addition, we also observed that a treatment protocol with drugs with high adverse effects and with a high potential of merozoite suppression can be beneficial to patients. However, an optimal control strategy that seeks to maximise immune cells has no potential to improve the treatment of blood stage malaria.

Keywords: malaria modelling, chloroquine chemotherapy, optimal control, *Plasmodium falciparum*.

1 Introduction

Malaria remains a major public health problem in most tropical countries, particularly sub-Saharan Africa. It has been estimated that between 300 million and 500 million individuals are infected annually and between 1.5 million and 2.7 million people die of malaria every year [1]. Malaria is caused by the protozoan *Plasmodium* and is transmitted to humans by female *Anophele* mosquitoes. Of the four species of plasmodia infecting

humans, *P. falciparum* accounts for the most severe and often potentially lethal form of malaria. Malaria parasites injected into the human host by mosquitoes initially migrate to the liver where they develop into schizonts which rupture, releasing a large number of daughter merozoites into the blood stream. There, each merozoite invades a fresh erythrocyte to renew the cycle. The erythrocyte cycle maintains infection and directly generates disease symptoms [2, 3].

The infection of humans by malaria solicits immunity development, such that individuals that are repeatedly exposed to *P. falciparum* infection acquire partial immunity. Consequently, non-immune children in areas of high endemicity suffer severe malaria, while adults suffer fewer clinical malaria episodes [3]. Naturally acquired immunity is not completely understood. However, several studies [2–6] concluded that both cell-mediated and antibody-dependent immunity are required for adequate protection. Both types of responses are critically dependent on CD4+ T cells. The two main facets of CD4+ T cells that are functionally distinguished by the cytokines they solicit, that is, (i) Th1-type which mainly induce γ -interferon (IFN- γ), and (ii) Th2-type which induce interleukine-4 (IL-4) and IL-5. Both the Th1 and Th2 responses seem to be required to regulate the infection of humans with *P. falciparum* malaria. However, they need to be adequately tuned in intensity and on time [2]. It has been proposed in murine malaria that innate and adaptive responses are required for parasite elimination [5]. The difference between lethal and non-lethal is explained by the expression of cytokines stimulated by the infection, such that production of IFN- γ , IL-12 and TNF- α responses are associated with non-lethal malaria and even elimination of infection. However, overproduction of IFN- γ or TNF- α predisposes to severe pathology [4, 5, 7].

Chloroquine (CQ) has remained the drug of choice for the chemosuppression and radical cure of malaria particularly in the tropics, primarily because it is cheap, rapidly effective and readily available [8]. However, the wide spread emergence of CQ-resistance *P. falciparum* strains has led to studies to counter the threat of CQ resistant strains through development of combinations of antimalarials [9, 10], which are now recommended by world health organisation (WHO). Antimalarial combination therapy is the simultaneous use of two (sulfadoxine-pyrimethamine, sulfalene-pyrimethamine, proguanil-dapsone, etc.) or more blood schizontocidal drugs with independent modes of action. The concept is based on the potential of two or more schizontocidal drugs to improve therapeutic efficacy and delay the development of resistance to the individual components [9, 10]. Other multiple therapies include a non-antimalarial medicine to enhance the antimalarial effect of a blood schizontocidal drug, such as the combination of CQ and chlorpheniramine (CP). However, the major disadvantage of combination treatments is the increased risk of adverse effects and increased cost of treatment.

Optimal controls have vastly been used in determining control strategies of disease dynamics, especially in the control of human immunodeficiency virus and tuberculosis [1, 11–23]. In these studies, optimal control therapy strategies were explored using Pontryagin's maximum principle using dynamical models. However, up-to date, to the best of our knowledge no work has been done to seek optimal control schemes for malaria drugs despite frantic efforts to find effective treatment and vaccine schemes. Emergence of *P. falciparum* resistance to widely used antimalarial drugs such as CQ has made treat-

ment and control difficult. Therefore, the main thrust of this study is to determine how CQ treatment in combination with CP (or an malaria drug that reduce reproduction of merozoites in parasitised erythrocytes) should be initiated, investigate drug percentage usage, and effective treatment in the face of emerging malaria drug resistant strains with aid of a model that incorporates the cellular and humoral immune response mechanisms in an elaborate way.

This paper is organised as follows, in Section 2 we present a basic malaria model [24]. We incorporate malaria drug administration in Section 3 and develop the objective functional to determine an optimal control strategy in the treatment of malaria. Existence and characterisation of the optimal control are carried out in Section 4 and 5, respectively. The optimality system and its proof are given in Section 6. In Section 7 we present the numerical simulations of the optimal system and concluding remarks are provided in Section 8.

2 Malaria intra-host model

Here we present a malaria model proposed by Chiyaka et al. [24], which models the interaction of (i) uninfected red blood cells (X), (ii) infected red blood cells (Y), (iii) immune cells (B), (iv) merozoites (M), and (v) antibodies (A). Red blood cells are recruited naturally at a constant rate such that their natural turn over is $\frac{\lambda_x}{\mu_x}$ and are further recruited at a rate σ in response to the population of infected red blood cells, which is induced by infected red blood cells. Red blood cells are infected by merozoites at a rate β and infected cells die or burst at rate u_y . Bursting of infected cells release r daughter merozoites per infected cells. Infection of red blood cells is counteracted by parasite specific antibodies, such that the increase of antibodies result in the reduction of infected cells. This effect is represented by the term, $(\frac{1}{1+c_0A})$, while ω represents removal of red blood cells bound to merozoites by immune cells. Immune cells kill infected red blood cells at rate k_y . The life expectancy of the merozoites is $\frac{1}{\mu_m}$ and are eliminated by immune cells at rate $k_m B$. The natural turn over of immune cells is $\frac{\lambda_B}{\mu_B}$, and more immune cells proliferate at the site of infection in proportion to the density of infected red blood cells and merozoites at rates p_y and p_m with proliferation saturation limits of K_0 and K_1 , respectively. Antibodies are secreted at rate η , this secretion is induced by immune cells and depends on the density of merozoites in the blood, that is as the population of merozoites increase more antibodies will be secreted. Merozoite specific antibodies decay at a rate μ_A . These assumptions lead to the following system of equations:

$$\frac{dX(t)}{dt} = \lambda_x + \sigma Y(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right) - \mu_x X(t) - \omega X(t)M(t)B(t), \quad (1)$$

$$\frac{dY(t)}{dt} = \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right) - u_y Y(t) - k_y B(t)Y(t), \quad (2)$$

$$\frac{dM(t)}{dt} = \frac{r u_y Y(t)}{1 + c_1 B(t)} - \mu_m M(t) - k_m B(t)M(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right), \quad (3)$$

$$\frac{dB(t)}{dt} = \lambda_b + \left(p_y \frac{Y(t)}{K_0 + Y(t)} + p_m \frac{M(t)}{K_1 + M(t)} \right) B(t) - \mu_b B(t), \quad (4)$$

$$\frac{dA(t)}{dt} = \eta B(t) \left(\frac{M(t)}{K_1 + M(t)} \right) - \mu_a A(t). \quad (5)$$

Interested readers may refer to [24] for the mathematical properties of model.

