A singularly perturbed vector-bias malaria model incorporating bed-net control

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Abstract

A malaria transmission disease model with host selectivity and Insecticide-treated bed nets (ITNs), as an intervention for controlling the disease, is formulated. Since the vector is an insect, the vector time scale is faster than the host time scale. This leads to a singularly perturbed model with two distinctive intrinsic time scales, two-slow for the host and one-fast for the vector. The basic reproduction number $\mathfrak{R}_o$ is calculated and the local stability analysis is performed at equilibria of the model when the perturbation parameter $\epsilon > 0$. The model is analyzed when $\epsilon \to 0$ using asymptotic expansions technique. The dynamics on the slow surface indicate that the infected vectors decays fast when $\epsilon = 0.001$ according to the numerical simulations.

Keywords: Malaria; vector-bias effect; bed-net control; fast-slow dynamical systems.

1 Introduction

Malaria infectious disease is one of the major public health problem in the poorest area of the world such as sub-Saharan Africa, which is caused by four species of Plasmodium protozoan parasites and it is transmitted to humans as a result of bites of female Anopheles mosquitoes. Despite the promising results of control policies that have led to reducing the number of cases and deaths, malaria remains one of the most widespread human infection. Serious complications affecting kidney, brain, lungs are consequences of malaria disease. It causes an estimated 300 to 500 million cases and 1.5 to 2.7 million deaths each year worldwide [1]. Africa shares 80% of the cases and 90% of deaths as most cases and deaths occur in sub-Saharan Africa [2]. Many intervention strategies such as Dichlorodiphenyltrichloroethane (DDT), antimalarial drugs, larvicides, insecticides and choppy preventive treatment are used to eradicate malaria in Europe, North America, and

parts of Asia and South-Central America in the early 20th century. Insecticide-treated bed nets (ITNs) is the most chosen tool to decline malaria transmission and lessen disease burden [3, 4]. To understand the disease transmission spread, mathematical models are devoted to simulate the spread of the disease through a population and hence make a prediction on the long-term of the disease spread. Malaria is a mosquito-borne disease in which its dynamics are strongly related to the interaction between humans and mosquitoes. Consequently, malaria mathematical models are usually consisting of coupling two models for the host (humans) and vectors (mosquitoes), respectively [5–16].

Some mosquitoes exhibit host selectivity which means blood-sucking mosquitoes may prefer to choose infected hosts [17]. Recent studies indicate that malaria parasite manipulate a host to be more attractive to mosquitoes via chemical substances [18–22]. The attractiveness is considered in the following way: the mosquito arrives at a human at random and bits him with probability p if he is infectious, and with a probability l if he is susceptible with $p > l$. Picking humans in different probabilities represents the so-called vector-bias model [19]. In order to reduce virus spread, it is necessary to limit the contact between infectious and susceptible individuals [23]. This can be done using ITNs which is one of the most effective non-pharmaceutical interventions (NPIs) for preventing disease spread. In many African parts, it is shown that ITNs succeeded in reducing the death of children under five years from causes of the disease by about 20% [24, 25].

On the other hand, many biological processes involve actions on very intrinsic time scales which, in consequence, lead to rapid changes in number of variables while the others act more slowly. Such processes transform the model to what is called a singular perturbed model [26, 27]. In this paper, we rely on the fact that vector dynamics are much faster than host dynamics as discussed in [28–30]. We formulate and analyze a malaria model taking into account three aspects. The first is the host selectivity represented in a vector-bias term for the infectious host. Second, the ITNs interventions represented in the bed-net users for population. Third, singularly perturbation due to the fact that the vector is an insect which in turn operates much faster than the host. The baseline of our model is the model proposed in [19], which is extended here to include both singular perturbation aspect and bed-net usage adopted from [31, 32]. The rest of the paper is organized as follows. In Section 2, the formulation of the model is presented. The existence of disease-free equilibrium and endemic equilibrium and their local stability analysis at them is shown in Section 3 when the perturbation parameter $0 < \epsilon < 1$. In Section 4, the model is analyzed when $\epsilon \to 0$. Numerical simulations are reported in Section 5. Finally, we conclude in Section 6.

2 Model formulation

Consider the following system of nonlinear ordinary differential equations [19]

$$\begin{aligned}
\dot{S}_h &= \mu N_h - \frac{l\beta}{pI_h + lS_h} S_h I_v - \mu S_h + \nu I_h, \\
\dot{I}_h &= \frac{l\beta}{pI_h + lS_h} S_h I_v - (\mu + \nu) I_h, \\
\dot{S}_v &= \eta N_v - \frac{p\alpha}{pI_h + lS_h} I_h S_v - \eta S_v, \\
\dot{I}_v &= \frac{p\alpha}{pI_h + lS_h} I_h S_v - \eta I_v,
\end{aligned} \tag{2.1}$$

where the dots denote the derivative with respect to the time t and S_h, I_h, S_v and I_v are susceptible humans, infected humans, susceptible mosquitoes, and infected mosquitoes, respectively. All parameters are strictly positive and their description is given in Table 1.

Table 1: Biological description and values of parameters in model (2.1).

Parameter	Description	Values	Source
μ	Birth and death rate of humans	1/70 $(year^{-1})$	[19]
l	Prob. that a mosquito arrives at human at random and picks him in case he is susceptible	0-1	Varying
p	Prob. that a mosquito arrives at human at random and picks him in case he is infected	0-1	Varying
β_{max}	Maximum transmission rate in humans	0.1	[25]
β_{min}	Minimum transmission rate in humans	0	[25]
ν	Recovery rate of infectious humans	1/4 $(year^{-1})$	[25]
η_n	Natural mortality rate in mosquitoes	1/14 $(year^{-1})$	[38]
η_b	Maximum ITNs-induced death rate in mosquitoes	1/14	Assumed
b	Proportion of ITNs usage	53/100	[37]
α_{max}	Maximum transmission rate in mosquitoes	0.4	Assumed
α_{min}	Minimum transmission rate in mosquitoes	0	[25]
N_h	Total size of human population	200000	[19]
N_v	Total size of mosquito population	mN_h	[19]
$m = \frac{N_v}{N_h}$	Number of female mosquito per human host	1-2	[39]

In model (2.1), the host population is formed of two classes, susceptible and infectious with total population size $N_h = S_h + I_h$. Similarly, the vector population is grouped into two classes, susceptible and infectious with total population size $N_v = S_v + I_v$. All the newborn individuals are assumed to be susceptible and

there is no vertical transmission of the disease. We assume that mosquitoes reach humans with equal probability, but the biting will be with probability p if the human is infectious and with probability l if he is susceptible [19]. Hence, when a human is bitten, the probability that this human is infected is given by the ratio between the total bitten infectious humans and the total bitten humans, $\frac{pI_h}{pI_h+lS_h}$, whereas the probability that this human is susceptible is given by the ratio between the total bitten susceptible humans and the total bitten humans $\frac{lI_h}{pI_h+lS_h}$. The incidence function for humans is given by $\frac{\beta pI_h}{pI_h+lS_h}$ and the incidence function for mosquitoes is given by $\frac{\alpha lI_h}{pI_h+lS_h}$. If $p = l$, then the model is without vector-bias and the nonlinear incidence becomes standard. If p increases, then a vector-bias effect increases. Following [31, 32], the biting rate of mosquitoes is modeled by a linearly decreasing function of the proportion of ITNs adopters b as follows:

$$\beta(b) = \beta_{max} - b(\beta_{max} - \beta_{min}), \;\; 0 \leq b \leq 1,$$

where $b = 0$ means that no one uses bed-nets, while $b = 1$ means all host population are users. The goal of insecticide treated bed-nets is to reduce the probability that mosquitoes bite humans, that is b should reduce the contact rats β and α and increase the death rate η. Thus, we also assume that

$$\alpha(b) = \alpha_{max} - b(\alpha_{max} - \alpha_{min}), \;\; 0 \leq b \leq 1.$$

