11th World Congress on Computational Mechanics (WCCM XI)
5th European Conference on Computational Mechanics (ECCM V)
6th European Conference on Computational Fluid Dynamics (ECFD VI)
E. Oñate, J. Oliver and A. Huerta (Eds)

# OPTIMAL CONTROL OF TWO AGE STRUCTURED MALARIA MODEL WITH MODEL PARAMETER UNCERTAINTY

**GASPER G. MWANGA[†] AND HEIKKI HAARIO[*]**

[†] Department of Mathematics and Physics
Lappeenranta University of Technology (LUT)
Box 20, FIN-53851, Lappeenranta, Finland
e-mail: mwanga.gasper@gmail.com

[*] Department of Mathematics and Physics
Lappeenranta University of Technology (LUT)
Box 20, FIN-53851, Lappeenranta, Finland
e-mail: heikki.haario@lut.f

**Key words:** Malaria, asymptomatic malaria, Optimal control, Parameter uncertainty.

**Abstract.** Mathematical models usually involve parameters which are to be estimated from noisy measurements. Furthermore, a common pitfall for many epidemiological models is the absence of real data; model-based conclusions have to be based on uncertain parameter values, often available from literature only, without reliable uncertainty quantification. These uncertainties propagate into any conclusions based on modeling. Here we study the robustness of optimal control under such parameter uncertainty, using a two-age-classes mathematical model of malaria transmission with asymptomatic malaria carriers. The model incorporates four controls: the use of Long Lasting Insecticide Nets, indoor residual spraying, treatment of symptomatic and asymptomatic individuals. For a given model simulation we generate the synthetic noisy data so that a plausible variability of the epidemiological dynamics is covered. By Markov chain Monte Carlo (MCMC) simulations this variability is mapped to model parameter distributions. The optimal control algorithm is then run using different parameter values sampled from the MCMC parameter posterior. Here we study different ways of implementing this approach and demonstrate by numerical simulations the robustness of control: the main conclusions of the optimal control remain unchanged, even if inevitable variability remains in the control profiles provided that there is effective control scenario. The results provide a promising framework for the designing of cost-effective strategies for disease controls with multiple interventions, even under considerable uncertainty of model parameters.

## 1 INTRODUCTION

This paper propose a two-age-classes (child and adult) model of malaria transmission with asymptomatic carrier to study the effect of different control practices using an optimal control approach. Contrast from other existing papers which applied optimal control to malaria transmission models (see., e.g, [1]), we use an age structured model since disease morbidity, mortality, and severity of infections differ across the age profile. Furthermore, the control policies and the impact of the control measure which may be optimal for a specific age group may not necessarily be directly applicable to the other age group. Nevertheless, epidemiological models are often plagued with poorly known parameter values. The objective of the current work is to apply an optimal control approach to study combinations of different control strategies to prevent and control malaria, together with an uncertainty quantification of the optimal control results.

We first start with the formulation of the mathematical model. Secondly, we present the analysis of the parameter uncertainties using Markov chain Monte Carlo (MCMC) method. Finally, we study the robustness of optimal control in the presence of parameter uncertainties. We run the optimal control algorithm several times for different parameter values sampled from the MCMC posterior. Another option, aimed at minimizing the CPU costs, is to run the optimal control algorithm using a few 'extreme' points of the parameter posterior distribution extracted by the principal component analysis (PCA) method.

## 2 DESCRIPTION OF THE MODEL

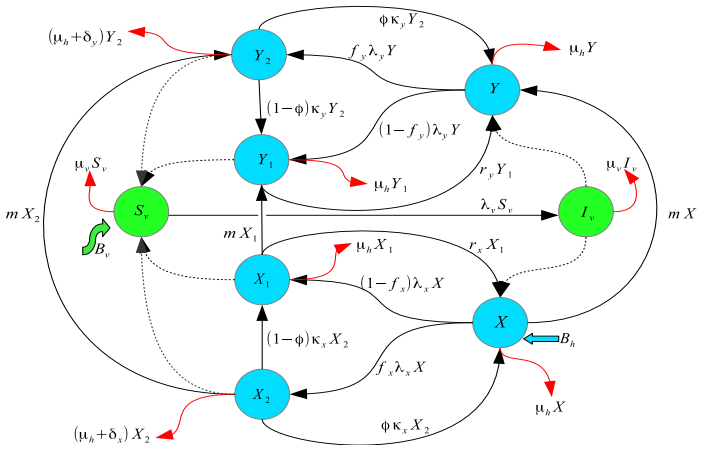


**Figure 1**: The flux diagram illustrating the transmission of malaria parasites in humans and mosquitoes. X and Y represents susceptible child and adult humans respectively while subscript 1 and 2 represents asymptomatic and symptomatic infection respectively. $S_v$ and $I_v$ denotes susceptible and infectious mosquitoes respectively. The dotted line represents infection while the continuous line represents the constant transition rates between different compartments.

The model developed in this paper combines two sub-models, the vectorial dynamics and the human host dynamics. The adult female mosquitoes are categorized into uninfected (susceptible) mosquitoes, $S_v$ and the infected mosquitoes, $I_v$. Therefore the total mosquito population $N_v = S_v + I_v$. Since the interest of the model is to study the effect of various interventions to control the spread of malaria, we assume that the vector population is comprised of only female Anopheles mosquitoes.