3 Treatment of malaria with antimalarial drugs

The administration of malaria drug, CQ, interact with parasitized erythrocytes. The drug diffuses into parasite lysosomal and becomes protonated in the acidic environment. It raises the pH of lysosome, inhibiting the polymerase that converts toxic free haem to a harmless by-product. It makes the survival and development of parasite difficult by preventing its digestion of haemoglobin and by reducing its supply of amino acids. Since CQ-resistant *P. falciparum* strains are rampant in sub-Saharan Africa we consider the administration of CQ in combination with CP to enhance CQ to suppress merozoites reproduction in erythrocytes. Therefore administration of CQ in combination with CP reduces the burst size r of infected red blood cells to $(1 - \gamma(t))r$, where $\gamma(t)$ is the normalised CQ and CP dosage as a function of time.

$$\frac{dX(t)}{dt} = \lambda_x + \sigma Y(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right) - \mu_x X(t) - \omega X(t)M(t)B(t), \quad (6)$$

$$\frac{dY(t)}{dt} = \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right) - u_y Y(t) - k_y B(t)Y(t), \quad (7)$$

$$\frac{dM(t)}{dt} = \frac{(1 - \gamma(t))r u_y Y(t)}{1 + c_1 B(t)} - \mu_m M(t) - k_m B(t)M(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right), \quad (8)$$

$$\frac{dB(t)}{dt} = \lambda_b + \left(p_y \frac{Y(t)}{K_0 + Y(t)} + p_m \frac{M(t)}{K_1 + M(t)} \right) B(t) - \mu_b B(t), \quad (9)$$

$$\frac{dA(t)}{dt} = \eta B(t) \left(\frac{M(t)}{K_1 + M(t)} \right) - \mu_a A(t). \quad (10)$$

We define our objective functional as

$$J(\gamma(t)) = \int_0^{t_f} [B(t) - G_1 M(t) - G_2 \gamma(t)^2] dt. \quad (11)$$

The first term represents the benefit of immune cells. The parameters G_1 and G_2 represent the weight constants on the benefit and cost on the merozoite population and the control, respectively. Our goal is to maximise the benefit based on the number of immune cells and treatment while minimising the merozoite population and the systemic cost (adverse effects and cost of treatment) of drug chemotherapy. The value $\gamma(t) = 1$ represents

maximal use of chemotherapy and the maximal cost is represented by $\gamma(t)^2$. We therefore seek an optimal control γ^* such that

$$J(\gamma^*) = \max\{J(\gamma) \mid \gamma \in \mathcal{U}\},$$

where, $\mathcal{U} = \{\gamma(t) \mid \gamma(t) \text{ is measurable: } 0 \leq a \leq \gamma(t) \leq b \leq 1, t \in [0, t_f]\}$. The basis framework of this problem is to characterise the optimal control and prove the existence of the optimal control and uniqueness of the optimality system.

4 Existence of an optimal control

The existence of an optimal control is proved by a result from Fleming and Rishel [25]. The boundedness of solutions of system of Eqs. (6)–(10) for a finite time interval is used to prove the existence of an optimal control.

For biological relevance of the model we impose restrictions that the growth of $X(t)$ and $B(t)$ is bounded, therefore we use $X(t) < X_{\max}$ and $B(t) < B_{\max}$, where X_{\max} and B_{\max} are the maximum numbers of RBCs and immune cells, respectively. The upper bounds of the solutions of the system of Eqs. (6)–(10) are determined.

$$\begin{aligned} \frac{dY^*}{dt} &= \frac{\beta X_{\max} M^*}{1 + a_0 A_{\min}}, & Y(0)^* &= Y_0^*, \\ \frac{dM^*}{dt} &= \frac{r u_y Y^*}{1 + c_1 B_{\min}}, & M(0)^* &= M_0^*, \\ \frac{dA^*}{dt} &= \eta B_{\max} \left(\frac{M^*}{K_1 + M^*} \right), & A(0)^* &= A_0^*. \end{aligned}$$

Note: (i) the upper bound of Y^* is obtained when $A^* = A_{\min}$, where $0 \leq A_{\min} \leq A^*$, (ii) the most positive value of M^* is obtained with B_{\min} , ($0 \leq B_{\min} < B_{\max}$) and its worth noting that $0 \leq \left(\frac{M^*}{K_1 + M^*}\right) < 1$. Therefore, the supersolutions Y^* , M^* , and A^* are bounded on a finite time interval.

To determine existence of an optimal control to our problem, we use a result from [25, Thm. 4.1, pp. 68–69], where the following properties must be satisfied:

1. The set of controls and corresponding state variables is nonempty.
2. The control set \mathcal{U} is convex and closed.
3. The right hand side of the state system is bounded by a linear function in the state and control.
4. The integrand of the functional is concave on \mathcal{U} and is bounded above by $c_2 - c_1 |\gamma|^\kappa$, where $c_1, c_2 > 0$ and $\kappa > 1$.

An existence result in [26, Thm. 9.2.1]) for the system of Eqs. (6)–(10) for bounded coefficients is used to give Condition 1. The control set is closed and convex by definition. The right hand side of the state system (Eqs. (6)–(10)) satisfies Condition 3 since the state solution are *a priori* bounded. The integrand in the objective functional, $B(t) - G_1 M(t) -$

$G_2\gamma(t)^2$, is Lebesgue integrable and concave on \mathcal{U} . Furthermore, $c_1, c_2 > 0$ and $\kappa > 1$, hence satisfying

$$B(t) - G_1M(t) - G_2\gamma(t)^2 \leq c_2 - c_1|\gamma|^\kappa,$$

therefore the optimal control exist, since the states are bounded.

5 Characterisation

Since there exists an optimal control for maximising the functional (11) subject to Eqs. (6)–(10), we use Pontryagin's maximum principle to derive the necessary conditions for this optimal control. The Lagrangian is defined as,

$$\begin{aligned} L = & B(t) - (G_1M(t) + G_2\gamma(t)^2) \\ & + \lambda_1 \left[\lambda_x + \sigma Y(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0A(t)} \right) - \mu_x X(t) - \omega X(t)M(t)B(t) \right] \\ & + \lambda_2 \left[\beta \left(\frac{X(t)M(t)}{1 + c_0A(t)} \right) - \mu_y Y(t) - k_y B(t)Y(t) \right] \\ & + \lambda_3 \left[\frac{(1 - \gamma(t))ru_y Y(t)}{1 + c_1B(t)} - \mu_m M(t) - k_m B(t)M(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0A(t)} \right) \right] \\ & + \lambda_4 \left[\lambda_b + \left(p_y \frac{Y(t)}{K_0 + Y(t)} + p_m \frac{M(t)}{K_1 + M(t)} \right) B(t) - \mu_b B(t) \right] \\ & + \lambda_5 \left[\eta B(t) \frac{M(t)}{K_1 + M(t)} - \mu_a A(t) \right] + w_1(t)(b - \gamma(t)) + w_2(t)(\gamma(t) - a), \quad (12) \end{aligned}$$

where $w_1(t) \geq 0$, $w_2(t) \geq 0$ are penalty multipliers satisfying $w_1(t)(b - \gamma(t)) = 0$ and $w_2(t)(\gamma(t) - a) = 0$ at the optimal γ^* .

Theorem 1. *Given an optimal control γ^* and solutions of the corresponding state system (6)–(10), there exist adjoint variables λ_i , $i = 1, \dots, 5$, satisfying*

$$\frac{d\lambda_1}{dt} = -\frac{\partial L}{\partial X} = (\lambda_1 + \lambda_3 - \lambda_2) \left(\beta \frac{M(t)}{1 + c_0A(t)} \right) + \lambda_1 \left(\mu_x + \omega M(t)B(t) \right), \quad (13)$$

$$\begin{aligned} \frac{d\lambda_2}{dt} &= -\frac{\partial L}{\partial Y} \\ &= -\lambda_1\sigma + \lambda_2(\mu_y + k_y B(t)) - \lambda_3 \left(\frac{(1 - \gamma(t))r\mu_y}{1 + c_1B(t)} \right) - \lambda_4 \left(\frac{p_y K_0 B(t)}{(K_0 + Y(t))^2} \right), \quad (14) \end{aligned}$$

$$\begin{aligned} \frac{d\lambda_3}{dt} &= -\frac{\partial L}{\partial M} \\ &= G_1 + (\lambda_1 + \lambda_3 - \lambda_2) \left(\beta \frac{X(t)}{1 + c_0A(t)} \right) + \lambda_1 (\omega X(t)B(t)) \\ &\quad + \lambda_3 (\mu_m + k_m B(t)) - B(t) \frac{K_1}{K_1 + M(t)} \left(\lambda_4 \left(\frac{p_m}{K_1 + M(t)} \right) + \lambda_5 \eta \right), \quad (15) \end{aligned}$$

$$\begin{aligned}\frac{d\lambda_4}{dt} &= -\frac{\partial L}{\partial B} \\ &= -1 + \lambda_1(\omega X(t)M(t)) + \lambda_2 k_y Y(t) + \lambda_3 \left(\frac{(1-\gamma(t))r\mu_y c_1 Y(t)}{(1+c_1 B(t))^2} - k_m M(t) \right) \\ &\quad - (p_m \lambda_4 + \eta \lambda_5) \left(\frac{M(t)}{M(t) + K_1} \right) - \lambda_4 \left(p_y \frac{Y(t)}{K_0 + Y(t)} - \mu_b \right),\end{aligned}\quad (16)$$

$$\begin{aligned}\frac{d\lambda_5}{dt} &= -\frac{\partial L}{\partial A} \\ &= (\lambda_2 - \lambda_1 - \lambda_3) \left(\beta c_0 \frac{X(t)M(t)}{(1+c_0 A(t))^2} \right) + \lambda_5 \mu_a,\end{aligned}\quad (17)$$

transversality conditions $\lambda_i(t_f) = 0$ for $i = 1, \dots, 5$.

