

Mathematical Analysis of Ivermectin as a Malaria Control Method

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1 Abstract

Malaria epidemics are detrimental to the health of many people and economies of many countries. There exist methods of malaria control, but the fight against the disease is far from being over. The history of mathematical modeling of malaria spread is more than hundred years old. Recently, a model was proposed in the literature that captures the dynamics of malaria transmission by taking into account the behavior and life cycle of the mosquito and its interaction with the human population. We modify this model by including the effect of an anti-parasitic medication, ivermectin, on several threshold parameters, which can determine the spread of malaria. The modified model takes a form of a system of nonlinear ordinary differential equations. We investigate this model using applied dynamical systems techniques. We were able to show that that exist parameter regimes such that careful use of ivermectin can curtail the spread of malaria without harming the mosquito population. Otherwise, the ivermectin either eradicates the mosquito population, or has little to no effect on the spread of malaria. We suggest that ivermectin can be very effective when used as a malaria control method in conjunction with other methods such as reduction of breeding sites.

2 Introduction

2.1 Background

Malaria, a disease caused by a mosquito-borne parasite, results in hundreds of thousands of deaths each year, primarily in sub-Saharan Africa. According to the 2014 WHO report [1] there were about 198 million cases of malaria in 2013, resulting in approximately 584,000 deaths, 90% of which occurred in sub-Saharan Africa. Roughly 78% of malaria related deaths were in children under five years of age. In addition to causing a large number of deaths, malaria can also damage the active and potential work force in a country,

24 hindering economic growth. Malaria is seen predominantly in areas with poor economic conditions to begin
25 with, making it challenging for the economy to flourish. Because of the detrimental effects of malaria, it is
26 clear that ongoing research for control methods for malaria can save future lives and boost the economies of
27 nations at risk. Malaria has been a recurring issue since as early as 1324 BC when it was said to have played
28 part in the death of the boy Pharaoh Tutankhamen [2]. Although the number of malaria infections a year
29 have dropped from 227 million in 2000 to 198 million in 2013 [3], there are still many areas where malaria
30 is prevalent.

31 As a response to this epidemic, several mathematicians have developed models in search of understanding
32 of malaria dynamics. The research began as early as 1911, when the Ross-Macdonald was the first to
33 create a model demonstrating the interaction between mosquitoes and humans which perpetuates malaria.
34 Although we will not go into depth about the history of malaria models, those interested may see [4] -
35 [6] for details. In 2012, as a part of this ongoing research, a Susceptible-Infectious-Susceptible model for
36 malaria that accounts for the interactions between the human and mosquito populations was created in [7] to
37 account for the complex dynamics of the disease. This model was among the first models which consider the
38 population dynamics of the mosquito population. Other models which consider the population dynamics of
39 the mosquito include [8], [9]. Specifically, the model in [7] considers factors related to local carrying capacity
40 of the mosquito population, as well as mosquito birth rates, that ultimately affect how the disease spreads
41 through the human population. The new, rich dynamics of the system provide valuable insight into what
42 factors most directly affect the spread of malaria, and make it possible to study many additional control
43 strategies.

44 In [7] the existence of zero, one, or two endemic steady states, Hopf bifurcations, and backwards (subcrit-
45 ical) bifurcations were shown. Furthermore, the effect of certain parameters, such as the carrying capacity
46 and birthrate mentioned above, on these phenomena was studied. Here we adapt the model used by [7]
47 account for the use of another control strategy in the form of medication. In particular, we investigate the
48 pharmaceutical drug *ivermectin*, a widely accepted broad-spectrum antiparasitic drug. Ivermectin has been
49 identified in [10] to cause infertility and death in the anopheles mosquito. When a mosquito bites a human
50 who has recently ingested ivermectin, it will die within 48-72 hours. If the concentration of ivermectin is
51 too weak, the mosquito will not die, but its eggs will not be fertile. Some recent studies [11]-[13] suggest
52 that ivermectin could be used as an additional control method for malaria. Here we study the possible
53 effects of ivermectin on malaria control and the mosquito population. We show that the medication can
54 eradicate malaria in certain cases without detrimental effects to the mosquito population. Although some

55 may argue that this complete eradication of mosquitoes is a viable solution, from an ecological stand point,
56 such action could be quite dangerous. Mosquitoes are a food source for predators and provide pollination
57 in any environments in which they reside, thus, their total disappearance could have a negative effect on an
58 ecological system. Although this effect could be studied further, we assume in this paper that the eradication
59 of mosquitoes is not desirable.

60 2.2 Ideas behind the Model

61 Malaria is caused by the parasite *Plasmodium* and is not transmissible by human to human contact. However,
62 a mosquito biting an infected human becomes infected and therefore can spread the disease to other humans.
63 Diseases such as malaria which are spread by a secondary source are referred to as *vector-borne* disease. In
64 the case of malaria, the female mosquito is the vector which spreads the disease. Since the female mosquitoes
65 rely on blood meals to reproduce, the transmission of malaria is driven by the life cycle of the mosquito.
66 The vector-borne transmission of malaria is of great importance in regards to understanding, and hopefully
67 controlling, the spread of the disease. In particular, the female *Anopheles* mosquito transmits or receives
68 the parasite while biting a human as part of the mosquito's reproductive cycle [14]. This is an important
69 distinction from many other diseases, as both mosquitoes and humans are intimately tied to one another
70 in both reception and transmission of the parasite. Thus, understanding the life cycle of the parasite-
71 bearing mosquito population directly influences the understanding of the dynamics of malaria in the human
72 population. Accordingly, a mathematical model for malaria must take into account the dynamics of the
73 disease, as well as the life cycles of mosquitoes, and their interaction with the human population.

74 It is important that only the life cycles of the female mosquitoes is relevant, as only the females transmit
75 the disease to humans. To model the spread of Malaria, the life of the mosquito can be split into three stages;
76 resting, questing, and fed. The life cycle of the mosquito starts in the resting stage, enters the questing stage
77 upon maturity where it begins searching for a blood-meal to reproduce, and if a meal is successfully taken,
78 enters into the fed stage. Examining the life of a mosquito, and specifically the reproduction process, it
79 is apparent that mosquitoes reproduce only after taking a blood-meal. After reproducing, the mosquitoes
80 re-enter the resting stage, and the cycle continues. It should also be noted that a mosquito is not guaranteed
81 a blood-meal while questing. It is possible for a mosquito to fail to take a meal, and live to attempt another
82 meal, and also to die within the questing stage.

83 Relating ivermectin to the life cycle structure introduced above, the drug would affect mosquitoes during
84 the transition from the questing stage to the fed stage. We focus here on the effect of the drug killing

85 mosquitoes that take a blood-meal from a medicated human. Essentially, ivermectin creates a break in the
86 life cycle of the mosquito, removing a mosquito from the system between the questing and fed stages. It
87 should also be noted that using ivermectin does not directly prevent disease transmission to people who
88 have taken the drug, or help cure infected individuals. Rather, the medication kills the mosquito, stopping
89 it from transmitting the disease after biting a person with ivermectin in their blood.

90 **3 The Model**

91 **3.1 The Model, Variables, and Parameters**

92 The mathematical model used here is a nonlinear system of ordinary differential equations. The primary
93 feature of the model is its focus on the life cycles of the mosquito vectors in the transmission of malaria.
94 The model itself is based on the model in [7], but includes additional features related to the administration
95 of the drug ivermectin, and its effect on the spread of the disease. The inclusion of the intricate life cycle
96 of the mosquitoes within the model allows for a realistic interpretation of the effects the drug would have if
97 administered in areas of the world struggling with the disease. The original model by [7] takes into account
98 the three stages of mosquito life described above; resting, questing, and fed. Further, each stage of mosquito
99 as well as the human population can be either susceptible or infected. The model utilizes parameters such as
100 flow rates of mosquitoes to and from human habitats, probabilities of mosquitoes successfully taking blood
101 from a human, and birth and death rates to capture the dynamics of the disease as accurately as possible.

102 For the portion of the model related to humans, birth and death are constant and transitions between
103 susceptible and infected are considered. Susceptible humans that have blood taken by an infected mosquito
104 become infected, and infected humans can also naturally recover at a slow rate. Within the mosquito
105 population, the vectors are born and die, and also transfer between each of the three life cycles, as well as
106 being either infected or susceptible. Susceptible mosquitoes can become infected by feeding on an infected
107 human. The variables and parameters used in the model are described in the Tables 1 and 2 respectively.
108 For a more technical, in depth description of the model, see [7].

109 As described above, the effect of ivermectin on the transmission of malaria is that mosquitoes which
110 take a blood meal from a medicated human will die before returning to the breeding site and successfully
111 reproducing. We assume that staggered doses of ivermectin will be given consistently to some portion M
112 of the population, thus that portion of the population will always have a large enough concentration of the

Description	Original Variable	Dimensionless Variable
Total human population	$N_h(t)$	
Susceptible humans	$S_h(t)$	
Infected humans	$I_h(t)$	i_h
Susceptible resting mosquitoes	$S_r(t)$	s_r
Susceptible questing mosquitoes	$S_q(t)$	s_q
Susceptible fed mosquitoes	$S_f(t)$	s_f
Infected resting mosquitoes	$I_r(t)$	i_r
Infected questing mosquitoes	$I_q(t)$	i_q
Infected fed mosquitoes	$I_f(t)$	i_f
Total mosquito population	$N_m(t)$	

Table 1: The variables for systems (1) and (5).