The total human population $N_h$ is divided into six classes: susceptible children ($X$), susceptible adults ($Y$), asymptomatic infected children ($X_1$), symptomatic infected children ($X_2$), asymptomatic infected adults ($Y_1$) and symptomatic infected adults ($Y_2$). Hence, $N_h = X+X_1+X_2+Y+Y_1+Y_2$. The human hosts are recruited in the susceptible children subpopulation at a density dependent birth rate $B_h = \Lambda_h N_h$. Thus, we assume there is no immigration of humans in the population. The malaria transmission rate from infected mosquitoes to susceptible human is defined as, $\lambda_i = (1 - \alpha_i u_1)\beta_h I_v$ and from infected humans to susceptible mosquitoes as $\lambda_v = \beta_v[(1 - \alpha_x u_1)(X_1 + X_2) + (1 - \alpha_y u_1)(Y_1 + Y_2)]$ where $i = x, y$ denoting children and adults respectively. $\beta_h = ba/N_h$ where, $a$ denotes the rate of mosquito bites and $b$ denotes the probability that an individual acquire infection from a bite. $u_1(t) \in [0, 1]$ is the time dependent control effort for the use of Long Lasting Insecticide Nets (LLINs) to protect individuals from mosquito bites and $\alpha_i$ is the measure of the effectiveness of LLINs in protecting children ($i = x$) and adults ($i = y$). $\beta_v = ca/N_h$ where $c$ is the probability that a mosquito acquire malaria parasite (gametocytes) from biting an infectious individual.

The model further assumes that upon infection a proportion, $f_i$, of infected human are symptomatic and the remain proportion, $1 - f_i$ are asymptomatic. The natural mortality rate of humans is denoted by $\mu_h$. The disease induced death rate for symptomatic individuals is denoted as $\delta_i$. In addition regardless of the infection status the rate of progress from childhood to adulthood is assumed to be $m$.

The model further assumes that the individuals in the symptomatic infectious state clears malaria parasite to enter susceptible class at the rate $\phi\kappa_i$ and the remaining fraction $(1 - \phi)\kappa_i$ enters the asymptomatic class. Here $\kappa_i = r_i + u_2(t)\rho$, where $r_i$ is the naturally clearance rate and $u_2(t)\rho$ is the clearance rate after taking chemotherapy. $u_2(t) \in [0, 1]$ is the time dependent treatment effort of symptomatic individuals with drugs of efficacy $\rho$. It is assumed that due to the fact that adult individuals living in malaria endemic regions acquires immunity which is capable of clearing the infections then $r_x < r_y$. The asymptomatic individual clears infection at the rate $\eta_i = \nu_i + u_3(t)\rho$, where $1/\nu_i$ is the longevity of asymptomatic infection ( $1/\nu_y > 1/\nu_x$ , due to acquisition of immunity) and $u_3(t) \in [0, 1]$ is the time dependent control for screening and treating asymptomatic infected individuals.

Finally, the life expectancy of the mosquitoes is given as $1/d_m$. $d_m = \mu_v + \alpha_v u_4(t)$ where, $u_4(t) \in [0, 1]$ is the mosquito adulticide effort using Indoor Residual Spraying (IRS) with killing efficacy $\alpha_v$; and $\mu_v$ is the natural mortality rate of the mosquitoes.

The compartmental mathematical model for malaria transmission and control is rep-

resented by the following system of non-linear ordinary differential equations:

$$\begin{aligned}
\frac{\mathrm{d}X}{\mathrm{d}t} &= \Lambda_h N_h + (\nu_x + \rho u_3)X_1 + \phi(r_x + u_2\rho)X_2 - \lambda_x X - (m + \mu_h)X, \\
\frac{\mathrm{d}X_1}{\mathrm{d}t} &= (1 - f_x)\lambda_x X + (1 - \phi)(r_x + u_2\rho)X_2 - (m + \nu_x + u_3\rho + \mu_h)X_1, \\
\frac{\mathrm{d}X_2}{\mathrm{d}t} &= f_x\lambda_x X - (m + r_x + u_2\rho + \mu_h + \delta_x)X_2, \\
\frac{\mathrm{d}Y}{\mathrm{d}t} &= mX + (\nu_y + u_3\rho)Y_1 + \phi(r_y + u_2\rho)Y_2 - \lambda_y Y - \mu_h Y, \\
\frac{\mathrm{d}Y_1}{\mathrm{d}t} &= (1 - f_y)\lambda_y Y + (1 - \phi)(r_y + u_2\rho)Y_2 + mX_1 - (\nu_y + u_3\rho + \mu_h)Y_1, \\
\frac{\mathrm{d}Y_2}{\mathrm{d}t} &= f_y\lambda_y Y + mX_2 - (r_y + u_2\rho + \mu_h + \delta_y)Y_2, \\
\frac{\mathrm{d}S_v}{\mathrm{d}t} &= \Lambda_v N_v - \lambda_v S_v - (\mu_v + \alpha_v u_4)S_v, \\
\frac{\mathrm{d}I_v}{\mathrm{d}t} &= \lambda_v S_v - (\mu_v + \alpha_v u_4)I_v.
\end{aligned} \tag{1}$$

## 3 APPLICATION OF OPTIMAL CONTROL TO THE MODEL

The goal of the application of optimal control is to minimize the number of humans infected with malaria while keeping the costs of control as low as possible. To achieve this objective we must incorporates relative costs associated with each policy (control) or combination of policies directed towards controlling the spread of malaria. We define the objective function as

$$J = \min_{u \in \Gamma} \int_0^T G(t, u, v)dt; \tag{2}$$

subject to the state system defined in equation (1). Here $v$ is the solution of state system (1) computed at a control value $u$. In precise we define $G(t, u, v) = g(t, u, v) + h(t, u)$. The use of LLINs control protects both infected and susceptible humans while the treatment effort $u_2(t)\rho$ acts on symptomatic individuals who normally reports at the healthy facilities and the control effort $u_3(t)\rho$ focuses on the screening and treatment of asymptomatic individual. Let $C_{d1}$, $C_{d2}$ and $C_p$ be the individual costs of treatment of symptomatic individuals, screening and treatment of asymptomatic individuals, and using LLINs respectively. Furthermore, let $A_1$ and $A_2$ be the relative weights of asymptomatic and symptomatic infections respectively. Then $g(t, u, v)$ is written as follows;

$$g(t, v, u) = A_1(X_1 + Y_1) + A_2(X_2 + Y_2) + C_p u_1 N_h + C_{d1} u_2(X_2 + Y_2) + C_{d2} u_3(X_1 + Y_1). \tag{3}$$