Proof. The form of the adjoint equation and transversality conditions are standard results from Pontryagin's maximum principle [25, 27]; therefore, solutions to the adjoint system exist and are bounded. To determine the interior maximum of our lagrangian, we take the partial derivate of L with respect to $\gamma(t)$ and set it to zero. Thus,

$$\frac{\partial L}{\partial \gamma(t)} = -2G_2 \gamma(t)^* - \lambda_3 \left(\frac{r\mu_y Y(t)}{1+c_1 B(t)} \right) - w_1(t) + w_2(t) = 0. \quad (18)$$

Making $\gamma(t)^*$ subject of formulae

$$\gamma(t)^* = -\lambda_3 \left(\frac{r\mu_y Y(t)}{(1+c_1 B(t))2G_2} \right) + \frac{w_2(t) - w_1(t)}{2G_2}. \quad (19)$$

To determine an explicit expression for the control without $w_1(t)$ and $w_2(t)$, a standard optimality technique is utilized. The following three cases are considered to determine a specific characterisation of the optimal control.

(i) On the set $\{t | a < \gamma(t)^* < b\}$, $w_1(t) = w_2(t) = 0$. Hence the optimal control is

$$\gamma(t)^* = -\lambda_3 \left(\frac{r\mu_y Y(t)}{(1+c_1 B(t))2G_2} \right). \quad (20)$$

(ii) On the set $\{t | a = \gamma(t)^*\}$, $w_1(t) = 0$, hence

$$a = \gamma(t)^* = -\lambda_3 \left(\frac{r\mu_y Y(t)}{(1+c_1 B(t))2G_2} \right) + \frac{w_2(t)}{2G_2},$$

this implies that

$$-\lambda_3 \left(\frac{r\mu_y Y(t)}{(1+c_1 B(t))2G_2} \right) \leq a, \quad \text{since } w_2(t) \geq 0. \quad (21)$$

(iii) On the set $\{t \mid b = \gamma(t)^*\}$, $w_2(t) = 0$, hence

$$b = \gamma(t)^* = -\lambda_3 \left(\frac{r\mu_y Y(t)}{(1 + c_1 B(t))2G_2} \right) - \frac{w_1(t)}{2G_2},$$

this implies that

$$-\lambda_3 \left(\frac{r\mu_y Y(t)}{(1 + c_1 B(t))2G_2} \right) \geq b, \quad \text{since } w_1(t) \geq 0. \quad (22)$$

Combining these three cases, the optimal control is characterised as,

$$\gamma(t)^* = \min \left\{ \max \left\{ a, \frac{1}{2G_2} (-\lambda_3) \left(\frac{r\mu_y Y(t)}{1 + c_1 B(t)} \right) \right\}, b \right\}. \quad (23)$$

We consider the optimal system next. □

6 The optimal system

The optimality system consists of the state system coupled with the adjoint system with the initial conditions, the transversality conditions and the characterisation of the optimal control.

$$\frac{dX(t)}{dt} = \lambda_x + \sigma Y(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right) - \mu_x X(t) - \omega X(t)M(t)B(t), \quad (24)$$

$$\frac{dY(t)}{dt} = \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right) - u_y Y(t) - k_y B(t)Y(t), \quad (25)$$

$$\begin{aligned} \frac{dM(t)}{dt} = & \left[1 - \min \left\{ \max \left\{ a, \frac{1}{2G_2} (-\lambda_3) \left(\frac{r\mu_y Y(t)}{1 + c_1 B(t)} \right) \right\}, b \right\} \right] \left(\frac{ru_Y Y(t)}{1 + c_1 B(t)} \right) \\ & - \mu_m M(t) - k_m B(t)M(t) - \beta \left(\frac{X(t)M(t)}{1 + c_0 A(t)} \right), \end{aligned} \quad (26)$$

$$\frac{dB(t)}{dt} = \lambda_b + \left(p_y \frac{Y(t)}{K_0 + Y(t)} + p_m \frac{M(t)}{K_1 + M(t)} \right) B(t) - \mu_b B(t), \quad (27)$$

$$\frac{dA(t)}{dt} = \eta B(t) \left(\frac{M(t)}{K_1 + M(t)} \right) - \mu_a A(t). \quad (28)$$

$$\frac{d\lambda_1}{dt} = (\lambda_1 + \lambda_3 - \lambda_2) \left(\beta \frac{M(t)}{1 + c_0 A(t)} \right) + \lambda_1 (\mu_x + \omega M(t)B(t)), \quad (29)$$

$$\begin{aligned} \frac{d\lambda_2}{dt} = & -\lambda_1 \sigma + \lambda_2 (\mu_y + k_y B(t)) - \lambda_4 \left(\frac{p_y K_0 B(t)}{(K_0 + Y(t))^2} \right) \\ & - \lambda_3 \left[1 - \min \left\{ \max \left\{ a, \frac{1}{2G_2} (-\lambda_3) \left(\frac{r\mu_y Y(t)}{1 + c_1 B(t)} \right) \right\}, b \right\} \right] \left(\frac{r\mu_y}{1 + c_1 B(t)} \right), \end{aligned} \quad (30)$$

$$\begin{aligned} \frac{d\lambda_3}{dt} = & G_1 + (\lambda_1 + \lambda_3 - \lambda_2) \left(\beta \frac{X(t)}{1 + c_0 A(t)} \right) + \lambda_1 \left(\omega X(t) B(t) \right) \\ & + \lambda_3 (\mu_m + k_m B(t)) - B(t) \frac{K_1}{K_1 + M(t)} \left(\lambda_4 \left(\frac{p_m}{K_1 + M(t)} \right) + \lambda_5 \eta \right), \end{aligned} \quad (31)$$

$$\begin{aligned} \frac{d\lambda_4}{dt} = & -1 + \lambda_1 \left(\omega X(t) M(t) \right) + \lambda_2 k_y Y(t) \\ & + \lambda_3 \left[\left(1 - \min \left\{ \max \left\{ a, \frac{1}{2G_2} (-\lambda_3) \left(\frac{r\mu_y Y(t)}{1 + c_1 B(t)} \right) \right\}, b \right\} \right) \right. \\ & \quad \times \left. \left(\frac{r\mu_y c_1 Y(t)}{(1 + c_1 B(t))^2} \right) - k_m M(t) \right] \\ & - (p_m \lambda_4 + \eta \lambda_5) \left(\frac{M(t)}{M(t) + K_1} \right) - \lambda_4 \left(p_y \frac{Y(t)}{K_0 + Y(t)} - \mu_b \right), \end{aligned} \quad (32)$$

$$\frac{d\lambda_5}{dt} = (\lambda_2 - \lambda_1 - \lambda_3) \left(\beta c_0 \frac{X(t) M(t)}{(1 + c_0 A(t))^2} \right) + \lambda_5 \mu_a. \quad (33)$$

With $X(0) = X_0, Y^*(0) = Y_0^*, M^*(0) = M_0^*, B(0) = B_0, A^*(0) = A_0^*$ and $\lambda_i(t_f) = 0$ for $i = 1, \dots, 5$.