Parameter	Description
a_v	Fed mosquitoes rate of return to the breeding site.
$\alpha_v(N_h)$	Rate of mosquito attraction to humans.
$\mu_h, \mu_u, \mu_v, \mu_w$	Human and mosquito death rates.
$\lambda_v(S_r)$	birth rate of the resting mosquitoes (note: no other mosquitoes give birth).
r_h	Human recovery rate from malaria.
β_v	Flow rate of susceptible and questing mosquitoes to humans.
β_h	Flow rate of infectious and questing mosquitoes to humans.
p	Probability of blood being taken from a susceptible human by a susceptible mosquito.
q	Probability of blood being taken from an infected human by a susceptible mosquito.
p_1	Probability of blood being taken from an infected human by an infectious mosquito.
q_1	Probability of blood being taken from a susceptible human by an infectious mosquito.
M	The portion of humans which have mosquito killing levels ivermectin in their blood.
L	The mosquito carrying capacity in the local environment.

Table 2: The parameter descriptions for system (1).

113 drug in their system to kill the mosquitoes. The result is the following model,

$$\dot{S}_h = \mu_h N_h + r_h I_h - \beta_h S_h I_f - \mu_h S_h, \quad (1a)$$

$$\dot{I}_h = \beta_h S_h I_f - (\mu_h + r_h) I_h, \quad (1b)$$

$$\dot{S}_r = p \beta_v S_h S_f (1 - M) - (a_v + \mu_v) S_r, \quad (1c)$$

$$\dot{S}_q = a_v \lambda_v(S_r) S_r + a_v \lambda_v(I_r) I_r + a_v S_r - (\mu_v + \alpha_v(N_h)) S_q, \quad (1d)$$

$$\dot{S}_f = \alpha_v(N_h) S_q - (\mu_v + \beta_v N_h) S_f, \quad (1e)$$

$$\dot{I}_r = (p_1 \beta_h N_h I_f + q \beta_v I_h S_f) (1 - M) - (a_v + \mu_v) I_r, \quad (1f)$$

$$\dot{I}_q = a_v I_r - (\mu_v + \alpha_v(N_h)) I_q, \quad (1g)$$

$$\dot{I}_f = \alpha_v(N_h) I_q - (\mu_v + \beta_h N_h) I_f. \quad (1h)$$

114 with the equations for the total populations of mosquitoes and humans

$$\dot{N}_h = 0, \tag{2a}$$

$$\begin{aligned} \dot{N}_m = & p\beta_v S_h S_f (1 - M) + a_v (\lambda_v(S_r) S_r + \lambda_v(I_r) I_r) \\ & - ((1 - p_1)(\beta_h N_h I_f) + (1 - q)(\beta_v N_h S_f))(1 - M) - \mu_v N_m. \end{aligned} \tag{2b}$$

115 The effect of ivermectin is captured through the scaling of the questing mosquitoes which successfully take
 116 a blood meal by ratio of the humans medicated with the drug. In the system, the two terms in which are
 117 scaled are $p\beta_v S_h S_f$ in Equation (1c) and $p_1\beta_h N_h I_f + q\beta_v I_h S_f$ in Equation (1f). Ultimately, we assume that
 118 any mosquito taking blood from a medicated human dies before reaching the next stage of the life cycle. So
 119 we change the original model by scaling the mosquitoes entering the fed life stage by a constant $(1 - M)$.
 120 In this constant, M represents a proportion of the human population which are medicated with the drug
 121 ivermectin.

122 The system (1) also requires appropriate initial conditions in the form

$$(S_h(0), I_h(0), S_r(0), S_q(0), S_f(0), I_r(0), I_q(0), I_f(0)).$$

123 3.2 Positivity, Uniqueness of Solution, and Boundedness

124 Since the variables in this model represent populations, their values are non-negative. Therefore, we use a
 125 reasonable domain $\mathcal{D} \subset \mathbb{R}^8$,

$$\begin{aligned} \mathcal{D} = \{ & (S_h, I_h, S_r, S_q, S_f, I_r, I_q, I_f) : S_h \geq 0, I_h \geq 0, N_h \geq S_h + I_h \geq 0, S_r \geq 0, S_q \geq 0, S_f \geq 0, \\ & I_r \geq 0, I_q \geq 0, I_f \geq 0, N_m \geq S_r + S_q + S_f + I_r + I_q + I_f \geq 0 \}. \end{aligned}$$

126 Since the right hand side of the equations in (1) and (2) and their partial derivatives are continuous in \mathcal{D} , it
 127 can be verified by standard techniques as in [15] that for any initial condition in \mathcal{D} with

$$S_r(0) + S_q(0) + S_f(0) + I_r(0) + I_q(0) + I_f(0) = N_m(0) \text{ and } S_h + I_h = N_h,$$

128 there exists a unique solution to the system for all t . Also note that if $N_m(0) > 0$ then $N_m(t) > 0$ for all t
 129 and if $N_m(0) = 0$ then $N_m(t) = 0$ for all t . The same holds for the human population, N_h . Additionally we

130 note the following result for the mosquito population.

131 **Theorem 3.1.** *The closed set $\Phi = \{(S_r, S_q, S_f, I_r, I_q, I_f) \in \mathbb{R}^6 : N_m = S_r + S_q + S_f + I_r + I_q + I_f \leq \frac{2a_v\lambda_0 L}{\mu_v}\}$*
 132 *is positively invariant and attracting with respect to the system (1).*

133 *Proof.* See [7, Theorem 2.1]. □

134 3.3 Reparameterization and Nondimensionalization

135 We now scale the model by introducing dimensionless variables. Noting that $S_h = N_h - I_h$, we introduce
 136 the new variables:

$$\begin{aligned} s_r &= \frac{S_r}{L}, & s_q &= \frac{p\beta_v N_h \alpha(N_h)}{L(a_v + \mu_v)(\mu_v + \beta_v N_h)} S_q, & s_f &= \frac{p\beta_v N_h}{L(a_v + \mu_v)} S_f, & \tau &= (a_v + \mu_v)t, \\ i_r &= \frac{I_r}{L}, & i_q &= \frac{\mu_v + \alpha_v(N_h)}{a_v L} I_q, & i_f &= \frac{(\mu_v + \alpha_v(N_h))(\mu_v + \beta_h N_h)}{a_v L \alpha_v(N_h)} I_f, & i_h &= \frac{I_h}{N_h}, \end{aligned} \quad (3)$$

137 and the dimensionless parameter groupings:

$$\begin{aligned} \beta &= \frac{a_v \alpha_v(N_h) \beta_h L}{(a_v + \mu_v)(\mu_v + \alpha_v(N_h))(\mu_v + \beta_h N_h)}, & \delta &= \frac{a_v \alpha_v(N_h) \beta_h N_h p_1}{(a_v + \mu_v)(\mu_v + \alpha_v(N_h))(\mu_v + \beta_h N_h)}, & \mu &= \frac{\mu_h + r_h}{a_v + \mu_v}, \\ \sigma &= \frac{q}{p}, & \alpha &= \frac{a_v \alpha_v(N_h) \beta_h N_h p}{(a_v + \mu_v)^2 (\mu_v + \beta_v N_h)}, & \gamma &= \frac{\mu_v + \beta_v N_h}{a_v + \mu_v}, & \rho &= \frac{\mu_v + \alpha_v(N_h)}{a_v + \mu_v}, & \epsilon &= \frac{\mu_v + \beta_h N_h}{a_v + \mu_v}, \end{aligned} \quad (4)$$

138 to yield new parameters for the model. System (1) now takes the form:

$$\dot{i}_h = \beta(1 - i_h)i_f - \mu i_h, \quad (5a)$$

$$\dot{s}_r = (1 - i_h)s_f(1 - M) - s_r, \quad (5b)$$

$$\dot{s}_q = \alpha\lambda_0(s_r(1 - s_r) + i_r(1 - i_r)) + \alpha s_r - \rho s_q, \quad (5c)$$

$$\dot{s}_f = \gamma(s_q - s_f), \quad (5d)$$

$$\dot{i}_r = (\delta i_f + \sigma I s_f)(1 - M) - i_r, \quad (5e)$$

$$\dot{i}_q = \rho(i_r - i_q), \quad (5f)$$

$$\dot{i}_f = \epsilon(i_q - i_f), \quad (5g)$$

139 where the dots now represent the derivative with respect to τ . A feasible region for the parameter space is

140 $\Gamma = \{0 \leq \beta < L/N_h, \mu > 0, 0 < \alpha < \rho < 1, 0 \leq \delta < 1, \epsilon > 0, \rho > 0, \gamma > 0, \lambda_0 > 0\}$, for details see [7]. The
 141 system (5) requires an initial condition in the form $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0))$.