The death rate of mosquitoes is modeled by a linearly increasing function of b as follows:

$$\eta(b) = \eta_n + b\eta_b, \;\; 0 \leq b \leq 1.$$

Instead of dealing with the actual population, we scale model (2.1) to deal with portion of quantities by normalizing them in the form $s_h = \frac{S_h}{N_h}, i_h = \frac{I_h}{N_h}, s_v = \frac{S_v}{N_v}, i_v = \frac{I_v}{N_v}, m = \frac{N_v}{N_h}$. Taking into account that $N_h = S_h + I_h$ and $N_v = S_v + I_v$, model (2.1) is rewritten in the following form

$$\begin{aligned}
\dot{s}_h &= \mu - \frac{ml\beta(b)}{pi_h + ls_h} s_h i_v - \mu s_h + \nu i_h, \\
\dot{i}_h &= \frac{ml\beta(b)}{pi_h + ls_h} s_h i_v - (\mu + \nu) i_h, \\
\dot{s}_v &= \eta(b) - \frac{p\alpha(b)}{pi_h + ls_h} i_h s_v - \eta(b) s_v, \\
\dot{i}_v &= \frac{p\alpha(b)}{pi_h + ls_h} i_h s_v - \eta(b) i_v.
\end{aligned} \tag{2.2}$$

Note that the total population sizes N_h and N_v do not appear in the equations of model (2.2). Since $s_v + i_v = 1$, model (2.4) is reduced to the following system of

equations

$$\begin{aligned}
\dot{s}_h &= \mu - \frac{ml\beta(b)}{pi_h + ls_h} s_h i_v - \mu s_h + \nu i_h, \\
\dot{i}_h &= \frac{ml\beta(b)}{pi_h + ls_h} s_h i_v - (\mu + \nu) i_h, \\
\dot{i}_v &= \frac{p\alpha(b)}{pi_h + ls_h} i_h(1 - i_v) - \eta(b) i_v.
\end{aligned} \tag{2.3}$$

In fact, there is a difference in time ecologies between infectious agents and the host's response. In other words, in vector disease transmission models the vector population time scale is much more expeditious than the host population time scale, therefore, we introduce the quantities $\alpha^*(b) = \frac{\alpha(b)}{\epsilon}$ and $\eta^*(b) = \frac{\eta(b)}{\epsilon}$ to model (2.3), where $\epsilon \in [0, 1]$ is the perturbation parameter. This means that both the transmission and the death rates of mosquitoes are very high compared to those of humans. Singular perturbation is often identified by a small parameter in front of the highest derivative such that the order of the system drops by one when this parameter tends to zero. In view of the above assumptions, model (2.3) now takes the following form (keeping old variables notations S_h, I_h, and I_v for convenience)

$$\begin{aligned}
\dot{S}_h &= \mu - \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - \mu S_h + \nu I_h, \\
\dot{I}_h &= \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - (\mu + \nu) I_h, \\
\epsilon \dot{I}_v &= \frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b) I_v,
\end{aligned} \tag{2.4}$$

with initial conditions $S_h(0) = S_{ho}, I_h(0) = I_{ho}$ and $I_v(0) = I_{vo}$. The model makes biological sense in the region

$$\Omega = \{(S_h, I_h, I_v) \in \mathbb{R}^3_+, 0 < S_h + I_h \leq 1, 0 < I_v \leq 1\}.$$

2.1 Positivity and boundedness of solutions

All parameters in model (2.4) are strictly positive since the model represents populations of both humans and mosquitoes. Thus, given non-negative initial values, it can be shown that the solutions of the model are non-negative. We now show that the solutions in Ω remain in Ω for all $t > 0$, that is Ω is positively invariant set.

Theorem 1. *The solutions S_h, I_h, and I_v of malaria model (2.4) with non-negative initial conditions in the feasible region Ω, remain non-negative in Ω for all $t > 0$.*

Proof. We will proceed as [33, 34]. It is easy to see that $S_h > 0$ for all $t \geq 0$. If not, let there exists $t^* > 0$ such that $S_h(t^*) = 0$, $\dot{S}_h(t^*) \leq 0$ and $S_h, I_h, I_v > 0$ for $0 < t < t^*$. Then from the first equation of model (2.4), we have

$$\begin{aligned} \dot{S}_h(t^*) &= \mu - \frac{ml\beta(b)}{pI_h(t^*) + lS_h(t^*)} S_h(t^*) I_v(t^*) - \mu S_h(t^*) + \nu I_h(t^*), \\ &= \mu + \nu I_h(t^*) > 0, \end{aligned}$$

which is a contradiction. Hence, $S_h(t) > 0$.
Now assume that $I_h(t^*) = 0$. Multiplying both sides of the second equation of model (2.4) by $e^{(\mu+\nu)t}$, we obtain

$$e^{(\mu+\nu)t}\dot{I}_h + e^{(\mu+\nu)t}(\mu+\nu)I_h = \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v.$$

Here on the left side stands the derivative of the function $e^{(\mu+\nu)t}(\mu+\nu)I_h$. Hence, integrating this equality on the interval $[0, t]$ we get

$$e^{(\mu+\nu)t} I_h(t) - I_h(0) = \int_0^t e^{(\mu+\nu)s} \frac{ml\beta(b)}{pI_h(s) + lS_h(s)} S_h(s) I_v(s) ds.$$

Putting $t = t^*$, we obtain

$$I_h(t^*) = e^{-(\mu+\nu)t^*} I_h(0) + \int_0^{t^*} e^{-(\mu+\nu)(t^*-s)} \frac{ml\beta(b)}{pI_h(s) + lS_h(s)} S_h(s) I_v(s) ds.$$

Hence $I_h(t^*) > 0$, which is a contradiction.
Finally, we assume that $I_v(t^*) = 0$. Then the third equation in model (2.4) at $t = t^*$ results in the following relation

$$\begin{aligned} \epsilon \dot{I}_v(t^*) &= \frac{p\alpha^*(b)}{pI_h(t^*) + lS_h(t^*)} I_h(t^*)(1 - I_v(t^*)) - \eta^*(b) I_v(t^*), \\ &= \frac{p\alpha^*(b)}{pI_h(t^*) + lS_h(t^*)} I_h(t^*) > 0, \end{aligned}$$

which means that $I_v(t)$ is strictly monotonically increasing in t^*, which is a contradiction. These steps prove that there is no such t^* where any of S_h, I_h, I_v turns into zero. Since at the initial values the components are positive, due to the continuity of the functions every component is positive for all t. □

In Theorem 1 we have proved the positivity of the solution, which means the model is bounded from below. In the following we consider its boundedness from above.

Theorem 2. *The region Ω is positively invariant with respect to the model (2.4) with non-negative initial conditions in Ω.*

Proof. Since the total population size for humans equals $N_h(t) = S_h(t) + I_h(t)$, we obtain

$$\begin{aligned} \dot{N}_h(t) &= \dot{S}_h(t) + \dot{I}_h(t), \\ &= \mu - \mu(S_h + I_h), \\ &= \mu - \mu N_h. \end{aligned}$$

This leads to $N_h(t) = e^{-\mu t}N_h(0) + (1 - e^{-\mu t})$. A standard comparison theorem [35] can be then used to show that $\dot{N}_h(t) \leq 1$ if $N_h(0) \leq 1$. As a consequence, I_v is also bounded from the third equation of model (2.4) if $I_v(0) \leq 1$. Thus, the region Ω is positively invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (2.4) in Ω. In this region, the model is epidemiologically and mathematically well-posed [36]. Thus, every solution of the basic model (2.4) with initial conditions in Ω remains in Ω for all $t > 0$. □

Throughout this paper, we consider model (2.4) with initial values in Ω.