6.1 Uniqueness of the optimality system

The state system and adjoint system have finite upper bounds. These bounds are needed in the uniqueness proof of the optimality system.

Lemma 1. *The function $u^*(s) = \min(\max(s, a), b)$ is Lipschitz continuous in s , where $a < b$ are some fixed positive constants*

Theorem 2. *For t_f sufficiently small, bounded solutions to the optimality system are unique.*

Proof. Suppose $(X, Y, M, B, A, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)$ and $(\bar{X}, \bar{Y}, \bar{M}, \bar{B}, \bar{A}, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4, \bar{\lambda}_5)$ are two different solutions of our optimality system. Let $X = e^{\lambda t} p_1, Y = e^{\lambda t} p_2, M = e^{\lambda t} p_3, B = e^{\lambda t} p_4, A = e^{\lambda t} p_5, \lambda_1 = e^{-\lambda t} q_1, \lambda_2 = e^{-\lambda t} q_2, \lambda_3 = e^{-\lambda t} q_3, \lambda_4 = e^{-\lambda t} q_4, \lambda_5 = e^{-\lambda t} q_5$. Similarly, let $\bar{X} = e^{\lambda t} \bar{p}_1, \bar{\lambda}_1 = e^{-\lambda t} \bar{q}_1$, and so forth. Further we let

$$\gamma(t)^* = \min \left\{ \max \left\{ a, \frac{-1}{2G_2} q_3 \left(\frac{r\mu_y p_2}{1 + c_1 p_4 e^{\lambda t}} \right) \right\}, b \right\}, \quad (34)$$

and

$$\bar{\gamma}(t)^* = \min \left\{ \max \left\{ a, \frac{-1}{2G_2} \bar{q}_3 \left(\frac{r\mu_y \bar{p}_2}{1 + c_1 \bar{p}_4 e^{\lambda t}} \right) \right\}, b \right\}, \quad (35)$$

$$|\gamma(t)^* - \bar{\gamma}(t)^*| \leq \frac{r\mu_y}{2G_2} \left| \left(\frac{(1 + c_1 \bar{p}_4 e^{\lambda t}) q_3 p_2 - (1 + c_1 p_4 e^{\lambda t}) \bar{q}_3 \bar{p}_2}{(1 + c_1 p_4 e^{\lambda t})(1 + c_1 \bar{p}_4 e^{\lambda t})} \right) \right|. \quad (36)$$

Substituting $X = e^{\lambda t} p_1$ into the first ODE, the state equation becomes

$$e^{\lambda t}(\dot{p}_1 + \lambda p_1) = \lambda x + \sigma p_2 e^{\lambda t} - \beta \left(\frac{p_1 p_3 e^{2\lambda t}}{1 + c_0 p_5 e^{\lambda t}} \right) - \mu_x p_1 e^{\lambda t} - \omega p_1 p_3 p_4 e^{3\lambda t}. \quad (37)$$

Also, substituting $\lambda_1 = e^{-\lambda t} q_1$ in the equation of $\frac{d\lambda_1}{dt}$, the adjoint equation becomes

$$e^{-\lambda t}(\dot{q}_1 - \lambda q_1) = (q_1 + q_3 - q_2) \left(\frac{\beta p_3}{1 + c_0 p_5 e^{\lambda t}} \right) + (\mu_x + \omega p_3 p_4 e^{2\lambda t}) q_1 e^{-\lambda t}. \quad (38)$$

Now we subtract the equations for M and \bar{M} , λ_1 and $\bar{\lambda}_1$. Then multiply each equation by appropriate difference of functions ($p_1 - \bar{p}_1$ and $q_1 - \bar{q}_1$, respectively) and integrate from 0 to t_f we get

$$\begin{aligned} & \frac{1}{2}(p_1 - \bar{p}_1)^2 + \lambda \int_0^{t_f} (p_1 - \bar{p}_1)^2 dt \\ &= \sigma \int_0^{t_f} (p_2 - \bar{p}_2)(p_1 - \bar{p}_1) dt - \mu_x \int_0^{t_f} (p_1 - \bar{p}_1)^2 dt \\ & \quad - \beta \int_0^{t_f} e^{\lambda t} \left(\frac{p_1 p_3}{1 + c_0 p_5 e^{\lambda t}} - \frac{\bar{p}_1 \bar{p}_3}{1 + c_0 \bar{p}_5 e^{\lambda t}} \right) (p_1 - \bar{p}_1) dt \\ & \quad - \omega \int_0^{t_f} e^{2\lambda t} (p_1 p_3 p_4 - \bar{p}_1 \bar{p}_3 \bar{p}_4) (p_1 - \bar{p}_1) dt. \end{aligned} \quad (39)$$

Following the same procedure for the remaining state variables and adjoint variables, for Y and \bar{Y} , M and \bar{M} , B and \bar{B} , A and \bar{A} the following equations are obtained.

$$\begin{aligned} & \frac{1}{2}(p_2 - \bar{p}_2)^2 + \lambda \int_0^{t_f} (p_2 - \bar{p}_2)^2 dt \\ &= -\mu_y \int_0^{t_f} (p_2 - \bar{p}_2)^2 dt - k_y \int_0^{t_f} e^{\lambda t} (p_2 p_4 - \bar{p}_2 \bar{p}_4) (p_2 - \bar{p}_2)^2 dt \\ & \quad - \beta \int_0^{t_f} e^{\lambda t} \left(\frac{p_1 p_3}{1 + c_0 p_5 e^{\lambda t}} - \frac{\bar{p}_1 \bar{p}_3}{1 + c_0 \bar{p}_5 e^{\lambda t}} \right) (p_2 - \bar{p}_2) dt, \end{aligned} \quad (40)$$

$$\begin{aligned} & \frac{1}{2}(p_3 - \bar{p}_3)^2 + \lambda \int_0^{t_f} (p_3 - \bar{p}_3)^2 dt \\ &= r\mu_y \int_0^{t_f} \left(\frac{(1 - \gamma^*)p_2}{1 + c_1 p_4 e^{\lambda t}} - \frac{(1 - \bar{\gamma}^*)\bar{p}_2}{1 + c_1 \bar{p}_4 e^{\lambda t}} \right) (p_3 - \bar{p}_3) dt \end{aligned}$$

$$\begin{aligned}
& -\mu_m \int_0^{t_f} (p_3 - \bar{p}_3)^2 dt - k_m \int_0^{t_f} e^{\lambda t} (p_3 p_4 - \bar{p}_3 \bar{p}_4) (p_3 - \bar{p}_3) dt \\
& - \beta \int_0^{t_f} e^{\lambda t} \left(\frac{p_3 p_4}{1 + c_0 p_5 e^{\lambda t}} - \frac{\bar{p}_3 \bar{p}_4}{1 + c_0 \bar{p}_5 e^{\lambda t}} \right) (p_3 - \bar{p}_3) dt, \tag{41}
\end{aligned}$$

$$\begin{aligned}
& \frac{1}{2} (p_4 - \bar{p}_4)^2 + \lambda \int_0^{t_f} (p_4 - \bar{p}_4)^2 dt \\
& = p_y \int_0^{t_f} e^{\lambda t} \left(\frac{p_2 p_4}{K_0 + p_2 e^{\lambda t}} - \frac{\bar{p}_2 \bar{p}_4}{K_0 + \bar{p}_2 e^{\lambda t}} \right) (p_4 - \bar{p}_4) dt \\
& + p_m \int_0^{t_f} e^{\lambda t} \left(\frac{p_3 p_4}{K_1 + p_3 e^{\lambda t}} - \frac{\bar{p}_3 \bar{p}_4}{K_1 + \bar{p}_3 e^{\lambda t}} \right) (p_4 - \bar{p}_4) dt \\
& - \mu_b \int_0^{t_f} (p_4 - \bar{p}_4)^2 dt, \tag{42}
\end{aligned}$$

$$\begin{aligned}
& \frac{1}{2} (p_5 - \bar{p}_5)^2 + \lambda \int_0^{t_f} (p_5 - \bar{p}_5)^2 dt \\
& = \eta \int_0^{t_f} e^{\lambda t} \left(\frac{p_3 p_4}{K_1 + p_3 e^{\lambda t}} - \frac{\bar{p}_3 \bar{p}_4}{K_1 + \bar{p}_3 e^{\lambda t}} \right) (p_5 - \bar{p}_5) dt \\
& - \mu_a \int_0^{t_f} (p_5 - \bar{p}_5)^2 dt. \tag{43}
\end{aligned}$$

These estimates utilize upper bounds on the solutions. They involve separating terms that involve squares, several multiplied terms, and quotients.