142 4 The Existence and Linear Stability of Steady States

143 4.1 The Disease Free System

144 In the absence of malaria, $i_h = 0, i_r = 0, i_q = 0, i_f = 0$, and our model (5) reduces to:

$$\dot{s}_r = s_f(1 - M) - s_r, \quad (6a)$$

$$\dot{s}_q = \alpha\lambda_0 s_r(1 - s_r) + \alpha s_r - \rho s_q, \quad (6b)$$

$$\dot{s}_f = \gamma(s_q - s_f). \quad (6c)$$

145 We identify a threshold parameter \mathcal{R}^* with the properties stated in the Theorems (4.1) and (4.2), where

$$\mathcal{R}^* = \frac{\alpha\lambda_0}{\frac{\rho}{1-M} - \alpha}. \quad (7)$$

146 **Theorem 4.1.** *The threshold parameter \mathcal{R}^* has the following properties:*

- 147 • If $\mathcal{R}^* \leq 1$, there exists only the trivial steady state, $E_0 = (s_r^*, s_q^*, s_f^*) = (0, 0, 0)$.
- 148 • If $\mathcal{R}^* > 1$, there exists, in addition to the trivial steady state E_0 , a non-trivial steady state

$$E_1 = (s_r^*, s_q^*, s_f^*) = \left(1 - \frac{1}{\mathcal{R}^*}, \frac{1 - \frac{1}{\mathcal{R}^*}}{1 - M}, \frac{1 - \frac{1}{\mathcal{R}^*}}{1 - M}\right). \quad (8)$$

149 *Proof.* We find the steady state solutions to system (6) by setting the right hand side of that system equal
 150 to zero and solving the resulting system of equations. It is straightforward calculation to verify that the
 151 existence of realistic steady state solutions as given by (7) and that if $\mathcal{R}^* > 1$ then E_1 as given in (8) exists.
 152 When $\mathcal{R}^* = 1$, E_1 reduces to the trivial steady state E_0 , and when $\mathcal{R}^* < 1$, E_1 is not a realistic steady
 153 state. □

154 **Remark 4.1.** From a biological standpoint, Theorem 4.1 states that the threshold parameter \mathcal{R}^* has the
 155 following effect on the mosquito population. If $\mathcal{R}^* < 1$, the mosquito population will die out over time. If

156 $\mathcal{R}^* = 1$, the mosquito population will remain constant. Finally, when $\mathcal{R}^* > 1$ the mosquito population will
 157 grow to the carrying capacity of the environment.

158 **Theorem 4.2.** *The trivial steady state always exists and is linearly stable to small perturbations. Let*

$$Y = \gamma + \rho + 1 > 0, \quad Z = \gamma + \rho + \gamma\rho > 0, \quad X = \gamma(\rho - \alpha(1 - M)) > 0 \quad \text{since } \rho > \alpha, M < 1. \quad (9)$$

159 *Then when $\mathcal{R}^* > 1$, the non-trivial steady state E_1 is linearly stable to small perturbations whenever*

$$YZ - X(\mathcal{R}^* - 1) > 0$$

160 *and can be driven to instability via a Hopf bifurcation at the point in the parameter space where*

$$YZ - X(\mathcal{R}^* - 1) = 0.$$

161 *Proof.* Stability of steady state solutions to the system (5) is determined by the signs of the eigenvalues of
 162 the linearized system at the steady state, namely

$$\begin{pmatrix} \dot{s}_r \\ \dot{s}_q \\ \dot{s}_f \end{pmatrix} = J(s_r^*, s_q^*, s_f^*) \begin{pmatrix} s_r \\ s_q \\ s_f \end{pmatrix} = \begin{pmatrix} -1 & 0 & 1 - M \\ \alpha(\lambda_0 + 1) - 2\alpha\lambda_0 s_r^* & -\rho & 0 \\ 0 & \gamma & -\gamma \end{pmatrix} \begin{pmatrix} s_r \\ s_q \\ s_f \end{pmatrix},$$

163 where $J(s_r^*, s_q^*, s_f^*)$ is the Jacobian matrix of the system evaluated at the steady state. If k is an eigenvalue
 164 of $J(s_r^*, s_q^*, s_f^*)$ then k is a solution to the characteristic equation

$$k^3 + Yk^2 + Zk + \rho\gamma + 2\gamma\alpha\lambda_0 s_r^*(1 - M) - \gamma\alpha(\lambda_0 + 1)(1 - M) = 0, \quad (10)$$

165 where Y and Z are as stated in Equation (9). It then follows that at E_0 , $s_r^* = 0$, and all solutions to Equation
 166 (10) have negative real parts when $\mathcal{R}^* \leq 1$. Additionally, when $\mathcal{R}^* > 1$ the solution to (10) has positive
 167 real parts, so perturbations grow exponentially and at E_1 , $s_r^* = 1 - \frac{1}{\mathcal{R}^*}$. Routh - Hurwitz stability criterion
 168 tells us that solutions of Equation (10) have negative real parts when $YZ - X(\mathcal{R}^* - 1) > 0$, and a Hopf
 169 Bifurcation occurs where $X(\mathcal{R}^* - 1) = YZ$. □

170 **Remark 4.2.** From a biological standpoint, Theorem 4.2 says the following. If there are no mosquitoes in
 171 the environment, introducing a small number mosquitoes will have no long term effect on the population of

172 mosquitoes, they will simply die out again shortly. Similarly, if there is a living population of mosquitoes
 173 ($\mathcal{R}^* > 1$) introducing or killing a small number mosquitoes will have no long term effect on the population
 174 of mosquitoes unless $YZ - X(\mathcal{R}^* - 1) > 0$. In the later case, introducing or killing some mosquitoes may
 175 have a long term effect on the population of mosquitoes.

176 **Remark 4.3.** We note that the condition $YZ - X(\mathcal{R}^* - 1) > 0$ is equivalent to

$$1 - \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma\rho) + \gamma\rho}{\gamma\alpha(\lambda_0 + 1)} < M < 1$$

177 in terms of M . Additionally, in the case that $M = 0$, it was found in [7] that $YZ - X(\mathcal{R}^* - 1) > 0$ is
 178 equivalent to

$$0 < \lambda_0(\gamma) < \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma\rho) + \gamma(\rho - \alpha)}{\alpha\gamma}$$

179 in the (γ, λ_0) space. Thus the conditions for a Hopf Bifurcation to occur are both

$$\lambda_0(\gamma) \geq \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma\rho) + \gamma(\rho - \alpha)}{\alpha\gamma} \quad \text{and} \quad 0 < M = 1 - \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma\rho) + \gamma\rho}{\gamma\alpha(\lambda_0(\gamma) + 1)}.$$

180 **Theorem 4.3.** *The trivial steady state E_1 is globally and asymptotically stable whenever $\mathcal{R}^* \leq 1$.*

181 *Proof.* See [18]. □

182 4.2 The Basic Reproduction Number

183 In a disease model, an essential threshold parameter is the basic reproduction number \mathcal{R}_0 which is a measure
 184 of the average number of secondary cases of the disease caused by a single infected individual in an otherwise
 185 susceptible population [16]. It is generally assumed that when $\mathcal{R}_0 < 1$ the disease disappears from a
 186 community and when $\mathcal{R}_0 > 1$ the disease remains and spreads throughout the community. The critical case
 187 in which $\mathcal{R}_0 = 1$ leaves the community with a constant number of infected individuals. In some cases, there
 188 is a possibility of backward bifurcation which complicates disease control because $\mathcal{R}_0 < 1$ may not be enough
 189 to curtail the spread of the disease. This phenomena is discussed further in Section 4.5.

190 To calculate \mathcal{R}_0 we use the next generation method where \mathcal{R}_0 is the spectral radius of the next generation
 191 matrix. The spectral radius is the eigenvalue with the largest absolute value. As in [16], [17] we calculate
 192 $\tilde{\mathcal{R}}_0$ to be the spectral radius of the next generation matrix $\mathcal{M} = \mathcal{F}\mathcal{V}^{-1}$ where

$$\mathcal{F} = \begin{pmatrix} 0 & 0 & 0 & \beta_h N_h \\ q\beta_v S_f^*(1-M) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} \mu_h + r_h & 0 & 0 & 0 \\ 0 & a_v + \mu_v & 0 & -p_1\beta_h N_h(1-M) \\ 0 & -a_v & \mu_v + \alpha_v(N_h) & 0 \\ 0 & 0 & -\alpha_v(N_h) & \mu_v + \beta_h N_h \end{pmatrix}$$

From these we obtain the eigenvalue

$$\tilde{\mathcal{R}}_0 = \sqrt{\frac{\beta_v \beta_h N_h S_f^*(1-M)}{\mu_v(r_h + \mu_h)} q \frac{a_v \alpha_v(N_h)}{a_v \alpha_v(N_h) \left(1 + \frac{\beta_h N_h(1-p_1(1-M))}{\mu_v}\right) + (\mu_v + \beta_h N_h)(a_v + \alpha_v(N_h) + \mu_v)}}$$

and, in dimensionless parameters,

$$\tilde{\mathcal{R}}_0 = \sqrt{\frac{s_f^* \sigma \beta (1-M)}{(1-\delta(1-M))\mu}} = \sqrt{\frac{\sigma \beta (\mathcal{R}^* - 1)}{(1-\delta(1-M))\mu \mathcal{R}^*}}$$

We note here that, since $\mathcal{R}^* > 1$ and $0 \leq \delta(1-M) < 1$, $\tilde{\mathcal{R}}_0$ is a positive real number. Also note that when $0 < \tilde{R}_0 \leq 1$, $0 < \tilde{\mathcal{R}}_0^2 \leq 1$ and when $1 < \tilde{\mathcal{R}}_0$, $1 < \tilde{\mathcal{R}}_0^2$. We use the value $\mathcal{R}_0 = \tilde{\mathcal{R}}_0^2$, which coincides with the value of the basic reproduction number which can be obtained by seeking conditions for the existence of a steady state as in [7]. That is, we use the value

$$\mathcal{R}_0 = \frac{s_f^* \sigma \beta (1-M)}{(1-\delta(1-M))\mu} = \frac{\sigma \beta (\mathcal{R}^* - 1)}{(1-\delta(1-M))\mu \mathcal{R}^*}. \quad (11)$$

The squaring of $\tilde{\mathcal{R}}_0$ to obtain \mathcal{R}_0 is due to the fact that the transmission of malaria takes place via the mosquito, so the mosquito must bite two humans to transmit the disease. That is, the mosquito must first bite the single introduced infectious individual and then bite one of the susceptible individuals.

4.3 Existence of Steady States

Theorem 4.4. *In the presence of malaria there is a trivial steady state,*

$$E_0 = (0, 0, 0, 0, 0, 0),$$

205 a disease free steady state,

$$E_{df} = (i_h^*, s_r^*, s_q^*, s_f^*, i_r^*, i_q^*, i_f^*) = \left(0, 1 - \frac{1}{\mathcal{R}^*}, \frac{1 - \frac{1}{\mathcal{R}^*}}{1 - M}, \frac{1 - \frac{1}{\mathcal{R}^*}}{1 - M}, 0, 0, 0\right),$$

206 where \mathcal{R}^* is defined in (7) and either zero one or two endemic steady states,

$$E_e = (i_h^*, s_r^*, s_q^*, s_v^*, u_r^*, i_q^*, i_v^*),$$

207 whose existence are determined by the size of the threshold parameter \mathcal{R}_0 and the value of the parameters

$$A_1 = 1 - \frac{\rho\beta s_r^*}{\mu\alpha\lambda_0(1 - M)} \quad \text{and} \quad A_2 = s_r^*(1 - \frac{1}{\mathcal{R}^*} - s_r^*) = s_r^{*2}(\mathcal{R}_0 - 1). \quad (12)$$

208 When E_e exists it can be written in terms of i_f^* , the scaled endemic steady state of infectious, fed, mosquitoes.

209 *Proof.* The steady states of the malaria model are found by setting the right hand side of (5) equal to zero

210 and solving the resulting system of equations. Some algebra shows that the resulting constant solutions, i_h^* ,

211 s_r^* , s_q^* , s_f^* , i_r^* , i_q^* , and i_f^* , can be written in terms of i_f^* as follows.

$$\begin{aligned} i_h^*(i_f^*) &= \frac{\beta i_f^*}{\beta i_f^* + \mu}, & s_r^* &= \frac{\mu(1 - \delta(1 - M))}{\sigma\beta}, & i_r^* &= i_q^* = i_f^*, \\ s_q^*(i_f^*) &= s_f^*(i_f^*) = s_r^* \left(\frac{1}{1 - M}\right) \left(1 + \frac{\beta i_f^*}{\mu}\right), \end{aligned} \quad (13)$$

212 where i_f^* is a positive solution to the equation

$$i_f^{*2} - A_1 i_f^* - A_2 = 0, \quad (14)$$

213 with A_1 and A_2 given by (12). Solving for i_f^* we obtain

$$i_{f1,2}^* = \frac{A_1 \pm \sqrt{A_1^2 + 4A_2}}{2}, \quad (15)$$

214 whose existence as a real and positive solution is determined by the size and sign of A_1 and A_2 , leading to

215 the possibility of zero, one, or two solutions. \square

216 **Remark 4.4.** From a biological standpoint, Theorem 4.4 states that the following situations are possible.

217 There can be no mosquitoes and thus no malaria. There can be mosquitoes but no malaria. There can
 218 be mosquitoes and malaria. And lastly, when there are mosquitoes and malaria, there are situations in
 219 which the infected portion of the human population can fluctuate, sometimes quite a bit, by increasing or
 220 decreasing the infected mosquito population. The parameters A_1 and A_2 determine which of these cases
 221 occurs.

222 **Remark 4.5.** As can be seen in Figure 1, the various possibilities for the number and sizes of endemic
 223 steady states, depending on the signs of our threshold parameters A_1 , A_2 , and Δ where $\Delta = A_1^2 + 4A_2$ are
 224 as follows:

225 1. If $A_2 > 0$, $A_1 < 0$, and $\Delta > 0$ then there is a unique endemic steady state defined by

$$\begin{aligned}
 i_h^* &= \frac{\alpha\lambda_0\sigma\beta(1-M) - \rho\beta(1-\delta(1-M)) + \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2}}{\alpha\lambda_0\sigma\beta(1-M) - \rho\beta(1-\delta(1-M)) + \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2} + 2\mu\alpha\lambda_0\sigma(1-M)}, \\
 s_r^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta}, \\
 s_q^* = s_f^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta(1-M)} \left(1 + \frac{\beta \left(\sigma\alpha\lambda_0(1-M) - \rho(1-\delta(1-M)) + \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2} \right)}{2\mu\alpha\lambda_0\sigma(1-M)} \right), \\
 i_r^* = i_q^* = i_f^* &= \frac{\sigma\alpha\lambda_0(1-M) - \rho(1-\delta(1-M)) + \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2}}{2\alpha\lambda_0\sigma(1-M)}.
 \end{aligned}
 \tag{16}$$

226 2. If $A_2 > 0$, $A_1 = 0$, and $\Delta > 0$ the unique endemic steady state is defined by

$$\begin{aligned}
 i_h^* &= \frac{(1-\delta(1-M))\sqrt{\mathcal{R}_0-1}}{(1-\delta(1-M))\sqrt{\mathcal{R}_0-1} + \sigma}, \\
 s_r^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta}, \\
 s_q^* = s_f^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta(1-M)} \left(1 + \frac{(1-\delta(1-M))\sqrt{\mathcal{R}_0-1}}{\sigma} \right), \\
 i_r^* = i_q^* = i_f^* &= \frac{\mu(1-\delta(1-M))\sqrt{\mathcal{R}_0-1}}{\sigma\beta}.
 \end{aligned}
 \tag{17}$$

227 3. If $A_2 > 0$, $A_1 > 0$, and $\Delta > 0$ the unique endemic steady state is represented by the equations in (16),
 228 however, the steady state values will differ numerically since there is a change in the sign of A_1 .

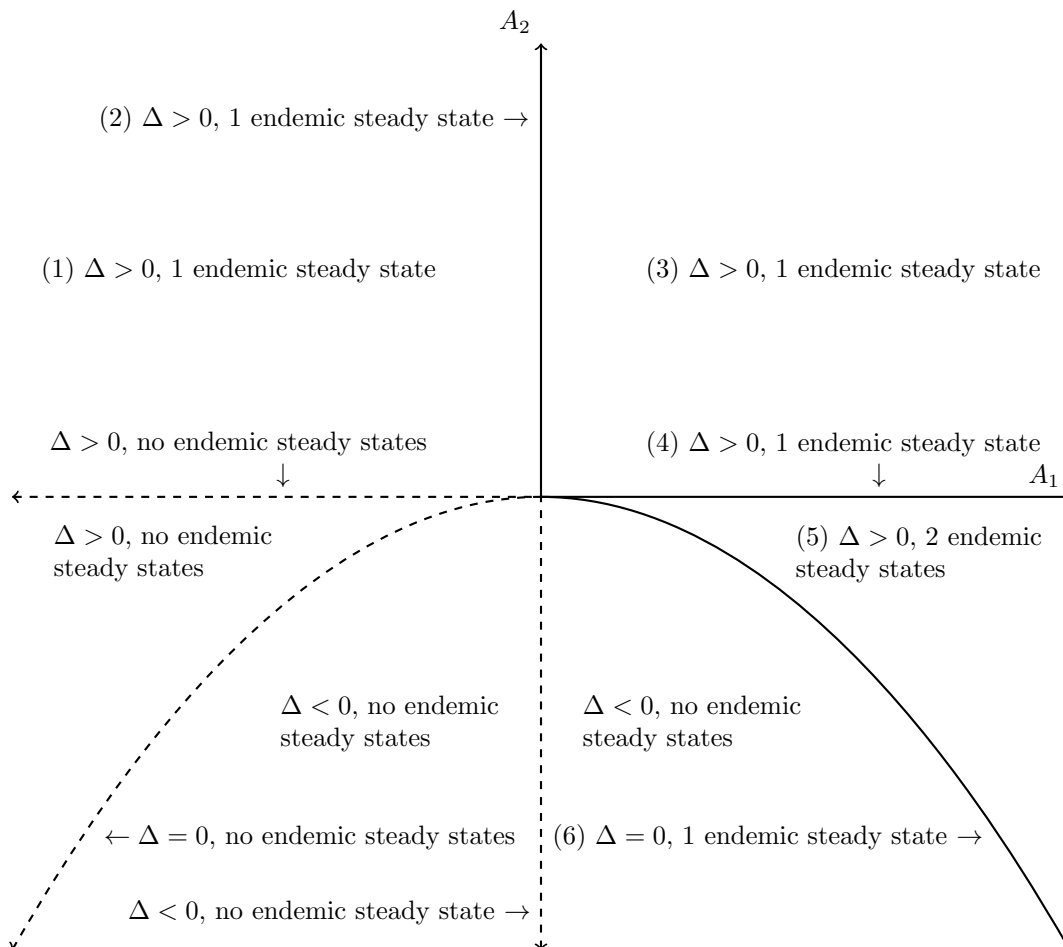


Figure 1: The A_1 , A_2 parameter space showing the possible number of endemic steady state solutions to Equation (5). Note that $\Delta = A_1^2 + 4A_2$, the discriminant of Equation (15). Lines which are broken contain no realistic endemic steady states, while lines which are solid contain realistic endemic steady states. We note here that the condition $\mathcal{R}_0 > 1$ is equivalent to $A_2 > 0$ and $\mathcal{R}_0 < 1$ is equivalent to $A_2 < 0$. Here we can see that by changing the signs of A_1 , A_2 , and Δ , all of which depend on M , we can control the number of realistic endemic steady states. Figure adapted from [7].