3 Analysis of model (2.4) in case $\epsilon > 0$

The equilibria of model (2.4) are the solution of the following algebraic equations

$$\begin{aligned} \mu - \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - \mu S_h + \nu I_h = 0, \\ \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - (\mu + \nu) I_h = 0, \\ \frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b) I_v = 0. \end{aligned} \tag{3.1}$$

Hence, model (2.4) has the disease-free equilibrium point $E^0(1, 0, 0)$ and an endemic equilibrium point $E^*(S_h^*, I_h^*, I_v^*)$ with components will be discussed later.
An important threshold in epidemiology is the basic reproduction number $\mathfrak{R}_o$ [40–45]. It is defined as the average number of secondly infectious produced by a single primary infectious introduced into the susceptible population. Following the next generation matrix approach proposed in [41], we can easily calculate $\mathfrak{R}_o$

as follows. In model (2.4), the disease states I_h and I_v define the vector-valued functions $\tilde{F}$ and $\tilde{V}$ as follows

$$\tilde{F} = \begin{pmatrix} \frac{ml\beta(b)}{pI_h+lS_h} S_h I_v \\ \frac{p\alpha^*(b)}{pI_h+lS_h} I_h S_v \end{pmatrix}, \tilde{V} = \begin{pmatrix} -(\mu+\nu)I_h \\ -\eta^*(b) \end{pmatrix}.$$

The Jacobian matrices of $\tilde{F}$ and $\tilde{V}$ evaluated at the disease-free equilibrium are given by

$$D\tilde{F}(E^0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \; D\tilde{V}(E^0) = \begin{pmatrix} V & 0 \\ m\beta(b) & 0 \end{pmatrix},$$

where

$$F = \begin{pmatrix} 0 & m\beta(b) \\ \frac{p\alpha^*(b)}{l} & 0 \end{pmatrix}, V = \begin{pmatrix} (\mu+\nu) & 0 \\ 0 & \eta^*(b) \end{pmatrix}.$$

Now, $\mathfrak{R}_o$ is defined as the spectral radius of

$$FV^{-1} = \frac{1}{(\mu+\nu)\eta^*(b)} \begin{pmatrix} 0 & m\beta(b) \\ \frac{p\alpha^*(b)}{l} & 0 \end{pmatrix} \begin{pmatrix} -\eta^*(b) & 0 \\ 0 & -(\mu+\nu) \end{pmatrix}.$$

Accordingly, it is given by

$$\mathfrak{R}_o = \frac{mp\beta(b)\alpha^*(b)}{l\eta^*(b)(\mu+\nu)}.$$

Note that some references use the square-root for $\mathfrak{R}_o$ which is obtained from direct calculations such as in [46]. As it is clear, we can quantify that higher values of $\beta(b)$ and $\alpha^*(b)$ allow the outbreak of the disease. From the expression for $\mathfrak{R}_o$, we can see the impact of bed-net usage in reducing the the disease burden. This can be seen by differentiating $\mathfrak{R}_o$ with respect to b which gives

$$\frac{d\mathfrak{R}_o}{db} = -mp\left(\frac{\alpha^*(b)(\beta_{max}-\beta_{min}) + \beta(b)(\alpha_{max}-\alpha_{min})}{l\eta^*(b)(\mu+\nu)} + \frac{\eta_b\alpha^*(b)\beta(b)}{l\eta^*(b)^2(\mu+\nu)}\right) < 0.$$

As it is clear, the bed-net usage decreases $\mathfrak{R}_o$ and hence, reduces the disease burden. Now, we discuss the local stability of equilibria.

Proposition 1. *The disease-free equilibrium $E^0(1,0,0)$ of model (2.4) is locally asymptotically stable if $\mathfrak{R}_o < 1$ and unstable if $\mathfrak{R}_o > 1$.*

Proof. See Appendix A. □

For the existence of the endemic equilibrium $E^*(S_h^*, I_h^*, I_v^*)$ in Ω, its components should satisfy Eq. (3.1) which can be rewritten in the following form

$$\begin{aligned} \mu - \theta_v^* S_h^* - \mu S_h^* + \nu I_h^* &= 0, \\ \theta_v^* S_h^* - \theta I_h^* &= 0, \\ \theta_h^*(1 - I_v^*) - \eta^*(b) I_v^* &= 0, \end{aligned}$$

where

$$\theta_v^* = \frac{ml\beta(b)I_v^*}{pI_h^* + lS_h^*}, \quad \theta_h^* = \frac{p\alpha^*(b)I_h^*}{pI_h^* + lS_h^*}, \quad \text{and} \quad \theta = \mu + \nu. \tag{3.2}$$

Hence, we obtain $S_h^* = \frac{\theta\mu}{\theta(\theta_v^*+\mu)-\nu\theta_v^*}$, $I_h^* = \frac{\theta_v^*\mu}{\theta(\theta_v^*+\mu)-\nu\theta_v^*}$, and $I_v^* = \frac{\theta_v^*}{\theta_h^*+\eta^*(b)}$. As a consequence we obtain

$$\theta_h^* = \frac{p\alpha^*(b)\theta_v^*}{p\theta_v^* + l\theta}, \tag{3.3}$$

$$\theta_v^* = \frac{ml\beta(b)\theta_h^*(\theta(\theta_v^* + \mu) - \nu\theta_v^*)}{\mu(\theta_h^* + \eta^*(b))(p\theta_v^* + l\theta)}. \tag{3.4}$$

Substituting Eq.(3.3) into Eq.(3.4) we get the quadratic equation

$$\gamma_1 \theta_v^{*2} + \gamma_2 \theta_v^* + \gamma_3 = 0,$$

where $\gamma_1 = \mu p^2(\alpha^*(b) + \eta^*(b))$, $\gamma_2 = \mu l\theta p(2\eta^*(b) + \alpha^*(b)) - \mu mlp\beta^*(b)\alpha^*(b)$, and $\gamma_3 = \mu l^2\eta^*(b)\theta^2(1 - \mathfrak{R}_o)$. We may state the following proposition

Proposition 2. *Model (2.4) has the following possible numbers of endemic equilibria. It may have*

- *a unique endemic equilibrium if* $\gamma_3 < 0 (\mathfrak{R}_o > 1)$,
- *a unique endemic equilibrium if* $\gamma_2 < 0$ *and either* $\gamma_3 = 0$ *or* $\gamma_2^2 - 4\gamma_1\gamma_3 = 0$,
- *two endemic equilibria if* $\gamma_3 > 0$, $\gamma_2 < 0$, *and* $\gamma_2^2 - 4\gamma_1\gamma_3 > 0$,
- *else, there are none.*

In order to discuss stability of E^* of model (2.4), the additive compound matrices proposed in [47] is used as shown in Appendix B.

4 Analysis of model (2.4) with singular perturbation

The main thrust of our consideration now is the following singularly perturbed system

$$\begin{aligned} \dot{S}_h &= f(S_h, I_h, I_v, 0), \\ \dot{I}_h &= g(S_h, I_h, I_v, 0), \\ \epsilon \dot{I}_v &= z(S_h, I_h, I_v, 0), \end{aligned} \tag{4.1}$$

where

$$\begin{aligned} f &= \mu - \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - \mu S_h + \nu I_h, \\ g &= \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - (\mu + \nu) I_h, \\ z &= \frac{p\alpha^*(b)}{pI_h + lS_h} I_h (1 - I_v) - \eta^*(b) I_v. \end{aligned}$$

Recall that the slow surface of system (4.1) is described by the equation

$$z(S_h, I_h, I_v, 0) = 0. \tag{4.2}$$

Let $I_v = \phi(S_h, I_h)$ be an isolated root of equation (4.2). The subsets S^{st}, and S^{uns} of S defined by

$$\frac{\partial z}{\partial I_v}(S_h, I_h, \phi(S_h, I_h), 0) < 0, (> 0), \tag{4.3}$$

are called the stable (unstable) leaf of S. The breakdown surface of S is defined by

$$\frac{\partial z}{\partial I_v}(S_h, I_h, \phi(S_h, I_h), 0) = 0.$$

In an ϵ-neighborhood of $S^{st}(S^{uns})$ there exists a stable (unstable) slow manifold. This means that the slow surface is an approximation to the slow integral manifold (for $\epsilon = 0$) [50]. Taking the limit $\epsilon \to 0$ of system (2.4) we obtain the reduced (slow) system

$$\begin{aligned} \dot{S}_h &= \mu - \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - \mu S_h + \nu I_h, \\ \dot{I}_h &= \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - (\mu + \nu) I_h, \\ 0 &= \frac{p\alpha^*(b)}{pI_h + lS_h} I_h (1 - I_v) - \eta^*(b) I_v. \end{aligned} \tag{4.4}$$