The function $h(t, u)$ is chosen to have a quadratic cost on the controls as is done in other epidemiological models with controls (see., e.g, [1]). Thus,

$$h(t, u) = \frac{1}{2}\sum_{j=1}^{4} W_j u_j(t)^2, \tag{4}$$

where, $W_j$ is the weight constant associated with the control measure $u_j$. Our goal is to find the optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{u_1,u_2,u_3,u_4 \in \Gamma} J(u_1, u_2, u_3, u_4), \tag{5}$$

for $\Gamma = \{(u_1, u_2, u_3, u_4)$ such that $u_1, u_2, u_3, u_4$ are measurable with $0 \leq u_j \leq 1$, for $t \in [0, T], j = 1, 2, 3, 4\}$ subject to the state system given in equation (1). If we write the state system (1) as $\dot{v} = M(t, u(t), v(t))$ together with equations (2) to (4); following the Pontryagings Maximum Principle [2], the Hamiltonian function $\mathcal{H}$ is written as

$$\mathcal{H}(t, v, u, z) = G(t, u, v) + M(t, u, v)Z, \tag{6}$$

where $Z$ is the adjoint variable.

Hence, taking the negative derivative of a Hamiltonian function $\mathcal{H}$ with respect to the state variables results to a costate (or adjoint) system. That is, from Eqn (6)

$$\dot{Z} = -\mathcal{H}_v(t, v, u, z); \quad Z(T) = 0. \tag{7}$$

Thus we obtain the following costate system

$$\begin{aligned}
\dot{Z}_1 =& - C_p u_1 - \lambda_x(x-1)[Z_1 - (1-f_x)Z_2 - f_x Z_3] + (m + \mu_h - \Lambda_h)Z_1 - mZ_4 \\
& - \lambda_y y[Z_4 - (1-f_y)Z_5 - f_y Z_6] + \lambda_m S_v[Z_8 - Z_7], \\
\dot{Z}_2 =& - A_1 - C_p u_1 - C_{d2} u_3 - \lambda_x x[Z_1 - (1-f_x)Z_2 - f_x Z_3] - \eta_x Z_1 + \theta_1 Z_2 \\
& - \lambda_y y[Z_4 - (1-f_y)Z_5 - f_y Z_6] - mZ_5 + [Z_7 - Z_8]S_v(\theta_{vx} - \lambda_m), \\
\dot{Z}_3 =& - A_2 - C_p u_1 - C_{d1} u_2 - \kappa_x[\phi Z_1 + (1-\phi)Z_2] + \theta_2 Z_3 - mZ_6 \\
& - \lambda_x x[Z_1 - (1-f_x)Z_2 - f_x Z_3] - \lambda_y y[Z_4 - (1-f_y)Z_5 - f_y Z_6] \\
& + [Z_7 - Z_8]S_v(\theta_{vx} - \lambda_m), \\
\dot{Z}_4 =& - C_p u_1 - \lambda_x x[Z_1 - (1-f_x)Z_2 - f_x Z_3] + (\mu_h - \Lambda_h)Z_4 + \lambda_m S_v[Z_8 - Z_7] \\
& - \lambda_y(y-1)[Z_4 - (1-f_y)Z_5 - f_y Z_6], \\
\dot{Z}_5 =& - A_1 - C_p u_1 - C_{d2} u_3 - \lambda_x x[Z_1 - (1-f_x)Z_2 - f_x Z_3] - \eta_y Z_4 + \theta_3 Z_5 \\
& - \lambda_y y[Z_4 - (1-f_y)Z_5 - f_y Z_6] + [Z_7 - Z_8]S_v(\theta_{vy} - \lambda_m), \\
\dot{Z}_6 =& - A_2 - C_p u_1 - C_{d1} u_2 - \kappa_y[\phi Z_4 + (1-\phi)Z_5] + [Z_7 - Z_8]S_v(\theta_{vy} - \lambda_m) \\
& + \theta_4 Z_6 - \lambda_x x[Z_1 - (1-f_x)Z_2 - f_x Z_3] - \lambda_y y[Z_4 - (1-f_y)Z_5 - f_y Z_6], \\
\dot{Z}_7 =& \lambda_v[Z_7 - Z_8] + (d_m - \Lambda_v)Z_7, \\
\dot{Z}_8 =& \theta_{vx} X[Z_1 - (1-f_x)Z_2 - f_x Z_3] + \theta_{vy} Y[Z_4 - (1-f_y)Z_5 - f_y Z_6] + (d_m - \Lambda_v)Z_8
\end{aligned} \tag{8}$$

with transversality condition $Z_i(T) = 0$, $i = 1, 2, \ldots 8$, where $\lambda_m = \beta_v[(1 - \alpha_x u_1)(x_1 + x_2) + (1 - \alpha_y u_1)(y_1 + y_2)]$, $\theta_1 = m + \eta_x + \mu_h - \Lambda_h$, $\theta_2 = m + r_x + u_2\rho + \mu_h + \delta_x - \Lambda_h$, $\theta_3 = \eta_y + \mu_h - \Lambda_h$, $\theta_4 = r_y + u_2\rho + \mu_h + \delta_y - \Lambda_h$, $\kappa_x = r_x + u_2\rho$, $\kappa_y = r_y + u_2\rho$,

$\eta_x = \nu_x + u_3\rho$, $\eta_y = r_y + u_3\rho$, $\theta_{vx} = (1-\alpha_x u_1)\beta_v$, $\theta_{vy} = (1-\alpha_y u_1)\beta_v$, $d_m = \mu_v + \alpha_v u_4$ and $x = X/N_h, x_1 = X_1/N_h, x_2 = X_2/N_h, y = Y/N_h, y_1 = Y_1/N_h, y_2 = Y_2/N_h$.