229

4. If $A_2 = 0$, $A_1 > 0$, and $\Delta > 0$ the unique endemic steady state is defined by

$$\begin{aligned}
 i_h^* &= \frac{\beta\alpha\lambda_0\sigma(1-M) - \beta\rho(1-\delta(1-M))}{\beta\alpha\lambda_0\sigma(1-M) - \beta\rho(1-\delta(1-M)) + \mu\alpha\lambda_0\sigma(1-M)}, \\
 s_r^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta}, \\
 s_q^* = s_f^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta(1-M)} \left(1 + \frac{\beta(\alpha\lambda_0\sigma(1-M) - \rho(1-\delta(1-M)))}{\mu\alpha\lambda_0\sigma(1-M)} \right), \\
 i_r^* = i_q^* = i_f^* &= \frac{\alpha\lambda_0\sigma(1-M) - \rho(1-\delta(1-M))}{\alpha\lambda_0\sigma(1-M)}.
 \end{aligned} \tag{18}$$

230

5. If $A_2 < 0$, $A_1 > 0$, and $\Delta > 0$ the model has feasible endemic steady states defined by

$$\begin{aligned}
 i_{h1,2}^* &= \frac{\alpha\lambda_0\sigma\beta(1-M) - \rho\beta(1-\delta(1-M)) \pm \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2}}{\alpha\lambda_0\sigma\beta(1-M) - \rho\beta(1-\delta(1-M)) \pm \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2} + 2\mu\alpha\lambda_0\sigma(1-M)}, \\
 s_{r1,2}^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta}, \\
 s_{q1,2}^* = s_{f1,2}^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta(1-M)} \left(1 + \frac{\beta(\sigma\mu\alpha\lambda_0 - \rho((1-M)^{-1} - \delta) \pm \sqrt{\Delta(\alpha\lambda_0\sigma)^2})}{2\mu\alpha\lambda_0\sigma} \right), \\
 i_{r1,2}^* = i_{q1,2}^* = i_{f1,2}^* &= \frac{\sigma\alpha\lambda_0(1-M) - \rho(1-\delta(1-M)) \pm \sqrt{\Delta(\alpha\lambda_0\sigma(1-M))^2}}{2\alpha\lambda_0\sigma(1-M)}.
 \end{aligned} \tag{19}$$

231

6. If $A_2 < 0$, $A_1 > 0$, and $\Delta = 0$ the unique endemic steady state is defined by

$$\begin{aligned}
 i_h^* &= \frac{\beta\sigma\alpha\lambda_0(1-M) - \beta\rho(1-\delta(1-M))}{\sigma\alpha\lambda_0(1-M) - \rho(1-\delta(1-M)) + 2\mu\sigma\alpha\lambda_0(1-M)}, \\
 s_r^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta}, \\
 s_q^* = s_f^* &= \frac{\mu(1-\delta(1-M))}{\sigma\beta(1-M)} \left(1 + \frac{\beta(\sigma\alpha\lambda_0(1-M) - \rho(1-\delta(1-M)))}{2\mu\sigma\alpha\lambda_0(1-M)} \right), \\
 i_r^* = i_q^* = i_f^* &= \frac{\sigma\alpha\lambda_0(1-M) - \rho(1-\delta(1-M))}{2\sigma\alpha\lambda_0(1-M)}.
 \end{aligned} \tag{20}$$

232

Otherwise there exists no endemic steady states. Thus the importance of seeking values of M between zero

233

and one which can change A_1 , A_2 , and Δ so that there exists no endemic steady state is clear.

234

4.4 Stability of Steady States

235

We now analyze the linear stability of the system in (5). We linearize the system about the steady state

236

$(i_h^*, s_r^*, s_q^*, s_f^*, i_r^*, i_q^*, i_f^*)$ to obtain:

$$\begin{array}{l}
237 \\
238
\end{array}
\begin{pmatrix} \dot{i}_h \\ \dot{s}_r \\ \dot{s}_q \\ \dot{s}_f \\ \dot{i}_r \\ \dot{i}_q \\ \dot{i}_f \end{pmatrix} = \begin{pmatrix} -(\beta i_f^* + \mu) & 0 & 0 & 0 & 0 & 0 & \beta(1 - i_h^*) \\ -s_f^*(1 - M) & -1 & 0 & (1 - i_h^*)(1 - M) & 0 & 0 & 0 \\ 0 & \alpha\lambda_0(1 - 2s_r^*) + \alpha & -\rho & 0 & \alpha\lambda_0(1 - 2i_r^*) & 0 & 0 \\ 0 & 0 & \gamma & -\gamma & 0 & 0 & 0 \\ \sigma s_f^*(1 - M) & 0 & 0 & \sigma i_h^*(1 - M) & -1 & 0 & \delta(1 - M) \\ 0 & 0 & 0 & 0 & \rho & -\rho & 0 \\ 0 & 0 & 0 & 0 & 0 & \epsilon & -\epsilon \end{pmatrix} \begin{pmatrix} i_h \\ s_r \\ s_q \\ s_f \\ i_r \\ i_q \\ i_f \end{pmatrix}.$$

239 **Proposition 4.1.** *The trivial steady state is linearly stable to small perturbations whenever $\mathcal{R}^* \leq 1$ and*
240 *unstable when $\mathcal{R}^* > 1$.*

241 *Proof.* To determine the linear stability of the trivial steady state we find the eigenvalues of the Jacobian
242 matrix evaluated at $E_0 = (0, 0, 0, 0, 0, 0, 0)$,

$$243 \quad J(E_0) = \begin{pmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & \beta \\ 0 & -1 & 0 & 1 - M & 0 & 0 & 0 \\ 0 & \alpha(\lambda_0 + 1) & -\rho & 0 & \alpha\lambda_0 & 0 & 0 \\ 0 & 0 & \gamma & -\gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & \delta(1 - M) \\ 0 & 0 & 0 & 0 & \rho & -\rho & 0 \\ 0 & 0 & 0 & 0 & 0 & \epsilon & -\epsilon \end{pmatrix}.$$

244 If k is an eigenvalue of $J(E_0)$, k is a solution to the characteristic equation

$$(\mu + k)(k^3 + Xk^2 + Yk + Z(1 - \mathcal{R}^*)) (k^3 + X_1k^2 + Y_1k + Z_1) = 0, \tag{21}$$

245 where X, Y, Z are defined in Equation (9) and

$$X_1 = \epsilon\rho(1 - \delta(1 - M)), \quad Y_1 = \epsilon + \rho + 1, \quad Z_1 = \epsilon\rho + \epsilon + \rho. \tag{22}$$

246 Note that $X_1 > 0$ since $0 \leq \delta < 1$ and $M < 1$.

247 We can see that the characteristic equation takes the form of three polynomials, multiplied together. It

248 is clear that $Y_1 Z_1 - X_1 > 0$ so Routh-Hurwitz tells us that the roots of the right hand cubic in (21) have
 249 negative real parts. Additionally, since $\mu > 0$, $(\mu + k)$ has only solutions with negative real parts. Finally,
 250 Theorem 4.2 with $s_r^* = 0$ tells us the left cubic in Equation (21) has only negative real parts when $\mathcal{R}^* \leq 1$
 251 but has solutions with positive real parts when $\mathcal{R}^* > 1$. Thus the trivial steady state is unstable to small
 252 perturbations whenever $\mathcal{R}^* > 1$, and is stable whenever $\mathcal{R}^* \leq 1$. \square

253 **Proposition 4.2.** *When $\mathcal{R}^* > 1$, the disease free steady state exists and is linearly stable to small perturba-*
 254 *tions whenever $YZ - X(\mathcal{R}^* - 1) > 0$ and $\mathcal{R}_0 < 1$ but can become unstable via Hopf Bifurcation, even when*
 255 *$\mathcal{R}_0 < 1$ at the point where $YZ - X(\mathcal{R}^* - 1) = 0$. The disease free steady state is always linearly unstable*
 256 *whenever $\mathcal{R}_0 > 1$.*

Proof. To determine the linear stability of the disease free steady state we find the eigenvalues of the Jacobian matrix evaluated at $E_{df} = (0, s_r^*, s_q^*, s_f^*, 0, 0, 0)$. If k is an eigenvalue of

$$J(E_{df}) = \begin{pmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & \beta \\ -s_f^*(1-M) & -1 & 0 & (1-M) & 0 & 0 & 0 \\ 0 & \alpha\lambda_0(1-2s_r^*) + \alpha & -\rho & 0 & \alpha\lambda_0 & 0 & 0 \\ 0 & 0 & \gamma & -\gamma & 0 & 0 & 0 \\ \sigma s_f^*(1-M) & 0 & 0 & 0 & -1 & 0 & \delta(1-M) \\ 0 & 0 & 0 & 0 & \rho & -\rho & 0 \\ 0 & 0 & 0 & 0 & 0 & \epsilon & -\epsilon \end{pmatrix},$$

257 then k is a solution to the characteristic polynomial

$$(k^3 + Xk^2 + Yk + Z(\mathcal{R}^* - 1)) = 0, \quad (23)$$

258 or

$$(k^4 + (Y_1 + \mu)k^3 + (\mu Y_1 + Z_1)k^2 + (\mu Z_1 + Y_1)k + X_1\mu(1 - \mathcal{R}_0)) = 0, \quad (24)$$

259 where X, Y, Z are defined in Equation (9) and X_1, Y_1, Z_1 are defined in Equation (22). It can immediately
 260 be seen that whenever $\mathcal{R}_0 > 1$, $\mu(1 - \mathcal{R}_0) < 0$ and thus there is at least one sign change in the coefficients

261 of the characteristic equation. Hence there is at least one positive real value for k and so E_{df} is linearly
 262 unstable to small perturbations whenever $\mathcal{R}_0 > 1$. When $\mathcal{R}_0 \leq 1$, $\mu(1 - \mathcal{R}_0) \geq 0$, thus all the coefficients
 263 of Equation (24) are non-negative, so Descartes rule of signs tells us that there are no positive real values k
 264 which satisfy the characteristic equation. We now use Routh - Hurwitz criteria to show that all solutions to
 265 (24) have negative real parts whenever $\mathcal{R}_0 \leq 1$. To do this we must show

$$(Y_1 + \mu)(\mu Y_1 + Z_1)(\mu Z_1 + X_1) > (\mu Z_1 + X_1)^2 + (Y_1 + \mu)^2 \mu X_1 (1 - \mathcal{R}^*). \quad (25)$$

266 We subtract the right hand side of Equation (25) from the left hand side and simplify to obtain

$$(\mu Z_1 + X_1)(Y_1 Z_1 - X_1) + (Y_1 + \mu)^2 \mu X_1 \mathcal{R}_0 + (Y_1 + \mu) \mu^2 (Y_1 Z_1 - X_1) > 0, \text{ since } (Y_1 Z_1 - X_1) > 0. \quad (26)$$

267 Thus any eigenvalues with positive real parts must be generated by Equation (23). This polynomial is the
 268 same as the polynomial in Equation (9) so the relevant results of Theorem 4.2 carry over and E_{df} is unstable
 269 to small perturbations even when $\mathcal{R}_0 < 1$ whenever

$$\lambda_0(\gamma) \geq \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma\rho) + \gamma(\rho - \alpha)}{\alpha\gamma} \quad \text{and} \quad 0 < M < 1 - \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma\rho) + \gamma\rho}{\gamma\alpha(\lambda_0(\gamma) + 1)}.$$

270

□

271 **Remark 4.6.** The endemic steady state E_e studied in [7] can be linearly stable to or unstable to small
 272 perturbations and when instabilities occur, they are oscillatory, caused by a Hopf Bifurcation. For details
 273 and proof see [7, Proposition 3.10].

274 4.5 Backward Bifurcation

275 For \mathcal{R}_0 , there exists a threshold value $\mathcal{R}_0^{bb} < 1$ such that when $\mathcal{R}_0 < \mathcal{R}_0^{bb} < 1$ or $\mathcal{R}_0^{bb} < \mathcal{R}_0 < 1$ and $A_1 \leq 0$
 276 there exists no endemic steady states, but when $\mathcal{R}_0^{bb} < \mathcal{R}_0 < 1$ and $A_1 > 0$ there exists two endemic steady
 277 states where

$$\mathcal{R}_0^{bb} = 1 - \left(\frac{A_1}{2s_r^*} \right)^2 = 1 - \left(\frac{\beta(\sigma\alpha\lambda_0(1-M) - \rho(1 - \delta(1-M)))}{2\mu(1 - \delta(1-M))\alpha\lambda_0(1-M)} \right)^2. \quad (27)$$

278 We compute the value of \mathcal{R}_0^{bb} by setting $\Delta = 0$. From here we can see that when $\mathcal{R}_0 < \mathcal{R}_0^{bb} < 1$, $\Delta < 0$
 279 and thus there are no endemic steady states. Also when $\mathcal{R}_0^{bb} < \mathcal{R}_0 < 1$ and $A_1 \leq 0$ we can see $\Delta > 0$ but
 280 since $A_1 \leq 0$ there are no endemic steady states. Furthermore, when $\mathcal{R}_0^{bb} < \mathcal{R}_0 < 1$ and $A_1 > 0$ we can see
 281 $\Delta > 0$ and $A_2 < 0$. In this case there exist two endemic steady states, even though $\mathcal{R}_0 < 1$. Thus a control
 282 method focusing solely on driving \mathcal{R}_0 below one will not always be effective unless $\mathcal{R}_0 < \mathcal{R}_0^{bb} < 1$. To prove
 283 the existence of backwards bifurcation, the techniques of [7, Theorem 3.6] could be used.

284 4.6 Finding Critical M Values

285 If $M = 0$, the model regresses to its original form in [7]. Additionally, the realistically non feasible case
 286 of $M = 1$ is trivial, because it most certainly causes the mosquito population to die out, resulting in the
 287 trivial steady state. We now develop the following Theorems and Remarks to search for critical values of
 288 $0 < M < 1$ such that the mosquito population is not destroyed (i.e. $\mathcal{R}^* > 1$) but the disease will die out
 289 ($\mathcal{R}_0 < 1$ or $\mathcal{R}_0 < \mathcal{R}_0^{bb} < 1$).

290 **Remark 4.7.** By setting A_1, A_2 , and Δ each equal to zero, we can solve for M to find the critical values
 291 $0 < M_{A_1}, M_{A_2}, M_\Delta < 1$ such that A_1, A_2 , and Δ change signs. Note that it is possible for A_2 and Δ to
 292 change signs multiple times. From there we can easily determine the values of M such that A_1, A_2 , and Δ
 293 are positive, negative, or zero. This method is used in Section 5 where we do some numerical simulations.

294 **Theorem 4.5.** *There is a threshold parameter*

$$M_{\mathcal{R}^*} = 1 - \frac{\rho}{(1 + \lambda_0)\alpha} \quad (28)$$

295 *such that when $M \geq M_{\mathcal{R}^*}$, there exists only the trivial steady state E_0 .*

296 *Proof.* Setting $\mathcal{R}^* = 1$ in Equation (7), we then solve the resulting equation for M to obtain (28). It is
 297 then clear that $M \geq 1 - \frac{\rho}{(1 + \lambda_0)\alpha}$ is equivalent to $\mathcal{R}^* \leq 1$ and thus only the trivial steady state exists when
 298 $M \geq M_{\mathcal{R}^*}$. □

299 **Theorem 4.6.** *There is a threshold parameter*

$$M_{\mathcal{R}_0} = 1 - \frac{\mu}{s_f^* \sigma \beta + \delta \mu}, \quad (29)$$

300 *such that whenever $M > M_{\mathcal{R}_0}$, $\mathcal{R}_0 < 1$ and whenever $M < M_{\mathcal{R}_0}$, $\mathcal{R}_0 > 1$.*

Parameter	μ_h	r_h	μ_v	a_v	$\alpha_v(N_h)$	p	q	p_1	β_h	β_v
Value Used	$\frac{1}{60*365}$	$\frac{1}{80}$	$\frac{1}{21}$.5	.5	.8	.9	.9352	$4.4524(10^{-6})$	$3.8221(10^{-6})$
Source	[19]	[20]	[21]	[20]	[9]	[7]	[7]	[7]	[7]	[7]

Table 3: Realistic parameter values.

Parameter	β	δ	ϵ	σ	α	γ	ρ	μ
Value	.0377	.7043	.9	1.125	.1276	.7849	1	.0229

Table 4: Nondimensionalized parameter values.

301 *Proof.* Setting $\mathcal{R}_0 = 1$ in Equation (11), we then solve the resulting equation for M to obtain (29). From
 302 here it is clear that whenever $M > M_{\mathcal{R}_0}$, $\mathcal{R}_0 < 1$ and whenever $M < M_{\mathcal{R}_0}$, $\mathcal{R}_0 > 1$. \square

303 **Remark 4.8.** Whenever $A_1 > 0$, the model (5) undergoes a backward (subcritical) bifurcation at $\mathcal{R}_0 = 1$.
 304 Due to this, it is not so simple to find a bound on M such that malaria is cured. We can find a critical value
 305 of M as stated in Theorem 4.6 such that \mathcal{R}_0 is less than 1, but that does not guarantee the disease goes
 306 away in all cases. The result of Theorem 4.6 are still helpful because whenever $\mathcal{R}_0 > 1$, malaria will surely
 307 persist. Additionally, when $A_1 \leq 0$, we are in the region with no backwards bifurcation, so driving \mathcal{R}_0 below
 308 1 cures the disease. Thus, when $M > \max(M_{A_1}, M_{\mathcal{R}_0})$, there exists no endemic steady states. We also note
 309 that when $A_2 = 0$, $\mathcal{R}_0 = 1$ thus $M_{\mathcal{R}_0} = M_{A_2}$.

310 **Remark 4.9.** In the case in which $M_{\mathcal{R}_0} < M < M_{A_1}$, the number of endemic steady states depends on the
 311 sign of Δ . When $\Delta < 0$ there exist no endemic steady states, and when $\Delta > 0$, and $A_2 < 0$ the persistence
 312 or resolution of malaria depends on the initial values $i_h(0)$ and $i_f(0), i_r(0), i_q(0)$.

313 5 Numerical Simulations

314 To illustrate the capabilities of ivermectin we now give an example using realistic values for the original and
 315 dimensionless parameters in Tables 3 and 4 respectively. In addition, we fix $L = 5000$, $N_h = 100000$, and
 316 vary λ_0 . For each λ_0 , we find the critical values $M_{A_1}, M_{A_2} = M_{\mathcal{R}_0}, M_{\mathcal{R}^*}$, and M_Δ , thus determining whether
 317 the disease spreads, based on the value of M .

318 Figure 2 displays the persistence of the mosquito population and the lack of disease when $\lambda_0 = 8$. Thus,
 319 if λ_0 is low enough, the disease is not present in the community. However, raising λ_0 to 12 results in a high
 320 level of disease as in Figure 3.

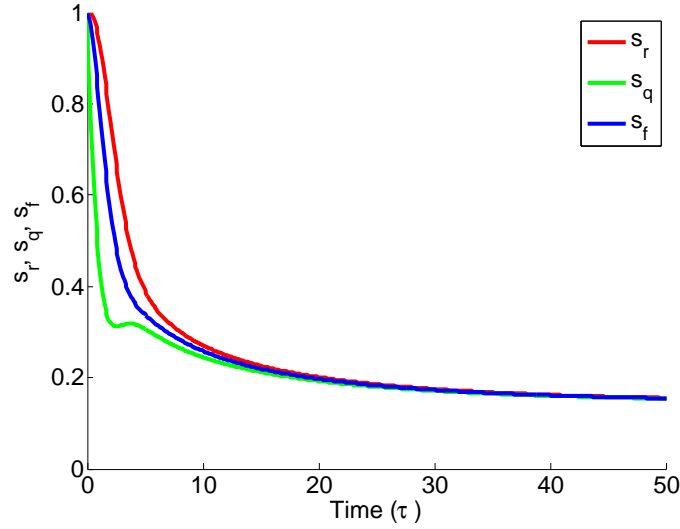


Figure 2: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 8$ and $M = 0$ we get the values $\mathcal{R}_0 = .6956$ and $\mathcal{R}^* = 1.1340$. Thus the mosquitoes survive and there is no disease, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0, 1, 1, 1, 0, 0, 0)$.

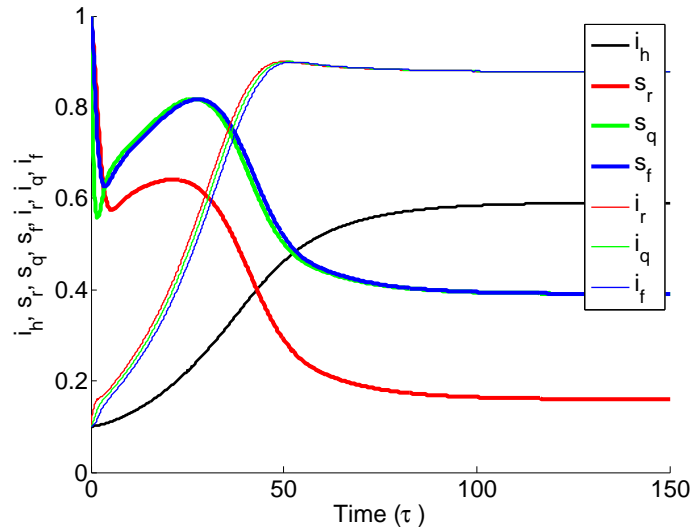


Figure 3: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 12$ and $M = 0$ we get the values $\mathcal{R}_0 = 2.6948$ and $\mathcal{R}^* = 1.7552$. Thus the mosquitoes survive and malaria is prevalent, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, .1, .1, .1)$.

321 When $\lambda_0 = 12, 18,$ and $100,$ Figures 4, 5, and 6 respectively display the regions in the M space for which
 322 ivermectin can curtail the spread of malaria with or without killing the mosquito population. The signs of
 323 $A_1, A_2,$ and Δ as well as the size of \mathcal{R}^* in each region can be seen in Table 5.

Region	A_1	A_2	Δ	\mathcal{R}^*	Result
(0,A)	+	+	+	> 1	Unique endemic steady state
(A,B)	+	-	+	> 1	Backward Bifurcation zone
(B,C)	+	-	-	> 1	No endemic steady states
(C,D)	+	-	-	< 1	Only trivial steady state
(D,E)	+	-	-	< 1	Only trivial steady state
(E,1)	-	-	+	< 1	Only trivial steady state

Table 5: The resulting steady states when M is in the region listed in the first columns. For a given λ_0 , the values of A , B , C , D , and E can be seen in Figures 4, 5, and 6.

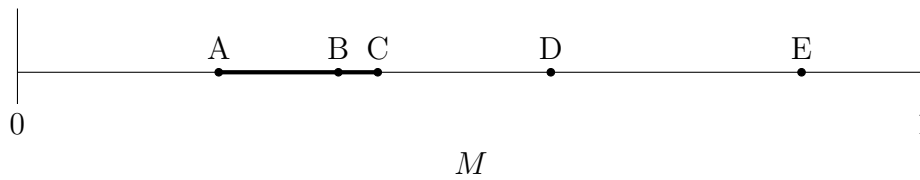


Figure 4: The parameters are as in Tables 3 and 4 with $\lambda_0 = 12$, $A = .2219$, $B = .3538$, $C = .3972$, $D = .588$, and $E = .8644$. The signs of A_1 , A_2 , and Δ as well as the size of \mathcal{R}^* in each region can be seen in Table 5. The thick region between A and C is the region in which curing malaria with ivermectin may be possible, without killing the mosquitoes.

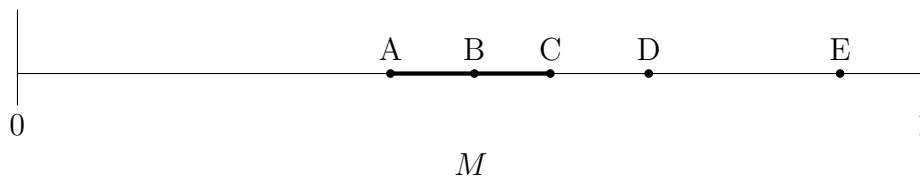


Figure 5: The parameters are as in Tables 3 and 4 with $\lambda_0 = 18$, $A = .4112$, $B = .5037$, $C = .5875$, $D = .6959$, and $E = .9069$. The signs of A_1 , A_2 , and Δ and the size of \mathcal{R}^* in each region are as in Table 5.

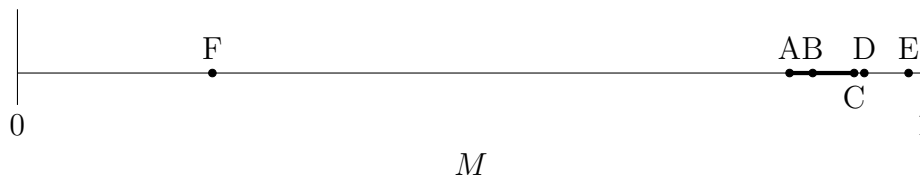


Figure 6: The parameters are as in Tables 3 and 4 with $\lambda_0 = 100$, $F = .2149$, $A = .8512$, $B = .8767$, $C = .9224$, $D = .9336$, and $E = .9824$. The signs of A_1 , A_2 , and Δ and the size of \mathcal{R}^* in each region are as in Table 5. When $M < F$, the model displays oscillatory instability in the steady states due to the Hopf Bifurcation. However, when $M > F$, the Hopf Bifurcation does not occur, and the steady state is stable.

324 The region represented by the thick line between A and C is the region in which eliminating malaria
325 with ivermectin may be possible, without killing the mosquitoes. The region to the right of C is the area in

326 which ivermectin can curtail the spread of malaria, but only by killing all the mosquitoes. The area to the
 327 left of A is the region in which ivermectin will have no effect on the spread of malaria. In Figure 6, F is the
 328 point in the M space at which a Hopf bifurcation occurs when $\lambda_0 = 100$.

329 Figures 7-10 demonstrate the possible effects of ivermectin in the presence of disease when $\lambda_0 = 12$.

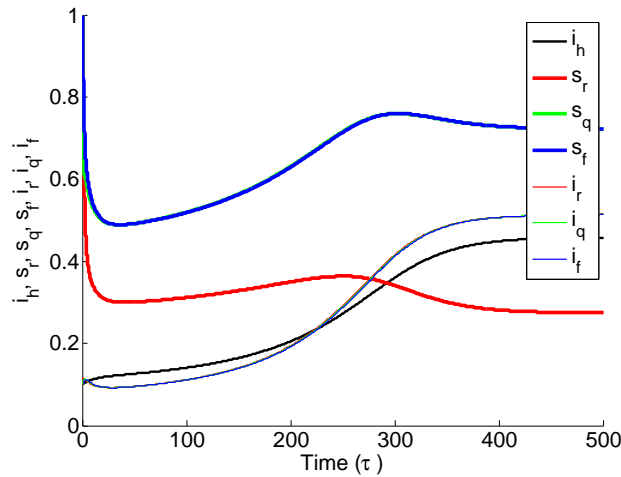


Figure 7: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 12$ and $M = .3$ we get the values $\mathcal{R}_0 = .5493$ and $\mathcal{R}^* = 1.177$. Although $\mathcal{R}_0 < 1$, there is still an endemic steady state, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, 1, 1, 1)$.

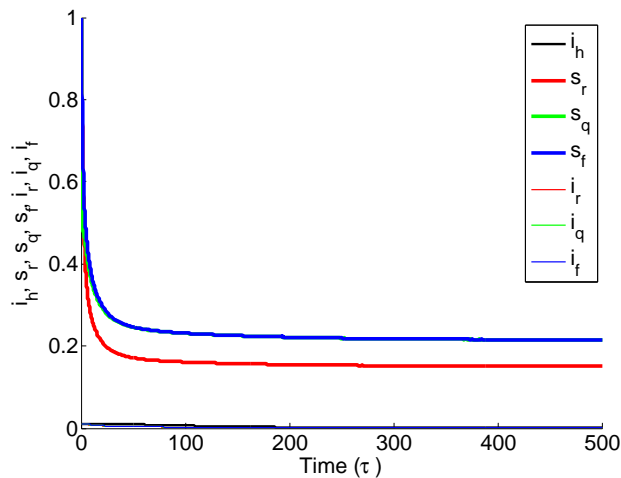


Figure 8: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 12$ and $M = .3$ we get the values $\mathcal{R}_0 = .5493$ and $\mathcal{R}^* = 1.177$. Although \mathcal{R}_0 did not change from Figure 7, there is no endemic steady state, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.01, 1, 1, 1, .01, .01, .01)$. We find the threshold for the initial conditions of $i_h(0), i_r(0), i_q(0), i_f(0)$ to be about .081 when $M = .3$. That is, when $i_h(0), i_r(0), i_q(0), i_f(0) > .081$, the disease flourishes. However, when $i_h(0), i_r(0), i_q(0), i_f(0) < .081$, the disease dies out over time.

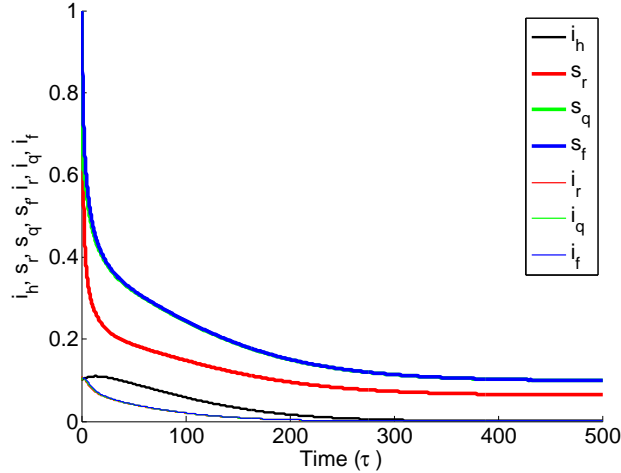


Figure 9: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 12$ and $M = .36$ we get the values $\mathcal{R}_0 = .2121$ and $\mathcal{R}^* = 1.0671$. Thus, the malaria outbreak is curtailed without killing of the entire mosquito population. It is however, important to note that the mosquito population is reduced in size, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, .1, .1, .1)$.

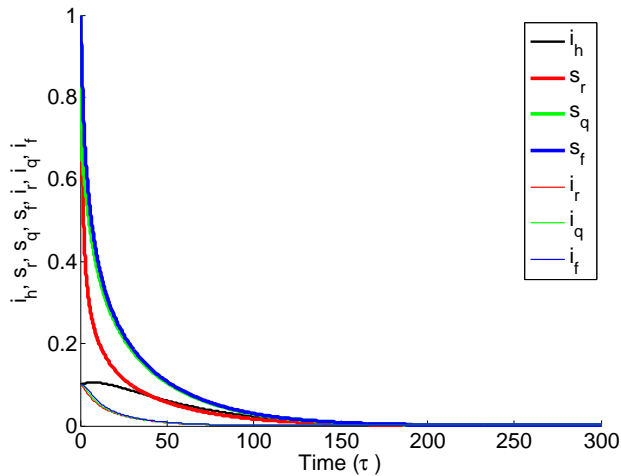


Figure 10: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 12$ and $M = .45$ we get the values $\mathcal{R}_0 = -.3147$ and $\mathcal{R}^* = .9057$. Thus, the malaria outbreak is curtailed at the cost of killing of the entire mosquito population, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, .1, .1, .1)$.

330 When $\lambda_0 = 100$, numerical simulations demonstrating the oscillations caused by the Hopf bifurcation at

331 $M_{Hopf} = .2149$ can be seen in Figures 11 and 12.

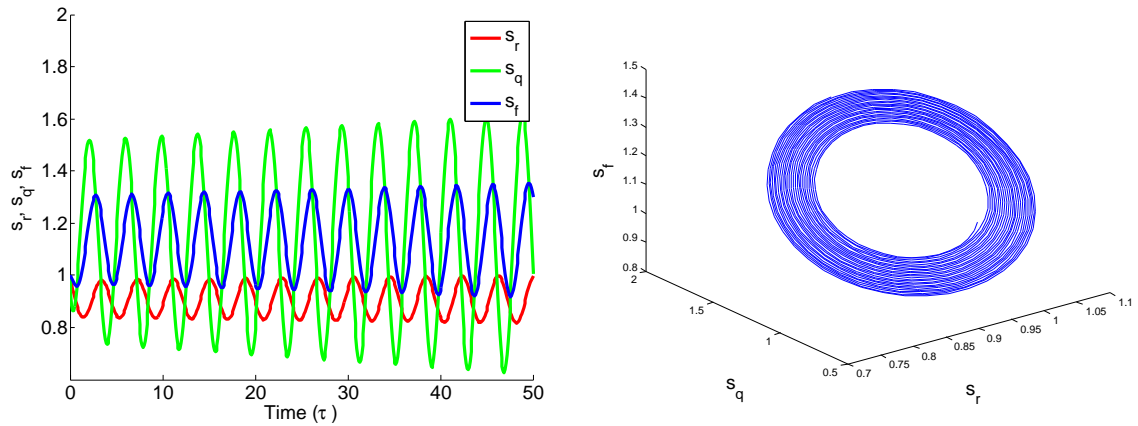


Figure 11: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 100$ and $M = .2$ there are oscillatory solutions as a result of a Hopf bifurcation at $\lambda_0 = 78.2939$, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0, 1, 1, 1, 0, 0, 0)$. Here we calculate the eigenvalues of Equation (10) to be -2.7994 , $0.0072 + 1.6157i$, and $0.0072 - 1.6157i$, so we have a periodic orbit.

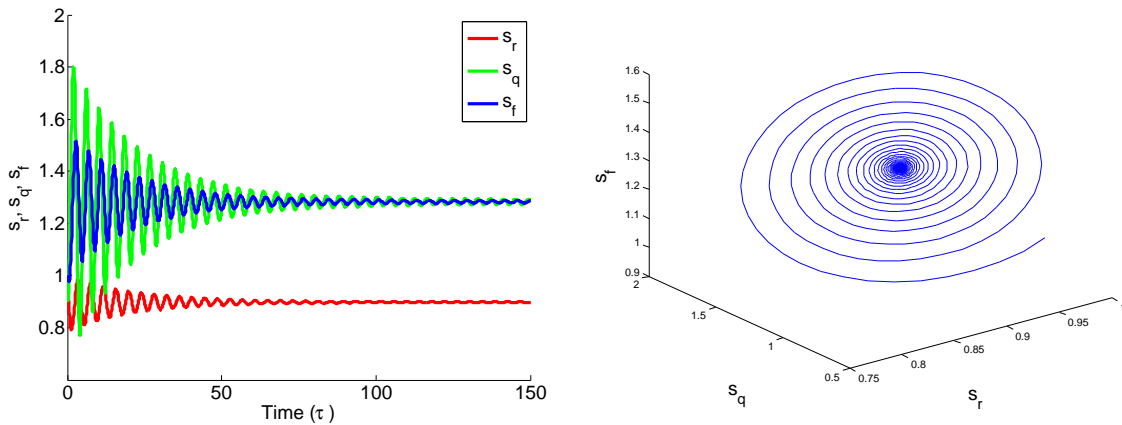


Figure 12: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 100$ and $M = .3$, the oscillatory solutions are curtailed because when $\lambda_0 = 100$, $M_{Hopf} = .2149$ and $M > .2149$. This is demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0, 1, 1, 1, 0, 0, 0)$. Here we calculate the eigenvalues of Equation (10) to be -2.6975 , $-0.0437 + 1.5271i$ and $-0.0437 - 1.5271i$, so we have a stable equilibrium.

6 Biological Implications, and Conclusions

From our system analysis and numerical simulations, we can conclude that there are potentially realistic situations in which ivermectin can be used to curtail the spread of malaria. We suggest that ivermectin would be particularly useful when combined with other methods of malaria control, such as the reduction of breeding sites and use of mosquito nets, since lowering λ_0 not only lowers the amount of medication needed, but also widens the range of values of M that can be used to cure malaria, without killing the local population of mosquitoes. In addition, the existence of backwards bifurcation suggests that early intervention may be particularly important when using ivermectin to fight malaria. Our numerical simulations showed that in some cases it doesn't take much medication to curtail the spread of the disease when the initial conditions are small enough, but higher levels are needed once the disease has taken hold of a population.

Our results also suggest that a drug similar to ivermectin, but with a longer half life, could be particularly useful. The parameter M loosely represents the percentage of the population with ivermectin present in their body at any given time. Ivermectin only stays in a humans blood at a concentration strong enough to kill mosquitoes for about two weeks. Due to this, even keeping as little as 30% of the population medicated at anytime would be logistically challenging. Thus, if a drug with a similar effect, but a longer half life were to be discovered, it would be substantially easier to keep higher percentages of people medicated.

The presence of oscillations in the steady states, which are not produced by seasonal forces, was first discovered in [7]. Our adapted model with consideration of the drug ivermectin, shows that there is the possibility of eliminating the occurrence of the Hopf bifurcation, and thus eliminating the oscillatory solutions. In fact, we find that relatively low levels of ivermectin are required to eliminate the occurrence of these oscillations.

The analysis in [7] noted the importance of the parameter λ_0 in the control of malaria. The parameter λ_0 is able to move the solutions to our equation through the A_1, A_2 parameter space, changing the number of endemic steady states to be 0, 1 or 2. We now note, that even in cases where λ_0 cannot be changed, or lowered sufficiently, certain levels of M can also move us through the A_1, A_2 space to areas with no endemic steady states. Perhaps the most important thing to note is that in some cases we are able to do this without lowering \mathcal{R}^* below zero, killing the mosquitoes. Thus we conclude that ivermectin may be use useful tool in combating the spread of malaria, particularly in conjunction with other methods, and can curtail the spread of malaria without annihilating the local mosquito population.

361 **6.1 Further Investigation**

362 The parameter space of this model is so vast that one could spend substantial time exploring the possible
363 outcomes in regards to λ_0 and M . In particular, one could search for specific regions in the parameter space
364 where malaria can be eliminated by changes in λ_0 and M and regions in which it cannot. In addition to
365 further numerical study of the parameter space, one could make modifications to the model to make it more
366 accurate or study different scenarios. For example, one may wish to investigate a model in which disease
367 related deaths are considered in the human population, or in which multiple populations of humans interact.
368 In addition, as an anonymous reviewer suggested, one could modify the current model to take into account
369 the waning efficiency of the drug over time. The authors of [7] have already written an additional paper [8]
370 in which a more intricate model is studied. These modifications could be made to either model, or the model
371 in this paper.

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