This is a two-dimensional dynamical system on the manifold of solutions of the third equation. The quasi-steady state in model (2.4), which is the case when $\epsilon = 0$, is given by the equation

$$I_v = \frac{\alpha^*(b) I_h}{\eta^*(b)(pI_h + lS_h) + \alpha^*(b) pI_h}. \tag{4.5}$$

As we can see from Eq.(4.5), there is a functional dependency between two infected populations. Substituting for I_v in the equations of model (2.4), equations for S_h and I_h are given as follows

$$\begin{aligned} \dot{S}_h &= \mu - \frac{mlp\alpha^*(b)\beta(b) S_h I_h}{(pI_h + lS_h)(\eta^*(b)(pI_h + lS_h) + \alpha^*(b) pI_h)} - \mu S_h + \nu I_h, \\ \dot{I}_h &= \frac{mlp\alpha^*(b)\beta(b) S_h I_h}{(pI_h + lS_h)(\eta^*(b)(pI_h + lS_h) + \alpha^*(b) pI_h)} - (\mu + \nu) I_h. \end{aligned} \tag{4.6}$$

Equations (4.6) mean that we may formulate vector host transmission as equations of hosts only. Transform the slow time t to the fast time scale by ϵ where the fast time is $\tau = \frac{t}{\epsilon}$ we get the equivalent fast system

$$\begin{aligned} S_h' &= \epsilon(\mu - \frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - \mu S_h + \nu I_h), \\ I_h' &= \epsilon(\frac{ml\beta(b)}{pI_h + lS_h} S_h I_v - (\mu + \nu) I_h), \\ I_v' &= \frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b) I_v, \end{aligned} \tag{4.7}$$

where the dash denotes the derivatives with respect to τ. By taking the limit $\epsilon \to 0$ in system (4.7), we obtain the layer problem

$$\begin{aligned} S_h' &= 0, \\ I_h' &= 0, \\ I_v' &= \frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b) I_v. \end{aligned} \tag{4.8}$$

System (4.8) is a one-dimensional dynamical system in the fast variable I_v with the slow variables S_h and I_h acting as parameters. We can analyze the dynamics of model (2.4) using geometric singular perturbation theory, which was founded by Fenichel ([51]), by combining the dynamics of the reduced problem (4.4), which is a differential algebraic system, and the dynamics of the layer problem (4.8). We note that the the reduced fast system (4.8) determines the fast dynamics of I_v through

$$I_v' = \frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b) I_v, \tag{4.9}$$

which can be solved explicitly for $I_v(\tau)$, since S_h and I_h are constants, in the form

$$I_v(\tau; S_h, I_h) = \frac{-Ce^{-\tau(K+\eta^*(b))} + K}{K + \eta^*(b)}, \tag{4.10}$$

where $K = \frac{p\alpha^*(b)I_h}{pI_h + lS_h}$ and C is the integration constant. Meanwhile, we have

$$S_h(\tau) = S_h(0), \;\; I_h(\tau) = I_h(0).$$

The critical manifold S is the algebraic part of the slow (reduced) problem (4.4) which is given by the equation

$$S = \{(S_h, I_h, I_v) \in \mathbb{R}^3_+ : \frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b)I_v = 0\}. \tag{4.11}$$

The local stability of points (S_h, I_h, I_v) in S, which are the equilibria of the layer problem (4.8), depends on the sign of $\frac{\partial z}{\partial I_v}$. That is we obtain

$$\frac{\partial z}{\partial I_v}(\frac{p\alpha^*(b)}{pI_h + lS_h} I_h(1 - I_v) - \eta^*(b)I_v) = -(\frac{p\alpha^*(b)I_h}{pI_h + lS_h} + \eta^*(b)) < 0,$$

Accordingly, equilibria of the layer problem (4.8) are locally stable. If $\frac{\partial z}{\partial I_v}(S_h, I_h, I_v, 0)$ is uniformly bounded away from zero for all $(S_h, I_h, I_v) \in S_0$, where $S_0 \subset S$ is compact, the critical manifold S_0 is normally hyperbolic [52]. The flow of the reduced problem is slow and constrained to the manifold S. By solving for I_v we have

$$I_v = \frac{\alpha^*(b)I_h}{\eta^*(b)(pI_h + lS_h) + \alpha^*(b)pI_h}.$$

It is necessary to note that neither the manifold nor the dynamics on the manifold depend on ϵ. Outside from a neighborhood of the critical manifold S for small ϵ, Fenichel theory assures that there exists a locally invariant manifold S^ϵ close to the critical manifold S for compact subsets of S where $\frac{\partial z}{\partial I_v} \neq 0$. Outside the manifold, the system will follow the fast trajectories. Thus, we evaluate $\frac{\partial z}{\partial I_v}$ on the critical manifold. The part of S where $\frac{\partial z}{\partial I_v} < 0$ is called the attractive part of the critical manifold. In our case since we have $\frac{\partial z}{\partial I_v} < 0$ hence, the whole critical manifold is attractive. The scenario of the dynamics of model (2.4) when $\epsilon \to 0$ is as follows. There is a rapid settlement of the vector population to a quasi steady-state value on a time scale of order ϵ followed by a slower transformation of the host population on a time scale of order 1. In what follows, we describe these processes by formulating outer and inner solutions and match them together.

4.1 Outer solution

Consider the following expansion

$$\begin{aligned} S_h &= S_h^0(t) + O(\epsilon), \\ I_h &= I_h^0(t) + O(\epsilon), \\ I_v &= I_v^0(t) + \hat{I_v}^0(\tau) + O(\epsilon), \end{aligned} \tag{4.12}$$

where $\tau = t/\epsilon$ and $\lim_{\tau\to 0} \hat{I}_v(\tau) = 0$. Substituting expansion (4.12) in model (2.4) and equating leading order of ϵ^0 we obtain

$$\begin{aligned} \frac{dS_h^0(t)}{dt} &= \mu - \frac{ml\beta(b)}{pI_h^0 + lS_h^0} S_h^0 I_v^0 - \mu S_h^0 + \nu I_h^0, \\ \frac{dI_h^0(t)}{dt} &= \frac{ml\beta(b)}{pI_h^0 + lS_h^0} S_h^0 I_v^0 - (\mu+\nu) I_h^0, \\ 0 &= \frac{p\alpha^*(b)}{pI_h^0 + lS_h^0} I_h^0(1 - I_v^0) - \eta^*(b) I_v^0, \end{aligned} \tag{4.13}$$

which is again a differential algebraic system to the leading order. Thus we have from the third equation

$$I_v^0(t) = \frac{\alpha^*(b) I_h^0(t)}{\eta^*(b)(pI_h^0(t) + lS_h^0(t)) + \alpha^*(b) pI_h^0(t)}, \tag{4.14}$$

consequently, we obtain the system

$$\begin{aligned} \frac{dS_h^0}{dt} &= \mu - \frac{mlp\alpha^*(b)\beta(b) S_h^0 I_h^0}{(pI_h^0 + lS_h^0)(\eta^*(b)(pI_h^0 + lS_h^0) + \alpha^*(b) pI_h^0)} - \mu S_h^0 + \nu I_h^0, \\ \frac{dI_h^0}{dt} &= \frac{mlp\alpha^*(b)\beta(b) S_h^0 I_h^0}{(pI_h^0 + lS_h^0)(\eta^*(b)(pI_h^0 + lS_h^0) + \alpha^*(b) pI_h^0)} - (\mu+\nu) I_h^0, \end{aligned} \tag{4.15}$$

with initial conditions $S_h^0(0) = S_{h0}$ and $I_h^0(0) = I_{h0}$. There is a mismatch in the initial condition such that $I_v^0(0) \neq I_{v0}$ which can be justified by imposing $\hat{I_v^0}$ where $I_v^0(0) = \hat{I_{v0}} - I_v^0(0)$ and $\lim_{\tau\to\infty} \hat{I}_{v0}(\tau) = 0$. Note that

$$\begin{aligned} S_h^0(t) &= S_h^0(\epsilon\tau) = S_h^0(0) + \epsilon\tau S_h^0(0) + O(\epsilon^2), \\ I_h^0(t) &= I_h^0(\epsilon\tau) = I_h^0(0) + \epsilon\tau I_h^0(0) + O(\epsilon^2), \\ I_v^0(t) &= I_v^0(\epsilon\tau) = I_v^0(0) + \epsilon\tau I_v^0(0) + O(\epsilon^2). \end{aligned} \tag{4.16}$$