Note:

$$\begin{aligned}
& \beta \int_0^{t_f} e^{\lambda t} \left(\frac{p_1 p_2}{1 + c_0 p_5 e^{\lambda t}} - \frac{\bar{p}_1 \bar{p}_3}{1 + c_0 \bar{p}_3 e^{\lambda t}} \right) (p_1 - \bar{p}_1) dt \\
& = \beta \int_0^{t_f} e^{\lambda t} \left(\frac{p_1 p_2 - \bar{p}_1 \bar{p}_2}{(1 + c_0 p_5 e^{\lambda t})(1 + c_0 p_5 e^{\lambda t})} \right) (p_1 - \bar{p}_1) dt \\
& + \beta c_0 \int_0^{t_f} e^{2\lambda t} \left(\frac{p_1 p_3 \bar{p}_5 - \bar{p}_1 \bar{p}_3 p_5}{(1 + c_0 p_5 e^{\lambda t})(1 + c_0 p_5 e^{\lambda t})} \right) (p_1 - \bar{p}_1) dt \\
& \leq (c_1 e^{\lambda t_f} + c_2 e^{2\lambda t_f}) \int_0^{t_f} [(p_1 - \bar{p}_1)^2 + (p_3 - \bar{p}_3)^2 + (p_5 - \bar{p}_5)^2] dt, \tag{44}
\end{aligned}$$

$$\begin{aligned} & \omega \int_0^{t_f} e^{2\lambda t} (p_1 p_3 p_4 - \bar{p}_1 \bar{p}_3 \bar{p}_4) (p_1 - \bar{p}_1) dt, \\ & \leq c_3 e^{2\lambda t_f} \int_0^{t_f} [(p_1 - \bar{p}_1)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2] dt, \end{aligned} \quad (45)$$

$$\begin{aligned} & r^{\mu_y} \int_0^{t_f} \left(\frac{(1 - \gamma^*) p_2}{1 + c_1 p_4 e^{\lambda t}} - \frac{(1 - \bar{\gamma}^*) \bar{p}_2}{1 + c_1 \bar{p}_4 e^{\lambda t}} \right) (p_3 - \bar{p}_3) dt \\ & \leq c_4 e^{2\lambda t_f} \int_0^{t_f} [(p_1 - \bar{p}_1)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (q_3 - \bar{q}_3)^2] dt. \end{aligned} \quad (46)$$

This shows uniqueness and the combination of the integrals produces

$$\begin{aligned} & \frac{1}{2} (p_1 - \bar{p}_1)^2(t_f) + \frac{1}{2} (p_2 - \bar{p}_2)^2(t_f) + \frac{1}{2} (p_3 - \bar{p}_3)^2(t_f) + \frac{1}{2} (p_4 - \bar{p}_4)^2(t_f) \\ & + \frac{1}{2} (p_5 - \bar{p}_5)^2(t_f) + \frac{1}{2} (q_1 - \bar{q}_1)^2(0) + \frac{1}{2} (q_2 - \bar{q}_2)^2(0) \\ & + \frac{1}{2} (q_3 - \bar{q}_3)^2(0) + \frac{1}{2} (q_4 - \bar{q}_4)^2(0) + \frac{1}{2} (q_5 - \bar{q}_5)^2(0) \\ & + \lambda \int_0^{t_f} [(p_1 - \bar{p}_1)^2 + 2(p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2 \\ & \quad + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2] dt \\ & \leq (\lambda - \hat{C}_1 - \hat{C}_2 e^{3\lambda t_f}) \\ & \quad \times \int_0^{t_f} [(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2] dt \\ & \quad + \int_0^{t_f} [(q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2] dt. \end{aligned} \quad (47)$$

Thus, from the expression (47), using the non-negativity of the variable expressions evaluated at the initial and the final time and simplifying, the inequality is reduced to

$$\begin{aligned} & (\lambda - \hat{C}_1 - \hat{C}_2 e^{3\lambda t_f}) \int_0^{t_f} [(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 \\ & \quad + (p_5 - \bar{p}_5)^2 + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 \\ & \quad + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2] dt \leq 0, \end{aligned} \quad (48)$$

where \hat{C}_1 , and \hat{C}_2 depend on the coefficients and the bounds of $p_1, p_2, p_3, p_4, p_5, q_1, q_2, q_3, q_4, q_5$. If λ is chosen such that $\lambda > \hat{C}_1 + \hat{C}_2$ and $t_f < \frac{1}{3\lambda} \ln(\frac{\lambda - \hat{C}_1}{\hat{C}_2})$, then $p_1 = \bar{p}_1, p_2 = \bar{p}_2, p_3 = \bar{p}_3, p_4 = \bar{p}_4, p_5 = \bar{p}_5, q_1 = \bar{q}_1, q_2 = \bar{q}_2, q_3 = \bar{q}_3, q_4 = \bar{q}_4, q_5 = \bar{q}_5$. Hence the solution is unique for small time. \square

The uniqueness for a small time interval is usual in “two-point” boundary value problems due to opposite time orientations; the state equations have initial conditions and the adjoint equations have final time conditions. The optimal control $\gamma(t)^*$ are characterized in terms of the unique solution of the optimality system. The above optimal controls give an optimal treatment strategy for the malaria infected patient under treatment with CQ and CP.

7 Numerical simulations

The optimality system is solved using an iterative method with Runge–Kutta fourth order scheme coded in Matlab. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then those state values are used to solve the adjoint equations backward in time, and the iterations continue until convergence.

Table 1. Table of parameters used in the model. Est means estimated.

Name	Definition	Value	Units	Reference
λ_x	Supply of RBC	41664.0	$\text{mm}^{-3}\text{day}^{-1}$	[24, 28]
σ	Rate of recruitment of RBC	0.009	day^{-1}	[24]
β	Rate of infection	0.08	$\text{mm}^{-3}\text{day}^{-1}$	[24]
c_0	Efficiency of antibodies	0.6	Scalar factor	[24]
μ_x	Death rate of RBCs	0.8	day^{-1}	[24]
u_y	Death rate of IRBCs	1.0	day^{-1}	[24]
k_y	Immunosensitivity of IRBC	0.9	day^{-1}	[24]
k_m	Rate at which RBCs are eliminated	1.2×10^{-5}	$\text{mm}^{-3}\text{day}^{-1}$	[24]
r	Merozoites released per each bursting	16.0	Scalar factor	[24, 29, 30]
c_1	Parasite production suppression	0.85	day^{-1}	[24]
μ_m	Death rate of merozoites	3.0	day^{-1}	[24]
λ_b	Supply rate of immune cells	30.0	$\text{mm}^{-3}\text{day}^{-1}$	[24]
p_y	Immunogenicity of IRBCs	0.05	$\text{mm}^{-3}\text{day}^{-1}$	[24].
p_m	Immunogenicity of merozoites	0.05	day^{-1}	[24]
K_0	Immune cells stimulation constant	2000.0	Scalar factor	[24]
K_1	Immune cells stimulation	1500.0	Scalar factor	[24]
μ_b	Death rate of immune cells	1.53	$\text{mm}^{-3}\text{day}^{-1}$ Scalar	[24]
μ_a	Decay of antibodies	0.4	day^{-1}	[24]
η	Rate of increase of antibodies	0.6	mm^{-3} Scalar	[24]