Finally, we obtain the gradient formula by taking the derivative of the Hamiltonian function $\mathcal{H}$ Eqn (6) with respect to the controls (see. eg. [3])

$$\nabla J(u(t)) = \mathcal{H}_u(t, v, u, z). \tag{9}$$

Applying the first order optimality condition for optimization problem, $\mathcal{H}_u(t, v, u^*, z) = 0$, $u^*$ is the optimal control. Then this lead to a linear equation which can be solved for $u_i^*$; afterward the control constraint, $0 \le u_i^* \le 1$ is applied to obtain the following characterization equation,

$$u_j^* = \max\{0, \min(1, \zeta_j)\},\ j = 1, 2, 3, 4 \tag{10}$$

$$\text{where } \zeta_1 = \frac{C_p N_h + \beta_h I_v(V_x + V_y) + \beta_v S_v(Z_7 - Z_8)[\alpha_x(X_1 + X_2) + \alpha_y(Y_1 + Y_2)]}{-W_1}$$

$$\zeta_2 = \frac{C_{d1}(X_2 + Y_2) + \rho\{X_2[\phi Z_1 + (1-\phi)Z_2 - Z_3] + Y_2[\phi Z_4 + (1-\phi)Z_5 - Z_6]\}}{-W_2}$$

$$\zeta_3 = \frac{C_{d2}(X_1 + Y_1) + \rho[X_1(Z_1 - Z_2) + Y_1(Z_4 - Z_5)]}{-W_3},\ \zeta_4 = \frac{\alpha_v[S_v Z_7 + I_v Z_8]}{W_4}.$$

with $V_x = \alpha_x X(Z_1 - (1-f_x)Z_2 - f_x Z_3)$ and $V_y = \alpha_y Y(Z_4 - (1-f_y)Z_5 - f_y Z_6)$.

## 4 NUMERICAL RESULTS AND DISCUSSION

For the numerical simulation we use the following model parameter and weights values. $\mu_h = 1/(60\times365)$ [4, 5], $r_y = 0.01-0.05$ [6, 7], $r_x = 0.5r_y$, $f_x = 0.4$, $f_y = 0.6$, $b = 0.03-0.5$ [6, 7, 8], $c = 0.09-0.5$ [6, 7, 9], $\phi = 0.8$, $a = 0.2-0.5$, [1, 7, 10], $\nu_x = 1/(180)$, $\nu_y = 1/(365)$, $\mu_v = 0.04-0.5$ [6, 12], $m = 1/(12\times365)$ [11], $\Lambda_h = \mu_h$, $\Lambda_v = 1/16$, $\delta_x = 70/(1000\times365)$, $\delta_y = 50/(1000\times365)$, $\rho = 1/80$ [5], $\alpha_x = 0.6$, $\alpha_y = 0.4$ and $\alpha_v = 1/12$. $T = 400$, $C_p = 5/T$, $C_{d1} = 10/T$, $C_{d2} = 30/T$, $W_1 = 100$, $W_2 = 60$, $W_3 = 120$, $W_4 = 150$, $A_1 = 50/T$ and $A_1 = 500/T$.

### 4.1 Model sensitivity using MCMC

To study the model sensitivity, the Markov chain Monte Carlo (MCMC) method is used. The MCMC method takes into account all the uncertainties in the data and give out all the parameterization of the model that statistically fit the data 'equally well'. That is, MCMC gives the distribution of parameter values instead of a single point estimate as is traditionally done using maximum a posteriori estimation method (MAP) like least square method. To use MCMC we need model observation (that is, data) to estimate parameters. Since we do not have real data, we generate the synthetic data. We first simulate model (1) using literature value given above, and initial state variable $X = 5000$,

$X_1 = 400$, $X_2 = 500$, $Y = 5500$, $Y_1 = 600$, $Y_2 = 500$, $S_v = 10000$, $I_v = 1500$ to produce the approximately known dynamics of malaria disease. For those parameters given in ranges, the middle value is used. Note, since the aim is to characterize the internal uncertainty structure of the model parameters, during this process all control variables are set to zero. Then the synthetic data is created by adding a relative noise to the model response to cover the plausible variability of the epidemiological dynamics of malaria. For the MCMC sampling an effective adaptive MCMC method called Delayed Rejection Adaptive Metropolis (DRAM) algorithm is used [13]. Note further that for the MCMC sampling flat priors in the ranges given above is used. The DRAM algorithm is run for 30,000 iterations. For the purpose of studying the effect of parameter uncertainty in an optimal control problem, the independent model parameters $b$, $c$, $\mu_v$, $r_x$, $r_y$, $\nu_x$, and $\nu_y$ are estimated while the rest of the parameters are fixed.

The parameter posterior distribution (or chain) and the predictive distribution of state variables for the case of zero controls, are plotted in Figures 2 and 3 respectively. Figure 2 shows that all samples mixes well from the beginning to the end of the simulation runs. Furthermore, the MCMC results revealed a strong correlation between parameters $c$ and $\mu_v$, which means neither of the parameter can be identified by itself, hence the fraction $w = c/\mu_v$ is identified (Figure 2 ). Figure 3 shows that the community is not disease-free, but there is stable endemic situation which is sensitive to the uncertainty in the model parameter values. The light gray part shows the predictive distributions for state variables calculated from MCMC samples, the bold line shows a single prediction estimated by the Least Square Method (MAP) and the red circles are synthetic data (Figure 3).