As a consequence, we get

$$\frac{d\hat{I_v^0}}{d\tau} = -(\eta^*(b)(pI_{h0} + lS_{h0}) + \alpha^*(b)pI_{h0})\hat{I_v^0},$$

which gives

$$\hat{I_v^0} = (I_{v0} - \frac{\alpha^*(b)I_{h0}}{\eta^*(b)(pI_{h0} + lS_{h0}) + \alpha^*(b)pI_{h0}})e^{-(\eta^*(b)(pI_{h0}+lS_{h0})+\alpha^*(b)pI_{h0})\tau}.$$

The expansion given in (4.12) is asymptotic as can be seen from the following theorem.

Theorem 3. *For sufficiently small $\epsilon > 0$, there exists a constant $L_1 > 0$ independent of ϵ such that*

$$\|X - X^0\|_\infty \leq \epsilon L_1,$$

where $X^\epsilon(t) = (S_h(t), I_h(t), I_v(t))$, $X^0(t,\tau) = (S_h^0(t), I_h^0(t), I_v^0(t) + \hat{I}_v^0(\tau))$, and $\|.\|_\infty$ denotes the uniform norm in $[0,\infty)$. Moreover, there exist two constants $L_2, L_3 > 0$ such that for $t > \epsilon L_2$ for which

$$\|X^\epsilon - \hat{X^0}\|_\infty \leq \epsilon L_3,$$

where $\hat{X}^\epsilon(t) = (S_h^0(t), I_h^0(t), I_v^0(t))$.

Proof. See [53]. □

4.2 Inner solution

Now for times $\tau = O(\epsilon)$, both S_h and I_h adjust from their initial values to values consistent with the outer solution just found above. Define the inner variables $s_h(\tau,\epsilon) = S_h(t,\epsilon)$, $i_h(\tau,\epsilon) = I_h(t,\epsilon)$, and $i_v(\tau,\epsilon) = I_v(t,\epsilon)$. Again we seek an asymptotic expansion in the form

$$\begin{aligned} s_h &= s_h^0(t) + \hat{s}_h^0 + O(\epsilon), \\ i_h &= i_h^0(t) + \hat{i}_h^0 + O(\epsilon), \\ i_v &= i_v^0(t) + O(\epsilon), \end{aligned} \tag{4.17}$$

where $\tau = t/\epsilon$ and $\lim_{\tau\to\infty}(\hat{s}_h^0, \hat{i}_h^0) = 0$. Thus we have

$$\begin{aligned} 0 &= \mu - \frac{ml\beta(b)}{pi_h^0 + ls_h^0} s_h^0 i_v^0 - \mu s_h^0 + \nu i_h^0, \\ 0 &= \frac{ml\beta(b)}{pi_h^0 + ls_h^0} s_h^0 i_v^0 - (\mu + \nu) i_h^0, \\ \frac{di_v^0}{dt} &= \frac{p\alpha^*(b)}{pi_h^0 + ls_h^0} i_h^0(1 - i_v^0) - \eta^*(b) i_v^0. \end{aligned} \tag{4.18}$$

The first two equations give $s_h^0 = 0$ and $i_h^0 = 1$. This means that the inner solution for the human variables remain constant. Substituting in the third equation we get for mosquito variable

$$\frac{di_v^0}{dt} = \alpha^*(b)(1 - i_v^0) - \eta^*(b)i_v^0,$$

which has the solution along with the initial condition

$$i_v^0 = \frac{\alpha^*(b) - C_1 e^{-(\alpha^*(b)+\eta^*(b))\tau}}{\alpha^*(b) + \eta^*(b))},$$

where C_1 is the integration constant.

4.3 Matching outer and inner solutions

To determine an accurate approximation to the solution of a singularly perturbed problem, asymptotic matching is used here. Assume that both outer and inner expansions are valid for $\epsilon \ll t \ll 1$. Thus, the expansions are linked together and must agree asymptotically when $t \to 0$ and $\tau \to \infty$ as $\epsilon \to 0$. The matching condition is

$$\begin{aligned}
\lim_{\tau\to\infty} s_{h0}(\tau) &= \lim_{t\to 0} S_{h0}(t) = s_h(0), \\
\lim_{\tau\to\infty} i_{h0}(\tau) &= \lim_{t\to 0} I_{h0}(t) = i_h(0), \\
\lim_{\tau\to\infty} i_{v0}(\tau) &= \lim_{t\to 0} I_{v0}(t) = \frac{\alpha^*(b)}{\alpha^*(b) + \eta^*(b)}.
\end{aligned} \tag{4.19}$$

Now we can obtain a uniform solution $\widehat{S_{h0}}$, $\widehat{I_{h0}}$, and $\widehat{I_{v0}}$ as follows

$$\begin{aligned}
\widehat{S_{h0}} &= S_{h0}(t) + s_{h0}(\frac{t}{\epsilon}) - S_h(0), \\
\widehat{I_{h0}} &= I_{h0}(t) + i_{h0}(\frac{t}{\epsilon}) - I_h(0), \\
\widehat{I_{v0}} &= \frac{\alpha^*(b) - C_1 e^{-(\alpha^*(b)+\eta^*(b))\frac{t}{\epsilon}}}{\alpha^*(b) + \eta^*(b)}.
\end{aligned} \tag{4.20}$$