We carry simulations to determine the impact of systemic costs and drug percentage usage on the treatment strategy. Simulations in Fig. 1 were aimed to find out the impact of a treatment scheme that has varying levels of merozoite population suppression with fixed systemic cost weights. The investigation (Fig. 2) also, aimed to explore a scheme

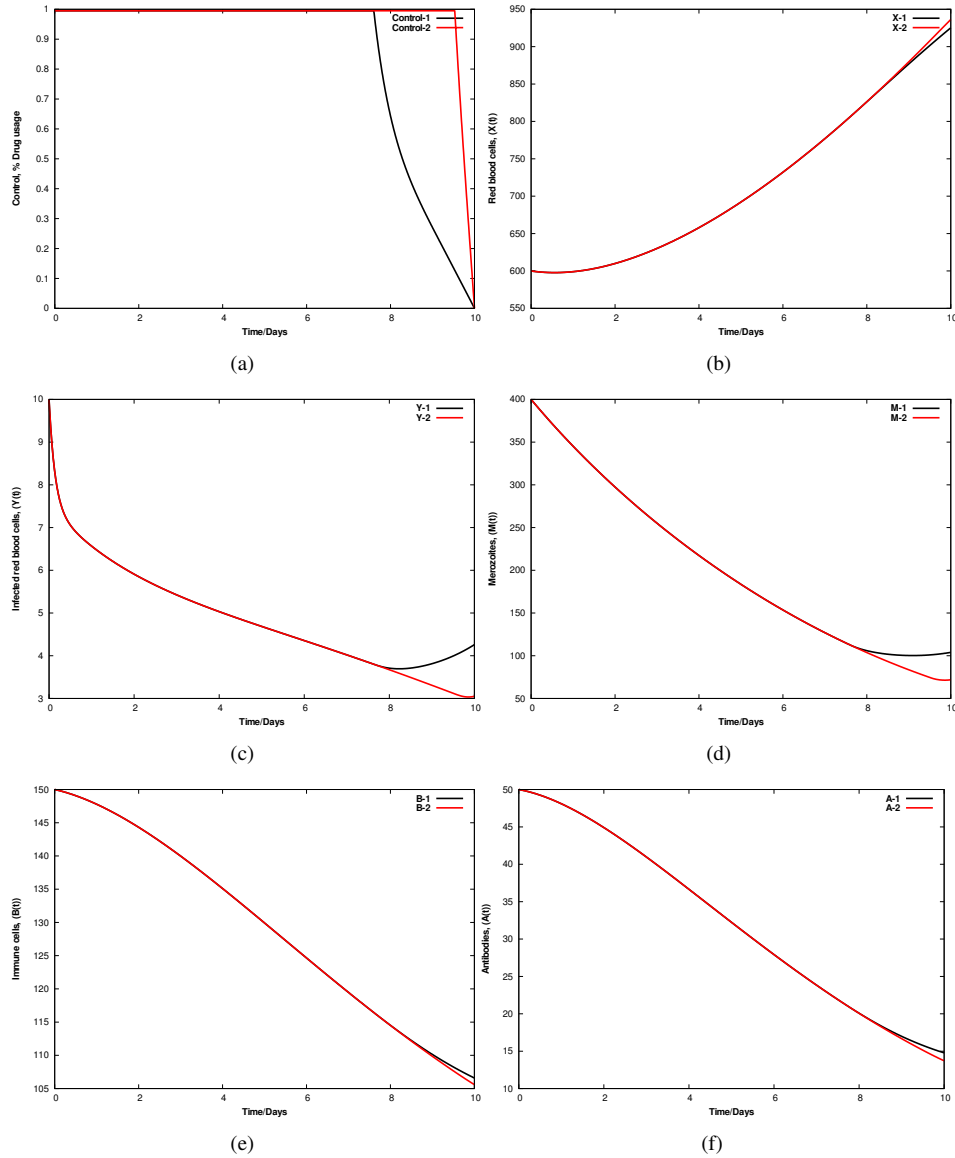


Fig. 1. Graphs of the numerical solutions to the optimality system, showing propagation of the (a) % drug usage, (b) red blood cells, (c) infected red blood cells, (d) merozoites, (e) immune cells, and (f) antibodies when treatment is administered for 10 days. Initial conditions when treatment is initiated are: $X(0) = 600.0$, $Y(0) = 10.0$, $M(0) = 400.0$, $B(0) = 150.0$, $A(0) = 50$. The value of the weights used are (i) $G_1 = 1.25$, $G_2 = 75.0$ for Control-1, X-1, Y-1, M-1, B-1 and A-1, (ii) $G_1 = 12.5$, $G_2 = 75.0$ for Control-2, X-2, Y-2, M-2, B-2 and A-2.

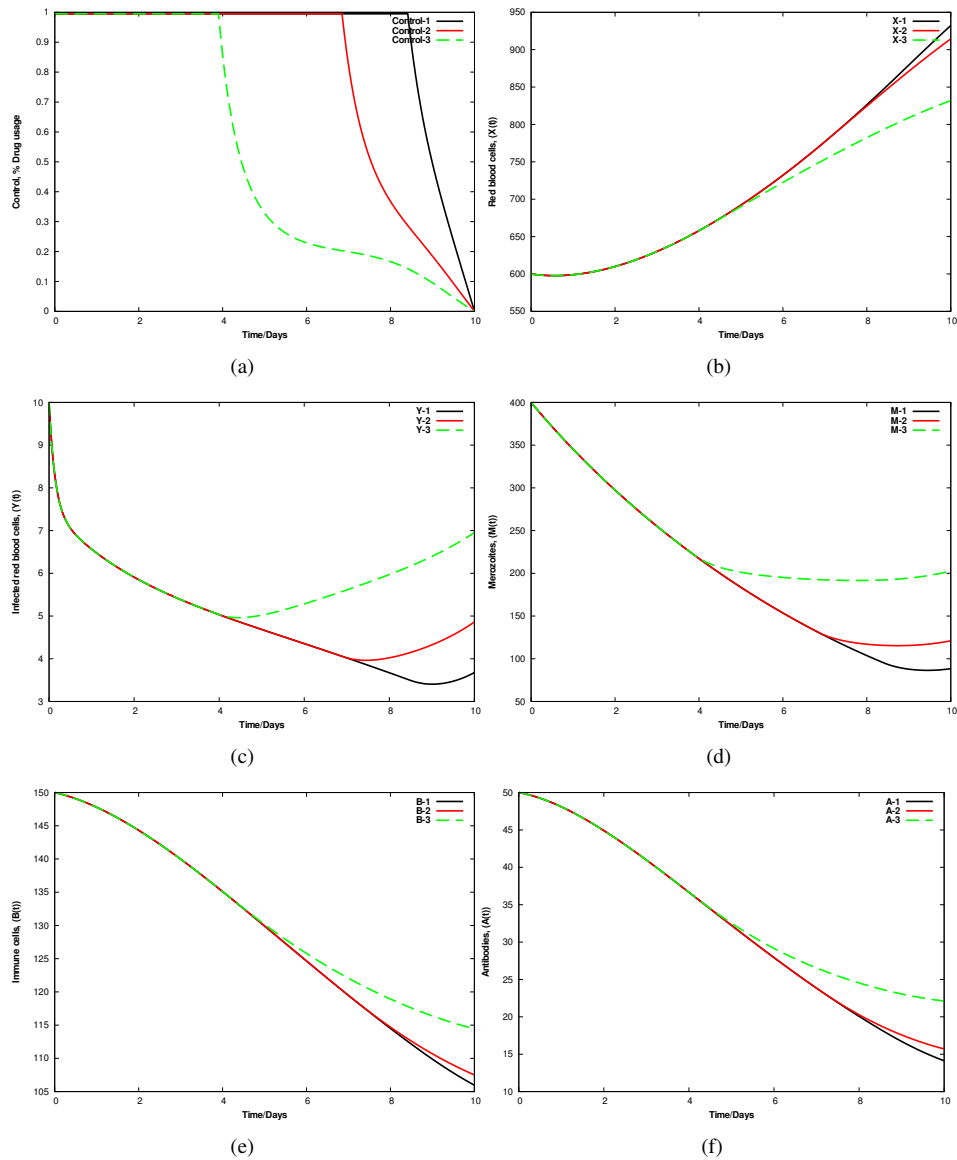


Fig. 2. Graphs of the numerical solutions to the optimality system, showing propagation of (a) % drug usage, (b) red blood cells, (c) infected red blood cells, (d) merozoites, (e) immune cells, and (f) antibodies when treatment is administered for 10 days. Initial conditions when treatment is initiated are: $X(0) = 600.0$, $Y(0) = 10.0$, $M(0) = 400.0$, $B(0) = 150.0$, $A(0) = 50$. The value of the weights used are (i) $G_1 = 2.5$, $G_2 = 75.0$ for Control-1, X-1, Y-1, M-1, B-1 and A-1, (ii) $G_1 = 2.5$, $G_2 = 250.0$ for Control-2, X-2, Y-2, M-2, B-2 and A-2, and (iii) $G_1 = 2.5$, $G_2 = 750.0$ for Control-3, X-3, Y-3, M-3, B-3 and A-3.

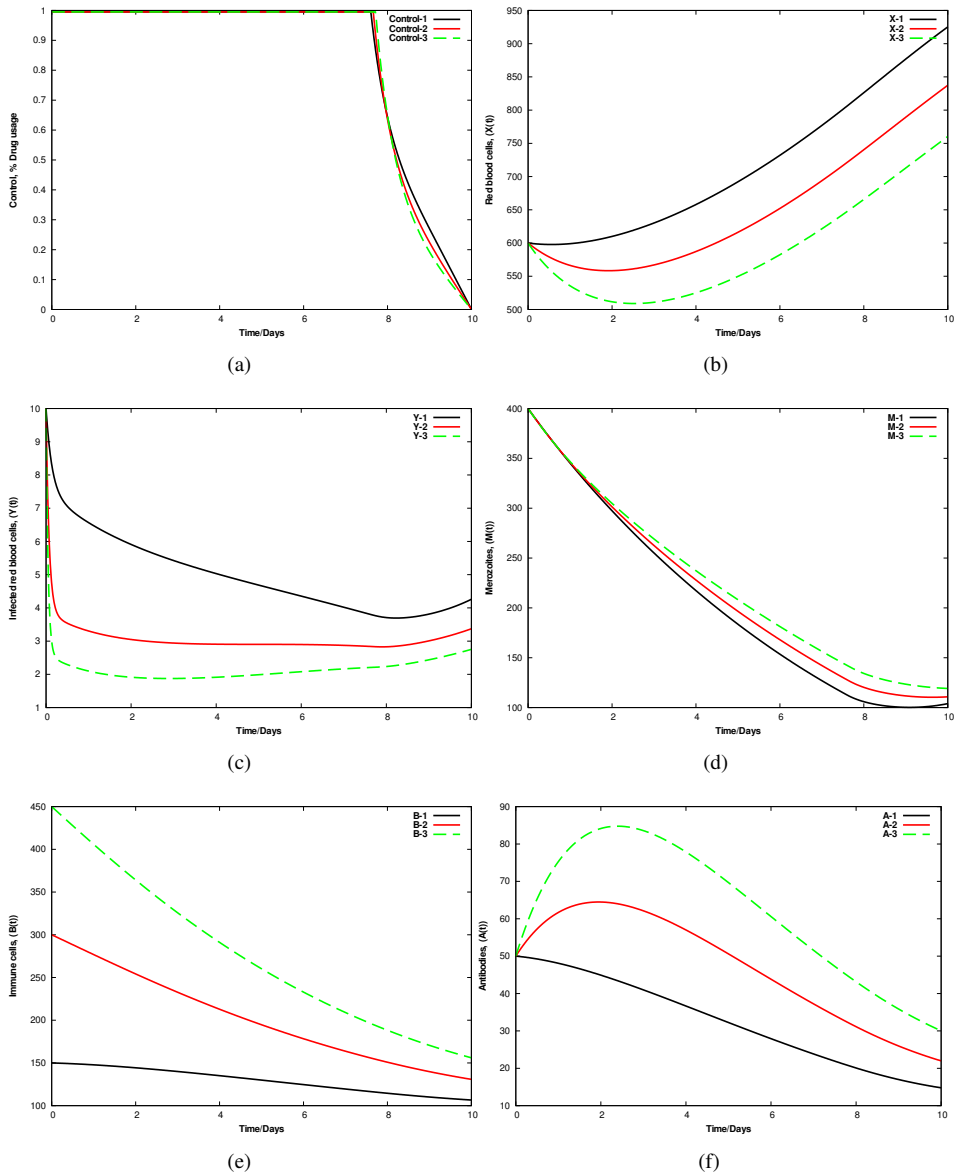


Fig. 3. Graphs of the numerical solutions to the optimality system, showing propagation of (a) % drug usage, (b) red blood cells, (c) infected red blood cells, (d) merozoites, (e) immune cells, and (f) antibodies when treatment is administered for 10 days. Initial conditions when treatment is initiated are: $X(0) = 600.0$, $Y(0) = 10.0$, $M(0) = 400.0$, $A(0) = 50$, $G_1 = 1.25$, $G_2 = 75.0$. With (i) $B(0) = 150.0$ for Control-1, X-1, Y-1, M-1, B-1 and A-1, (ii) $B(0) = 300.0$ for Control-2, X-2, Y-2, M-2, B-2 and A-2, and (iii) $B(0) = 450.0$ for Control-3, X-3, Y-3, M-3, B-3 and A-3.

with a fixed merozoite population suppression, which probe the effect of different systemic cost weights. And then to ascertain if initial disease conditions has a contributing factor in determining a treatment scheme. In Fig. 1 we fix the value of G_2 at 75.0 (the weight of the optimal control) and vary the weight of merozoites (G_1) from 1.25 to 12.5 in the objective functional. In Fig. 2 three values (75.0, 250.0, and 750.0) of G_2 are used while the value of G_1 is fixed at 2.5 and in Fig. 3 three initial values (150.0, 300.0, and 450.0) of immune cells (B) are used with G_1 and G_2 fixed at 1.25 and 75.0, respectively.

In Fig. 1, increasing G_1 from 1.25 to 12.5 achieves maximal drug administration close to 10 days with out early withdrawal of therapy, while when the value G_1 is equivalent to 1.25, therapy is continuous within the first 8 days after which therapy is tapped off. Increasing the value of G_1 implies increasing the minimisation of merozoites in the objective functional. This effect is accompanied by reduction in infected red blood cells and merozoites while red blood cells are boosted. Contrary, fixing G_1 and increasing G_2 (in Fig. 2), that is increasing treatment systemic costs of malarial drugs or if the adverse effects are increased forces treatment to be withdrawn early. The effects of increasing the weight G_2 are counteracted by increasing G_1 , hence suggesting that a therapy with high systemic costs combined with the high potential to suppress merozoites could be administered for a longer time. This has more benefits than a strategy with high systemic costs but with low suppression of merozoites. Fig. 3 suggests that starting with different amounts of immune cells does not significantly affect treatment schedule, drug percentage usage and treatment interval but affect levels of red blood cells (infected and uninfected) and merozoites. It is expected that as immune cells are increased then merozoites will be reduced, but here, results suggest that as the immune cells are increased only the levels of antibodies are increased, this propels the reduction of infected red blood cells. However, the rate of recovery of uninfected red blood cells is slow as well as the clearance of merozoites.

This study suggests that a malarial therapy that seeks to minimise merozoites population with less side effects is more beneficial to patients. Also a treatment scheme with high systemic costs but with high suppression of merozoite reproduction has the potential to give positive treatment results since high merozoite suppression seems to compensate for high systemic costs. However, a treatment scheme that seeks to maximise the immune cells does not significantly improve the treatment of malaria.

8 Conclusion

Recently, optimal control studies [31, 32] addressed optimal control strategies of malaria in a population. Okosun et al. [32] derived conditions under which it is optimal to eradicate the disease and examine the impact of a possible combined vaccination and treatment strategies on the disease transmission. The study [31], predicated factors that are critical in the transmission of malaria in a population (the contact rate and the biting rate). Their optimal scheme expored the effectiveness of spraying of insecticides in a population and the contribution of immigrants to the spread of malaria. They showed that immigrants have no significant contribution to the spread of the disease.

In this study, we used techniques and ideas of optimal control to design malaria treatment therapy protocols in the human body, unlike in the rest of the studies that looked at malaria transmission and treatment in a human population. We presented a malaria immune model and then constructed an optimal problem with an objective to maximise immune cell benefits and minimise the merozoite population and treatment systemic costs. We derived optimal treatment schemes by solving the optimality system. Results in this study suggest that administration of malarial drugs with less adverse effects and high suppression of merozoites or administration of malaria therapy with high systemic costs and high suppression of merozoites might be beneficial to malaria patients.

Acknowledgments

GM is supported by the University of Cape Town, Health Science Faculty and also thanks Prof. S. Lenhart for optimal control materials.

References

1. D. Butler, J. Maurice, C. O'Brien, Time to put malaria on global agenda, *Nature*, **386**, pp. 535–536, 1997.
2. I. Angulo, M. Frenso, Cytokines in the pathogenesis of and protection against malaria, *Clin. Diagn. Lab. Immunol.*, **9**(6), pp. 1145–1152, 2002.
3. R. Chattopadhyay, A. Sharma, V.K. Srivastava, S.S. Pati, S.K. Sharma, B.S. Das, C.E. Chitnis, *Plasmodium falciparum* infection elicits both variant-specific and cross-reactive antibodies against variant surface antigens, *Infect. Immunol.*, **71**(2), pp. 597–607, 2003.
4. K. Artavanis-Tsakonas, J.E. Tongren, E.M. Riley, The war between the malaria parasite and the immune system: immunity, immunoregulation and immunopathology: Review, *Clin. Exp. Immunol.*, **133**, pp. 145–152, 2003.
5. D. Dodoo, F.M. Omer, J. Todd, B.D. Akanmori, K.A. Koram, E.M. Riley, Absolute levels and ratios of proinflammatory and anti-inflammatory cytokine production in vitro predict immunity to *plasmodium falciparum* malaria, *J. Infect. Dis.*, **185**, pp. 971–9, 2002.
6. D.L. Doolan, S.L. Hoffman, IL-12 and NK Cells are required for antigen-specific adaptive immunity against malaria initiated by CD8+ T cells in the *Plasmodium yoelii* model, *J. Immunol.*, **163**, pp. 884–892, 1999.
7. M. Hensmann, D. Kwiatkowski, Cellular basis of early response to *plasmodium falciparum*, *Infect. Immunol.*, **69**(4), pp. 2364–2371, 2001.
8. E.O. Farombi, Y.Y. Shyntum, G.O. Emerole, Influence of chloroquine treatment and *plasmodium falciparum* malaria infection on some enzymatic and non-enzymatic defense indices in humans, *Drug. Chem. Toxicol.*, **26**(1), pp. 59–71, 2003.
9. Guidelines for the treatment of malaria, World Health Organization, 2006.
10. N.J. White, Drug resistance in malaria, *Brit. Med. Bull.*, **54**(3), pp. 703–715, 1998.

11. B.M. Admas et al., Dynamic multidrug therapies for HIV: Optimal and STI control approaches, *Math. Biosci. Eng.*, **1**(2), pp. 22–241, 2004.
12. K.R. Fister, S. Lenhart, J.S. McNally, Optimizing chemotherapy in an HIV model, *Electron. J. Differ. Equ.*, **32**, pp. 1–12, 1998.
13. W. Garira, S.D. Musekwa, T. Shiri, Optimal control of combined therapy in a single strain HIV-1 model, *Electron. J. Differ. Equ.*, **52**, pp. 1–22, 2005.
14. H.R. Joshi, Optimal control of an HIV immunology model, *Optim. Control Appl. Methods*, **23**, pp. 199–213, 2002.
15. E. Jung, S. Lenhart, Z. Feng, Optimal control of treatments in a two-strain tuberculosis model, *Discrete Contin. Dyn. Syst., Ser. B*, **2**(4), pp. 473–482, 2002.
16. J. Karrakchou, M. Rahik, S. Gourari, Optimal control and infectiology: Application to an HIV/AIDS model, *Appl. Math. Comput.*, **177**, pp. 807–818, 2006.
17. D. Kirschner, G.F. Webb, A model for treatment strategy in the chemotherapy of AIDS, *Bull. Math. Biol.*, **58**(2), pp. 367–390, 1996.
18. D. Kirschner, G.F. Webb, A mathematical model of combined drug therapy of HIV infection, *J. Theor. Med.*, **1**, pp. 25–34, 1997.
19. H. Kwon, Optimal treatment strategies derived from a HIV model with drug resistant mutants, *Appl. Math. Comput.*, **188**(2), pp. 1193–1204, 2007.
20. S. Lenhart, J. Workman, *Optimal Control Applied to Biological Models*, Mathematical and Computational Biology, Chapman & Hall/CRC, 2007.
21. G. Magomedze, Recent progress in infectious disease modelling. With-in host modeling: Their complexities and limitations. A short communication, in: J.M. Tchuente, Z. Mukandavire (Eds.), *Advances in Disease Epidemiology*, Nova Science Publishers, New York, 2009, pp. 253–260.
22. G. Magomedze, Z. Mukandavire, C. Chiyaka, G. Musuka, Optimal control of an HIV heterosexual transmission model with condom use, *Math. Model. Anal.*, **14**(4), pp. 483–494, 2009.
23. G. Magomedze, W. Garira, E. Mwenje, C.P. Bhunu, Optimal control for HIV-1 triple therapy, *Int. J. Comput. Math.*, **88**(2), pp. 314–340, 2011.
24. C. Chiyaka, W. Garira, S. Dube, Modelling immune response and drug therapy in human malaria infection, *Comput. Math. Methods Med.*, **9**(2), pp. 143–163, 2008.
25. W.H. Fleming, R.W. Rishel, *Deterministic and Stochastic Optimal Control*, Springer, New York, 1975.
26. L.D. Lukes, *Differential Equations: Classical to Controlled*, Math. Sci. Eng., Vol. 162., Academic Press, New York, 1982.
27. L.S. Pontryagin, V.T. Boltyanskii, R.V. Gamkrelidze, E.F. Mishcheuko, *L.S. Pontryagin Selected Works, IV. The Mathematical Theory of Optimal Processes*, Class. Sov. Math., Gordon & Breach Science Publishers, New York, 1986.

28. R.M. Anderson, R.M. May, S. Gupta, Non-linear phenomena in host-parasite interactions, *Parasitology*, **99**, pp. S59–S79, 1989.
29. I.A. Clark, J.L. Virelizier, E.A. Carswell, P.R. Wood, Possible importance of macrophage-derived mediators in acute malaria, *Infect. Immun.*, **32**, pp. 1058–1066, 1981.
30. M.M. Elloso, H.C. van der Heyde, J.A. vande Waa, D.D. Manning, W.P. Weidanz, Inhibition of *Plasmodium falciparum* in vitro by human gamma delta T cells, *J. Immunol.*, **153**, pp. 1187–1194, 1994.
31. O.D. Makinde, K.O. Okosun, Impact of chemo-therapy on optimal control of malaria disease with infected immigrants, *Biosystems*, **104**, pp. 32–41, 2011.
32. K.O. Okosun, R. Ouifki, N. Marcus, Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity, *Biosystems*, 2011, doi:10.1016/j.biosystems.2011.07.006.