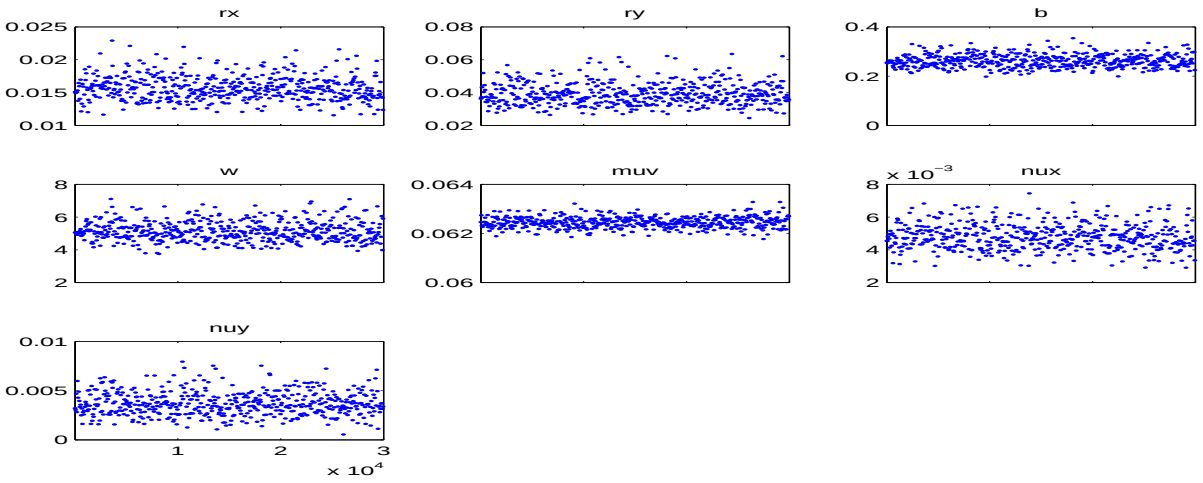


**Figure 2**: The plot of the chain for the fitted parameters for 30,000 samples shows that each chain mixes well. The vertical axis represents the parameter distribution and the horizontal axis is the number of simulation runs. Due to correlation between c and $\mu_v$, $w = c/\mu_v$ is estimated.

From various combinations of the controls, three strategies are formed and studied numerically. Strategy I, consists of the use of LLINs and treatment of symptomatic individuals,

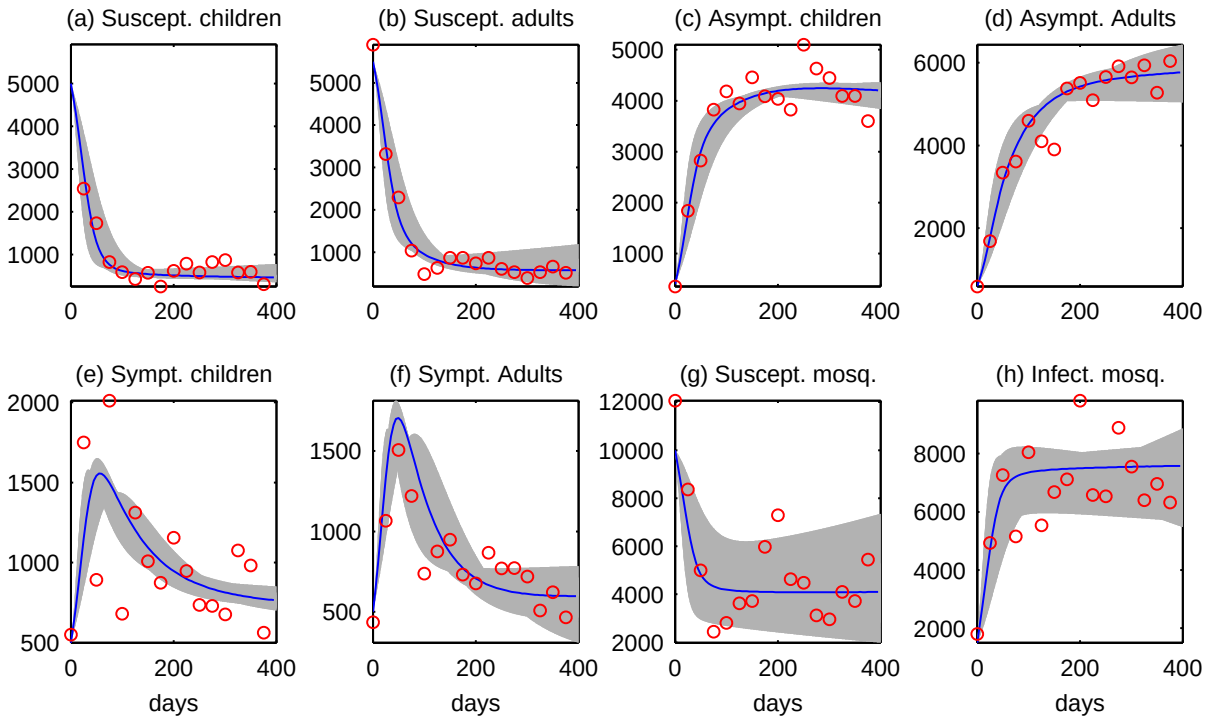


**Figure 3**: The predictive posterior distribution of state variables calculated from MCMC (light gray) and a single prediction by MAP estimate (blue bold line) for the case with no controls. The red circles are synthetic data

Strategy II combines the use of LLINs, IRS and treatment of symptomatic individuals and Strategy III combines all four controls, the use of LLINs, IRS and treatment of both symptomatic and asymptomatic individuals.

### 4.2 Numerical simulation: Optimal control with parameter uncertainty

We solve the optimality system, consisting of 16 ordinary differential equations from the state (1) and costate (8) equations, coupled with four control characterizations equations (10) in the presence of model parameter uncertainty in an iterative scheme as follows:

**Algorithm 1** : Optimal control with model parameter uncertainty

**S1:** Take a model parameter from the MCMC sub-chain selected for control runs.

**S2:** Assume a piecewise-constant control.

**S3:** Given initial condition of the state variables, simulate the state system (1) forward in time using Runge-Kutta of fourth order.

**S4:** Using transversality condition ($Z_i(T) = 0,\ i = 1, 2, \ldots, 8$), simulate the costate system (8) backward in time using Runge-Kutta of fourth order

**S5:** Update the control by entering the new state and costate solutions $\vec{v}$ and $\vec{z}$ respectively through the characterization equations (10).

**S6:** Check the stopping condition $\frac{\|\vec{v}^{i+1}-\vec{v}^{i}\|}{\|\vec{v}^{i+1}\|} < \epsilon$ if is attained; otherwise update the control using a convex combination of the current and previous control and return to S3. Here, $\vec{v}^{i}$ is the $i^{th}$ iterative solution of the state variable and $\epsilon$ is the arbitrarily small positive quantity.

**S7:** Repeat Step S1 to S6 until all parameter from the MCMC sub-chain are treated.

Selection of the parameter sample in step S1 (Algorithm 1 ) is rather a challenging task. The entire MCMC posterior parameter sample is required to reveal how model responds to the uncertainties in the parameters but this approach is expensive in terms of CPU running time. One can reduce the CPU cost by running the optimal control algorithm several times by using randomly selected parameter values from the MCMC posterior (see the gray region in Figures 4–8). To reduce further the CPU cost this paper presents an alternative approach of creating the MCMC sub-chain by using few 'extreme' points of the MCMC posterior distribution extracted by the Principal Component Analysis (PCA) method (see the dash lines in Figures 4–8). The PCA is used in such a way that the first points are at the tails of the sampled parameter distribution along the first principal axes, which captures the largest possible parameter variance. The next pair of points is taken from tails of the succeeding principal component which has the highest variance possible in a direction orthogonal to the first axes.

In Figures 4 – 8, the predictive state and control profiles calculated from the MAP estimate (solid line), randomly selected parameters (gray region) and deterministically chosen extreme points using PCA (red dash lines) from the MCMC posterior under different control strategies are compared.

**Strategy I:** The objective function is optimized by the use of LLINs control ($u_1$) and treatment of symptomatic individuals ($u_2$) only. The simulation results show that the disease persist in the community as the number of asymptomatic individuals increases

with time even though the controls are maintained at 100% throughout the control period (Figure 4). Figure 4 shows that in this control strategy, the model response is sensitive to the parameter uncertainties. This simulation results show that the use of strategy I to control malaria is not beneficial to the community.

**Strategy II:** The objective function is optimized by the use of LLINs control ($u_1$), IRS ($u_4$) and treatment of symptomatic individuals ($u_2$). With this optimal control strategy the number of mosquitoes and human with symptomatic infection decreases to zero after about 150 days of the control program but humans with asymptomatic infections persists in the community (Figure 5). The predictive distribution of state variables for asymptomatic children (Figure 5a) and adults (Figure 5b), and control profiles (Figure 7), are sensitive to the model parameter uncertainties. The results in this control scenario shows that if there is mosquito resurgence after stopping the control program will lead to rebound of malaria infection in the controlled community due to the presence of individuals with asymptomatic infection.

**Strategy III:** The objective function is optimized by the use of all four control measures: LLINs ($u_1$), treatment of symptomatic individuals ($u_2$), treatment of asymptomatic individuals ($u_3$) and use of IRS ($u_4$). In Figure 6, we observe that the control strategy resulted in a total decrease in the number of infected humans ($X_1, X_2, Y_1$ and $Y_2$) and mosquitoes ($S_v$ and $I_v$) to zero at the final time of the control program. In this control strategy, the model response is insensitive to the uncertainties in the model parameters (Figure 6). The uncertainties remains only in the control profiles (Figure 8). This control strategy produces the desired objective of the control program.

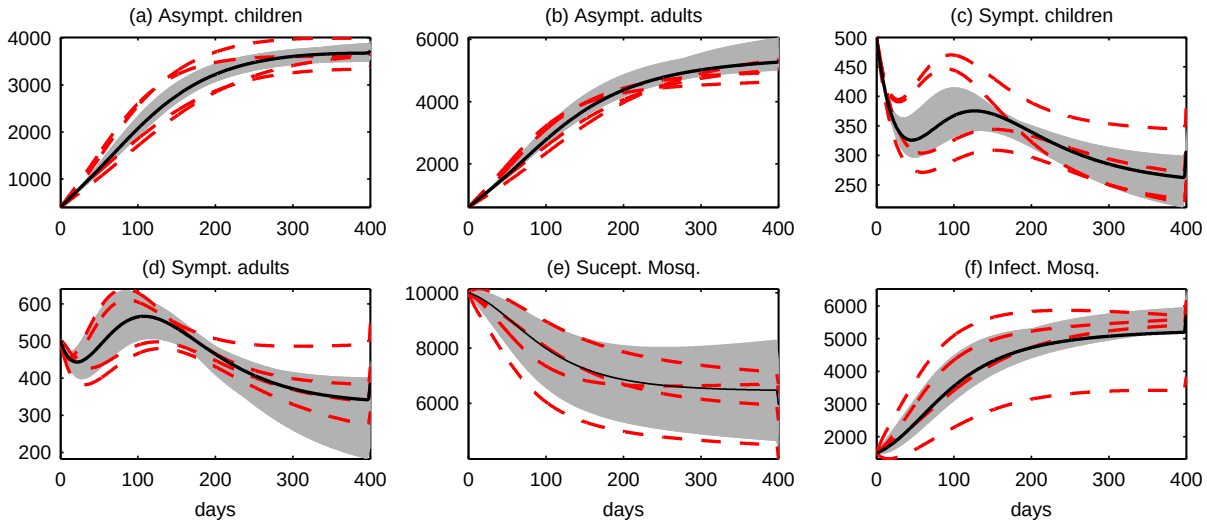


**Figure 4**: The predictive posterior distribution of state variables calculated from MCMC (light gray), by MAP estimate (bold line) and by using extreme points (dashed red line) for strategy I: $u_1 \neq 0$, $u_2 \neq 0$, $u_3 = 0$ and $u_4 = 0$

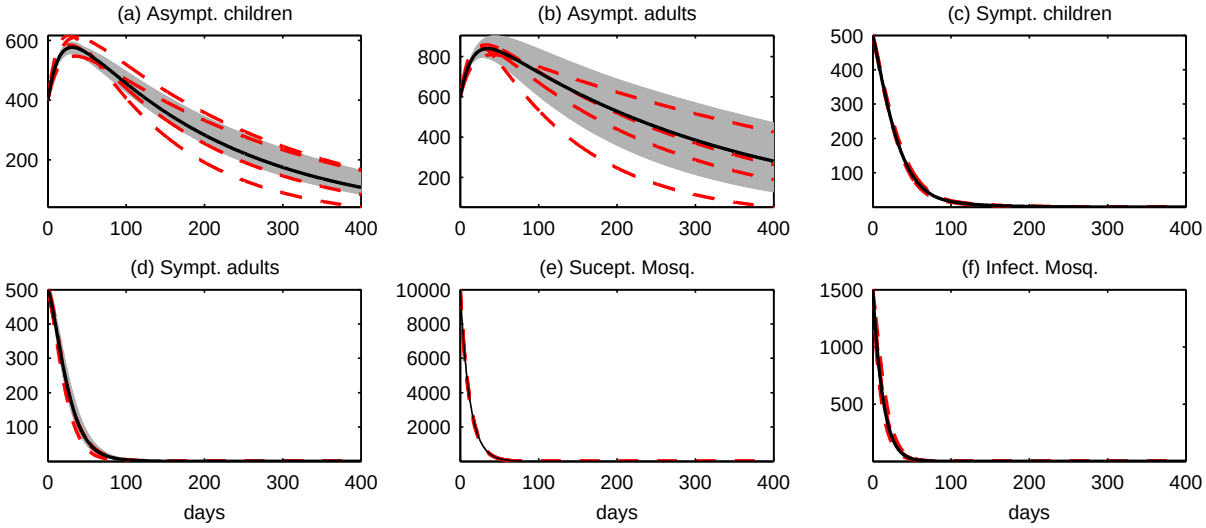


**Figure 5**: The predictive posterior distribution of state variables calculated from MCMC (light gray), by MAP estimate (bold line) and by using extreme points (dashed red line) for strategy II: $u_1 \neq 0$, $u_2 \neq 0$, $u_3 = 0$ and $u_4 \neq 0$

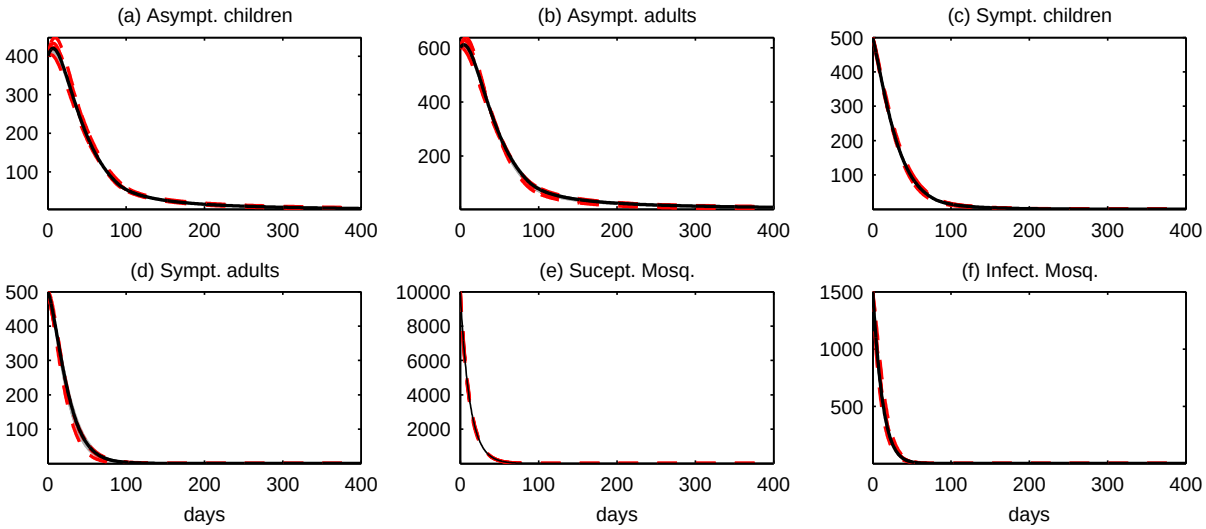


**Figure 6**: The predictive posterior distribution of state variables calculated from MCMC (light gray), by MAP estimate (bold line) and by using extreme points (dashed red line) for strategy III: $u_1 \neq 0$, $u_2 \neq 0$, $u_3 \neq 0$ and $u_4 \neq 0$

The same observation as in strategy III is made for the case of uncertainties in the weights value ($C_p$, $C_{d1}$, $C_{d2}$, $W_1$, $W_2$, $W_3$, $W_4$, $A_1$ and $A_1$) for the fixed model parameter values.

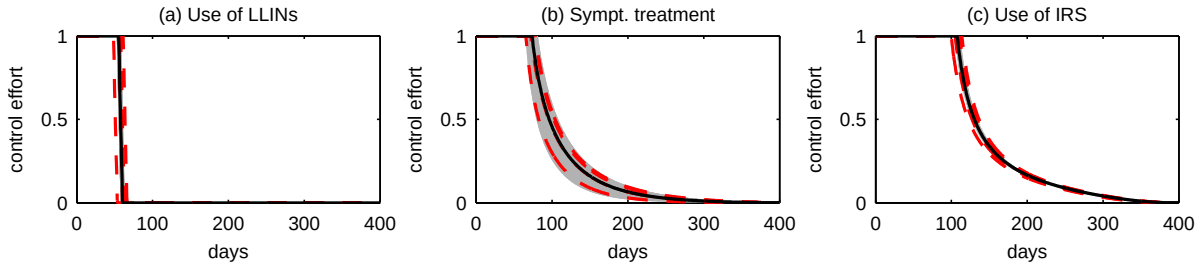


**Figure 7**: The control profiles using parameter posterior distribution calculated from MCMC (light gray), by MAP estimate (bold line) and by using extreme points (dashed red line) for strategy II: $u_1 \neq 0$, $u_2 \neq 0$, $u_3 = 0$ and $u_4 \neq 0$

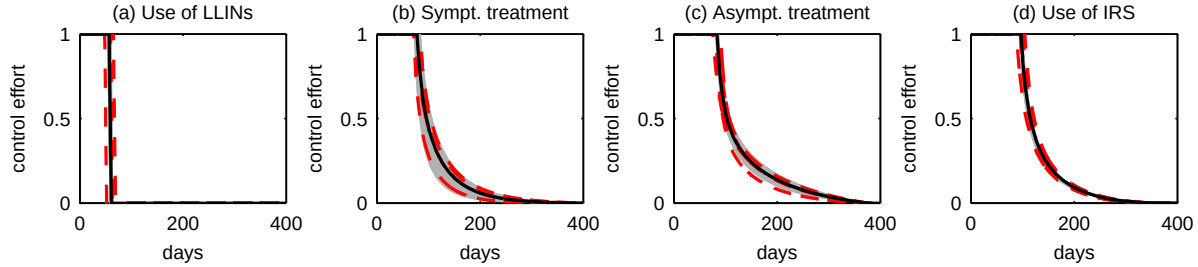


**Figure 8**: The control profiles using parameter posterior distribution calculated from MCMC (light gray), by MAP estimate (bold line) and by using extreme points (dashed red line) for strategy III: $u_1 \neq 0$, $u_2 \neq 0$, $u_3 \neq 0$ and $u_4 \neq 0$

## 5 CONCLUSION

In this article, a two age-stage model of malaria transmission which incorporates asymptomatic malaria carriers together with four control mechanisms is presented. The article discussed a way to incorporate parameter uncertainty into an optimal control problem. The approach utilizes the output from MCMC methods which is becoming popular in statistical model fitting problems. Numerical simulation was carried out to determine the best combination of four controls which provides the best strategy for malaria control in a community. It was observed in this scenario that combination of all four controls provides the best malaria control measure. It is further observed that the optimal model response is sensitive to the parameter uncertainty when the combination of the control is less than four. Analysis of numerical results revels further that even if different parameters are selected from the parameter posterior distribution lead to different optimal control profiles, the model response remains the same provided that the best control strategy is used.

## REFERENCES

[1] Agusto, F.B, Marcus N and Okosun, K.O. Application of optimal control to the epidemiology of malaria. *EJDE* (2012) **81**:1–22.

[2] Pontryagin, L.S., Boltyanskii, V.G., Gamkrelidze, R.V. and Mishchenko, E.F. *The Mathematical Theory of Optimal Process*. Wiley, New York (1962).

[3] Aniţa, S., Arnăutu, V. and Capasso, V. *An introduction to optimal control problems in life sciences and economics*. Springer (2011).

[4] Blayneh, K., Cao, Y. and Kwon, H. Optimal control of vector-borne diseases: treatment and prevention. *Discrete Contin. Dyn. Syst., Ser. B* (2009) **11**:587–611.

[5] Shim, E., Feng, Z., Castillo-Chavez, C. and others. Differential impact of sickle cell trait on symptomatic and asymptomatic malaria. *Math Biosci Eng.* (2012) **9**: 877–898.

[6] Menach, A.L., McKenzie, F.E., Flahault, A. and Smith, D.L. The unexpected importance of mosquito oviposition behaviour for malaria: non-productive larval habitats can be sources for malaria transmission. *Malaria J.* (2005) **4**: 23.

[7] Menach, A.L., McKenzie, F.E., Flahault, A. and Smith, D.L. Statics and dynamics of malaria infection in Anopheles mosquitoes. *Malaria J.* (2004) **3**: 13.

[8] Gu, W., Killeen, G.F., Mbogo, C.M. and Others. An individual-based model of Plasmodium falciparum malaria transmission on the coast of Kenya. *Trans R Soc Trop Med Hyg.* (2003) **97**: 43–50.

[9] Chitnis, N., Cushing, J.M. and Hyman, J.M. Bifurcation analysis of a mathematical model for malaria transmission. *SIAM J Appl Math.* (2006) **67**: 24–45.

[10] Dietz, K., Molineaux, L. and Thomas, A. A malaria model tested in the African savannah. *Bull World Health Organ.* (1974) **50**: 347–357.

[11] Aldila, D., Götz, T. and Soewono, E. An optimal control problem arising from a dengue disease transmission model. *Math Biosci.* (2013) **242**: 9–16.

[12] Gu, W., Mbogo, C.M., Githure, J.I. and Others. Low recovery rates stabilize malaria endemicity in areas of low transmission in coastal Kenya. *Acta Trop.* (2003) **86**: 71–81.

[13] Haario, H., Laine, M., Mira, A. and Saksman, E. DRAM: efficient adaptive MCMC. *Stat Comput.* (2006) **16**: 339–354.