Introducing the limits in (4.19), we obtain

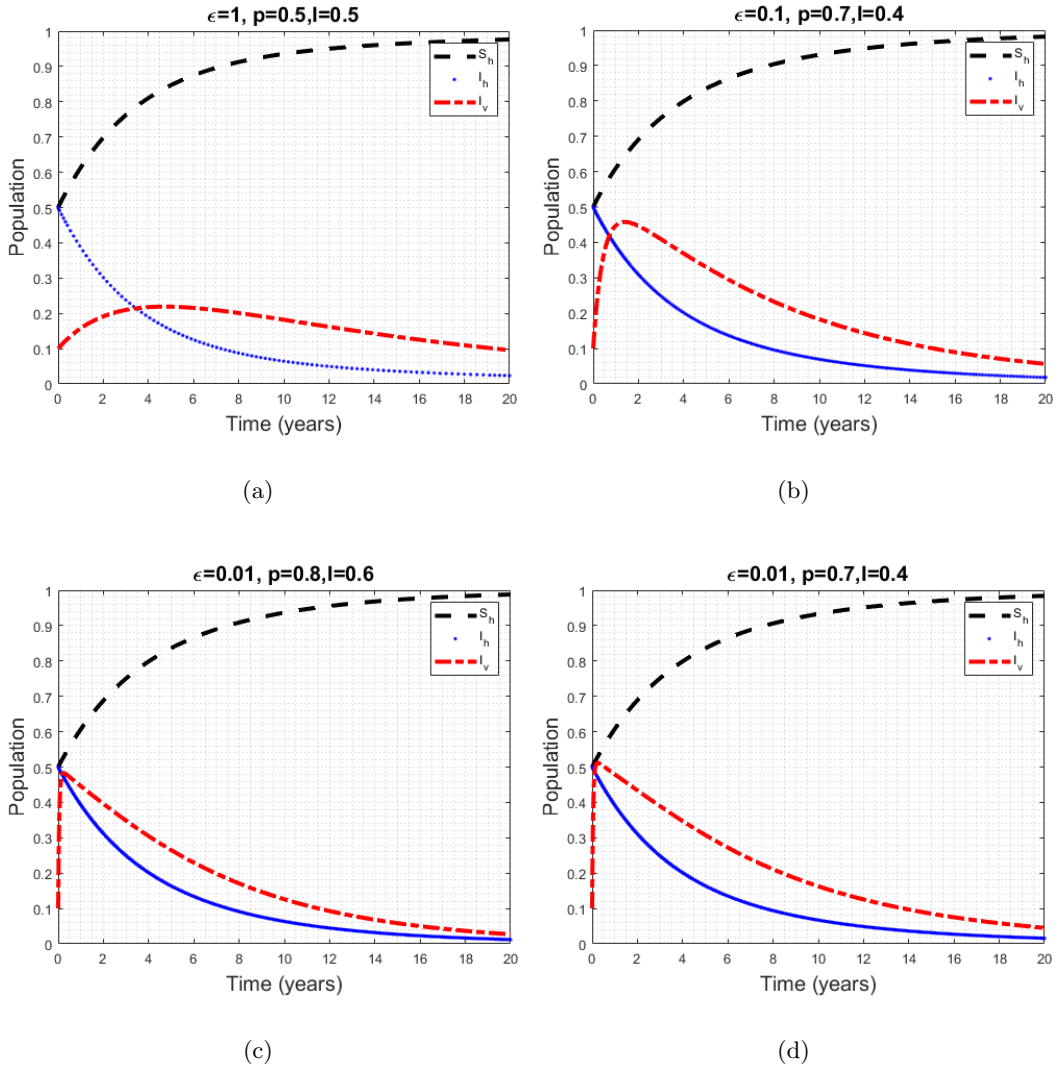
$$\begin{aligned}
\widehat{S_{h0}} &= S_{h0}(t), \\
\widehat{I_{h0}} &= I_{h0}(t), \\
\widehat{I_{v0}} &= \frac{\alpha^*(b) - C_1 e^{-(\alpha^*(b)+\eta^*(b))\frac{t}{\epsilon}}}{\alpha^*(b) + \eta^*(b)}.
\end{aligned} \tag{4.21}$$

Equations (4.21) mean that the outer solutions are the uniform solutions for human population while the inner solution is for the mosquitoes population.

5 Numerical simulations

In this section, we will investigate both the vector-bias effect and bed-net control on malaria disease transmission along with the perturbation effect numerically to confirm theoretical results obtained above. Since nonlinear Ordinary differential Equations (ODEs) may exhibit complicated behaviors over long time, more complicated numerical solvers such as the Runge-Kutta method have been developed to avoid the inaccuracy of standard methods such as Euler [54]. In this paper we use ODE45 Matlab tool, which is a six stage, fifth order Runge-Kutta method. Based on estimations and the literature, a set of parameter values is considered as shown in Table 1. The following cases are illustrated numerically.

1. Let $\epsilon = 1$, and $p = 1 = 0.5$, that is model (2.4) is neither singularly perturbed, nor biased. For an initial condition $(S_h(0), I_h(0), I_v(0)) = (0.5, 0.5, 0.1)$, the long-term behavior for a portion of population is plotted in Fig.(1)a. It can be seen that the number of both infected humans and mosquitoes decreases. For $\epsilon = 0.1$, $p = 0.7$, and $l = 0.4$, the peak of infected mosquitoes increases then suddenly decreases as seen in Fig.(1)b. Now let $\epsilon = 0.01$, $p = 0.8$, and $l = 0.6$. The peak of infection is increased then decreased as seen in Fig.(1)c. Finally, let $\epsilon = 0.01$, $p = 0.7$, and $l = 0.4$ as depicted in Fig.(1)d. Comparing Fig.(1)b with Fig.(1)d reveals that decreasing the perturbation parameter ϵ from 0.1 to 0.01 results in increasing the peak of infected vectors then suddenly reducing it to make the number of infected mosquitoes very small. In all parts of Fig.(1), the basic reproduction number $\mathfrak{R}_o$ is below one and the disease-free equilibrium $E^0(1, 0, 0)$ is locally stable.



(a) (b)

(c) (d)

Figure 1: Time profile of model (2.4) with parameter values taken from Table 1. where (a)$\epsilon = 1, p = l = 0.5$, (b)$\epsilon = 0.1, p = 0.7$, and $l = 0.4$, (c)$\epsilon = 0.01, p = 0.8$, and $l = 0.6$, (d) $\epsilon = 0.01, p = 0.7$, and $l = 0.4$. Here $\mathfrak{R}_o < 1$.

2. To examine both the vector-bias effect and bed-net control on the infected humans only in the presence of the perturbation parameter ϵ, we plot the long-term behavior of portion of the infected humans. Let us take $p = l = 0.5$, $p = 0.7$, $l = 0.4$, and $p = 0.8$, $l = 0.2$ while decreasing ϵ as follows.

In Fig.(2)a, we take $\epsilon = 1$ and in Fig.(2)b, $\epsilon = 0.5$, while in Fig.(2)c and Fig.(2)d, $\epsilon = 0.1$, and $\epsilon = 0.02$, respectively. As we can see, the epidemic outbreak does not take place at any of the values of p (the attractiveness of infectious humans to mosquitoes). The epidemic is eradicated more slowly for $p = 0.8$ and $q = 0.2$, while such behavior occurs faster for $p = 0.7$ and $q = 0.4$, then for $p = q = 0.5$. The same thing can be said when $\epsilon = 0.5, 0.1$, and 0.02. The notable thing is when reducing the value of ϵ, the epidemic is eradicated fast as we see in Fig.(2)(d) for $\epsilon = 0.02$.

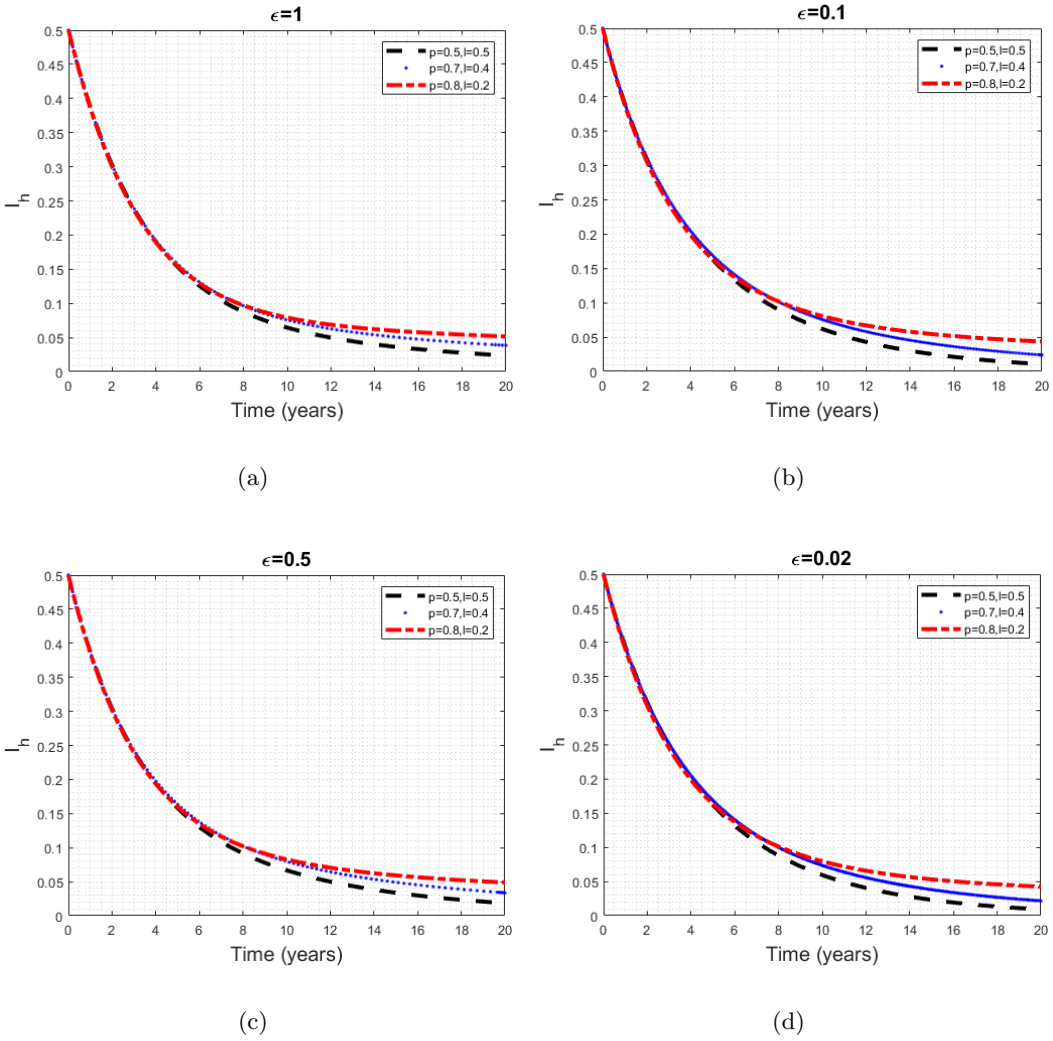
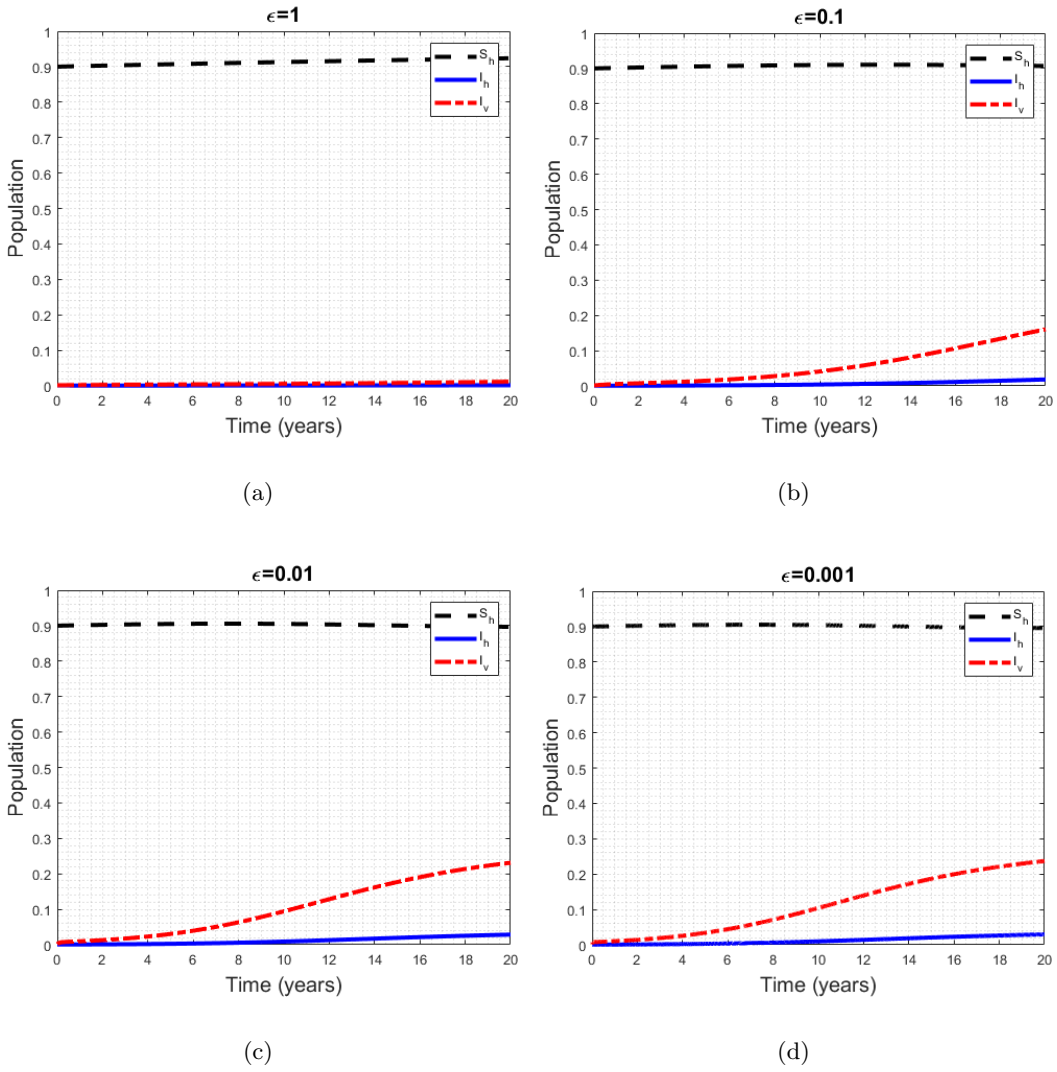


Figure 2: Time profile of the infected humans only of model (2.4) with parameter values taken from Table 1. with $p = 1 = 0.5$, $p = 0.7$, $l = 0.4$, and $p = 0.8$, $l = 0.2$ and (a)$\epsilon = 1$, (b)$\epsilon = 0.5$, (c)$\epsilon = 0.1$, and (d)$\epsilon = 0.02$.

3. Now fix $p = 0.87$ and $l = 0.13$ and the rest of parameters are taken from Table 1. According to Proposition 2, there exists a unique equilibrium point $E^* = (0.9998, 6.0128e-04, 0.0014)$ when $\Re_o = 2.0474 > 1$ and $\gamma_3 = -1.9302e-06 < 0$. Starting with and initial condition $(0.9, 6.0128e-04, 0.0014)$, we plot the long term behavior of model (3) with different per-

turbation parameter values as depicted in Fig.(3). For all parts of the figure a,b,c and d where $\epsilon = 1, 0.1, 0.01$, and 0.001, respectively, we see that E^* is locally stable. With high attractiveness p, both the number of infected vectors and infected humans increases when decreasing ϵ from 1 to 0.1, then it becomes stable from $\epsilon = 0.01$ to $\epsilon = 0.001$.

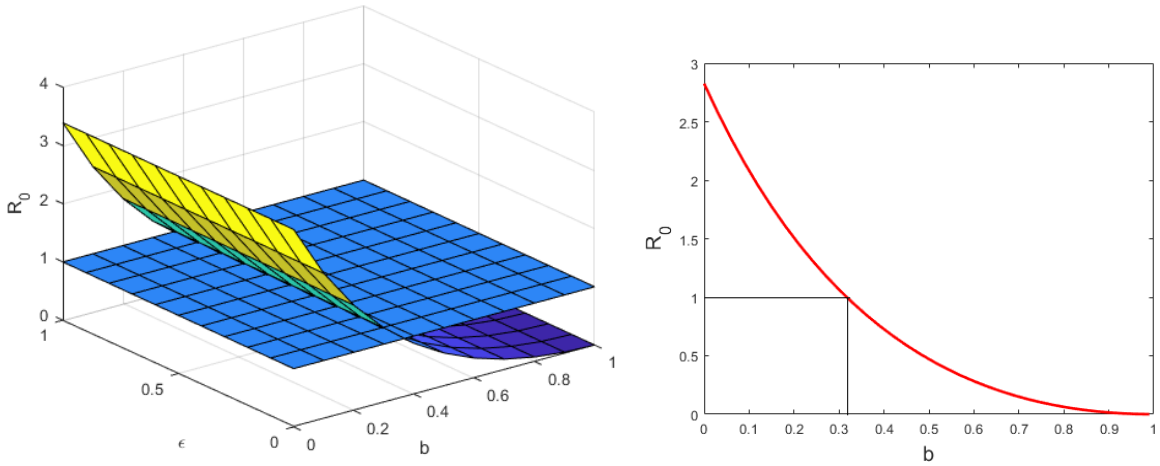


(a) (b)

(c) (d)

Figure 3: Time profile of model (2.4) with parameter values taken from Table 1 where $p = 0.87$, $l = 0.13$ and (a)$\epsilon = 1$, (b)$\epsilon = 0.1$, (c)$\epsilon = 0.01$, and (d)$\epsilon = 0.001$.

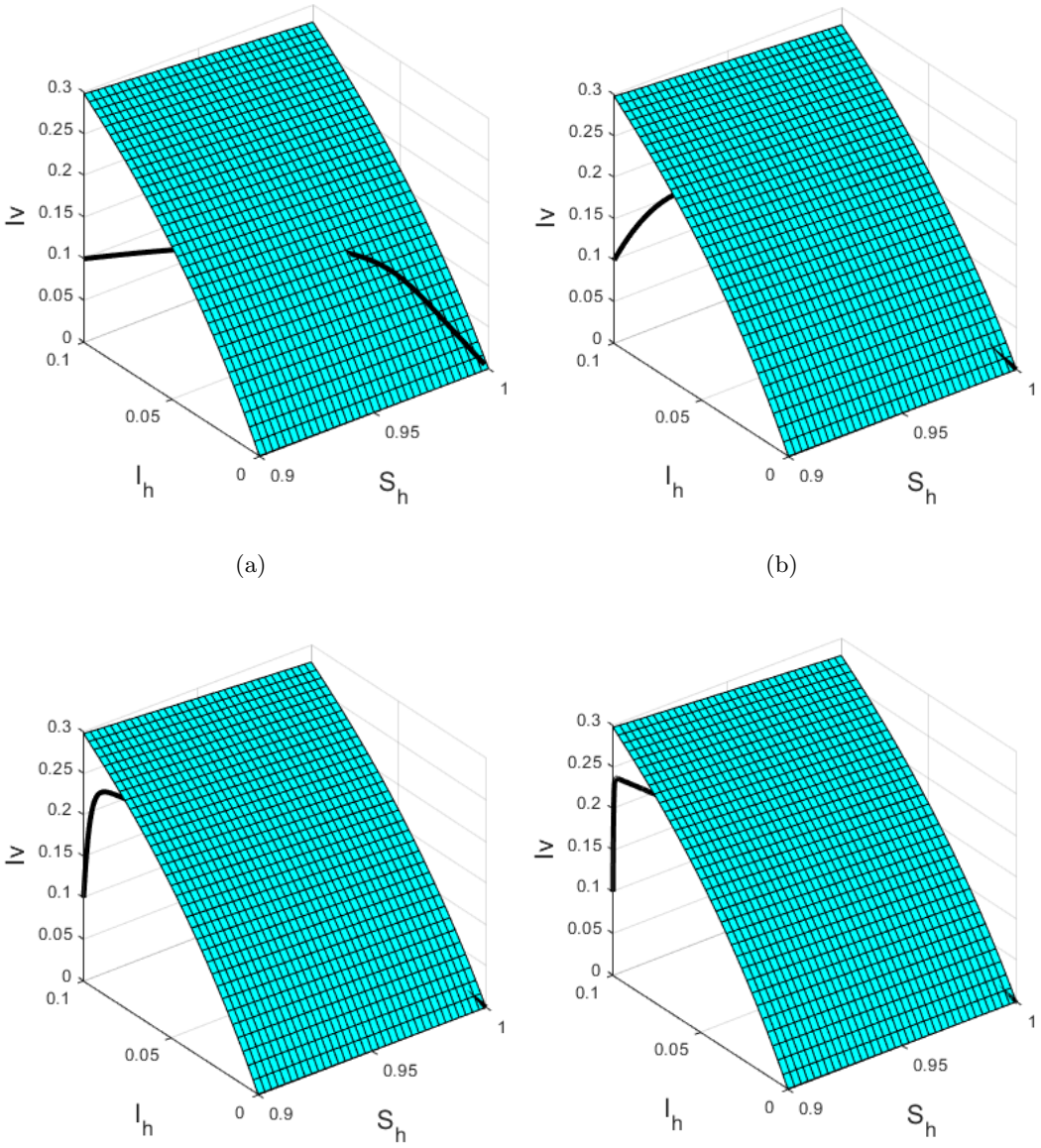
4. Take $p = 0.8$, $l = 0.6$ and keep the rest of parameters taken from Table 1, a surface plot for the basic reproduction number $\mathfrak{R}_o$ is represented in Fig.(4)a. As we can see, an increase of the bed-net usage b leads to a decline in the value of $\mathfrak{R}_o$, while a decrease in the perturbation parameter ϵ leads also to a decline in the value of $\mathfrak{R}_o$. With the same values for p and l, we plot the relation between b and $\mathfrak{R}_o$ in Fig.(4)b and as we can wee $\mathfrak{R}_o$ is a decreasing function of b. We also see that if over 30% of humans use ITNs, then $\mathfrak{R}_o$ can be reduced below one, and hence, malaria disease can be reduced.



(a) (b)

Figure 4: (a)Surface plot of $\mathfrak{R}_o$ of model (2.4) when $p = 0.8$ and $l = 0.6$ as a function of the perturbation parameter ϵ and bed-net usage b, (b) Relation between $\mathfrak{R}_o$ and b.

5. The trajectories of solution on the slow surface for $p = 0.8$ and $l = 0.4$ are plotted in Fig.(5)(a-d) with different perturbation parameter values; $\epsilon = 1, 0.1, 0.01$, and 0.001, respectively. We note that when $\epsilon = 0.001$, the portion of infectious mosquitoes decreases.



(a) (b)

(c) (d)

Figure 5: Slow surface dynamics with parameter values taken from Table 1 where $p = 0.8$, $l = 0.4$ and (a)$\epsilon = 1$, (b)$\epsilon = 0.1$, (c)$\epsilon = 0.01$, (d)$\epsilon = 0.001$ and an initial point $(0.9, 0.1, 0.1)$.

6 Conclusion

We modified a vector-bias model for malaria transmission proposed in (Chamchod et al. 2011), in which mosquitoes exhibit host selectivity. Several new interventions are currently being used to reduce malaria disease burden such as insecticide-treated bed-nets (ITNs). Since we are interested in reducing both the contact rate of humans and the contact rate of mosquitoes, we incorporated the bed-net usage b on both contact rates. Mosquitoes have a very short life cycle compared to humans, hence, host and vector dynamics act on two different time scales; slow for the host and fast for the vector. This is represented in our model by scaling both transmission and death rates of mosquitoes by the perturbation parameter $\epsilon \in [0, 1]$, that is, both the transmission and death rates of mosquitoes are very high compared to those of humans. As a consequence, the model is transformed into a singular perturbation model. The basic reproduction number $\mathfrak{R}_o$, a threshold to control malaria outbreak, is calculated using the next generation matrix method. Local stability analysis of the disease-free equilibrium and the endemic equilibrium is investigated when the singular perturbation parameter $0 < \epsilon < 1$. The disease-free equilibrium is locally stable if $\mathfrak{R}_o < 1$, that is, the disease dies out and the endemic equilibrium is locally stable if $\mathfrak{R}_o > 1$. The combination of these three modeling approaches, vector-bias, bed-net control, and singular perturbation, strongly affect the model dynamics. The peak of infection is reduced when $\epsilon \to 0$ while using bed-net control. We have seen that if over %30 of humans use ITNs, malaria disease burden can be reduced. Indeed, the increase of the bed-net usage b declines the value of $\mathfrak{R}_o$ when $\epsilon \to 0$ which have a great role in decreasing the portion of infected humans. We discussed the singular perturbation model when $\epsilon = 0$ by separating it into two subsystems, fast and slow then investigating them by asymptotic expansions and matching them. We point out that the deduced subsystems obtained here could be effective in obtaining more simpler models. Finally, the numerical simulations confirmed the theoretical analysis and revealed that the number of infected mosquitoes will be declined if the perturbation parameter $\epsilon = 0.001$. The proposed model can seen as a nonlinear control system, then different feedback control strategies can be used such as model predictive control (MPC) presented in [55].

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Appendix: