Modeling Mosquito-borne Diseases: An adventure through ODEs and integral equations

A Dissertation Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

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May 2021

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For my family and friends.

You gave me the courage to pursue my passion.

For my God.

You gave me my passion.

1 Corinthians 10:31

Acknowledgments

I do not know where to start or if I can even finish recognizing within this page all of the people that got me to this point.

I will begin with my amazing advisor, Dr. Olivia Prosper, for encouraging me and helping me believe that I could actually get a PhD. Thank you for the countless hours spent in your office and on Zoom, reading over my scribbles, and letting me walk you through my broken codes line-by-line to find all of the bugs. Thank you for being patient with me and for being invested in me as a person and not just as a student. Thank you for being so invested in my future that you invited me to finish my dissertation with you at the University of Tennessee. The move was hard, but worth it. I could not have asked for a better advisor.

A huge thanks to my mentors who helped me along the way: Carrie Manore, Katie Gurski, Mimi Teboh-Ewungkem, and Zhilan Feng. And thanks to my committee members: Judy Day, Lou Gross, and Suzanne Lenhart. Thank you to everyone in the math department at the University of Tennessee for welcoming me with open arms when I transferred universities. Especially Pam. You're amazing.

A big thanks to the many wonderful people I met at the University of Kentucky. First, to my fellow graduate students for all of those late night homework sessions (and chair races) in POT. Also, thank you to my professors for grading all of my long, drawn-out homework proofs and messy exams. And a huge shout-out to Christine, Sheri, and Rejeana - you are the real MVPs.

Thank you to my professors at Samford University, both in math and other classes. Drs. Metress and Johnson, thanks for accepting me into the Fellows Program. You made learning so interesting and pushed me beyond my comfort level. Thanks to Drs. Hynds, Kennedy, Powell, Patane, and Stanley for inspiring me to love math and encouraging me to pursue

graduate school. Also, to Mr. Kawell for teaching me to love programming and coding... even though that calendar project caused me so much grief.

And let me thank the people who started me on this journey, Mr. P and Ms. Stokes. You would not believe the impact you had on me. Your investment in your students goes above and beyond. I am forever grateful.

Thank you to my parents for raising me to love learning. And to my siblings for not quite understanding why I love math so much but going with it anyways. And thanks to my church family at LaGrange Baptist who have prayed for and encouraged me throughout my entire life.

And of course, thank you to my friends who let me rant, cry, and make corny math jokes all throughout this experience. In no particular order, thank you to the people who got me through the ups and downs of undergrad: Hannah, Rae, Chelsea, Kaleena, Tyler, Karson, and the Sams. And thank you to the people who got me through the ups and downs of grad school: Kalila, Camille, Kaelin, Hunter, Jessica, Kyle, Susanna, Matias, George, Deborah, and so many others. May God bless all of you.

Lastly, thank You, God, for Your good will, perfect timing, amazing grace, and constant reminders of Your love.

Abstract

In this work, we consider two types of mosquito-born disease modeling. First, we develop an ordinary differential equation (ODE) compartment model in order to investigate the effects of treatment on the spread of drug-resistant malaria. In order to investigate drug-resistance, we incorporate a drug-sensitive and drug-resistant parasite strain into a vector-borne disease model with treatment. In particular, we calculate reproduction and invasion numbers that will inform disease outcome and strain competition to be able to inform public health policies. We investigate the parameters associated with treatment in order to make recommendations for public health guidelines in the fight against malaria. Our results indicate that long-term population-level disease dynamics are insensitive to the effects of drug concentration in the blood on human susceptibility. That is, we see no correlation between pharmacokinetics and number of infections. On the other hand, we found that the parasite density, pharmacodynamics, in the human bloodstream significantly effects the magnitude of disease prevalence. We next investigate compartment stage durations. Many epidemiological ODE models inherently assume that the waiting times for each of the disease stages are exponentially distributed, which simplifies the model formulation and its analysis. However, this is not always the correct assumption and many methods have been developed to account for more biologically realistic waiting time distributions for each stage. We use malaria as a guiding example and formulate a two-strain vector-borne disease integral equation model with general waiting time distributions in order to more accurately capture the timing of within-human and between-human disease dynamics with treatment. We develop a novel numerical algorithm in order to simulate our model. Our results indicate that incorporating different assumptions on waiting times in each disease class significantly impact the outcome of disease persistence in populations.

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Chapter 1

Background

A vector-borne disease is a disease transmitted via a vector and can include parasitic, bacterial, or viral infections. Examples of vector-borne diseases include malaria, Dengue virus (which causes Dengue hemorrhagic fever), chikungunya virus, Zika virus, yellow fever, West Nile fever, and Lyme disease. Many vectors for these types of diseases are insects, like mosquitoes in the case of of malaria or ticks in the case of Lyme disease. According to the World Health Organization, 17% of all infectious diseases are caused by vector-borne diseases and cause more than 700,000 deaths every year [1]. Although many of these vector-borne diseases are preventable or have effective treatment regimes, human malaria is still a major concern in many parts of the world. In the following chapters, we will develop models to capture the spread of malaria in a human and mosquito population that focus on incorporating treatment.

1.1 Malaria

Human malaria is a parasitic vector-borne disease that spreads between human hosts and mosquito vectors. Specifically, the vector for human malaria is the female *Anopheles* mosquito. The female mosquito will search for a human to take a blood meal to produce eggs. If that human is infected with and harbors the gametocyte state of the malaria parasite, the mosquito will ingest the parasite in the form of male and female gametocytes. The parasite will then undergo sexual reproduction within the mosquito and eventually travel up to the

mosquito's salivary glands. The now-infectious mosquito can then come in contact with a non-infected, susceptible human, bite the human in the course of taking a blood meal, and release the parasite into the human bloodstream, where it will then travel to the liver and undergo asexual reproduction in red blood cells, causing them to burst. The cycle starts anew when a non-infected, susceptible female mosquito comes to take a blood meal from this now-infected human.

The World Health Organization reported that in 2020 there were approximately 229 million human malaria cases globally with 409,000 deaths (more than half of the estimated vector-borne disease deaths that occur every year) and 67% of the deaths occurred in children under the age of five years [2].

One of the challenges in controlling malaria is the emergence of drug resistance, which has been reported in several of the known human malaria parasite strains. Currently, there are five known malaria parasites that infect humans, all part of the genus *Plasmodium (P.)*. The most severe species, which causes the majority of malaria deaths, is *P. falciparum* and is prevalent in sub-Saharan Africa. Other species include *P. vivax* (present in Southeast Asia and Latin America), *P. ovale*, *P. malariae*, and *P. knowlesi*. Unfortunately, parasite drug-resistance to antimalarial medicines has been documented in three of the five malaria species known to affect humans, including *P. falciparum* [3]. Studies have been performed to determine the progression of drug resistance over time [4]. We must therefore evaluate new treatment regimes to combat malaria while avoiding further resistance or developing new resistance.

1.2 Between-host dynamics: Ross-Macdonald model

Human malaria is especially complex to model because it involves three organisms: humans, mosquitoes, and parasites. Many epidemiological models in the past have started with simplified versions of the system in order to better grasp basic dynamics. A mathematical model of mosquito-borne pathogen transmission was originally credited to Sir Ronald Ross and George Macdonald [5]. A simple example of a Ross-Macdonald model includes a population of susceptible humans (S_h), infected humans (I), and recovered humans (R)

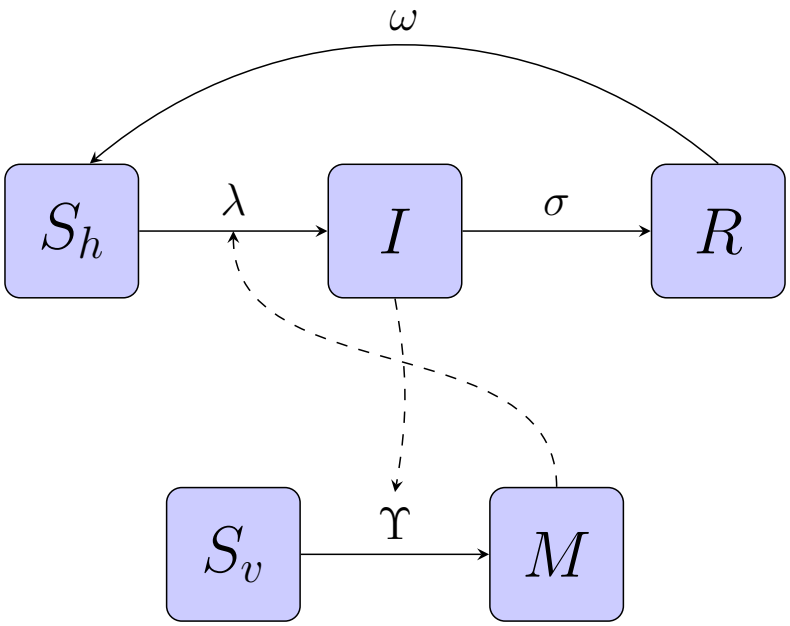


Figure 1.1: Example of Ross-Macdonald parasite transmission diagram where S_h represents the number of susceptible humans, I represents the number of infected humans, R represents the number of recovered humans, S_v represents the number of susceptible mosquitoes, and M represents the number of infected mosquitoes. Also, λ represents the force of infection from mosquitoes to humans, Υ represents the force of infection from humans to mosquitoes, σ is the rate at which individuals recover naturally from infection, and ω is the rate at which humans lose natural immunity and return to susceptibility.

as well as susceptible mosquitoes (S_v) and infected mosquitoes (M). The rate of human to mosquito parasite transmission is determined by a parameter β_v, which incorporates the mosquito biting rate and probability of transmitting the parasite. Likewise, the rate of mosquito to human infection is determined by a parameter β_h. We can use a diagram to represent the flow of humans as they move from being susceptible to infected to recovered and back to susceptible in the population, and mosquitoes as they move from being susceptible to infected. We call this an $SIRS$-SI model. See Figure 1.1 for a diagram of the human and mosquito population classes and transitions. Each box in the diagram represents one of these classes. Assuming we also have human and mosquito natural mortality rates, μ_h and μ_v, in every class, as well as per capita human and mosquito birth rates, Λ_h and Λ_v, replenishing the susceptible classes, we can write down the following system of Ordinary Differential Equations (ODEs) that describe the rate of change in each class:

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h - \lambda S_h - \mu_h S_h + \omega R \\
\frac{dI}{dt} &= \lambda S_h - \sigma I - \mu_h I \\
\frac{dR}{dt} &= \sigma I - \omega R - \mu_h R \\
\frac{dS_v}{dt} &= \Lambda_v - \Upsilon S_v - \mu_v S_v \\
\frac{dM}{dt} &= \Upsilon S_v - \mu_h M
\end{aligned} \tag{1.1}$$

where

$$\lambda = \beta_h \frac{M}{S_h + I + R} \qquad \text{and} \qquad \Upsilon = \beta_v \frac{I}{S_h + I + R}$$

and with initial conditions

$$\begin{aligned}
S_h(0) &= S_h^0 \\
I(0) &= I^0 \\
R(0) &= R^0 \\
S_v(0) &= S_v^0 \\
M(0) &= M^0.
\end{aligned}$$

We note that, if there are no infections in the population, then as $t \to \infty$, we reach the disease-free equilibrium (DFE):

$$\mathscr{E}_0 = (S_h^*, I^*, R^*, S_v^*, M^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_h}{\mu_h}, 0\right).$$

1.3 Within-host dynamics: pharmacokinetics and pharmacodynamics

In order to combat malaria, health experts have used treatments for humans infected with the parasite as well as other methods involving controlling the mosquito population. For instance, bed nets are highly encouraged in malaria endemic areas of the world, with insecticide-treated bed nets (ITNs) being introduced in some areas in order to protect humans from being bitten, as well as to kill feeding mosquitoes. Other techniques involve indoor spraying and removing mosquito egg-laying sites like pooled/stagnant water.

Lately, there has been a consensus in using artemisinin based combination therapies (ACTs) for treating uncomplicated malaria [6]. In order to understand treatment affects on population dynamics, we need to study what is happening with drug concentration and parasite load within a treated infected individual, i.e. pharmacokinetics and pharmacodynamics (PKPD). Pharmacokinetics (PK) is the branch of pharmacology concerned with the movement of drugs within the body while pharmacodynamics (PD) is the branch of pharmacology concerned with the effects of drugs and the mechanism of their action. We need to understand how drugs move through the bloodstream and interact with the parasites in the blood in order to better understand the effects of treatment on population dynamics and potential for parasite drug-resistance [7].

1.4 Strain competition and drug resistance

According to the World Health Organization, malaria parasites have demonstrated some degree of drug-resistance for almost every antimalarial medication currently available [2]. Previous studies have investigated the within-host effects of PKPD on drug resistance and

the effects of multi-strain infections [8, 9, 10]. For example, in [9], Bushman studies how within-host competition between parasite strains can delay the evolution of drug resistance in malaria. Her model explored the effects of within-host competition on drug resistance by incorporating an individual-based model dealing with within-host dynamics embedded into a between-host model for humans and mosquitoes. Her results indicated that a key factor in influencing drug resistance in *P. falciparum* is within-host competition between strains.

Other studies have investigated the effects of a treatment called IPT (Intermittent Preventive Treatment) on drug resistance. This type of treatment targets asymptomatic individuals, regardless of their malaria infection status. For IPT, individuals are treated with regularly spaced antimalarial drug doses. Some modeling studies have looked at the impact of treating pregnant women and children with IPT [11] and the potential for the spread of resistance via this treatment. Other studies have developed age-structured ODE models to investigate the role of IPT in averting malaria-induced mortality in children, and its related cost in promoting the spread of antimalarial drug resistance [12]. In particular, this study's results suggest that IPT can be effective in high transmission regions. However, in locations with drug-resistant strains circulating in the population, it can increase disease-induced deaths. Hence, it is important to study the potential effects of treatment on populations prior to incorporating it so as the reduce the risk of emergence of drug-resistance resulting in a higher loss of human life. More work must be done in order to better understand the effects of treatment on drug-resistance.

1.5 Summary

Many studies have investigated between-host dynamics and within-host dynamics separately. Our goal in the following two chapters is to investigate treatment in population dynamics and the proper choice of model structure to accurately capture the biological system's behavior. In particular, we will model the spread of drug-resistance and investigate the effects of treatment on the competition between drug-sensitive and drug-resistant malaria parasite strains in a population. In Chapter 2, we present an ODE model that captures some key elements of PKPD using multiple treated stages. In Chapter 3, we present an integral

equation model that allows for general distributions for waiting times. Finally, in Chapter 4, we briefly discuss how the integral equation model can be extended to include PKPD.

Chapter 2

Modeling Malaria with Treatment Using Ordinary Differential Equations

2.1 Motivation

In order to understand the role of treatment dynamics and spread of drug resistance in a population, we must link within- and between-host dynamics. Recently, studies have begun to study these types of models [13, 14, 15, 16, 17]. We build on this work and develop an ODE compartment model to investigate the effects of treatment pharmacokinetics and pharmacodynamics on the spread of drug-resistant malaria as described in Chapter 1. Due to parasite mutation, selection pressure from available drug treatments, and adherence to treatment regimens, drug-resistant malaria strains have emerged and become more prominent over time. Hence, we explicitly incorporate infection due to a drug-sensitive and a drug-resistant strain of the malaria parasite that accounts for changing drug concentrations and parasite densities within treated individuals. We discuss the competition between these two strains. Since resistant parasites are harder to clear (either naturally or through antimalarial treatment), we include two disease-induced mortality parameters in the human population for the corresponding sensitive and resistant strains. In the model, the compartments are categorized by malaria strain-type infection and treatment status. The treatment stage is broken up into n compartments through which individuals progress as the drug concentration and parasite density in their system declines after being treated. We break up these treated

compartments in a similar fashion to the "Linear Chain Trick (LTC)" [18], which builds off of a method that incorporates time lags in biological models [19]. This "trick" allows us to incorporate a gamma distributed waiting time for the total time spent in the treatment stage, as opposed to an exponential waiting time as is inherent in a single ODE compartment class with linear exit rate. Although the LTC requires the rates between stages of a class to be equal in order to fit to a gamma-distributed waiting time, the model we develop here allows for varying rates between stages. In [20], Lloyd considers the dynamical changes resulting from including non-exponentially distributed infectious periods. It is of interest to note that the competition between these two strains may depend on the number of treated compartments (i.e. the integer-shape of our gamma distribution).

2.2 Model Description

The model developed here is an extension of the Ross-Macdonald model for malaria transmission [5]. We incorporate treatment stages into the $SIRS$-SI model framework for vector-borne diseases discussed in Chapter 1 to create an $SITRS$-SI model. The model also includes compartments for both drug-sensitive and drug-resistant strains of the malaria parasite and explicitly includes disease-induced mortality in the human population. The model flowcharts are given in Figs. 2.2 and 2.1 and the definitions of parameters and variables are given in Tables 2.1 and 2.2. The model equations are described by Equations (2.3a) - (2.3c) and (2.4a) - (2.4b) for the mosquito population and (2.1a) - (2.1i) and (2.2a) - (2.2b) for the human population.

The model is a system of nonlinear ordinary differential equations that tracks the host and mosquito populations with host treatment stages incorporated into the framework. In the model, the compartments are categorized by malaria strain-type infection and treatment status. Upon being bitten by an infected mosquito, a susceptible human may be successfully infected with a drug-sensitive or drug-resistant parasite strain. We will denote "drug-sensitive-strain" by "s-" and "drug-resistant-strain" by "r-". A human infected with the sensitive strain may either become infected with the resistant strain or receive treatment and flow through the treatment stages based upon drug concentration and parasite density in the

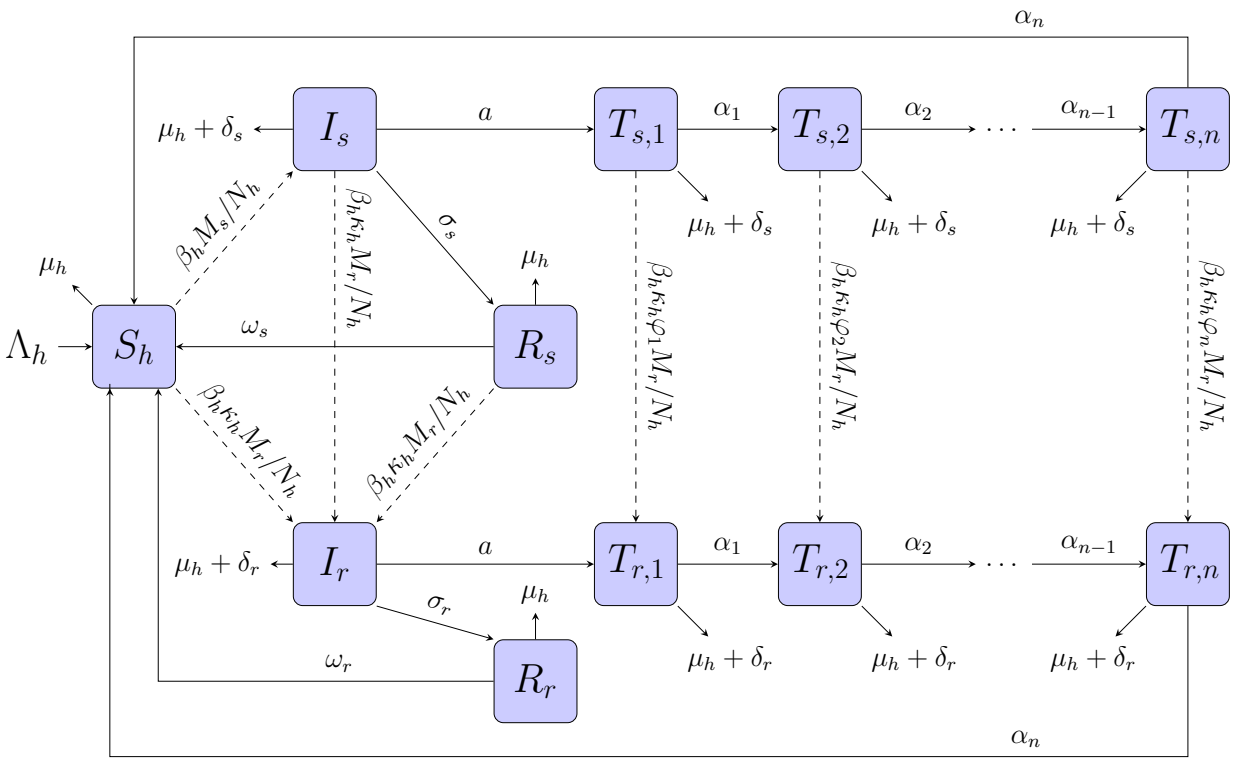


Figure 2.1: Transfer diagram for human infection in ODE model. Dashed lines represent parasite transmission via infected mosquitoes.

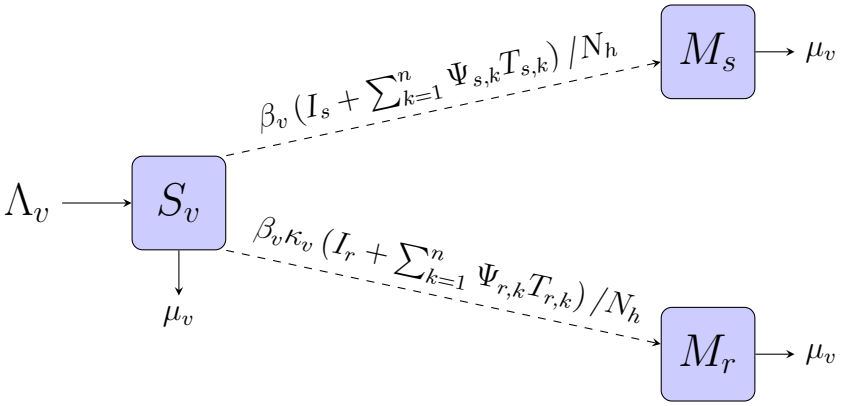


Figure 2.2: Transfer diagram for mosquito infection in ODE model. Dashed lines represent parasite transmission via infected humans

human bloodstream. During treatment, a human infected with the sensitive strain may pass into a treatment stage where the drug concentration dips below the threshold for protecting against the resistant strain. At this point, a human may be bitten by a mosquito infected with the resistant parasite strain and thus pass into the corresponding resistant-strain treatment compartment and then progress through the resistant-strain treatment stages. We assume that treated humans do not build-up natural immunity, and thus at the end of treatment, the human returns to the susceptible population. Alternatively, a human may not be treated, and either dies due to the disease or recovers independent of treatment, thereby boosting their immune system to provide temporary natural immunity. This immunity eventually fades and the untreated human returns to the susceptible population. Thus, the compartments for the human population at any time t are: susceptible (denoted S_h), infected with the sensitive or resistant strain (I_s or I_r, respectively), recovered without treatment from the sensitive or resistant strain (R_s or R_r, respectively), and treated at treatment stage k for the sensitive or resistant strain ($T_{s,k}$ or $T_{r,k}$, respectively). See Figure 2.1 for the transfer diagram for human infection.

We assume a constant birth rate into the susceptible human population as well as a constant natural death rate at all stages. Additionally, we account for disease-induced mortality as a function of parasite density in any stage associated with infection (i.e. the infected and treated stages). The equations governing the human dynamics are given by

$$\frac{dS_h}{dt} = \Lambda_h - \beta_h S_h \left(M_s + \kappa_h M_r\right)/N_h + \omega_s R_s + \omega_r R_r + \alpha_n(T_{s,n} + T_{r,n}) - \mu_h S_h \tag{2.1a}$$

$$\frac{dI_s}{dt} = \beta_h \left(S_h M_s - \kappa_h I_s M_r\right)/N_h - (a + \sigma_s + \delta_s + \mu_h) I_s \tag{2.1b}$$

$$\frac{dI_r}{dt} = \beta_h \kappa_h M_r (S_h + I_s + R_s)/N_h - (a + \sigma_r + \delta_r + \mu_h) I_r \tag{2.1c}$$

$$\frac{dT_{s,1}}{dt} = aI_s - (\alpha_1 + \delta_s + \mu_h) T_{s,1} - \beta_h \kappa_h \varphi_1 M_r T_{s,1}/N_h \tag{2.1d}$$

$$\frac{dT_{s,k}}{dt} = \alpha_{k-1} T_{s,k-1} - (\alpha_k + \delta_s + \mu_h) T_{s,k} - \beta_h \kappa_h \varphi_k M_r T_{s,k}/N_h \qquad \text{for } k = 2, \ldots, n \tag{2.1e}$$

$$\frac{dT_{r,1}}{dt} = aI_r - (\alpha_1 + \delta_r + \mu_h) T_{r,1} + \beta_h \kappa_h \varphi_1 M_r T_{s,1}/N_h \tag{2.1f}$$

$$\frac{dT_{r,k}}{dt} = \alpha_{k-1} T_{r,k-1} - (\alpha_k + \delta_r + \mu_h) T_{r,k} + \beta_h \kappa_h \varphi_k M_r T_{s,k}/N_h \qquad \text{for } k = 2, \ldots, n \tag{2.1g}$$

$$\frac{dR_s}{dt} = \sigma_s I_s - (\omega_s + \beta_h \kappa_h M_r/N_h + \mu_h) R_s \tag{2.1h}$$

$$\frac{dR_r}{dt} = \sigma_r I_r - (\omega_r + \mu_h) R_r \tag{2.1i}$$

The total human population is governed by

$$N_h = S_h + I_s + I_r + \sum_{k=1}^{n} (T_{s,k} + T_{r,k}) + R_s + R_r \tag{2.2a}$$

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \delta_s \left(I_s + \sum_{k=1}^{n} T_{s,k} \right) - \delta_r \left(I_r + \sum_{k=1}^{n} T_{r,k} \right) \tag{2.2b}$$

A susceptible mosquito may bite a human infected with either the sensitive or resistant strain and become infected with the sensitive or resistant strain, respectively. This means that the compartments for the mosquito population at any time t are: susceptible (denoted S_v), infected with the sensitive strain (M_s), and infected with the resistant strain (M_r). Thus, the total mosquito population is given by $N_v = S_v + M_s + M_r$.

We assume a constant total birth rate into the susceptible mosquito population as well as a constant per capita natural death rate at all stages. Disease-induced mortality is not considered for the mosquito population since mosquitoes already have a very short lifespan and hence are more likely to die due to natural causes than due to disease. Also, the difference in magnitude for the natural and disease-induced death rates is relatively small compared to the difference in magnitude for the natural and disease-induced death rates for the human population. See Figure 2.2 for the transfer diagram for mosquito infection. The equations governing the mosquito dynamics are given by

$$\frac{dS_v}{dt} = \Lambda_v - \beta_v S_v \left(I_s + \sum_{k=1}^{n} \Psi_{s,k} T_{s,k} + \kappa_v \left(I_r + \sum_{k=1}^{n} \Psi_{r,k} T_{r,k} \right) \right) / N_h - \mu_v S_v \tag{2.3a}$$

$$\frac{dM_s}{dt} = \beta_v S_v \left(I_s + \sum_{k=1}^{n} \Psi_{s,k} T_{s,k} \right) / N_h - \mu_v M_s \tag{2.3b}$$

$$\frac{dM_r}{dt} = \beta_v \kappa_v S_v \left(I_r + \sum_{k=1}^{n} \Psi_{r,k} T_{r,k} \right) / N_h - \mu_v M_r \tag{2.3c}$$

Table 2.1: Descriptions and dimensions of parameters for ODE model

Parameter	Description	Dimension
Λ_h	Total human birth rate	humans $\times T^{-1}$
Λ_v	Total mosquito birth rate	mosquitoes $\times T^{-1}$
μ_h	Natural human death rate	T^{-1}
μ_v	Natural mosquito death rate	T^{-1}
δ_s	Disease-induced death rate caused by drug-sensitive parasite	T^{-1}
δ_r	Disease-induced death rate caused by drug-resistant parasite	T^{-1}
β_h	Transmission rate of sensitive parasites from mosquitoes to humans	mosquito$^{-1} \times T^{-1}$
β_v	Transmission rate of sensitive parasites from humans to mosquitoes	human$^{-1} \times T^{-1}$
κ_h	Reduction factor of human transmission rate by drug-resistant parasite	1
κ_v	Reduction factor of mosquito transmission rate by drug-sensitive parasite	1
a	Treatment rate into first treated stage	T^{-1}
α_k	Rate of transition between treatment stage k and $k+1$ for $k = 1, \ldots, n-1$	T^{-1}
α_n	Rate of transition between treatment stage n and susceptible human population	T^{-1}
ω_s	Rate of loss of temporary immunity for those who naturally recovered from the drug-sensitive parasite	T^{-1}
ω_r	Rate of loss of temporary immunity for those who naturally recovered from the drug-resistant parasite	T^{-1}
σ_s	Rate of naturally clearing a drug-sensitive parasite infection	T^{-1}
σ_r	Rate of naturally clearing a drug-resistant parasite infection	T^{-1}
φ_k	Reduction factor of parasite transmission rate of the resistant strain from mosquito to human in treatment stage k (dependent on drug concentration)	1
$\Psi_{s,k}$	Reduction factor of parasite transmission rate of the sensitive strain from human in treatment stage k to mosquito (dependent on parasite density)	1
$\Psi_{r,k}$	Reduction factor of parasite transmission rate of the resistant strain from human in treatment stage k to mosquito(dependent on parasite density)	1

The total mosquito population is governed by

$$N_v = S_v + M_s + M_r \tag{2.4a}$$

$$\frac{dN_v}{dt} = \frac{dS_v}{dt} + \frac{dM_s}{dt} + \frac{dM_r}{dt} = \Lambda_v - \mu_v N_v. \tag{2.4b}$$

Another assumption we make is that the strains may differ in fitness. Thus, we scale the incidence term by κ_h for a new resistant human infection and κ_v for resistant mosquito infection. We assume that $0 \leq \kappa_h, \kappa_v \leq 1$, i.e. we reduce the likelihood of resistant-strain transmission for both the human and mosquito populations.

In order to scale the rate of infection for mosquitoes upon biting a treated human, we incorporate the piecewise-constant function Ψ as a function of within-human parasite density. We define $\Psi_s = [\Psi_{s,1}, \Psi_{s,2}, \ldots, \Psi_{s,n}]$ with $0 \leq \Psi_{s,k} \leq 1$ to be the scaling factor for mosquito infection from a treated human infected with the sensitive strain. Similarly, we define $\Psi_r = [\Psi_{r,1}, \Psi_{r,2}, \ldots, \Psi_{r,n}]$ with $0 \leq \Psi_{r,k} \leq 1$ to be the scaling factor for mosquito infection from a treated human infected with the resistant strain. In particular, $\Psi_{s,k}$ scales the mosquito infection rate from $T_{s,k}$ and $\Psi_{r,k}$ scales the mosquito infection rate from $T_{r,k}$. We assume the functions Ψ_s and Ψ_r are increasing functions of parasite density. That is, a higher parasite load implies a higher rate of infection. Since treatment reduces the parasite load in the blood, then as an individual progresses through the treatment stage with a single dose, we should see a decrease in parasite load and hence an increase in Ψ_s and Ψ_r so that $1 \geq \Psi_{s,1} \geq \Psi_{s,2} \geq \ldots, \Psi_{s,n} \geq 0$ and $1 \geq \Psi_{r,1} \geq \Psi_{r,2} \geq \ldots, \Psi_{r,n} \geq 0$. The drug concentration in the human bloodstream will also affect parasite transmission. Hence, we introduce the piecewise constant function $\varphi = [\varphi_1, \varphi_2, \ldots, \varphi_n]$ with $0 \leq \varphi_k \leq 1$ to account for a decrease in drug concentration in the sensitive strain treated class across the n stages. We note that a higher drug concentration should decrease the susceptibility to infection by the resistant strain, hence φ increases across treatment classes as the drug concentration in the human bloodstream decreases as individuals progress through treatment. That is, $0 \leq \varphi_1 \leq \varphi_2 \leq \cdots \leq \varphi_n \leq 1$. This assumes we treat with a single-dose protocol, although multiple doses could easily be implemented by decreasing φ_k at treatment stage k where a follow-up dose would be administered.

Table 2.2: Descriptions of state variables for ODE model

Variable	Description
N_v	Total mosquito population
S_v	Number of susceptible mosquitos
M_s	Number of mosquitos infected with the sensitive strain
M_r	Number of mosquitos infected with the resistant strain
N_h	Total human population
S_h	Number of susceptible humans
I_s	Number of humans infected with the sensitive strain
I_r	Number of humans infected with the resistant strain
$T_{s,k}$	Number of humans in treatment stage k for sensitive strain
$T_{r,k}$	Number of humans in treatment stage k for resistant strain
R_s	Number of humans naturally recovered from sensitive strain
R_r	Number of humans naturally recovered from resistant strain

As noted earlier, we assume that treated individuals do not develop temporary immunity once the drug has cleared the system. Instead, only humans who were infected but not treated develop a strong natural immunity if they survive to the recovered class. However, immunity to the sensitive strain does not necessarily confer immunity to the resistant strain. Hence those in the R_s class may still pass into the I_r class whereas individuals in the R_r class are protected from both strains. In particular, we assume no cross-immunity in the sensitive-to-resistant strain direction and perfect immunity in the resistant-to-sensitive strain direction. See Table 2.1 for a summary of parameters and Table 2.2 for a summary of the population variables.

2.3 Model Analysis

In this section, we derive the disease-free equilibrium (DFE) followed by the basic reproduction numbers for the sensitive and resistant strains (which determine the local stability of the DFE) and derive biological interpretations of the expressions. We also compute the sensitive-strain-only boundary equilibrium (SSE) and resistant strain only boundary equilibrium (RSE) and derive the invasion numbers for the two strains, which determine the stability of these equilibria and provide insight into the competition between these two strains.

2.3.1 Basic Reproduction Numbers

We compute the basic reproduction numbers for the sensitive parasite strain, $\mathscr{R}_s$, and the resistant parasite strain, $\mathscr{R}_r$ using the Next Generation Matrix (NGM) Approach by van den Driessche and Watmough [21]. We also provide a biological interpretation for the resulting threshold number. The NGM is formed by first arranging our ODE system so that the first k equations correspond with infected compartments and the remaining m equations correspond with the non-infected compartments:

$$\begin{aligned} x_i' &= f_i(x,y), \qquad && i = 1,\dots,k \qquad && \text{(infected compartments)} \\ y_j' &= g_j(x,y), \qquad && j = 1,\dots,m \qquad && \text{(non-infected compartments).} \end{aligned}$$

We then split our infected equations into terms responsible for new infections, $\mathscr{F}$, and terms related to other compartment transitions, $\mathscr{V}$, for $i = 1, \ldots, k$:

$$\begin{aligned} x_i' &= \mathscr{F}_i(x, y) - \mathscr{V}_i(x, y), \qquad && i = 1, \ldots, k \qquad && \text{(infected compartments)} \\ y_j' &= g_j(x, y), && j = 1, \ldots, m && \text{(non-infected compartments).} \end{aligned}$$

We then verify the following conditions:

- $\mathscr{F}_i(0, y) = 0$ and $\mathscr{V}_i(0, y) = 0$ for $y \geq 0$ and $i = 1, \ldots, k$.
- $\mathscr{F}_i(x, y) \geq 0$ for all $x, y \geq 0$.
- $\mathscr{V}_i(x, y) \leq 0$ whenever $x_i = 0$ for $i = 1, \ldots, k$.
- $\sum_{i=1}^{k} \mathscr{V}_i(x, y) \geq 0$ for all $x, y \geq 0$.

Next, we assume the disease-free system, $y' = g(0, y)$, has a unique DFE, $\mathscr{E}_0 = (0, y_0)$. We then compute two matrices F and V from linearizing the system around the DFE as follows:

$$F = \left[\frac{\partial \mathscr{F}_i(0,y_0)}{\partial x_j}\right] \qquad \text{and} \qquad V = \left[\frac{\partial \mathscr{V}_i(0,y_0)}{\partial x_j}\right].$$

The linear infected subsystem can be written as

$$x_j' = (F - V)x.$$

We then define the next generation matrix as

$$K = FV^{-1}$$

with $\mathscr{R}_0 = \rho(K)$, the spectral radius of K. In particular, F has only non-negative entries from its construction and V is a nonsingular M-matrix with $V^{-1} \geq 0$. The construction of our model in this chapter satisfies all of these conditions, and hence we use the NGM method to compute our reproduction numbers below. Using this DFE and the ordering in $\mathscr{E}$ (defined below), our NGM, K, becomes block triangular, where one block corresponds

to s-infected compartments and the other corresponds to r-infected compartments. Hence, $\rho(K)$ is the max of the spectral radius of each block. That is, $\rho(K) = \max\{\mathscr{R}_s, \mathscr{R}_r\}$, where $\mathscr{R}_s$ and $\mathscr{R}_r$ are defined after we compute the disease-free equilibrium.

The Disease-Free Equilibrium (DFE)

Let $\mathscr{E} = (M_r, I_r, T_{r,1}, \ldots, T_{r,n}, M_s, I_s, T_{s,1}, \ldots, T_{s,n}, S_h, S_v, R_s, R_r)$ be an equilibrium of the system described by (2.1a) - (2.1i) and (2.3a) - (2.3c). This ordering results in a block lower triangular matrix in our Next Generation Matrix Approach. This system has the DFE

$$\mathscr{E}_0 = (0, 0, 0, \ldots, 0, 0, 0, 0, \ldots, 0, S_h^*, S_v^*, 0, 0)\,.$$

That is, we have only susceptible populations while all other infected and recovered states are empty. To solve for the nonzero states, we set their corresponding differential equation to zero. To solve for S_h^*, we set equation (2.1a) to zero to get

$$0 = \Lambda_h - \mu_h S_h^* \qquad \Longrightarrow \qquad S_h^* = \frac{\Lambda_h}{\mu_h}.$$

Similarly, to solve for S_v^*, we set equation (2.3a) to zero to get

$$0 = \Lambda_v - \mu_v S_v^* \qquad \Longrightarrow \qquad S_v^* = \frac{\Lambda_v}{\mu_v}.$$

Thus, this system has the DFE

$$\mathscr{E}_0 = \left(0, 0, 0, \ldots, 0, 0, 0, 0, \ldots, 0, \frac{\Lambda_h}{\mu_h}, \frac{\Lambda_v}{\mu_v}, 0, 0\right)$$

where there are n treated compartments for both the sensitive and resistant parasite strains. Now we can define the reproduction numbers, $\mathscr{R}_s$ and $\mathscr{R}_r$, for the sensitive and resistant strains using the NGM.

The sensitive strain, $\mathscr{R}_s^2$

We use Mathematica for these symbolic computations and the script is available in the GitHub repository linked in Appendix B. We note that all assumptions for the NGM method are satisfied using the class ordering defined in $\mathscr{E}$. The resulting NGM matrix is block upper triangular where each block corresponds the sensitive and resistant strain infections. The sensitive strain reproduction number takes the form

$$\mathscr{R}_s^2 = v_s h_s \left[\frac{1}{c_s} + \frac{a\Psi_{s,1}}{c_s c_1} + \frac{a\alpha_1 \Psi_{s,2}}{c_s c_1 c_2} + \cdots + \frac{a\left(\prod_{k=1}^{n-1} \alpha_k\right) \Psi_{s,n}}{c_s \prod_{k=1}^{n} c_k} \right] S_h^* \tag{2.5}$$

where

$$h_s = \frac{\beta_h}{N_h^*}, \qquad v_s = \frac{\beta_v S_v^*}{\mu_v N_h^*}, \qquad c_s = a + \delta_s + \mu_h + \sigma_s, \qquad c_k = \alpha_k + \delta_s + \mu_h.$$

We define the following parameter groupings (evaluated at the SSE) that will be used in the analysis in this section:

$$\begin{aligned}
b_1 &:= 1 + \frac{a\Psi_1}{c_1} + \frac{a\alpha_1\Psi_2}{c_1 c_2} + \cdots + \frac{a\left(\prod_{k=1}^{n-1} \alpha_k\right) \Psi_n}{\prod_{k=1}^{n} c_k} \\
b_2 &:= 1 + \frac{a}{c_1} + \frac{a\alpha_1}{c_1 c_2} + \cdots + \frac{a\prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} c_k} \\
b_3 &:= 1 + \frac{a}{c_1} + \frac{a\alpha_1}{c_1 c_2} + \cdots + \frac{a\prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} c_k} + \frac{\sigma_s}{\omega_s + \mu_h} = b_2 + \frac{\sigma_s}{\omega_s + \mu_h} \\
B_1 &:= I_s + \sum_{k=1}^{n} \Psi_k T_{s,k} \\
B_2 &:= I_s + \sum_{k=1}^{n} T_{s,k} \\
B_3 &:= I_s + \sum_{k=1}^{n} T_{s,k} + R_s = B_2 + R_s.
\end{aligned} \tag{2.6}$$

We evaluate $\mathscr{R}_s^2$ at the DFE. That is, we set $S_h^* = N_h^* = \frac{\Lambda_h}{\mu_h}$ and $S_v^* = \frac{\Lambda_v}{\mu_v}$ so that

$$h_s = \frac{\beta_h}{\Lambda_h/\mu_h} \qquad \text{and} \qquad v_s = \frac{\beta_v(\Lambda_v/\mu_v)}{\mu_v(\Lambda_h/\mu_h)}.$$

Using b_1 defined in 2.6, we can simplify the reproduction number to

$$\mathscr{R}_s^2 = \frac{v_s h_s b_1 S_h^*}{c_s} = \frac{\beta_v(\Lambda_v/\mu_v)}{\mu_v(\Lambda_h/\mu_h)} \cdot \frac{\beta_h}{\Lambda_h/\mu_h} \cdot \frac{b_1}{c_s} \cdot \frac{\Lambda_h}{\mu_h} = \frac{\beta_v \beta_h \Lambda_v \mu_h}{\mu_v \Lambda_h \mu_v} \cdot \frac{b_1}{c_s}.$$

We can interpret the sensitive strain's basic reproduction number biologically. Note that $\frac{1}{c_s}$ accounts for the contribution of new s-infections from I_s, $\frac{a\Psi_{s,1}}{c_s c_1}$ accounts for the contribution of new s-infections from $T_{s,1}$, $\frac{a\alpha_1\Psi_{s,2}}{c_s c_1 c_2}$ accounts for the contribution of new s-infections from $T_{s,n}$, and so on. We note that the reproduction number breaks down into two components: the human component and the vector component. These components are due to the cycle in which an infected human must be bitten by a susceptible vector to produce more sensitive strain-infected vectors, and then that infected vector must bite and infect a susceptible human to produce a sensitive strain-infected human. Hence, the two components break down into the following human and vector components:

$$\mathscr{R}_s^v = v_s \frac{b_1}{c_s} \qquad \text{and} \qquad \mathscr{R}_s^h = h_s S_h^*$$

Note that $\mathscr{R}_s^v$ consists of the transmission term for human-to-mosquito transmission multiplied by the parameter groupings that scale transmission to mosquitoes throughout the infectious human classes as well as the ratio of susceptible mosquitoes to humans. Similarly, $\mathscr{R}_s^h$ consists of the mosquito-to-human transmission term multiplied by the population of susceptible humans.

The resistant strain, $\mathscr{R}_r^2$

Similarly, for the resistant strain, we have that the reproduction number takes the form

$$\mathscr{R}_r^2 = v_r h_r \left[\frac{1}{d_r} + \frac{a\Psi_{r,1}}{d_r d_1} + \frac{a\alpha_1\Psi_{r,2}}{d_r d_1 d_2} + \cdots + \frac{a\left(\prod_{k=1}^{n-1}\alpha_k\right)\Psi_{r,n}}{d_r \prod_{k=1}^{n} d_k} \right] S_h^* \tag{2.7}$$

where

$$h_r = \kappa_h h_s, \qquad v_r = \kappa_v v_s, \qquad d_r = a + \delta_r + \mu_h + \sigma_r, \qquad d_k = \alpha_k + \delta_r + \mu_h.$$

We define the following parameter groupings (evaluated at the RSE) that will be used in the analysis in this section:

$$
\begin{aligned}
g_1 &:= 1 + \frac{a\Psi_1}{d_1} + \frac{a\alpha_1\Psi_2}{d_1 d_2} + \cdots + \frac{a\left(\prod_{k=1}^{n-1}\alpha_k\right)\Psi_n}{\prod_{k=1}^{n} d_k} \\
g_2 &:= 1 + \frac{a}{d_1} + \frac{a\alpha_1}{d_1 d_2} + \cdots + \frac{a\prod_{k=1}^{n-1}\alpha_k}{\prod_{k=1}^{n} d_k} \\
g_3 &:= 1 + \frac{a}{d_1} + \frac{a\alpha_1}{d_1 d_2} + \cdots + \frac{a\prod_{k=1}^{n-1}\alpha_k}{\prod_{k=1}^{n} d_k} + \frac{\sigma_r}{\omega_r + \mu_h} = g_2 + \frac{\sigma_r}{\omega_r + \mu_h} \\
G_1 &:= I_r + \sum_{k=1}^{n} \Psi_k T_{r,k} \\
G_2 &:= I_r + \sum_{k=1}^{n} T_{r,k} \\
G_3 &:= I_r + \sum_{k=1}^{n} T_{r,k} + R_r = G_2 + R_r.
\end{aligned}
\tag{2.8}
$$

Again, we evaluate $\mathscr{R}_r^2$ at the DFE with $S_h^* = N_h^* = \frac{\Lambda_h}{\mu_h}$ and $S_v^* = \frac{\Lambda_v}{\mu_v}$ so that

$$
h_r = \kappa_h h_s = \frac{\kappa_h \beta_h}{\Lambda_h/\mu_h} \qquad \text{and} \qquad v_r = \kappa_v v_s = \frac{\kappa_v \beta_v (\Lambda_v/\mu_v)}{\mu_v(\Lambda_h/\mu_h)}.
$$

Using g_1 defined in 2.8, we can simplify the resistant strain reproduction number to

$$
\mathscr{R}_r^2 = \frac{v_r h_r g_1 S_h^*}{d_r} = \frac{\kappa_v \beta_v (\Lambda_v/\mu_v)}{\mu_v(\Lambda_h/\mu_h)} \cdot \frac{\kappa_h \beta_h}{\Lambda_h/\mu_h} \cdot \frac{g_1}{d_r} \cdot \frac{\Lambda_h}{\mu_h} = \frac{\kappa_v \beta_v \kappa_h \beta_h \Lambda_v \mu_h}{\mu_v \Lambda_h \mu_v} \cdot \frac{g_1}{d_r}.
$$

Again, we can interpret the resistant strain's basic reproduction number biologically. We can see the reproduction number break down into two components: the human component and the mosquito component. These components are due to the cycle in which an infected human must be bitten by a susceptible mosquito to produce more resistant strain-infected mosquitoes, and then that infected mosquito must bite and infect a human susceptible to the resistant strain to produce a resistant strain-infected human. We can see the two components break down into the following human and mosquito components:

$$
\mathscr{R}_r^v = v_r \frac{g_1}{d_r} \qquad \text{and} \qquad \mathscr{R}_r^h = h_r S_h^{**}
$$

Note that $\mathscr{R}_r^v$ consists of the transmission term for human-to-mosquito transmission multiplied by the parameter groupings that scale transmission to mosquitoes throughout the infectious human classes as well as the ratio of susceptible mosquitoes to humans. Similarly, $\mathscr{R}_r^h$ consists of the mosquito-to-human transmission term multiplied by the population of susceptible humans. Since $\mathscr{R}_s$ and $\mathscr{R}_r$ were computed using the NGM Method, we have the following theorem regarding the stability of the DFE:

Theorem 2.1 (Stability of the DFE)**.** *If $\mathscr{R}_s < 1$ and $\mathscr{R}_2 < 1$, then the disease-free equilibrium is locally asymptotically stable. If $\mathscr{R}_s > 1$ or $\mathscr{R}_r > 1$, then the disease-free equilibrium is unstable.*

2.3.2 Invasion Numbers

The basic reproduction numbers only determine the stability of the DFE. To determine the competitive outcome between the sensitive and resistant strains, we must also derive the invasion numbers, $\mathscr{R}_r^s$ and $\mathscr{R}_s^r$. We define $\mathscr{R}_r^s$ to be the threshold quantity for determining whether the resistant strain is able to invade the sensitive-strain boundary equilibrium and $\mathscr{R}_s^r$ to be the threshold quantity for determining whether the sensitive strain is able to invade the resistant-strain boundary equilibrium. Coexistence between the two strains could result if $\mathscr{R}_r^s > 1$ and $\mathscr{R}_s^r > 1$. Both of these thresholds are biologically interpretable. We adapt the Next Generation Approach to compute the invasion numbers by evaluating the next generation matrix at the sensitive-strain-only boundary equilibrium (SSE) and the resistant-strain-only boundary equilibrium (RSE) instead of the DFE, as described in [22].

Instead of dividing our compartments for the NGM into infected and non-infected classes, we instead divide our system into s-infected compartments, r-infected compartments, and non-infected compartments. In the case of the SSE, new infections only occur when an individual moves from S_h to I_s. In the case of the RSE, new infections occur when individuals from S_h, I_s, $T_{s,1}$, ..., $T_{s,n}$, and R_s become infected with the resistant strain and move to the appropriate r-infected classes as described in our model diagram in 3.1. In both instances, we get a block triangular NGM, in which one block corresponds to new s- (or r-) infections

in the presence of r- (or s-) infections whose eigenvalue, $\mathscr{R}_s^r$ (or $\mathscr{R}_r^s$), corresponds with the spectral radius of the NGM. We begin by computing the SSE and RSE.

The Sensitive-Strain Boundary Equilibrium (SSE)

Let $\mathscr{E} = (M_r, I_r, T_{r,1}, \ldots, T_{r,n}, M_s, I_s, T_{s,1}, \ldots, T_{s,n}, S_h, S_v, R_s, R_r)$ be an equilibrium of the system described by (2.1a) - (2.1i) and (2.3a) - (2.3c). We will need to solve this system for the sensitive-strain-only equilibrium. That is, we set $I_r = 0, M_r = 0, T_{r,1} = 0, \ldots, T_{r,n} = 0, R_r = 0$ and solve for nonzero quantities of the remaining compartments. The SSE for the system takes the form

$$\mathscr{E}_s = \left(0, 0, 0, \ldots, 0, M_s^\star, I_s^\star, T_{s,1}^\star, \ldots, T_{s,n}^\star, S_h^\star, S_v^\star, R_s^\star, 0\right)$$

where there are n treated compartments for both the sensitive and resistant parasite strains. To solve for the remaining nonzero compartments, we will set the corresponding differential equations to zero with the resistant strain compartments set to zero. The SSE equations are listed below in the order given in $\mathscr{E}_s$ with the total human population equation, $\frac{dN_h}{dt} = 0$, listed first:

$$0 = \Lambda_h - \mu_h N_h - \delta_s \left(I_s + \sum_{k=1}^{n} T_{s,k} \right) \tag{$N_h^\star$}$$

$$0 = \beta_v S_v \left(I_s + \sum_{k=1}^{n} \Psi_{s,k} T_{s,k} \right) / N_h - \mu_v M_s \tag{$M_s^\star$}$$

$$0 = \frac{\beta_h S_h M_s}{N_h} - c_s I_s \tag{$I_s^\star$}$$

$$0 = a I_s - c_1 T_{s,1} \tag{$T_{s,1}^\star$}$$

$$0 = \alpha_{k-1} T_{s,k-1} - c_k T_{s,k} \qquad \text{for } k = 2, \ldots, n \tag{$T_{s,k}^\star$}$$

$$0 = \Lambda_h - \frac{\beta_h S_h M_s}{N_h} + \omega_s R_s + \alpha_n T_{s,n} - \mu_h S_h \tag{$S_h^\star$}$$

$$0 = \Lambda_v - \beta_v S_v \left(I_s + \sum_{k=1}^{n} \Psi_{s,k} T_{s,k} \right) / N_h - \mu_v S_v \tag{$S_v^\star$}$$

$$0 = \sigma_s I_s - (\omega_s + \mu_h) R_s. \tag{$R_s^\star$}$$

First, note that we can easily solve for the treated and recovered classes as functions of the infected class as follows:

$$\begin{aligned} T_{s,1} &= \frac{a}{c_1} I_s \\ T_{s,2} &= \frac{a\alpha_1}{c_1 c_2} I_s \\ &\vdots \\ T_{s,n} &= \frac{a \prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} c_k} I_s \\ R_s &= \frac{\sigma_s}{\omega_s + \mu_h} I_s \end{aligned}$$

We can sum the treated compartments with I_s to get

$$B_2 = I_s + \sum_{k=1}^{n} T_{s,k} = \left(1 + \frac{a}{c_1} + \frac{a\alpha_1}{c_1 c_2} + \cdots + \frac{a \prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} c_k}\right) I_s = b_2 I_s.$$

We also sum the the recovered class with B_2 to get

$$B_3 = B_2 + R_s = b_2 I_s + \frac{\sigma_s}{\omega_s + \mu_h} I_s = \left(b_2 + \frac{\sigma_s}{\omega_s + \mu_h}\right) I_s = b_3 I_s.$$

We can then re-write the equilibrium equation $\frac{dN_h}{dt} = 0$ in terms of b_3 to get

$$0 = \Lambda_h - \mu_h N_h - \delta_s B_2 = \Lambda_h - \mu_h N_h - b_2 \delta_s I_s,$$

which implies that

$$N_h = \frac{\Lambda_h}{\mu_h} - \frac{b_2 \delta_s}{\mu_h} I_s.$$

We can also use the fact that N_h is the sum of the population at the SSE to get

$$N_h = S_h + I_s + \sum_{k=1}^{n} T_{s,k} + R_s = S_h + B_3 = S_h + b_3 I_s.$$

Setting these two equations for N_h equal, we obtain

$$\frac{\Lambda_h}{\mu_h} - \frac{b_2\delta_s}{\mu_h} I_s = S_h + b_3 I_s.$$

Solving for S_h gives us an equation for S_h as a function of I_s, as in the other treated and recovered compartments:

$$\begin{aligned} S_h &= \frac{\Lambda_h}{\mu_h} - \frac{b_2\delta_s}{\mu_h} I_s - b_3 I_s \\ &= \frac{\Lambda_h}{\mu_h} - \left(\frac{b_2\delta_s}{\mu_h} + b_3 \right) I_s. \end{aligned}$$

Now we can solve for S_v as a function of I_s. Note that

$$\begin{aligned} 0 &= \Lambda_v - \beta_v S_v \left(I_s + \sum_{k=1}^{n} \Psi_{s,k} T_{s,k} \right) / N_h - \mu_v S_v \\ &= \Lambda_v - \beta_v S_v B_1 / N_h - \mu_v S_v \\ &= \Lambda_v - S_v(\beta_v B_1 / N_h + \mu_v) \\ &= \Lambda_v - S_v(\beta_v b_1 I_s / N_h + \mu_v) \end{aligned}$$

which implies

$$\begin{aligned} S_v &= \frac{\Lambda_v}{\beta_v b_1 I_s / N_h + \mu_v} \\ &= \frac{\Lambda_v N_h}{\beta_v b_1 I_s + \mu_v N_h} \\ &= \frac{\Lambda_v \left(\frac{\Lambda_h}{\mu_h} - \frac{b_2\delta_s}{\mu_h} I_s \right)}{\beta_v b_1 I_s + \mu_v \left(\frac{\Lambda_h}{\mu_h} - \frac{b_2\delta_s}{\mu_h} I_s \right)} \\ &= \frac{\Lambda_v \left(\Lambda_h - b_2\delta_s I_s \right)}{\beta_v b_1 \mu_h I_s + \mu_v \left(\Lambda_h - b_2\delta_s I_s \right)} \\ &= \frac{\Lambda_v \left(\Lambda_h - b_2\delta_s I_s \right)}{\mu_v \Lambda_h + (\beta_v b_1 \mu_h - b_2\delta_s \mu_v) I_s}. \end{aligned}$$

Lastly, we solve for M_s. We start with the equation

$$\begin{aligned}
0 &= \beta_v S_v \left(I_s + \sum_{k=1}^{n} \Psi_{s,k} T_{s,k} \right) / N_h - \mu_v M_s \\
&= \beta_v S_v B_1 / N_h - \mu_v M_s \\
&= \beta_v B_1 \frac{S_v}{N_h} - \mu_v M_s \\
&= \beta_v B_1 \frac{\frac{\Lambda_v N_h}{\beta_v b_1 I_s + \mu_v N_h}}{N_h} - \mu_v M_s \\
&= \beta_v B_1 \frac{\Lambda_v}{\beta_v b_1 I_s + \mu_v N_h} - \mu_v M_s \\
&= \beta_v B_1 \frac{\Lambda_v}{\beta_v b_1 I_s + \mu_v \left(\frac{\Lambda_h}{\mu_h} - \frac{b_2 \delta_s}{\mu_h} I_s \right)} - \mu_v M_s \\
&= \beta_v B_1 \frac{\Lambda_v \mu_h}{\beta_v b_1 \mu_h I_s + \mu_v \left(\Lambda_h - b_2 \delta_s I_s \right)} - \mu_v M_s \\
&= \beta_v b_1 I_s \frac{\Lambda_v \mu_h}{\mu_v \Lambda_h + (\beta_v b_1 \mu_h - b_2 \delta_s \mu_v) I_s} - \mu_v M_s,
\end{aligned}$$

which implies

$$M_s = \frac{\beta_v b_1}{\mu_v} \left(\frac{\Lambda_v \mu_h}{\Lambda_h \mu_v + (\beta_v b_1 \mu_h - b_2 \delta_s \mu_v) I_s} \right) I_s.$$

Thus we have the following equations that depend on I_s:

$$\begin{aligned}
M_s &= \frac{\beta_v b_1}{\mu_v} \left(\frac{\Lambda_v \mu_h}{\Lambda_h \mu_v + (\beta_v b_1 \mu_h - b_2 \delta_s \mu_v) I_s} \right) I_s \\
T_{s,1} &= \frac{a}{c_1} I_s \\
T_{s,2} &= \frac{a \alpha_1}{c_1 c_2} I_s \\
&\vdots \\
T_{s,n} &= \frac{a \prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} c_k} I_s \\
S_h &= \frac{\Lambda_h}{\mu_h} - \left(\frac{b_2 \delta_s}{\mu_h} + b_3 \right) I_s \\
S_v &= \frac{\Lambda_v \left(\Lambda_h - b_2 \delta_s I_s \right)}{\Lambda_h \mu_v + (\beta_v b_1 \mu_h - b_2 \delta_s \mu_v) I_s} \\
R_s &= \frac{\sigma_s}{\omega_s + \mu_h} I_s.
\end{aligned}$$

Now we turn to the I_s equation. Notice that setting the ODE to zero yields

$$0 = \beta_h S_h M_s / N_h - c_s I_s,$$

which yields

$$\begin{aligned}
I_s &= \frac{\beta_h}{c_s}\frac{S_h}{N_h}M_s \\
&= \frac{\beta_h}{c_s}\frac{\frac{\Lambda_h}{\mu_h} - \left(\frac{b_2\delta_s}{\mu_h} + b_3\right)I_s}{\frac{\Lambda_h}{\mu_h} - \frac{b_2\delta_s}{\mu_h}I_s}\left(\frac{\beta_v b_1}{\mu_v}\left(\frac{\Lambda_v\mu_h}{\mu_v\Lambda_h + (\beta_v b_1\mu_h - b_2\delta_s\mu_v)I_s}\right)I_s\right) \\
&= \frac{\beta_h\beta_v b_1\Lambda_v\mu_h}{c_s\mu_v}\left(\frac{\Lambda_h - (b_2\delta_s + b_3\mu_h)I_s}{\Lambda_h - b_2\delta_s I_s}\right)\left(\frac{I_s}{\mu_v\Lambda_h + (\beta_v b_1\mu_h - b_2\delta_s\mu_v)I_s}\right).
\end{aligned}$$

This gives us the following cubic equation in I_s:

$$\begin{aligned}
0 &= \left[-c_s b_2\delta_s\mu_v(\beta_v b_1\mu_h - b_2\delta_s\mu_v)\right]I_s^3 \\
&\quad + \left[c_s\mu_v\Lambda_h(\beta_v b_1\mu_h - b_2\delta_s\mu_v) - c_s b_2\delta_s\mu_v^2\Lambda_h + \beta_v\beta_h b_1\Lambda_v\mu_h(b_2\delta_s + b_3\mu_h)\right]I_s^2 \\
&\quad + \left[c_s\mu_v^2\Lambda_h^2 - \beta_v\beta_h b_1\Lambda_v\mu_h\Lambda_h\right]I_s \\
&= I_s\Big(\left[-c_s b_2\delta_s\mu_v(\beta_v b_1\mu_h - b_2\delta_s\mu_v)\right]I_s^2 \\
&\qquad + \left[c_s\mu_v\Lambda_h(\beta_v b_1\mu_h - b_2\delta_s\mu_v) - c_s b_2\delta_s\mu_v^2\Lambda_h + \beta_v\beta_h b_1\Lambda_v\mu_h(b_2\delta_s + b_3\mu_h)\right]I_s \\
&\qquad + \left[c_s\mu_v^2\Lambda_h^2 - \beta_v\beta_h b_1\Lambda_v\mu_h\Lambda_h\right]\Big).
\end{aligned}$$

Since our underlying assumption for the SSE is that $I_s^* \neq 0$, then we reduce to the quadratic equation:

$$\begin{aligned}
0 &= A_s I_s^2 + B_s I_s + C_s \\
&= \left[-c_s b_2\delta_s\mu_v(\beta_v b_1\mu_h - b_2\delta_s\mu_v)\right]I_s^2 \\
&\quad + \left[c_s\mu_v\Lambda_h(\beta_v b_1\mu_h - b_2\delta_s\mu_v) - c_s b_2\delta_s\mu_v^2\Lambda_h + \beta_v\beta_h b_1\Lambda_v\mu_h(b_2\delta_s + b_3\mu_h)\right]I_s \\
&\quad + \left[c_s\mu_v^2\Lambda_h^2 - \beta_v\beta_h b_1\Lambda_v\mu_h\Lambda_h\right].
\end{aligned}$$

Now note that we can re-write each of the coefficients into useful parameter groupings. For the first coefficient, A_s, we have

$$\begin{aligned} A_s &= -c_s b_2 \delta_s \mu_v (\beta_v b_1 \mu_h - b_2 \delta_s \mu_v) \\ &= c_s b_2^2 \delta_s^2 \mu_v^2 - \beta_v c_s b_1 b_2 \delta_s \mu_h \mu_v \\ &= c_s b_2^2 \delta_s^2 \mu_v^2 \left(1 - \frac{\beta_v}{\mu_v} \frac{b_1}{b_2} \frac{\mu_h}{\delta_s}\right) \\ &= c_s b_2^2 \delta_s^2 \mu_v^2 \left(1 - Q_s\right) \end{aligned}$$

where we define

$$Q_s := \frac{\beta_v}{\mu_v} \frac{b_1}{b_2} \frac{\mu_h}{\delta_s}.$$

This parameter grouping will be useful for later analysis. Note that if $\delta_s = 0$, then $A_s = 0$, and our quadratic equation in I_s becomes linear. This means that at most one positive equilibrium is possible in this case. We note that disease induced mortality could cause a backward bifurcation at $\mathscr{R}_s = 1$ and could be studied in future work. For the second coefficient, B_s, we can re-write several parameter groupings in terms of our reproduction number, $\mathscr{R}_s^2$, as follows:

$$\begin{aligned} B_s &= c_s \mu_v \Lambda_h (\beta_v b_1 \mu_h - b_2 \delta_s \mu_v) - c_s b_2 \delta_s \mu_v^2 \Lambda_h + \beta_v \beta_h b_1 \Lambda_v \mu_h (b_2 \delta_s + b_3 \mu_h) \\ &= \beta_v c_s b_1 \mu_h \Lambda_h \mu_v - c_s b_2 \delta_s \Lambda_h \mu_v^2 - c_s b_2 \delta_s \Lambda_h \mu_v^2 + \beta_v \beta_h b_1 b_2 \delta_s \Lambda_v \mu_h + \beta_v \beta_h b_1 b_3 \Lambda_v \mu_h^2 \\ &= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\frac{\beta_v}{\mu_v} \frac{b_1}{b_2} \frac{\mu_h}{\delta_s} - 1 - 1 + \frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} + \frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \frac{\mu_h}{\delta_s} \frac{b_3}{b_2}\right] \\ &= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\left(\frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} - 1\right) + \left(\frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} + \frac{\beta_v}{\mu_v} \frac{b_1}{b_2} \frac{\mu_h}{\delta_s} - 1\right)\right] \\ &= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_s^2 - 1\right) + \left(\mathscr{R}_s^2 \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} + \frac{\beta_v}{\mu_v} \frac{b_1}{b_2} \frac{\mu_h}{\delta_s} - 1\right)\right] \\ &= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_s^2 - 1\right) + \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} \left(\mathscr{R}_s^2 + \frac{\beta_v}{\mu_v} \frac{b_1}{b_3} - \frac{\delta_s}{\mu_h} \frac{b_2}{b_3}\right)\right] \\ &= c_s b_2 \delta_s \Lambda_h \mu_v^2 \times \\ &\qquad \left[\left(\mathscr{R}_s^2 - 1\right) + \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} \left(\mathscr{R}_s^2 + \frac{c_s}{\beta_h b_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[\frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} - \frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \frac{\mu_v}{\beta_v} \frac{b_2}{b_1} \frac{\delta_s}{\mu_h}\right]\right)\right] \\ &= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_s^2 - 1\right) + \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} \left(\mathscr{R}_s^2 + \frac{c_s}{\beta_h b_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[\mathscr{R}_s^2 - \mathscr{R}_s^2 \frac{\mu_v}{\beta_v} \frac{b_2}{b_1} \frac{\delta_s}{\mu_h}\right]\right)\right] \end{aligned}$$

$$= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_s^2 - 1 \right) + \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} \mathscr{R}_s^2 \left(1 + \frac{c_s}{\beta_h b_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[1 - \frac{\mu_v}{\beta_v} \frac{b_2}{b_1} \frac{\delta_s}{\mu_h} \right] \right) \right]$$
$$= c_s b_2 \delta_s \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_s^2 - 1 \right) + \frac{\mu_h}{\delta_s} \frac{b_3}{b_2} \mathscr{R}_s^2 \left(1 + \frac{c_s}{\beta_h b_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[1 - \frac{1}{Q_s} \right] \right) \right].$$

Lastly, the coefficient C_s can be simplified to

$$\begin{aligned} C_s &= c_s \mu_v^2 \Lambda_h^2 - \beta_v \beta_h b_1 \Lambda_v \mu_h \Lambda_h \\ &= c_s \Lambda_h^2 \mu_v^2 \left(1 - \frac{\beta_v \beta_h}{\mu_v} \frac{b_1}{c_s} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \right) \\ &= c_s \Lambda_h^2 \mu_v^2 \left(1 - \mathscr{R}_s^2 \right). \end{aligned}$$

Now note that if $\mathscr{R}_s > 1$, then we can make the following conclusions about the signs of the coefficients of our I_s quadratic equation. First, note that since $\mathscr{R}_s^2 > 1$, then $1 - \mathscr{R}_s^2 < 0$ and hence $C_s < 0$.

Now let's consider the parameter grouping Q_s. If $Q_s < 1$, then $1 - Q_s > 0$. Hence $A_s > 0$. Note that $Q_s < 1$ also implies that $1 < 1/Q_s$ so that $1 - 1/Q_s < 0$. Note that if this makes $B_s < 0$, then we have that $A_s > 0$, $B_s < 0$, and $C_s < 0$. By Descartes' Rule of Signs, we know that we have one sign change between adjacent coefficients and hence one positive real root. If $1 - 1/Q_s < 0$ makes $B_s > 0$, then we have that $A_s > 0$, $B_s > 0$, and $C_s < 0$. Again, by Descartes' Rule of Signs, since we have one sign change between adjacent coefficients then we have one positive real root.

However, if $Q_s > 1$, then $1 - Q_s < 0$. Hence $A_s < 0$. Note that $Q_s > 1$ also implies that $1 > 1/Q_s$ so that $1 - 1/Q_s > 0$, which guarantees $B_s > 0$. Hence we have that $A_s < 0$, $B_s > 0$, and $C_s < 0$. By Descartes' Rule of Signs, since we have two sign changes between adjacent coefficients, then we have either two positive real roots or zero positive real roots. Using baseline parameters listed in Table 1 with $n = 3$, we compute $Q_s = 28.541 > 1$. Simulating our model confirms that $I_s > 0$ at equilibrium. Hence, we must have two positive real roots for our quadratic equation in I_s, a surprising result.

The Resistant-Strain Boundary Equilibrium (RSE)

As before, let $\mathscr{E} = (M_r, I_r, T_{r,1}, \ldots, T_{r,n}, M_s, I_s, T_{s,1}, \ldots, T_{s,n}, S_h, S_v, R_s, R_r)$ be an equilibrium of the system described by (2.1a) - (2.1i) and (2.3a) - (2.3c). We now solve this system for the resistant-strain-only equilibrium. That is, we set $I_s = 0, M_s = 0, T_{s,1} = 0, \ldots, T_{s,n} = 0, R_s = 0$ and solve for nonzero quantities of the remaining compartments. The RSE for the system takes the form

$$\mathscr{E}_r = \left(M_r^{\star\star}, I_r^{\star\star}, T_{r,1}^{\star\star}, \ldots, T_{r,n}^{\star\star}, 0, 0, 0, \ldots, 0, S_h^{\star\star}, S_v^{\star\star}, 0, R_r^{\star\star}\right)$$

where there are n treated compartments for both the sensitive and resistant parasite strains.

To solve for the remaining nonzero compartments, we will set the corresponding differential equations to zero with the sensitive strain compartments set to zero. We will also consider the total human population, N_h, in the SSE system to help us solve the equilibrium equations.

The RSE system, with $\frac{dN_h}{dt} = 0$ as the first equation listed followed by the order of non-zero compartments given in $\mathscr{E}_r$, is

$$0 = \Lambda_h - \mu_h N_h - \delta_r \left(I_r + \sum_{k=1}^{n} T_{r,k} \right) \tag{$N_h^{\star\star}$}$$

$$0 = \kappa_v \beta_v S_v \left(I_r + \sum_{k=1}^{n} \Psi_{r,k} T_{r,k} \right) / N_h - \mu_v M_r \tag{$M_r^{\star\star}$}$$

$$0 = \frac{\kappa_h \beta_h S_h M_r}{N_h} - d_r I_r \tag{$I_r^{\star\star}$}$$

$$0 = a I_r - d_1 T_{r,1} \tag{$T_{r,1}^{\star\star}$}$$

$$0 = \alpha_{k-1} T_{r,k-1} - d_k T_{r,k} \qquad \text{for } k = 2, \ldots, n \tag{$T_{r,k}^{\star\star}$}$$

$$0 = \Lambda_h - \frac{\kappa_h \beta_h S_h M_r}{N_h} + \omega_r R_r + \alpha_n T_{r,n} - \mu_h S_h \tag{$S_h^{\star\star}$}$$

$$0 = \Lambda_v - \kappa_v \beta_v S_v \left(I_r + \sum_{k=1}^{n} \Psi_{r,k} T_{r,k} \right) / N_h - \mu_v S_v \tag{$S_v^{\star\star}$}$$

$$0 = \sigma_r I_r - (\omega_r + \mu_h) R_r. \tag{$R_r^{\star\star}$}$$

Again, we can easily solve for the treated and recovered classes as functions of the infected class, I_r, as follows:

$$\begin{aligned} T_{r,1} &= \frac{a}{d_1} I_r \\ T_{r,2} &= \frac{a\alpha_1}{d_1 d_2} I_r \\ &\vdots \\ T_{r,n} &= \frac{a \prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} d_k} I_r \\ R_r &= \frac{\sigma_r}{\omega_r + \mu_h} I_r. \end{aligned}$$

We can sum the treated compartments with I_r to get

$$G_2 = I_r + \sum_{k=1}^{n} T_{r,k} = \left(1 + \frac{a}{d_1} + \frac{a\alpha_1}{d_1 d_2} + \cdots + \frac{a \prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} d_k} \right) I_r = g_2 I_r.$$

We can also sum the the recovered class with this expression to get

$$G_3 = G_2 + R_r = g_2 I_r + \frac{\sigma_r}{\omega_r + \mu_h} I_r = \left(g_2 + \frac{\sigma_r}{\omega_r + \mu_h} \right) I_r = g_3 I_r.$$

We can substitute G_2 into our ODE for N_h to get

$$0 = \Lambda_h - \mu_h N_h - \delta_r G_2 = \Lambda_h - \mu_h N_h - \delta_r g_2 I_r,$$

which implies that

$$N_h = \frac{\Lambda_h}{\mu_h} - \frac{\delta_r g_2}{\mu_h} I_r.$$

We can also use the fact that N_h is the sum of the population at the RSE to get

$$N_h = S_h + I_r + \sum_{k=1}^{n} T_{r,k} + R_r = S_h + G_3 = S_h + g_3 I_r.$$

Setting these two equations for N_h equal, we obtain

$$\frac{\Lambda_h}{\mu_h} - \frac{\delta_r g_2}{\mu_h} I_r = S_h + g_3 I_r.$$

Solving for S_h gives us an equation for S_h as a function of I_r, as in the other treated and recovered compartments:

$$\begin{aligned} S_h &= \frac{\Lambda_h}{\mu_h} - \frac{\delta_r g_2}{\mu_h} I_r - g_3 I_r \\ &= \frac{\Lambda_h}{\mu_h} - \left(\frac{\delta_r g_2}{\mu_h} + g_3 \right) I_r. \end{aligned}$$

Now we can solve for S_v as a function of I_r. Note that

$$\begin{aligned} 0 &= \Lambda_v - \kappa_v \beta_v S_v \left(I_r + \sum_{k=1}^{n} \Psi_{r,k} T_{r,k} \right) / N_h - \mu_v S_v \\ &= \Lambda_v - \kappa_v \beta_v S_v G_1 / N_h - \mu_v S_v \\ &= \Lambda_v - S_v (\kappa_v \beta_v G_1 / N_h + \mu_v) \\ &= \Lambda_v - S_v (\kappa_v \beta_v g_1 I_r / N_h + \mu_v), \end{aligned}$$

which implies

$$\begin{aligned} S_v &= \frac{\Lambda_v}{\kappa_v \beta_v g_1 I_r / N_h + \mu_v} \\ &= \frac{\Lambda_v N_h}{\kappa_v \beta_v g_1 I_r + \mu_v N_h} \\ &= \frac{\Lambda_v \left(\frac{\Lambda_h}{\mu_h} - \frac{\delta_r g_2}{\mu_h} I_r \right)}{\kappa_v \beta_v g_1 I_r + \mu_v \left(\frac{\Lambda_h}{\mu_h} - \frac{\delta_r g_2}{\mu_h} I_r \right)} \\ &= \frac{\Lambda_v \left(\Lambda_h - \delta_r g_2 I_s \right)}{\kappa_v \beta_v \mu_h g_1 I_r + \mu_v \left(\Lambda_h - \delta_r g_2 I_r \right)} \\ &= \frac{\Lambda_v \left(\Lambda_h - \delta_r g_2 I_r \right)}{\mu_v \Lambda_h + (\kappa_v \beta_v \mu_h g_1 - \delta_r g_2 \mu_v) I_r}. \end{aligned}$$

Lastly, we solve for M_r in terms of I_r. We start with the equation

$$\begin{aligned}
0 &= \kappa_v \beta_v S_v \left(I_r + \sum_{k=1}^{n} \Psi_{r,k} T_{r,k} \right) / N_h - \mu_v M_r \\
&= \kappa_v \beta_v S_v G_1 / N_h - \mu_v M_r \\
&= \kappa_v \beta_v G_1 \frac{S_v}{N_h} - \mu_v M_r \\
&= \kappa_v \beta_v G_1 \frac{\frac{\Lambda_v N_h}{\kappa_v \beta_v g_1 I_r + \mu_v N_h}}{N_h} - \mu_v M_r \\
&= \kappa_v \beta_v G_1 \frac{\Lambda_v}{\kappa_v \beta_v g_1 I_r + \mu_v N_h} - \mu_v M_r \\
&= \kappa_v \beta_v G_1 \frac{\Lambda_v}{\kappa_v \beta_v g_1 I_r + \mu_v \left(\frac{\Lambda_h}{\mu_h} - \frac{\delta_r g_2}{\mu_h} I_r \right)} - \mu_v M_r \\
&= \kappa_v \beta_v G_1 \frac{\Lambda_v \mu_h}{\kappa_v \beta_v \mu_h g_1 I_r + \mu_v \left(\Lambda_h - \delta_r g_2 I_r \right)} - \mu_v M_r \\
&= \kappa_v \beta_v g_1 I_r \frac{\Lambda_v \mu_h}{\mu_v \Lambda_h + (\kappa_v \beta_v \mu_h g_1 - \mu_v \delta_r g_2) I_r} - \mu_v M_r,
\end{aligned}$$

which implies

$$M_r = \frac{\kappa_v \beta_v g_1}{\mu_v} \left(\frac{\Lambda_v \mu_h}{\Lambda_h \mu_v + (\kappa_v \beta_v \mu_h g_1 - \mu_v \delta_r g_2) I_r} \right) I_r.$$

Thus we have the following equations that depend on I_r:

$$\begin{aligned}
M_r &= \frac{\kappa_v \beta_v g_1}{\mu_v} \left(\frac{\Lambda_v \mu_h}{\Lambda_h \mu_v + (\kappa_v \beta_v \mu_h g_1 - \mu_v \delta_r g_2) I_r} \right) I_r \\
T_{r,1} &= \frac{a}{d_1} I_r \\
T_{r,2} &= \frac{a \alpha_1}{d_1 d_2} I_r \\
&\vdots \\
T_{r,n} &= \frac{a \prod_{k=1}^{n-1} \alpha_k}{\prod_{k=1}^{n} d_k} I_r \\
S_h &= \frac{\Lambda_h}{\mu_h} - \left(\frac{\delta_r g_2}{\mu_h} + g_3 \right) I_r \\
S_v &= \frac{\Lambda_v \left(\Lambda_h - \delta_r g_2 I_r \right)}{\Lambda_h \mu_v + (\kappa_v \beta_v \mu_h g_1 - \mu_v \delta_r g_2) I_r} \\
R_r &= \frac{\sigma_r}{\omega_r + \mu_h} I_r.
\end{aligned}$$

Now we turn to the I_r equation. Notice that setting the ODE to zero yields

$$0 = \kappa_h \beta_h S_h M_r / N_h - d_r I_r,$$

which yields

$$\begin{aligned}
I_r &= \frac{\kappa_h \beta_h}{d_r} \frac{S_h}{N_h} M_r \\
&= \frac{\kappa_h \beta_h}{d_r} \frac{\frac{\Lambda_h}{\mu_h} - \left(\frac{g_2 \delta_r}{\mu_h} + g_3\right) I_r}{\frac{\Lambda_h}{\mu_h} - \frac{g_2 \delta_r}{\mu_h} I_r} \left(\frac{\kappa_v \beta_v g_1}{\mu_v} \left(\frac{\Lambda_v \mu_h}{\mu_v \Lambda_h + (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) I_r} \right) I_r \right) \\
&= \frac{\kappa_h \beta_h \kappa_v \beta_v g_1 \Lambda_v \mu_h}{d_r \mu_v} \left(\frac{\Lambda_h - (g_2 \delta_r + g_3 \mu_h) I_r}{\Lambda_h - g_2 \delta_r I_r} \right) \left(\frac{I_r}{\mu_v \Lambda_h + (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) I_r} \right).
\end{aligned}$$

This gives us the following cubic equation in I_r:

$$\begin{aligned}
0 &= \left[-d_r g_2 \delta_r \mu_v (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) \right] I_r^3 \\
&\quad + \left[d_r \mu_v \Lambda_h (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) - d_r g_2 \delta_r \mu_v^2 \Lambda_h + \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h (g_2 \delta_r + g_3 \mu_h) \right] I_r^2 \\
&\quad + \left[d_r \mu_v^2 \Lambda_h^2 - \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h \Lambda_h \right] I_r \\
&= I_r \left(\left[-d_r g_2 \delta_r \mu_v (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) \right] I_r^2 \right. \\
&\qquad + \left[d_r \mu_v \Lambda_h (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) - d_r g_2 \delta_r \mu_v^2 \Lambda_h + \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h (g_2 \delta_r + g_3 \mu_h) \right] I_r \\
&\qquad \left. + \left[d_r \mu_v^2 \Lambda_h^2 - \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h \Lambda_h \right] \right).
\end{aligned}$$

Since our underlying assumption for the RSE is that $I_r^{\star\star} \neq 0$, then we reduce to the quadratic equation:

$$\begin{aligned}
0 &= A_r I_r^2 + B_r I_r + C_r \\
&= \left[-d_r g_2 \delta_r \mu_v (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) \right] I_r^2 \\
&\quad + \left[d_r \mu_v \Lambda_h (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) - d_r g_2 \delta_r \mu_v^2 \Lambda_h + \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h (g_2 \delta_r + g_3 \mu_h) \right] I_r \\
&\quad + \left[d_r \mu_v^2 \Lambda_h^2 - \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h \Lambda_h \right].
\end{aligned}$$

Now note that we can re-write each of the coefficients into useful parameter groupings. For the first coefficient, A_r, we have

$$\begin{aligned} A_r &= -d_r g_2 \delta_r \mu_v (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) \\ &= d_r g_2^2 \delta_r^2 \mu_v^2 - \kappa_v \beta_v d_r g_1 g_2 \delta_r \mu_h \mu_v \\ &= d_r g_2^2 \delta_r^2 \mu_v^2 \left(1 - \frac{\kappa_v \beta_v}{\mu_v} \frac{g_1}{g_2} \frac{\mu_h}{\delta_r}\right) \\ &= d_r g_2^2 \delta_r^2 \mu_v^2 \left(1 - Q_r\right) \end{aligned}$$

where we define

$$Q_r := \frac{\kappa_v \beta_v}{\mu_v} \frac{g_1}{g_2} \frac{\mu_h}{\delta_r}.$$

This parameter grouping will be useful for later analysis. Again, we see that if $\delta_r = 0$, then $A_r = 0$ and hence our quadratic in I_r becomes linear so that we have at most one positive equilibrium in this case. Again, future work could study the possibility of a backward bifurcation at $\mathscr{R}_r = 1$ as a result of disease-induced mortality. For the second coefficient, B_r, we can re-write several parameter groupings in terms of our reproduction number, $\mathscr{R}_r^2$, as follows:

$$\begin{aligned} B_r &= d_r \mu_v \Lambda_h (\kappa_v \beta_v g_1 \mu_h - g_2 \delta_r \mu_v) - d_r g_2 \delta_r \mu_v^2 \Lambda_h + \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h (g_2 \delta_r + g_3 \mu_h) \\ &= \kappa_v \beta_v d_r g_1 \mu_h \Lambda_h \mu_v - d_r g_2 \delta_r \Lambda_h \mu_v^2 - d_r g_2 \delta_r \Lambda_h \mu_v^2 \\ &\quad + \kappa_v \beta_v \kappa_h \beta_h g_1 g_2 \delta_r \Lambda_v \mu_h + \kappa_v \beta_v \kappa_h \beta_h g_1 g_3 \Lambda_v \mu_h^2 \\ &= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\frac{\kappa_v \beta_v}{\mu_v} \frac{g_1}{g_2} \frac{\mu_h}{\delta_r} - 1 - 1 + \frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} + \frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \frac{\mu_h}{\delta_r} \frac{g_3}{g_2}\right] \\ &= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} - 1\right) + \left(\frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} + \frac{\kappa_v \beta_v}{\mu_v} \frac{g_1}{g_2} \frac{\mu_h}{\delta_r} - 1\right)\right] \\ &= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_r^2 - 1\right) + \left(\mathscr{R}_r^2 \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} + \frac{\kappa_v \beta_v}{\mu_v} \frac{g_1}{g_2} \frac{\mu_h}{\delta_r} - 1\right)\right] \\ &= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_r^2 - 1\right) + \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} \left(\mathscr{R}_r^2 + \frac{\kappa_v \beta_v}{\mu_v} \frac{g_1}{g_3} - \frac{\delta_r}{\mu_h} \frac{g_2}{g_3}\right)\right] \\ &= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_r^2 - 1\right) + \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} \times \right. \\ &\qquad \left. \left(\mathscr{R}_r^2 + \frac{d_r}{\kappa_h \beta_h g_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[\frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} - \frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \frac{\mu_v}{\kappa_v \beta_v} \frac{g_2}{g_1} \frac{\delta_r}{\mu_h}\right]\right)\right] \end{aligned}$$

$$
\begin{aligned}
&= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_r^2 - 1 \right) + \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} \left(\mathscr{R}_r^2 + \frac{d_r}{\kappa_h \beta_h g_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[\mathscr{R}_r^2 - \mathscr{R}_r^2 \frac{\mu_v}{\kappa_v \beta_v} \frac{g_2}{g_1} \frac{\delta_r}{\mu_h} \right] \right) \right] \\
&= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_r^2 - 1 \right) + \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} \mathscr{R}_r^2 \left(1 + \frac{d_r}{\kappa_h \beta_h g_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[1 - \frac{\mu_v}{\kappa_v \beta_v} \frac{g_2}{g_1} \frac{\delta_r}{\mu_h} \right] \right) \right] \\
&= d_r g_2 \delta_r \Lambda_h \mu_v^2 \left[\left(\mathscr{R}_r^2 - 1 \right) + \frac{\mu_h}{\delta_r} \frac{g_3}{g_2} \mathscr{R}_r^2 \left(1 + \frac{d_r}{\kappa_h \beta_h g_3} \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \left[1 - \frac{1}{Q_r} \right] \right) \right].
\end{aligned}
$$

Lastly, the coefficient C_r can be simplified to

$$
\begin{aligned}
C_r &= d_r \mu_v^2 \Lambda_h^2 - \kappa_v \beta_v \kappa_h \beta_h g_1 \Lambda_v \mu_h \Lambda_h \\
&= d_r \Lambda_h^2 \mu_v^2 \left(1 - \frac{\kappa_v \beta_v \kappa_h \beta_h}{\mu_v} \frac{g_1}{d_r} \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \right) \\
&= d_r \Lambda_h^2 \mu_v^2 \left(1 - \mathscr{R}_r^2 \right).
\end{aligned}
$$

Now note that if $\mathscr{R}_r^2 > 1$, then we can make the following conclusions about the signs of the coefficients of our I_r quadratic equation. First, note that since $\mathscr{R}_r^2 > 1$, then $1 - \mathscr{R}_r^2 < 0$ and hence $C_r < 0$.

Now let's consider the parameter grouping Q_r. If $Q_r < 1$, then $1 - Q_r > 0$. Hence, $A_r > 0$. Note that $Q_r < 1$ also implies that $1 < 1/Q_r$ so that $1 - 1/Q_r < 0$. Note that if this makes $B_r < 0$, then we have that $A_r > 0$, $B_r < 0$, and $C_r < 0$. By Descartes' Rule of Signs, we know that we have one sign change between adjacent coefficients and hence one positive real root. If $1 - 1/Q_r < 0$ makes $B_r > 0$, then we have that $A_r > 0$, $B_r > 0$, and $C_r < 0$. Again, by Descartes' Rule of Signs, since we have one sign change between adjacent coefficients then we have one positive real root.

However, if $Q_r > 1$, then $1 - Q_r < 0$. Hence, $A_r < 0$. Note that $Q_r > 1$ also implies that $1 > 1/Q_r$ so that $1 - 1/Q_r > 0$, which guarantees $B_r > 0$. Thus we have $A_r < 0$, $B_r > 0$, and $C_r < 0$. By Descartes' Rule of Signs, since we have two sign changes between adjacent coefficients, then we have either two positive real roots or zero positive real roots. Using baseline parameters listed in Table 1 with $n = 3$, we compute $Q_r = 17.125 > 1$. Simulating our model confirms that $I_r > 0$ at equilibrium. Hence, we must have two positive real roots for our quadratic equation in I_r.

The sensitive strain, $(\mathscr{R}_s^r)^2$

Now that we have computed the SSE and RSE, we can compute the invasion numbers, $\mathscr{R}_s^r$ and $\mathscr{R}_r^s$. Note that we square these numbers in our analysis, $(\mathscr{R}_s^r)^2$ and $(\mathscr{R}_r^s)^2$, but the interpretation still holds in that if $\mathscr{R}_s^r > 1$, then $(\mathscr{R}_s^r)^2 > 1$, and vice versa. The invasion number for the sensitive strain invading the resistant strain equilibrium takes the form

$$(\mathscr{R}_s^r)^2 = v_s h_s \left[\frac{1}{e_s} + \frac{a\Psi_{s,1}}{e_s e_1} + \frac{a\alpha_1 \Psi_{s,2}}{e_s e_1 e_2} + \cdots + \frac{a\left(\prod_{k=1}^{n-1} \alpha_k\right) \Psi_{s,n}}{e_s \prod_{k=1}^{n} e_k} \right] S_h^\star \tag{2.9}$$

where

$$h_s = \frac{\beta_h}{N_h^{\star\star}}, \qquad v_s = \frac{\beta_v S_v^{\star\star}}{\mu_v N_h^{\star\star}}, \qquad c_s = a + \delta_s + \mu_h + \sigma_s, \qquad c_k = \alpha_k + \delta_s + \mu_h$$

and

$$e_s = c_s + f_r, \qquad e_k = c_k + \varphi_k f_r, \qquad f_r = \frac{\kappa_h \beta_h}{N_h^{\star\star}} M_r^{\star\star}$$

Here, the compartments are evaluated at the RSE, instead of evaluated at the DFE as we did for the reproduction numbers. Notice, however, that if we evaluate $(\mathscr{R}_s^r)^2$ at the DFE, then we get the sensitive strain's basic reproduction number $\mathscr{R}_s^2$ from earlier.

The resistant strain, $(\mathscr{R}_r^s)^2$

The invasion number for the resistant strain invading the sensitive strain equilibrium takes the form

$$(\mathscr{R}_r^s)^2 = v_r h_r \left[\frac{1}{d_r} + \frac{a\Psi_{r,1}}{d_r d_1} + \frac{a\alpha_1 \Psi_{r,2}}{d_r d_1 d_2} + \cdots + \frac{a\left(\prod_{k=1}^{n-1} \alpha_k\right) \Psi_{r,n}}{d_r \prod_{k=1}^{n} d_k} \right] (S_h^\star + I_s^\star + R_s^\star) \tag{2.10}$$

$$+ v_r h_r \sum_{i=1}^{n} \left[\varphi_i \left(\frac{\Psi_{r,i}}{d_i} + \frac{\alpha_i \Psi_{r,i+1}}{d_i d_{i+1}} + \cdots + \frac{\left(\prod_{k=i}^{n-1} \alpha_k\right) \Psi_{r,n}}{\left(\prod_{k=i}^{n} d_k\right)} \right) T_{s,i}^\star \right] \tag{2.11}$$

where

$$h_s = \frac{\beta_h}{N_h^\star}, \qquad v_s = \frac{\beta_v S_v^\star}{\mu_v N_h^\star}, \qquad c_s = a + \delta_s + \mu_h + \sigma_s, \qquad c_k = \alpha_k + \delta_s + \mu_h$$

and where

$$h_r = \kappa_h h_s, \qquad v_r = \kappa_v v_s, \qquad d_r = a + \delta_r + \mu_h + \sigma_r, \qquad d_k = \alpha_k + \delta_r + \mu_h.$$

Here, the compartments are evaluated at the SSE. Notice, again, that if we evaluated $(\mathscr{R}_r^s)^2$ at the DFE, then we get the resistant strain's basic reproduction number $\mathscr{R}_r^2$ from earlier. Recalling our parameter groupings from earlier, we can rewrite this invasion number as

$$(\mathscr{R}_r^s)^2 = v_r h_r \left[\frac{g_1}{d_r}(S_h^s + I_s^s + R_s^s) + \sum_{i=1}^{n} \frac{\hat{g}_i}{d_r} T_{s,i}^s \right]$$

where

$$\hat{g}_i = \varphi_i \left(\frac{\Psi_{r,i}}{d_i} + \frac{\alpha_i \Psi_{r,i+1}}{d_i d_{i+1}} + \cdots + \frac{\left(\prod_{k=i}^{n-1} \alpha_k\right) \Psi_{r,n}}{\left(\prod_{k=i}^{n} d_k\right)} \right) \qquad \text{for} \qquad i = 1, \ldots, n.$$

Note that $\hat{g}_1 = \varphi_1(g_1 - 1)$.

Since $\mathscr{R}_s^r$ and $\mathscr{R}_r^s$ were computed using the NGM Method, we have the following theorem regarding the stability of the SSE and RSE:

Theorem 2.2 (Stability of the SSE and RSE)**.** *Suppose $\mathscr{R}_s > 1$ and $\mathscr{R}_r > 1$.*

The SSE is locally asymptotically stable if and only if $\mathscr{R}_r^s < 1$. The RSE is locally asymptotically stable if and only if $\mathscr{R}_s^r < 1$.

If $\mathscr{R}_s^r > 1$ and $\mathscr{R}_r^s < 1$, then the sensitive strain dominates. If $\mathscr{R}_s^r < 1$ and $\mathscr{R}_r^s > 1$, then the resistant strain dominates. If both $\mathscr{R}_s^r > 1$ and $\mathscr{R}_r^s > 1$, then the two strains can coexist. If both $\mathscr{R}_s^r < 1$ and $\mathscr{R}_r^s < 1$, then the dominant strain depends on initial conditions of the model.

2.4 Simulations and Discussion

In order to further investigate our model and understand the impact of parameters on disease outcome, we numerically simulate our model using MATLAB's ode45 solver. The baseline parameters that we use are listed in Appendix A in Table 1. The MATLAB code used in

this section can be found in the GitHub link listed in Appendix B. In these simulations, we scale by the total initial population size so that we simulate population density instead of total population.

2.4.1 Sensitivity Analysis

We investigate the parameters in our model by performing a global sensitivity analysis using latin hypercube sampling (LHS) and partial rank correlation coefficients (PRCCs) as described by Marino et al. in [23]. PRCCs are calculated by using the residuals of a regression procedure on the model after sampling parameter values. The PRCC describes the linear relationship between the LHS parameters and model output of interest after discounting the linear effects of other parameter changes. This sensitivity analysis involves studying a multi-dimensional parameter space in order to identify the impacts of parameter changes in system dynamics in our model, e.g. long-term behavior or equilibrium values. The LHS method we use for sampling parameter sets is a Monte Carlo method introduced by McKay et al. in [24] where sampling is performed independently for each parameter from a distribution and from equally probable intervals.

For our simulations, we sample and create 100,000 parameter sets and calculate the PRCCs for the infected and treated classes in the case of $n = 3$ treated classes using uniform distributions and bounds based on data from high and low transmission regions for malaria. We adapt the global sensitivity analysis MATLAB code from [23] for our model. See Table 1 for baseline parameter values and bounds used for the LHS. A PRCC will measure the degree of association between two random variables. In our analysis, the PRCC will measure association between a model parameter and the simulated approximate equilibrium value of the infected classes (I_s and I_r) as well as the treated classes ($T_{s,1}$, $T_{s,2}$, $T_{s,2}$, $T_{r,1}$, $T_{r,2}$, and $T_{r,3}$). These approximate equilibrium values are computed at time $t = 1000$ days in our simulations.

In Figure 2.3, we plot the PRCC values for each parameter in relation to the simulated equilibrium value for the sensitive and resistant strain infected classes (I_s and I_r). In Figure 2.4, we plot the PRCC values for each parameter in relation to the simulated equilibrium value for the sensitive and resistant strain treated classes ($T_{s,1}$, $T_{s,2}$, $T_{s,3}$, $T_{r,1}$, $T_{r,2}$ and

$T_{r,3}$). These figures are plotted with parameter sets split between those that have PRCC values above a threshold of 0.1 (*left)* and those below a threshold of 0.1 (*right).* Significant parameters (those with p-value < 0.01) are marked with a black dot.

First, we consider parameters with PRCC values greater than 0.1. Note the high PRCC values (*left* in both Figures 2.3 and 2.4) for the birth and death rates of mosquitoes (vectors), especially for the resistant-strain (I_r, $T_{r,1}$, $T_{r,2}$, and $T_{r,3}$). The positive PRCC value for Λ_v indicates that increasing the mosquito birth rate will increase the population in malaria-infected and treated human classes. The negative PRCC value for μ_v indicates that decreasing the mosquito death rate will increase the population in malaria-infected and treated human classes. Hence, a control method we could implement to decrease human malaria infections could include decreasing the mosquito birth rate by removing egg-laying sites like standing water near populated areas. We could also increase the mosquito death rate and cause a decrease in human infections by using mosquito insecticides, like in insecticide-treated bed nets (ITNs) or indoor residual spraying (IRS) as is recommended by the CDC [3].

We also see high positive PRCC values for the transmission rates, β_h and β_v. That is, if both the human-to-mosquito transmission and the mosquito-to-human transmission rates increase, then the populations in the infected classes, I_s and I_r, as well as all six treated classes for both strains will also increase. Hence, for control strategies, we can focus on decreasing the transmission rates, which incorporate the mosquito biting rate. Bed nets, as recommended by the CDC [3], can help decrease this transmission rate. The fitness parameters κ_h and κ_v also have high PRCC values. Recall that these fitness parameters scale the transmission rates for the resistant strain infection in order to account for biological trade-offs that come with the development of drug resistance for the malaria parasite. Notice that PRCC values for κ_h and κ_v are negative for the I_s and all three T_s classes and positive for the I_r and all three T_r classes. That is, as these fitness parameters increase, the population in the I_s and T_s classes will decrease and the population in the I_r and T_r classes will increase. Since this parameter is used to scale the resistant strain transmission, then this result follows from the fact that a higher fitness parameter means we have a higher rate of resistant strain transmission, which draws individuals away from the possibility of being infected with

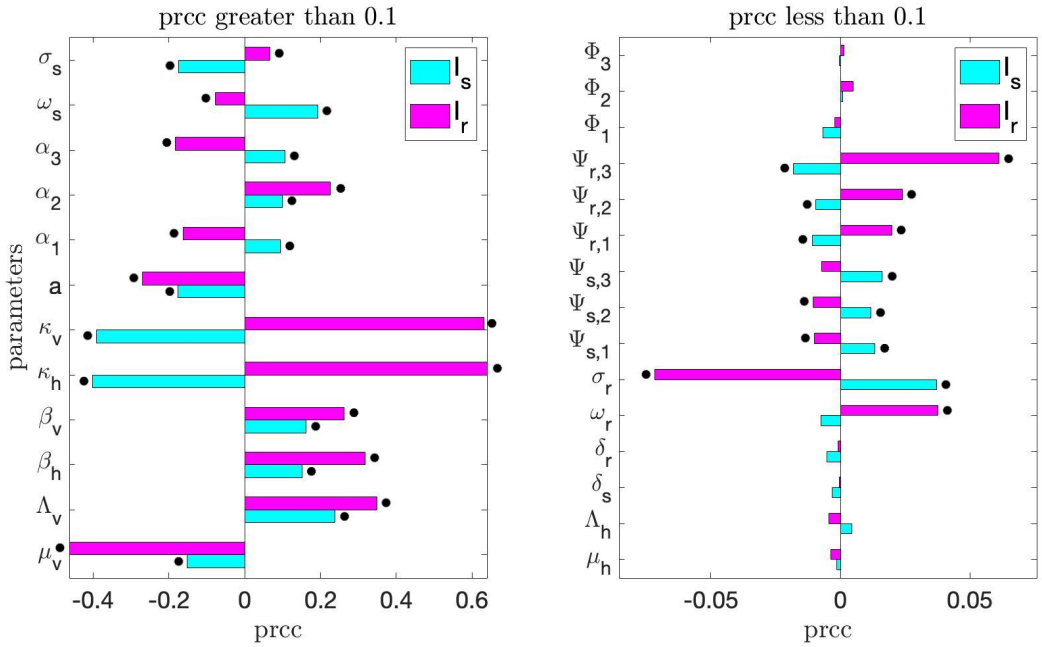


Figure 2.3: PRCCs for model parameters and Infected Classes' disease equilibrium (I_s and I_r) which is approximated numerically by running the model simulation to $t = 1000$ days. We compare PRCCs above a threshold of 0.1 (*left*) and those below 0.1 (*right*). These PRCCs were calculated using latin hypercube sampling with 100,000 parameter samples, $n = 3$ (three T_s classes and three T_r classes), increasing φ (represented by Φ in the above figure), and decreasing Ψ_s and Ψ_r. Significant parameters (those with p-value < 0.01) are marked with a black dot.

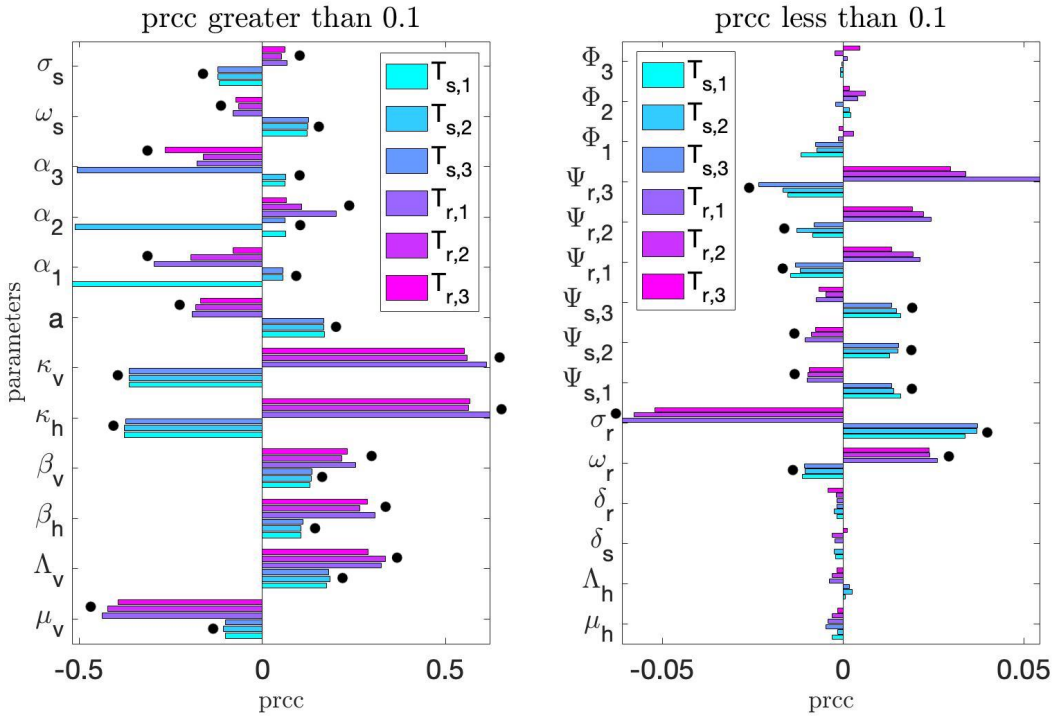


Figure 2.4: PRCCs for model parameters and Treated Classes' disease equilibrium ($T_{s,1}$, $T_{s,2}$, $T_{s,3}$, $T_{r,1}$, $T_{r,2}$, and $T_{r,3}$) approximated numerically by running the model simulation to $t = 1000$ days. We compare PRCCs above a threshold of 0.1 (*left*) and those below 0.1 (*right*). These PRCCs were calculated using latin hypercube sampling with 100,000 parameter samples, $n = 3$ (three T_s classes and three T_r classes), increasing φ (represented by Φ in the above figure), and decreasing Ψ_s and Ψ_r. Significant parameters grouped by strain-type (those with p-value < 0.01) are marked with a black dot.

the sensitive strain and move a higher number of people from the sensitive strain infected and treated classes into the resistant strain infected and treated classes. This result also highlights the fact that the transmission rate for the resistant strain plays a significant role in the number of resistant strain infections. And hence, to undermine resistance, we should focus on methods that will decrease this transmission rate, especially for the resistant strain of malaria.

We next notice the significance of parameters a, α_1, α_2, and α_3. Recall that a is the rate at which individuals move from I_s and I_r to their first treated classes, $T_{s,1}$ and $T_{r,1}$. Biologically we interpret this to be the rate of symptom onset and hence recognition of the need for treatment. A negative PRCC value indicates that as a increases, the infected class population decreases. Hence if we increase the rate of treatment (or decrease the time to recognize infection and start treatment), then we can decrease the total number of untreated infected individuals. We also see some interesting behavior in terms of the PRCC values for the α parameters. Recall that the α parameters measure the rate of exiting the corresponding treatment class. Notice that an increase in α_1, α_2, and α_3 corresponds to an increase in the I_s class, whereas only α_2 causes an increase in I_r while α_1 and α_3 cause a decrease in I_r. We consider the treated classes to determine what may account for this behavior. Notice that for the treated classes in Figure 2.4 (*left*), we see that, compared to the other classes, α_1 has a large negative PRCC value for $T_{s,1}$, α_2 has a large negative PRCC value for $T_{s,2}$, and α_3 has a large negative PRCC value for $T_{s,3}$. This means that increasing the rate at which we leave each sensitive-strain treated class will decrease the population in that treated class. However, there does not seem to be as strong of a correlation between the α's and the resistant-strain treated classes. Biologically, this relationship can be interpreted as follows: increasing the speed at which the drug works in the bloodstream will speed people along the recovery path and hence decrease the total number of treated (infectious) individuals.

Lastly, we note the high PRCC values for the rate of natural sensitive strain recovery (σ_s) and rate of return to susceptibility after sensitive strain recovery (sensitive strain infection immunity loss, ω_s). We see that σ_s has a negative PRCC for the I_s class as well as T_s classes, which indicates that decreasing the rate of natural sensitive strain recovery will decrease the sensitive strain infection class as well as the sensitive strain treatment classes.

However, we see the opposite behavior for the resistant strain classes. That is, σ_s has a positive PRCC for the I_r and T_r classes, although its magnitude is smaller than the PRCC for the sensitive strain classes. The opposite behavior occurs for the sensitive strain infection immunity loss parameter, ω_s. That is, the PRCC is positive for the sensitive strain infection and treatment classes, while negative for the resistant strain infection and treatment classes. Hence, an increase in the rate of s-infection immunity loss indicates we will increase our sensitive strain infections and decrease our resistant strain infections. This could be a result of the assumption in our model that the sensitive strain immunity while dwelling in R_s does not protect from resistant strain infections. The resistant strain does not have to compete with the sensitive strain for infecting individuals in R_s. Increasing ω_s depletes the R_s population and returns them to the S_h class, where the resistant strain now must compete with the sensitive strain for susceptible individuals. Hence, prolonging immunity to malaria will decrease the sensitive strain infections, while increasing the resistant strain infections.

Now we consider the less significant PRCC values that lie below the threshold of 0.1 in Figures 2.3 (*right*) and 2.4 (*right*). Note that the human natural mortality and birth rates (μ_h, Λ_h) as well as the human disease mortality rates (δ_s, δ_r) have very small PRCC values and hence do not pose much significance in our model outcome. Also, although the PRCCs are smaller in this case, we see the opposite behavior from σ_r and ω_r compared to the corresponding sensitive strain parameters. That is, σ_r has a positive PRCC for the I_s class as well as T_s classes, which indicates that increasing the rate of natural resistant strain recovery will increase the resistant strain infection class as well as the resistant strain treatment classes. Again, the opposite behavior occurs for the resistant strain infection immunity loss parameter, ω_r. That is, the PRCC for resistant strain infection immunity loss is negative for the sensitive strain infection and treatment classes, while positive for the resistant strain infection and treatment classes. Hence, an increase in the rate of resistant strain infection immunity loss indicates we will increase our resistant strain infections and decrease our sensitive strain infections. This can be explained by the increase in susceptible individuals for the resistant strain, which then draws away susceptible individuals from the sensitive strain.

We now turn to our PKPD parameters, φ, Ψ_s, and Ψ_r. Recall that φ scales susceptibility to the resistant strain for humans in the sensitive strain treated compartments based on drug concentration in the blood. Hence, as the drug concentration decays throughout the treated compartments, the possibility of resistant strain infection increases and hence φ increases. The PRCC values for φ_1, φ_2, and φ_3 are small and do not play a significant role in the sensitivity of our equilibrium.

On the other hand, the equilibrium is more sensitive to Ψ_s and Ψ_r. Recall that these parameters scale the mosquito transmission infection rate from biting humans in the sensitive strain treatment classes and the resistant strain treatment classes. As individuals advance through treatment, the parasite density in the blood will decrease. Hence, Ψ_s and Ψ_r will decrease across treatment stages to account for the decreased parasite presence and thus decreased probability of mosquito infection. We note that, although the PRCC values are small, we see a pattern develop. The PRCC for $\Psi_{s,1}$, $\Psi_{s,2}$, and $\Psi_{s,3}$ are positive for I_s, $T_{s,1}$, $T_{s,2}$, and $T_{s,3}$ and negative for I_r, $T_{r,1}$, $T_{r,2}$, and $T_{r,3}$. This could occur due to the fact that Ψ_s scales the transmission rate for s-infections, hence an increase in Ψ_s will lead to an increase in s-infected and s-treated individuals. Those infections are then drawing away individuals from being infected with the resistant strain, which already has reduced transmissibility as an assumption in our model. However, the opposite behavior occurs for Ψ_r. That is, the PRCC for $\Psi_{r,1}$, $\Psi_{r,2}$, and $\Psi_{r,3}$ are negative for I_s, $T_{s,1}$, $T_{s,2}$, and $T_{s,3}$ and positive for I_r, $T_{r,1}$, $T_{r,2}$, and $T_{r,3}$. This could occur due to the fact that Ψ_r scales the transmission rate for resistant strain infections, hence an increase in Ψ_r will lead to an increase in resistant strain infected and resistant strain treated individuals. Those infections are then drawing away individuals from being infected with the sensitive strain. We note that the highest PRCC occurs for $\Psi_{r,3}$ for both the resistant strain infected and resistant strain treated individuals. This could be a result of the Ψ_r decreasing across treatment classes. The parameter $\Psi_{r,3}$ would be the smallest of the Ψ_r parameters, and hence increasing it would have a larger effect overall on the transmission rate and increase the resistant strain infections and resistant strain treated populations. Hence, creating a treatment plan that acts quickly in decreasing parasite density in the blood can decrease resistant strain infections.

2.5 Conclusion

In summary, we created an $SITRS$-SI vector-borne disease Ordinary Differential Equation model in an effort to understand treatment dynamics, including within-host pharmacokinetics and pharmacodynamics, as well as the development and dynamics of drug resistance. We were able to derive important biological thresholds for determining disease persistence: the reproduction numbers for each strain ($\mathscr{R}_s$ and $\mathscr{R}_r$) and the invasion numbers ($\mathscr{R}_s^r$ and $\mathscr{R}_r^s$) that inform competitive outcomes between strains. In particular, these thresholds can be used to help public health experts determine which parameters in our model should be used to control persistence and prevalence of malaria as well as drug resistant parasite development. They can then use the information from these parameters to better inform public health strategies.

In our sensitivity analysis, we found that the most significant parameters in the model were those involving the birth and death rates of mosquitoes. Hence, controlling the mosquito population should be the first step in reducing the malaria burden in a population. However, we should also consider the treatment parameters and consider drug treatments that quickly deplete parasite density in infected humans so as to reduce the build-up of resistant strain infections. The effect of PKPD on reducing parasite load seems to be more crucial than the protective effect of a drug in the body fighting against resistant infection. More work is needed to determine whether this is a consequence of the model structure. For instance, if all T_s classes entered I_r upon r-infection, instead of entering the corresponding T_r classes, then sensitivity to the φ parameters might increase. This is a subject for future work.

Unfortunately, it seems that our treatment parameters dependent on parasite density, Ψ_s and Ψ_r, work in opposing each other. That is, increasing Ψ_s increases the number of sensitive strain infectious individuals, while it decreases the resistant strain infectious individuals. Similarly, increasing Ψ_r decreases the total number of sensitive strain infectious individuals while it increases the total number of resistant strain infectious individuals. We should then consider if there are some values for these treatment parameters that balance each other out to reduce the total number of malaria cases. One parameter to investigate

is a, the rate of treatment, as increasing this parameter decreases the number of untreated s-infected humans and untreated r-infected humans as well as treated r-infections.

It is important to remember that while antimalarial treatment is necessary in order to reduce malaria-induced mortality and morbidity, it also creates a selection-pressure for drug-resistant malaria parasites. This is one of the problems we face when dealing with a parasite-causing disease in that a random mutations or new variants in that organism that are advantageous allow that mutation or variant to spread. In order to combat the emergence of drug-resistance, we can adapt our treatment model by re-parameterizing it based on different treatment regimes via the treatment-related parameters φ_i, $\Psi_{s,i}$, $\Psi_{r,i}$, and α_i. We can then explore the public health impact of different dosing protocols using drugs with different pharmacokinetics and pharmacodynamics on the spread of drug-resistant malaria.

Chapter 3

Modeling Mosquito-borne disease with Integral Equations

3.1 Motivation

Many epidemiological models assume that the waiting times for each of the disease stages are exponentially distributed in order to simplify the model formulation and its analysis. However, this is not always the correct assumption and methods have been developed to account for the potential variability in waiting time distributions for each stage [25, 26, 18, 27]. It is important to create a more accurate representation of these waiting times when dealing with pharmacological responses due to disease treatment in order to capture the interaction between drug concentration and pathogen load within hosts. This interaction can help us model within-human pharmacodynamics and pharmacokinetics, which can help inform drug development and treatment in human populations. It is especially important to understand this interaction in order to reduce the spread and prevalence of drug-resistant parasite strains. We use malaria as a guiding example and formulate a two-strain $SITRS$-SI model with general waiting time distributions. This is the first step in developing a framework that allows us to more accurately capture the feedback between within-human and between-human disease dynamics in the presence of treatment. The model derivation described below allows for arbitrary survival probabilities in each class, which can be fit to data to more accurately represent the waiting time for each class as described by Feng et al.

in [26]. The following work expands the single-strain model we derived in [25] with general survival functions for the disease classes in a single-strain $SITRS$-SI model. It is important to fit the correct waiting times to each class since, as we shall see in our results, different waiting times can impact whether a disease persists or dies out in a population, even when the distribution of waiting times has the same mean.

In the past, vector-borne disease models have either focused on within-host or between-host disease dynamics, but not many have linked the two scales [28, 29, 30, 31, 32]. The motivation for this model was to determine the rates for moving through the sensitive-strain-infected, resistant-strain-infected, sensitive-strain-treated, resistant-strain-treated, sensitive-strain-recovered, and resistant-strain-recovered compartments in a two-strain $SITRS$-SI model. In most ODE models, it is assumed that there is an exponential waiting time in each of the compartments. This correlates to a survival probability that is described by a negative linear term in the corresponding ODE. However, this is not always the correct assumption. In the previous ODE model from Chapter 2, we were motivated by the linear chain trick to break up the treated compartments in order to provide a Gamma-distributed waiting time during the entire treatment period, if the rate at which individuals leave each treatment class, α_i, are equal. However, some waiting times might not reduce to an ODE as in the case with exponentially distributed waiting periods and Erlang-distributed waiting periods (i.e. Gamma-distributed waiting periods with integer shape parameter). Furthermore, deriving the correct ODE system directly from these distributions is not trivial when multiple survival scenarios are Gamma-distributed. The method described here will generalize the survival probabilities for each compartment so as to provide the framework to fit waiting times to relevant data, such as distributions of life-span and time to parasite clearance (natural or due due to treatment).

3.2 Model Description

We begin with the general structure for a two-strain $SITRS$-SI vector-borne disease population model to account for drug-sensitive and drug-resistant strains with resistant-strain dominance. Infected individuals move through the various stages of infection,

treatment, and recovery for the two strains before returning to the susceptible class at varying times. The method described here will account for the variability of individuals moving through the different compartments by using survival functions corresponding to probability distributions for compartment waiting times. Previous work on this topic is described in [25], which derives a single-strain mosquito-borne disease model with non-exponentially distributed infection and treatment stages. In [26], Feng et al. examined key underlying assumptions used in a widely cited Legrand model for Ebola. Their work emphasized the importance of creating a model framework based on appropriate disease stage durations for each class.

A desired application for this method is modeling the human population in a malaria transmission model. As an extension, we could model the different parasite loads in the human hosts. To add a pharmacological response with treatment drugs, we would need to model the drug concentration and parasite densities within individuals throughout the course of treatment.

Our model includes several human and vector populations. The human populations include S_h (susceptible), I_s (infected with drug-sensitive parasites), I_r (infected with drug-resistant parasites), T_s (treated for drug-sensitive parasites infection), T_r (treated for drug-resistant parasites infection), R_s (recovered from drug-sensitive parasite infection), and R_r (recovered from drug-resistant parasite infection) at time t. The vector populations include S_v (susceptible), M_s (infected with drug-sensitive parasites), and M_r (infected with drug-resistant parasites) at time t. We will consider exposed individuals as part of the corresponding infected classes. From here on, we will denote "drug-sensitive-strain" by "s-" and "drug-resistant-strain" by "r-". The model variables with descriptions are listed in Table 3.1.

One simplifying assumption we make is that the drug-resistant strain dominates the drug-sensitive strain. Hence, if a human is at first infected with the sensitive strain then becomes infected with a resistant strain, we assume the resistant strain takes over and that individual is only able to transmit the drug-resistant parasite. However, we assume that a vector will only become infected with one of the strains during its lifetime and will not change infection status from the sensitive to the resistant strain. In addition, we assume that recovering from

Table 3.1: Descriptions of state variables for Integral Equation model

Variable	Description
S_h	Number of susceptible humans
I_s	Number of humans infected with drug-sensitive strain
I_r	Number of humans infected with drug-resistant strain
T_s	Number of humans treated for drug-sensitive strain
T_r	Number of humans treated for drug-resistant strain
R_s	Number of humans recovered from drug-sensitive strain
R_r	Number of humans recovered from drug-resistant strain
S_v	Number of susceptible vectors
M_s	Number of vectors infected with drug-sensitive strain
M_r	Number of vectors infected with drug-resistant strain

the sensitive strain grants humans immunity only to the sensitive strain whereas recovering from the resistant strain grants immunity to both the sensitive and resistant strains. Additionally, an individual being treated for the sensitive strain can still become infected with the resistant strain and hence move from T_s to I_r.

In the model, an s-infected or r-infected mosquito can bite and infect a susceptible human, moving them from the S_h class to the human infection classes, I_s or I_r, depending on infection type. All of these individuals could be either symptomatic or asymptomatic. Individuals in the I_s class could die as a result of the disease, could die due to natural causes, may survive to progress to the R_s (s-immune) class, may be treated and move to the T_s (s-treatment) class, or may become infected with the resistant strain at some time point and hence progress to the I_r class. Individuals in the I_r class could die as a result of the disease, could die due to natural causes, may survive to progress to the R_r (s- and r-immune) class, or may be treated and move to the T_r (r-treatment) class.

We assume that the individuals who are symptomatic receive treatment with some probability and move to the T_s or T_r class (depending on infection type) or clear their infection naturally with a different probability and move to the R_s or R_r (again, depending on infection status). Those who are asymptomatic are assumed to only recover naturally through immune response (if recovery is successful). Individuals in the T_s class can also become infected with the resistant strain and move to I_r with the transmission rate scaled by the parameter ϕ to account for drug-concentration in the blood potentially preventing infection. Note that this component of the model differs from that in Chapter 2, which assumes that T_s individuals move to the corresponding T_r compartment if infected with the resistant strain. Here, we assume that if a T_s individual becomes infected with the resistant strain, then the drug concentration was not effective against the resistant strain parasite, and consequently we no longer track the drug concentration for the s-strain treatment.

Once the immune system (whether naturally or through treatment) clears enough of the parasite to render the individual non-infectious, the individual will progress to the recovered class for both the s- and r-infections (R_s and R_r). The time-frame for s-infection and r-infection will differ, and hence the recovery process will also differ. Those who recover from

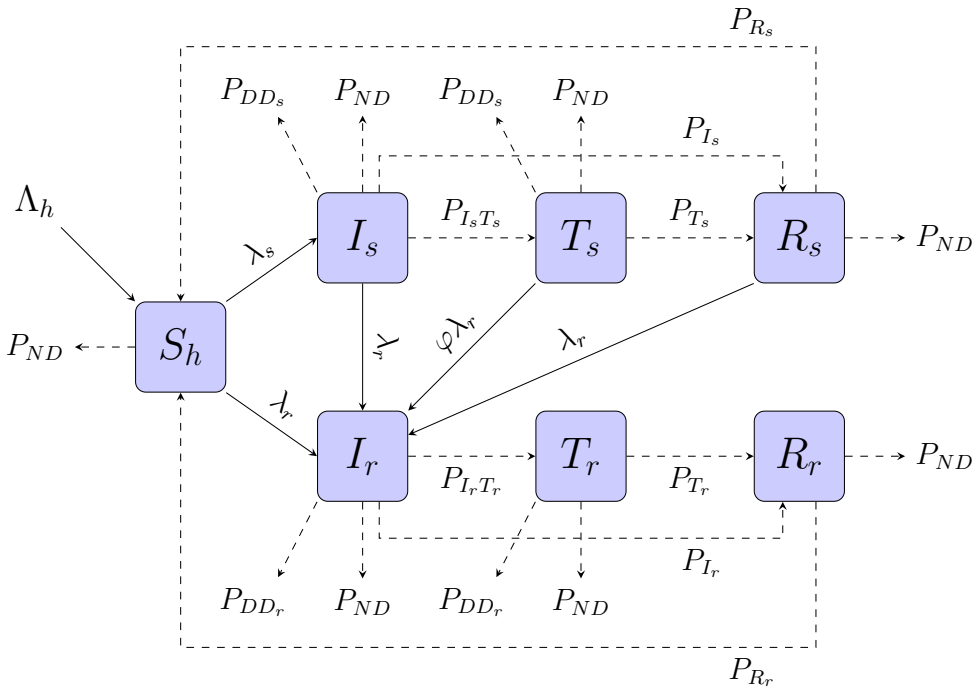


Figure 3.1: Transfer diagram for human populations in Integral Equation model with survival functions. Dashed lines labelled with survival functions P_m represent the probability of surviving in the current class and not progressing to the next class. The solid lines labelled with λ_s and λ_r represent the force of infection that moves humans to s- or r-infection classes.

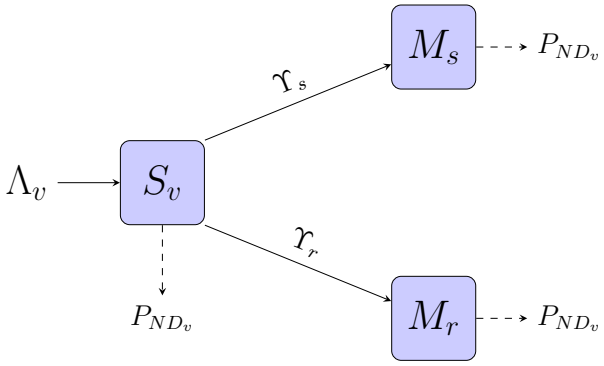


Figure 3.2: Transfer diagram for mosquito populations in Integral Equation model with survival functions. Dashed lines labelled with survival functions P_m represent the probability of surviving in the current class and not progressing to the next class. The solid lines labelled with Υ_s and Υ_r represent the force of infection that moves mosquitoes to s- or r-infection classes.

the sensitive strain are still susceptible to the resistant strain. That is, individuals can move from the R_s class to the I_r class if bitten by an r-infected mosquito in M_r.

Eventually, an individual's immunity will wane and they will return to the susceptible class, S_h, with some probability. An individual can also enter the S_h class via the human per capita birth rate, Λ_h. We assume natural death occurs in all human classes and disease-induced death occurs only in the infected and treated human classes. See Figure 3.1 for the transfer diagram for the human host.

The vector, in this case a mosquito, begins its journey in the susceptible vector class, S_v, which it enters via the vector birth rate Λ_v, and can bite and take a blood meal from either an s- or r-infected human. Doing so causes the vector to ingest one of the two parasite strains and hence move to the s-infected vector class, M_s, or the r-infected vector class, M_r. We assume only one type of infection for a vector (i.e. no co-infection with both strains) and that only natural death, not disease-induced death, occurs in all vector classes. See Figure 3.2 for the transfer diagram for the vector.

We will use the functions $\lambda_s(t)$ and $\lambda_r(t)$ to denote the force of infection from vectors to humans for s- and r-infection, respectively. Let

$$\lambda(t) = \lambda_s(t) + \lambda_r(t). \tag{3.1}$$

Similarly, we will use the functions $\Upsilon_s(t)$ and $\Upsilon_r(t)$ to denote the force of infection from humans to vectors for s- and r-infections, respectively. Let

$$\Upsilon(t) = \Upsilon_s(t) + \Upsilon_r(t). \tag{3.2}$$

For each epidemiological class, we will use integral equations to keep track of human and vector populations as well as their changes with time. This will allow us to incorporate arbitrary probability distributions for the time spent in each stage instead of assuming exponential waiting times, as is the underlying assumption in the construction of ordinary differential equations with linear exit rates. First, we must define survival functions for each survival scenario throughout the human and vector stages. See Table 3.2 for a list of possible

Table 3.2: Types of survival functions

Name	Function	Parameters
Exponential	$P(x) = \exp(-\mu x)$	mean $= \frac{1}{\mu}$
Gamma (Erlang)	$P(x) = \exp(-N\mu x) \sum_{n=1}^{N} \frac{(N\mu x)^{n-1}}{(n-1)!}$	mean $= \frac{1}{\mu}$, shape $= N$
Weibull	$P(x) = \exp(-(\mu x)^N)$	mean $= \frac{1}{\mu}$, shape $= N$
Gompertz	$P(x) = \exp(-N(e^{\mu x} - 1))$	mean $= \frac{1}{\mu}$, shape $= N$

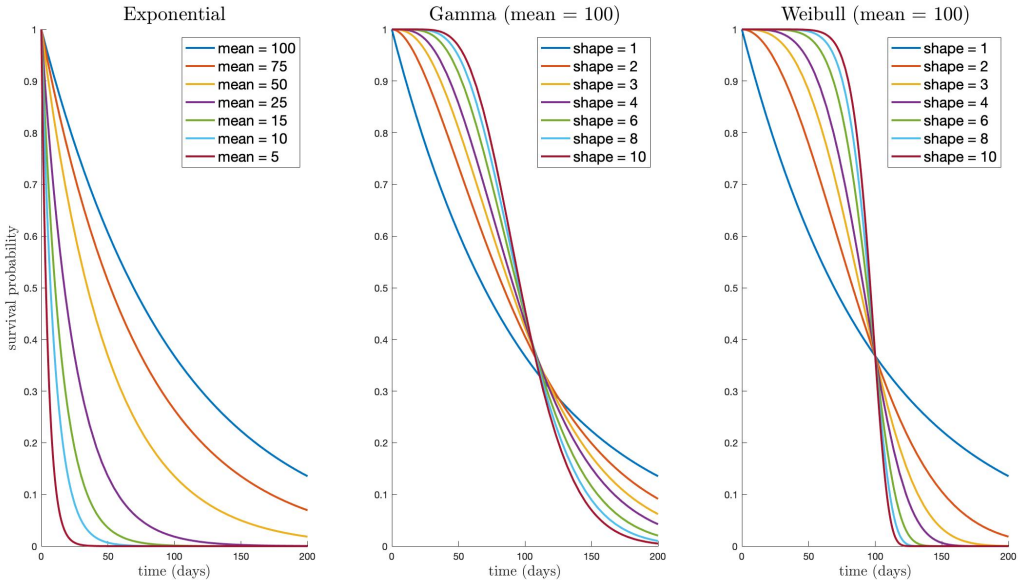


Figure 3.3: Examples of survival functions from Table 3.2.

survival functions (also known as the complement of the cumulative distribution function). See Figure 3.3 for visuals of these Survival Functions.

Let $P_m(x)$ denote the survival function for a probability distribution associated with scenario m. This represents the probability that an individual is still in the current class x time units after entering the class assuming scenario m. For the human stages, the subscript m could be I_kR_k (remain k-infected without recovering), I_kT_k (remain k-infected without being treated), T_kR_k (remain k-treated without recovering), R_kS_h (remain k-recovered without losing immunity), DD_k (remain in current class without succumbing to k-infection disease death), or ND (remain in current class without succumbing to natural death) where $k \in \{r, s\}$. For the vector stages, we assume only one survival scenario throughout all classes so that we have only one option for the subscript m, which is ND_v (remain in current class without succumbing to natural death). Note that we do not consider probability of transmission in these survival scenarios since we will be using the force of infection terms to track state transitions involving infection. See Table 3.3 for a summary of survival functions.

3.3 Model Derivation

In this section, we derive the human and mosquito (vector) population equations in the following order:

$$I_s,\ T_s,\ R_s,\ I_r,\ T_r,\ R_r,\ S_h,\ M_s,\ M_r,\ S_v$$

We will use a single label indicating which equation we are currently deriving and sub-labels indicating the pieces of the equation. That is, beginning with the number "3.4", we use "3.4" for I_s, "3.5" for T_s, etc. We use sub-labels for each compartment to identify components so that "a" labels the $flux$, "b" labels the product of survival functions, "c" labels the initial conditions, "d" labels the derivatives of the integral equation, "e" labels the derivative of the product of survival functions, and "f" labels other derivatives of interest.

Table 3.3: Summary of survival functions for Integral Equation model

Function	Description (humans)
$P_{I_sR_s}(x)$	Probability of not recovering from s-infection x time units after s-infection
$P_{I_rR_r}(x)$	Probability of not recovering from r-infection x time units after r-infection
$P_{I_sT_s}(x)$	Probability of not receiving treatment x time units after s-infection
$P_{I_rT_r}(x)$	Probability of not receiving treatment x time units after r-infection
$P_{T_sR_s}(x)$	Probability of not recovering from s-infection x time units after treatment
$P_{T_rR_r}(x)$	Probability of not recovering from r-infection x time units after treatment
$P_{R_sS_h}(x)$	Probability of not losing immunity x time units after s-recovery
$P_{R_rS_h}(x)$	Probability of not losing immunity x time units after r-recovery
$P_{ND}(x)$	Probability of not dying naturally x time units after entering the class
$P_{DD_s}(x)$	Probability of not dying due to disease x time units after s-infection
$P_{DD_r}(x)$	Probability of not dying due to disease x time units after r-infection
Function	Description (vectors)
$P_{ND_v}(x)$	Probability of not dying naturally x time units after entering the class

3.3.1 Derivation of human equations with general distributions

First, we need to establish a timeline for infection, recovery, treatment, and immunity loss according to Figure 3.1. Consider the case in which an individual travels through every compartment. Their path through the diagram in Figure 3.1 is $S_h \to I_s \to T_s \to R_s \to I_r \to T_r \to R_r \to S_h$. That is, we assume an individual is s-infected at time u_s, s-treated at time τ_s, s-recovered at time σ_s, r-infected at time u_r, r-recovered at time σ_r, and susceptible at time b. See Figure 3.4 for the timeline of this path.

However, in general we need only concern ourselves with the time of infection, treatment, and recovery without specifying whether it is an s- or r-infection, treatment, or recovery. This is because the variables $u_s, u_r, \tau_s, \tau_r, \sigma_s, \sigma_r$, and b act as dummy variables in our integrals and in particular do not overlap in the construction of our equations. Hence, to make computation easier, we simply use u, τ, and σ to denote times of infection, treatment, and recovery, regardless of the strain type. See Figure 3.5 for this simplified timeline.

It is important that we keep track of which paths an individual could take to account for all of the inflows and outflows in each class, which we will call the $flux$ of the class. We then consider the possible events in the two-strain $SITRS$ system at time t and construct integral equations for S_h, I_s, I_r, T_s, T_r, R_s, and R_r. We also compute their derivatives, and hence how the states are changing, in order to keep track of transitions from class to class apart from state transitions due to infection. Throughout, we will consider the interval $[0, t]$. For each class, we focus on its $flux$. That is, we are going to track all inflows and outflows of the class, which are the different ways of entering and exiting the class for every time point up to time t. After we compute the flux of the current class, we multiply it by the survival functions for the various survival scenarios in the current class. We then integrate over all time points up to time t to count the total population in the current class at time t.

As a general framework, we define the $flux$ at time u for a class c as $flux_c(u)$. We define the corresponding survival functions for a class $t - u$ units after entering the class as $Q_c(t - u)$. Integrating the product of $flux_c(u)$ and $Q_c(t - u)$ over all u on $[0, t]$ yields the

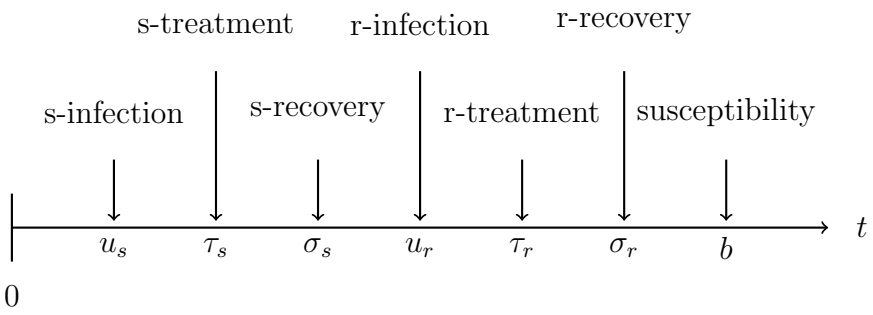


Figure 3.4: Timeline for human traveling the longest path through Figure 3.1:
$S_h \to I_s \to T_s \to R_s \to I_r \to T_r \to R_r \to S_h$

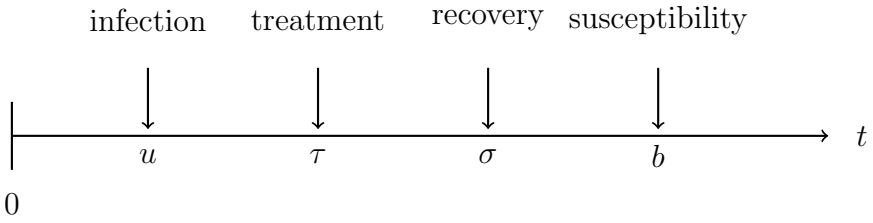


Figure 3.5: Shortened timeline for human traveling through Figure 3.1:
$S_h \to I \to T \to R \to S_h$

total number of individuals in class c at time t:

$$c(t) = c_0 Q_c(t) + \int_0^t flux_c(u) Q_c(t-u) du \tag{3.3}$$

where c_0 represents the initial population of class c and $c_0 Q_c(t)$ tracks the amount of the initial population still in the class at time t.

The I_s class

Since S_h depends on survival in the recovered class, we instead begin our derivation with I_s, whose inflow only depends on the force of s-infection and not a general survival scenario in S_h. We will look at the flux of I_s for all points $u \in [0, t]$. The terms contributing to the flux of I_s are entering s-infections from the S_h class and exiting r-infections to the I_r class. Thus the flux of I_s at infection time u is

$$flux_{I_s}(u) = \lambda_s(u) S_h(u) - \lambda_r(u) I_s(u). \tag{3.4a}$$

The survival scenarios corresponding to the I_s class are not recovering, not receiving treatment, not dying due to natural causes, and not dying due to s-infection.
The probabilities that an individual in the current population of I_s has not recovered from nor received treatment for the sensitive strain at time t are described by $P_{I_s R_s}(t-u)$ and $P_{I_s T_s}(t-u)$, respectively. The probabilities that they have not died due to natural causes nor due to s-infection at time t are described by $P_{ND}(t-u)$ and $P_{DDs}(t-u)$, respectively. The product of survival functions evaluated x time units after entering the I_s class is

$$Q_{I_s}(x) = P_{I_s R_s}(x) P_{I_s T_s}(x) P_{ND}(x) P_{DD_s}(x). \tag{3.4b}$$

Thus the total number of s-infections at time t is given by

$$I_s(t) = \tilde{I}_s^0(t) + \int_0^t flux_{I_s}(u) Q_{I_s}(t-u) du \tag{3.4}$$

where

$$\tilde{I}_s^0(t) = I_s^0 Q_{I_s}(t) \tag{3.4c}$$

denotes the number of initial s-infected people still present in the I_s class at time t. To track transitions to other classes, we compute the derivative of I_s to get

$$\frac{dI_s}{dt}(t) = \frac{d\tilde{I}_s^0}{dt}(t) + flux_{I_s}(t) + \int_0^t flux_{I_s}(u)\frac{dQ_{I_s}}{dt}(t-u)du, \tag{3.4d}$$

using the fact that $Q_{I_s}(0) = 1$. The derivative of our survival functions is

$$\begin{aligned}\frac{dQ_{I_s}}{dt} = \frac{dP_{I_sR_s}}{dt}P_{I_sT_s}P_{ND}P_{DD_s} + P_{I_sR_s}\frac{dP_{I_sT_s}}{dt}P_{ND}P_{DD_s} \\ + P_{I_sR_s}P_{I_sT_s}\frac{dP_{ND}}{dt}P_{DD_s} + P_{I_sR_s}P_{I_sT_s}P_{ND}\frac{dP_{DD_s}}{dt}.\end{aligned} \tag{3.4e}$$

For ease of notation, we define

$$dQ_{P_{I_sR_s}} = -\frac{dP_{I_sR_s}}{dt}P_{I_sT_s}P_{ND}P_{DD_s} \qquad dQ_{P_{I_sT_s}} = -P_{I_sR_s}\frac{dP_{I_sT_s}}{dt}P_{ND}P_{DD_s}. \tag{3.4f}$$

Note that the negative terms in the above definitions make $dQ_{P_{I_sR_s}}$ and $dQ_{P_{I_sT_s}}$ positive, since the derivatives of the survival probabilities are negative. Furthermore,

$$\begin{aligned}\frac{d\tilde{I}_s^0}{dt} &= I_s^0\ \frac{dQ_{I_s}}{dt} \\ &= I_s^0\left(\frac{dP_{I_sR_s}}{dt}P_{I_sT_s}P_{ND}P_{DD_s} + P_{I_sR_s}\frac{dP_{I_sT_s}}{dt}P_{ND}P_{DD_s}\right. \\ &\qquad \left. + P_{I_sR_s}P_{I_sT_s}\frac{dP_{ND}}{dt}P_{DD_s} + P_{I_sR_s}P_{I_sT_s}P_{ND}\frac{dP_{DD_s}}{dt}\right) \\ &= -I_s^0 dQ_{P_{I_sR_s}} - I_s^0 dQ_{P_{I_sT_s}} + I_s^0 P_{I_sR_s}P_{I_sT_s}\frac{dP_{ND}}{dt}P_{DD_s} + I_s^0 P_{I_sR_s}P_{I_sT_s}P_{ND}\frac{dP_{DD_s}}{dt}.\end{aligned}$$

We use the notation from 3.4f in the final line of the previous calculation.

The T_s class

Next, we consider the flux of T_s for all points τ assuming s-infection at time $u \geq 0$ where $\tau \in [u, t]$. The terms contributing to the flux of T_s are entering treated individuals from I_s (including the initial I_s^0 population) and exiting r-infected individuals to I_r with transmissions scaled by φ to account for drug-concentration in the human bloodstream that could fight off potential resistant infections. The rate at which s-infected individuals are treated $\tau - u$ units after s-infection is described by $dQ_{P_{I_sT_s}}(\tau - u)$ as defined in (3.4f). Thus the flux of T_s at treatment time τ is

$$flux_{T_s}(\tau) = I_s^0 dQ_{P_{I_sT_s}}(\tau) + \int_0^\tau flux_{I_s}(u) dQ_{P_{I_sT_s}}(\tau - u) du - \varphi\lambda_r(\tau) T_s(\tau). \tag{3.5a}$$

The survival scenarios corresponding to the T_s class are not recovering, not dying due to natural causes, and not dying due to s-infection. The probabilities that a person has not recovered, not died due to natural causes, and not died due to s-infection $t - \tau$ time units after treatment are $P_{T_sR_s}(t - \tau)$, $P_{ND}(t - \tau)$, and $P_{DD_s}(t - \tau)$, respectively. The product of our survival functions x time units after entering the T_s class is given by

$$Q_{T_s}(x) = P_{T_sR_s}(x) P_{ND}(x) P_{DD_s}(x). \tag{3.5b}$$

Then the total number of s-treated individuals at time t is given by

$$T_s(t) = \tilde{T}_s^0(t) + \int_0^t flux_{T_s}(\tau) Q_{T_s}(t - \tau) d\tau \tag{3.5}$$

where

$$\tilde{T}_s^0(t) = T_s^0 Q_{T_s}(t). \tag{3.5c}$$

Note that

$$\frac{dT_s}{dt}(t) = \frac{d\tilde{T}_s^0}{dt}(t) + flux_{T_s}(t) + \int_0^t flux_{T_s}(\tau) \frac{dQ_{T_s}}{dt}(t - \tau) d\tau \tag{3.5d}$$

where

$$\frac{dQ_{T_s}}{dt} = \frac{dP_{T_sR_s}}{dt}P_{ND}P_{DD_S} + P_{T_sR_s}\frac{dP_{ND}}{dt}P_{DD_s} + P_{T_sR_s}P_{ND}\frac{dP_{DD_s}}{dt}. \tag{3.5e}$$

Again, for ease of notation, we define

$$dQ_{P_{T_sR_s}} = -\frac{dP_{T_sR_s}}{dt}P_{ND}P_{DD_S}. \tag{3.5f}$$

Lastly for this compartment, we have

$$\begin{aligned}\frac{d\tilde{T}_s^0}{dt} &= T_s^0\frac{dQ_{T_s}}{dt} \\ &= T_s^0\left(\frac{dP_{T_sR_s}}{dt}P_{ND}P_{DD_S} + P_{T_sR_s}\frac{dP_{ND}}{dt}P_{DD_s} + P_{T_s}P_{ND}\frac{dP_{DD_s}}{dt}\right) \\ &= -T_s^0 dQ_{P_{T_sR_s}} + T_s^0 P_{T_sR_s}\frac{dP_{ND}}{dt}P_{DD_s} + T_s^0 P_{T_sR_s}P_{ND}\frac{dP_{DD_s}}{dt}.\end{aligned}$$

The R_s class

Now we look at the flux of R_s at all points σ assuming that an individual was infected with the sensitive strain at time u and, if diagnosed, treated at time τ. Note that $0 \le u \le \sigma \le t$ with $\tau \in [u, \sigma]$ if the individual receives treatment. The terms contributing to the flux of R_s are s-recoveries entering from I_s and T_s, and r-infections exiting to I_r. The rate of natural recovery from the sensitive strain at time σ is determined by $dQ_{P_{I_sR_s}}(\sigma - u)$ as defined in (3.4f) and the rate of recovering from the sensitive strain due to treatment at time σ is determined by $dQ_{P_{T_sR_s}}(\sigma - \tau)$ as defined in (3.5f). Thus the flux of R_s at recovery time σ is

$$\begin{aligned}flux_{R_s}(\sigma) = I_s^0 dQ_{P_{I_sR_s}}(\sigma) + \int_0^\sigma flux_{I_s}(u)dQ_{P_{I_sR_s}}(\sigma - u)du \\ + T_s^0 dQ_{P_{T_sR_s}}(\sigma) + \int_0^\sigma flux_{T_s}(\tau)dQ_{P_{T_sR_s}}(\sigma - \tau)d\tau - \lambda_r(\sigma)R_s(\sigma).\end{aligned} \tag{3.6a}$$

The survival scenarios corresponding to the R_s class are retaining s-immunity and not dying due to natural causes. The probabilities that a person has not lost s-immunity and has not died due to natural causes at time t are $P_{R_sS_h}(t - \sigma)$ and $P_{ND}(t - \sigma)$, respectively. The

product of survival functions x time units after entering the R_s class is given by

$$Q_{R_s}(x) = P_{R_sS_h}(x)P_{ND}(x). \tag{3.6b}$$

Then, the total number of s-recovered individuals at time t is given by

$$R_s(t) = \tilde{R}_s^0(t) + \int_0^t flux_{R_s}(\sigma)Q_{R_s}(t-\sigma)d\sigma \tag{3.6}$$

where

$$\tilde{R}_s^0(t) = R_s^0 Q_{R_s}(t) \tag{3.6c}$$

represents the number of initial s-recovered individuals still in the class at time t. Note that

$$\frac{dR_s}{dt}(t) = \frac{d\tilde{R}_s^0}{dt}(t) + flux_{R_s}(t) + \int_0^t flux_{R_s}(\tau)\frac{dQ_{R_s}}{dt}(t-\tau)d\tau \tag{3.6d}$$

where

$$\frac{dQ_{R_s}}{dt} = \frac{dP_{R_sS_h}}{dt}P_{ND} + P_{R_sS_h}\frac{dP_{ND}}{dt}. \tag{3.6e}$$

Again, for ease of notation, we define

$$dQ_{P_{R_sS_h}} = -\frac{dP_{R_sS_h}}{dt}P_{ND}. \tag{3.6f}$$

Lastly for this compartment, we have

$$\begin{aligned}
\frac{d\tilde{R}_s^0}{dt} &= R_s^0\frac{dQ_{R_s}}{dt} \\
&= R_s^0\left(\frac{dP_{R_sS_h}}{dt}P_{ND} + P_{R_sS_h}\frac{dP_{ND}}{dt}\right) \\
&= -R_s^0 dQ_{P_{R_sS_h}} + R_s^0 P_{R_sS_h}\frac{dP_{ND}}{dt}.
\end{aligned}$$

The I_r class

The flux in the I_r class consists of four inflows due to r-infection from S_h, I_s, T_s, and R_s. We will look at the flux of I_r for all points $u \in [0, t]$. That is, assume an individual becomes infected with the resistant strain at time u. Thus the flux of I_r at infection time u is

$$flux_{I_r}(u) = \lambda_r(u) \left[S_h(u) + I_s(u) + T_s(u) + R_s(u) \right]. \tag{3.7a}$$

The survival scenarios associated with the I_r class include not recovering from r-infection, not being treated for r-infection, not dying due to natural causes, and not dying due to the r-infection. The probabilities that the individual has not recovered from or been treated for the resistant strain at time t are described by $P_{I_rR_r}(t-u)$ and $P_{I_rT_r}(t-u)$, respectively. The probabilities that they have not died due to natural causes nor r-infection is described by $P_{ND}(t-u)$ and $P_{DD_r}(t-u)$, respectively. The product of survival functions evaluated x time units after entering the I_r class is

$$Q_{I_r}(x) = P_{I_rR_r}(x)P_{I_rT_r}(x)P_{ND}(x)P_{DD_r}(x). \tag{3.7b}$$

Thus, the total number of r-infections at time t is given by

$$I_r(t) = \tilde{I}_r^0(t) + \int_0^t flux_{I_r}(u) Q_{I_r}(t-u) du \tag{3.7}$$

where

$$\tilde{I}_r^0(t) = I_r^0 Q_{I_rR_r}(t) \tag{3.7c}$$

denotes the number of initial r-infected people still present in the I_r class at time t. Note that

$$\frac{dI_r}{dt}(t) = \frac{d\tilde{I}_r^0}{dt}(t) + flux_{I_r}(t) + \int_0^t flux_{I_r}(u) \frac{dQ_{I_r}}{dt}(t-u) du. \tag{3.7d}$$

The derivative of our survival functions is

$$\frac{dQ_{I_r}}{dt} = \frac{dP_{I_rR_r}}{dt}P_{I_rT_r}P_{ND}P_{DD_r} + P_{I_rR_r}\frac{dP_{I_rT_r}}{dt}P_{ND}P_{DD_r} + P_{I_rR_r}P_{I_rT_r}\frac{dP_{ND}}{dt}P_{DD_r} + P_{I_rR_r}P_{I_rT_r}P_{ND}\frac{dP_{DD_r}}{dt}. \quad (3.7e)$$

For ease of notation, we define

$$dQ_{P_{I_rR_r}} = -\frac{dP_{I_rR_r}}{dt}P_{I_rT_r}P_{ND}P_{DD_r} \qquad dQ_{P_{I_rT_r}} = -P_{I_rR_r}\frac{dP_{I_rT_r}}{dt}P_{ND}P_{DD_r}. \quad (3.7f)$$

Note the negative terms in the above definitions. Furthermore,

$$\begin{aligned}\frac{d\tilde{I}_r^0}{dt} &= I_r^0\ \frac{dQ_{I_r}}{dt} \\ &= I_r^0\left(\frac{dP_{I_rR_r}}{dt}P_{I_rT_r}P_{ND}P_{DD_r} + P_{I_rR_r}\frac{dP_{I_rT_r}}{dt}P_{ND}P_{DD_r} + P_{I_rR_r}P_{I_rT_r}\frac{dP_{ND}}{dt}P_{DD_r} + P_{I_rR_r}P_{I_rT_r}P_{ND}\frac{dP_{DD_r}}{dt}\right) \\ &= -I_r^0 dQ_{P_{I_rR_r}} - I_r^0 dQ_{P_{I_rT_r}} + I_r^0 P_{I_rR_r}P_{I_rT_r}\frac{dP_{ND}}{dt}P_{DD_r} + I_r^0 P_{I_rR_r}P_{I_rT_r}P_{ND}\frac{dP_{DD_r}}{dt}.\end{aligned}$$

The T_r class

For the T_r class, we will consider its flux at time τ for all time points $\tau \in [u, t]$ with $u \geq 0$. That is, we will assume treatment at time τ, assuming r-infection at time u. The flux of T_r consists of inflow from I_r. The rate of movement from I_r to T_r at time τ after r-infection at time u is described by $dQ_{P_{I_rT_r}}(\tau - u)$ as defined in (3.7f). Thus the flux of T_r at treatment time τ is

$$flux_{T_r}(\tau) = I_r^0 dQ_{P_{I_rT_r}}(\tau) + \int_0^\tau flux_{I_r}(u)dQ_{P_{I_rT_r}}(\tau - u)du. \quad (3.8a)$$

The survival scenarios associated with T_r are not recovering from r-infection, not dying due to natural causes, and not dying due to r-infection. The probability of not recovering at time t after given treatment at time τ is $P_{T_rR_r}(t - \tau)$. The probabilities of not dying due to natural causes and not dying due to r-infection are given by $P_{ND}(t - \tau)$ and $P_{DD_r}(t - \tau)$,

respectively. The product of our survival functions x time units after entering the T_r class is given by

$$Q_{T_r}(x) = P_{T_rR_r}(x)P_{ND}(x)P_{DD_r}(x). \tag{3.8b}$$

Then the total number of r-treated individuals at time t is given by

$$T_r(t) = \tilde{T}_r^0(t) + \int_0^t flux_{T_r}(\tau)Q_{T_r}(t-\tau)d\tau \tag{3.8}$$

where

$$\tilde{T}_r^0(t) = T_r^0 Q_{T_r}(t). \tag{3.8c}$$

Note that

$$\frac{dT_r}{dt}(t) = \frac{d\tilde{T}_r^0}{dt}(t) + flux_{T_r}(t) + \int_0^t flux_{T_r}(\tau)\frac{dQ_{T_r}}{dt}(t-\tau)d\tau \tag{3.8d}$$

where

$$\frac{dQ_{T_r}}{dt} = \frac{dP_{T_rR_r}}{dt}P_{ND}P_{DD_r} + P_{T_rR_r}\frac{dP_{ND}}{dt}P_{DD_r} + P_{T_rR_r}P_{ND}\frac{dP_{DD_r}}{dt}. \tag{3.8e}$$

Again, for ease of notation, we define

$$dQ_{P_{T_rR_r}} = -\frac{dP_{T_rR_r}}{dt}P_{ND}P_{DD_r}. \tag{3.8f}$$

Lastly for this compartment, we have

$$\begin{aligned}
\frac{d\tilde{T}_r^0}{dt} &= T_r^0\frac{dQ_{T_r}}{dt} \\
&= T_r^0\left(\frac{dP_{T_rR_r}}{dt}P_{ND}P_{DD_r} + P_{T_rR_r}\frac{dP_{ND}}{dt}P_{DD_r} + P_{T_rR_r}P_{ND}\frac{dP_{DD_r}}{dt}\right) \\
&= -T_r^0 dQ_{P_{T_rR_r}} + T_r^0 P_{T_rR_r}\frac{dP_{ND}}{dt}P_{DD_r} + T_r^0 P_{T_rR_r}P_{ND}\frac{dP_{DD_r}}{dt}.
\end{aligned}$$

The R_r class

Now for the R_r class. We will consider the flux at time σ, that is we will assume an individual recovers from the resistant strain at time σ assuming infection at time u and, if treated, with treatment at time τ. Note that $0 \leq u \leq \sigma \leq t$ with $\tau \in [u, \sigma]$ if the individual receives treatment. The flux of R_r consists of two inflows from I_r and T_r. The rate of movement from I_r to R_r is determined by $dQ_{P_{I_r R_r}}(\sigma - u)$ defined in (3.7f) and the rate of movement from T_r to R_r is given by $dQ_{P_{T_r R_r}}(\sigma - \tau)$ defined in (3.8f). Thus the flux of R_r at recovery time σ is

$$\begin{aligned} flux_{R_r}(\sigma) = I_r^0 dQ_{P_{I_r R_r}}(\sigma) + \int_0^\sigma flux_{I_r}(u) dQ_{P_{I_r R_r}}(\sigma - u) du \\ + T_r^0 dQ_{P_{T_r R_r}}(\sigma) + \int_0^\sigma flux_{T_r}(\tau) dQ_{P_{T_r R_r}}(\sigma - \tau) d\tau. \end{aligned} \tag{3.9a}$$

The survival scenarios associated with R_r are retaining immunity and not dying due to natural causes. The probabilities of remaining immune and not dying due to natural causes in R_r at time t are given by $P_{R_r S_h}(t - \sigma)$ and $P_{ND}(t - \sigma)$, respectively. The product of survival functions x time units after entering the R_r class is given by

$$Q_{R_r}(x) = P_{R_r S_h}(x) P_{ND}(x). \tag{3.9b}$$

Then the total number of r-recovered individuals at time t is given by

$$R_r(t) = \tilde{R}_r^0(t) + \int_0^t flux_{R_r}(\sigma) Q_{R_r}(t - \sigma) d\sigma \tag{3.9}$$

where

$$\tilde{R}_r^0(t) = R_r^0 Q_{R_r}(t) \tag{3.9c}$$

represents the number of initial r-recovered individuals still in the class at time t. Note that

$$\frac{dR_r}{dt}(t) = \frac{d\tilde{R}_r^0}{dt}(t) + flux_{R_r}(t) + \int_0^t flux_{R_r}(\tau) \frac{dQ_{R_r}}{dt}(t - \tau) d\tau \tag{3.9d}$$

where

$$\frac{dQ_{R_r}}{dt} = \frac{dP_{R_rS_h}}{dt}P_{ND} + P_{R_r}\frac{dP_{ND}}{dt}. \tag{3.9e}$$

We define

$$dQ_{P_{R_rS_h}} = -\frac{dP_{R_rS_h}}{dt}P_{ND}. \tag{3.9f}$$

Lastly for this compartment, we have

$$\begin{aligned}\frac{d\tilde{R}_r^0}{dt} &= R_s^0\frac{dQ_{R_r}}{dt}\\ &= R_r^0\left(\frac{dP_{R_rS_h}}{dt}P_{ND} + P_{R_rS_h}\frac{dP_{ND}}{dt}\right)\\ &= -R_r^0 dQ_{P_{R_rS_h}} + R_r^0 P_{R_rS_h}\frac{dP_{ND}}{dt}.\end{aligned}$$

The S_h class

Now that we have equations (3.4)–(3.9), we can construct the integral equation for the susceptible class, $S_h(t)$. To count the number of individuals in the S_h class at time t, we must describe the flux of S_h for all time points $b \in [0, t]$. The flux of S_h includes inflow from the per capita birth rate $\Lambda_h(t)$, individuals losing immunity from R_s, and individuals losing immunity from R_r, as well as outflow due to s-infection and r-infection. Assuming an individual recovers at time σ, then the rates from R_s and R_r to S_h are determined by $dQ_{P_{R_sS_h}}(b-\sigma)$ defined in (3.6f) and $dQ_{P_{R_rS_h}}(b-\sigma)$ defined in (3.9f), respectively. Thus the flux of S_h at time b is

$$\begin{aligned}flux_{S_h}(b) = \Lambda_h(b) - &\left[\lambda_s(b) + \lambda_r(b)\right]S_h(b)\\ &+ R_s^0 dQ_{P_{R_sS_h}}(b) + \int_0^b flux_{R_s}(\sigma)dQ_{P_{R_sS_h}}(b-\sigma)d\sigma\\ &+ R_r^0 dQ_{P_{R_rS_h}}(b) + \int_0^b flux_{R_r}(\sigma)dQ_{P_{R_rS_h}}(b-\sigma)d\sigma.\end{aligned} \tag{3.10a}$$

The only survival scenario associated with the S_h class is not dying due to natural causes. The probability of not dying at time t due to natural causes after entering the S_h class at time b is given by $P_{ND}(t-b)$. For the sake of consistency, we define the "product" of survival functions x time units after entering the S_h class as

$$Q_{S_h}(x) = P_{ND}(x). \tag{3.10b}$$

Thus, the total number of susceptible individuals at time t is given by

$$S_h(t) = \tilde{S}_h^0(t) + \int_0^t flux_{S_h}(b) Q_{S_h}(t-b) db \tag{3.10}$$

where

$$\tilde{S}_h^0(t) = S_h^0 Q_{S_h}(t) \tag{3.10c}$$

represents the number of initial susceptible individuals still in the class at time t. Since outflow of S_h to I_s and I_r is determined by the forces of infection, then we have no need to take a derivative to determine transition rates. However, we compute the derivative for consistency. Note that

$$\frac{dS_h}{dt}(t) = \frac{d\tilde{S}_h^0}{dt}(t) + flux_{S_h}(t) + \int_0^t flux_{S_h}(b) \frac{dQ_{S_h}}{dt}(t-b) db \tag{3.10d}$$

where

$$\frac{dQ_{S_h}}{dt} = \frac{dP_{ND}}{dt}. \tag{3.10e}$$

Lastly for this compartment, we have

$$\frac{d\tilde{S}_h^0}{dt} = S_h^0 \frac{dQ_{S_h}}{dt} = S_h^0 \frac{dP_{ND}}{dt}.$$

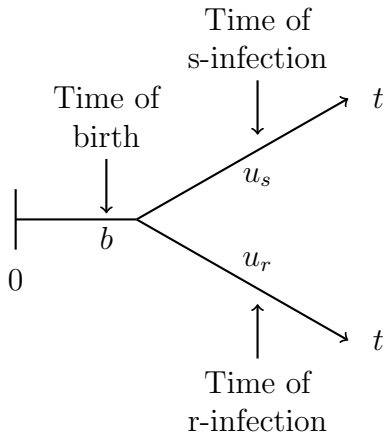


Figure 3.6: Timeline for mosquito traveling through the flow diagram: $S_v \to M_s$ and $S_v \to M_r$.

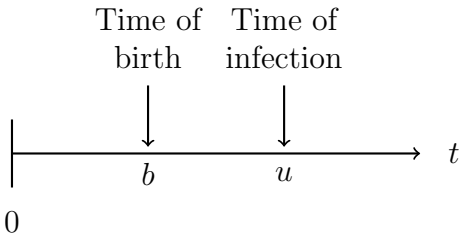


Figure 3.7: Shortened timeline for mosquito traveling through the flow diagram: $S_v \to M$.

3.3.2 Derivations of mosquito equations with general distributions

Now we derive equations for the mosquito population, which we represent with a two-strain SI compartment model. Again, we need to establish a timeline for infection according to Figure 3.2. In the case of vectors, they can follow the path $S_v \to M_s$ or the path $S_v \to M_r$. Hence we have two timelines to consider as seen in Figure 3.6, where b represents time of birth (i.e. susceptibility), u_s represents time of s-infection, and u_r represents time of r-infection.

However, in general we need only concern ourselves with a time of birth and a time of infection without specifying whether it is an s- or r-infection. This is because the variables u_s, and u_r act as dummy variables in our integrals and in particular do not overlap in the construction of our equations. Hence, to make computation easier, we simply use u to denote a time of infection regardless of the strain type. See Figure 3.7 for this simplified timeline.

We need to write equations for S_v, M_s, and M_r at time t. We can also calculate their derivatives for comparisons with survival functions that reduce our integral equations to ODEs. Throughout, we will consider the interval $[0, t]$.

As we did for the human system, we are going to focus on each compartment's $flux$. After calculating the $flux$, we must multiply by the relevant survival functions, then integrate over all time points up to time t to count the total vector population in the current class at time t. We will use the same framework as we used for the human population described in Equation 3.3.

The M_s class

We begin our derivation with the infected mosquito class as we did with the human system derivation. First we determine the flux of M_s for all infection times $u \in [0, t]$. The term contributing to the $flux$ of M_s is entering s-infections from the S_v class. Recall that the human-to-mosquito force of infection is given by Υ_s and Υ_r for s- and r- infection, respectively. Thus the $flux$ of M_s at infection time u is

$$flux_{M_s}(u) = \Upsilon_s(u) S_v(u). \tag{3.11a}$$

The survival scenario corresponding to the M_s class is not dying due to natural causes. The probability that a vector has not died due to natural causes at time t after infection at time u is described by $P_{ND_v}(t-u)$. To keep with previous naming conventions, and for the option of including additional survival scenarios for the vector in future models, we label the "product" of survival functions evaluated x time units after entering the M_s class as

$$Q_{M_s}(x) = P_{ND_v}(x). \tag{3.11b}$$

Thus the total number of vector s-infections at time t is given by

$$M_s(t) = \tilde{M}_s^0(t) + \int_0^t flux_{M_s}(u) Q_{M_s}(t-u) du \tag{3.11}$$

where

$$\tilde{M}_s^0(t) = M_s^0 Q_{M_s}(t) \tag{3.11c}$$

denotes the number of initial s-infected vectors still present in the M_s class at time t. For comparisons with other models with specific distributions, we calculate the derivative of our function as

$$\frac{dM_s}{dt}(t) = \frac{d\tilde{M}_s^0}{dt}(t) + flux_{M_s}(t) + \int_0^t flux_{M_s}(u) \frac{dQ_{M_s}}{dt}(t-u) du. \tag{3.11d}$$

The derivative of our survival function is

$$\frac{dQ_{M_s}}{dt} = \frac{dP_{ND_v}}{dt}. \tag{3.11e}$$

Furthermore,

$$\frac{d\tilde{M}_s^0}{dt} = M_s^0 \left(\frac{dQ_{M_s}}{dt} \right) = M_s^0 \left(\frac{dP_{ND_v}}{dt} \right).$$

The M_r class

Now we derive the M_r class. First, we look at the $flux$ of M_r for all points of infection $u \in [0, t]$. The term contributing to the $flux$ of M_r is entering r-infections from the S_v class. Thus the flux of M_r at infection time u is

$$flux_{M_r}(u) = \Upsilon_r(u) S_v(u). \tag{3.12a}$$

The survival scenario corresponding to the M_r class is not dying due to natural causes. The probability that a vector has not died due to natural causes at time t after infection at time u is described by $P_{ND_v}(t-u)$. Again, for the model's established naming convention, the "product" of survival functions evaluated x time units after entering the M_r class is

$$Q_{M_r}(x) = P_{ND_v}(x) \tag{3.12b}$$

Thus the total number of vector r-infections at time t is given by

$$M_r(t) = \tilde{M}_r^0(t) + \int_0^t flux_{M_r}(u) Q_{M_r}(t-u) du. \tag{3.12}$$

where

$$\tilde{M}_r^0(t) = M_r^0 Q_{M_r}(t) \tag{3.12c}$$

denotes the number of initial r-infected vectors still present in the M_r class at time t. The derivative of our M_r class is

$$\frac{dM_r}{dt}(t) = \frac{d\tilde{M}_r^0}{dt}(t) + flux_{M_r}(t) + \int_0^t flux_{M_r}(u) \frac{dQ_{M_r}}{dt}(t-u) du \tag{3.12d}$$

and the derivative of our survival function is

$$\frac{dQ_{M_r}}{dt} = \frac{dP_{ND_v}}{dt}. \tag{3.12e}$$

Furthermore,

$$\frac{d\tilde{M}_r^0}{dt} = M_r^0 \left(\frac{dQ_{M_r}}{dt} \right) = M_r^0 \left(\frac{dP_{ND_v}}{dt} \right).$$

The S_v class

Lastly, we need to construct the general $S_v(t)$ equation. To count the number of vectors in the S_v class at time t, we must describe the $flux$ of S_v for all time points $b \in [0, t]$. The $flux$ of S_v includes inflow from births via the function $\Lambda_v(t)$ as well as outflow via s-infections and r-infections. Thus the $flux$ of S_v at time b is

$$flux_{S_v}(b) = \Lambda_v(b) - [\Upsilon_s(b) + \Upsilon_r(b)] S_v(b). \tag{3.13a}$$

The only survival scenario associated with the S_v class is not dying due to natural causes. The probability of not dying at time t due to natural causes after entering the S_v class at time b is given by $P_{ND_v}(t-b)$. The survival function x time units after entering the S_v class is given by

$$Q_{S_v}(x) = P_{ND_v}(x). \tag{3.13b}$$

Thus, the total number of susceptible individuals at time t is given by

$$S_v(t) = \tilde{S}_v^0(t) + \int_0^t flux_{S_v}(b) Q_{S_v}(t-b) db \tag{3.13}$$

where

$$\tilde{S}_v^0(t) = S_v^0 Q_{S_v}(t) \tag{3.13c}$$

represents the number of initial susceptible individuals still in the class at time t. Note that

$$\frac{dS_v}{dt}(t) = \frac{d\tilde{S}_v^0}{dt}(t) + flux_{S_v}(t) + \int_0^t flux_{S_v}(b) \frac{dQ_{S_v}}{dt}(t-b) db \tag{3.13d}$$

where

$$\frac{dQ_{S_v}}{dt} = \frac{dP_{ND_v}}{dt}. \tag{3.13e}$$

Lastly for this compartment, we have

$$\frac{d\tilde{S}_v^0}{dt} = S_v^0\left(\frac{dQ_{S_v}}{dt}\right) = S_v^0\left(\frac{dP_{ND_v}}{dt}\right).$$

3.3.3 The full model

To summarize, equations (3.4) – (3.10) give the full human model with general distributions:

$$I_s(t) = \tilde{I}_s^0(t) + \int_0^t flux_{I_s}(u)Q_{I_s}(t-u)du \tag{3.4}$$

$$T_s(t) = \tilde{T}_s^0(t) + \int_0^t flux_{T_s}(\tau)Q_{T_s}(t-\tau)d\tau \tag{3.5}$$

$$R_s(t) = \tilde{R}_s^0(t) + \int_0^t flux_{R_s}(\sigma)Q_{R_s}(t-\sigma)d\sigma \tag{3.6}$$

$$I_r(t) = \tilde{I}_r^0(t) + \int_0^t flux_{I_r}(u)Q_{I_r}(t-u)du \tag{3.7}$$

$$T_r(t) = \tilde{T}_r^0(t) + \int_0^t flux_{T_r}(\tau)Q_{T_r}(t-\tau)d\tau \tag{3.8}$$

$$R_r(t) = \tilde{R}_r^0(t) + \int_0^t flux_{R_r}(\sigma)Q_{R_r}(t-\sigma)d\sigma \tag{3.9}$$

$$S_h(t) = \tilde{S}_h^0(t) + \int_0^t flux_{S_h}(b)Q_{S_h}(t-b)db. \tag{3.10}$$

The equations (3.4a) – (3.10a) give us the flux for each human compartment:

$$flux_{I_s}(u) = \lambda_s(u)S_h(u) - \lambda_r(u)I_s(u) \tag{3.4a}$$

$$flux_{T_s}(\tau) = I_s^0 dQ_{P_{I_sT_s}}(\tau) + \int_0^\tau flux_{I_s}(u)dQ_{P_{I_sT_s}}(\tau-u)du - \varphi\lambda_r(\tau)T_s(\tau) \tag{3.5a}$$

$$\begin{aligned} flux_{R_s}(\sigma) = {} & I_s^0 dQ_{P_{I_sR_s}}(\sigma) + \int_0^\sigma flux_{I_s}(u)dQ_{P_{I_sR_s}}(\sigma-u)du \\ & + T_s^0 dQ_{P_{T_sR_s}}(\sigma) + \int_0^\sigma flux_{T_s}(\tau)dQ_{P_{T_sR_s}}(\sigma-\tau)d\tau \\ & - \lambda_r(\sigma)R_s(\sigma) \end{aligned} \tag{3.6a}$$

$$flux_{I_r}(u) = \lambda_r(u)\left[S_h(u) + I_s(u) + T_s(u) + R_s(u)\right] \tag{3.7a}$$

$$flux_{T_r}(\tau) = I_r^0 dQ_{P_{I_rT_r}}(\tau) + \int_0^\tau flux_{I_r}(u) dQ_{P_{I_rT_r}}(\tau - u)du \tag{3.8a}$$

$$\begin{aligned} flux_{R_r}(\sigma) = {} & I_r^0 dQ_{P_{I_rR_r}}(\sigma) + \int_0^\sigma flux_{I_r}(u) dQ_{P_{I_rR_r}}(\sigma - u)du \\ & + T_r^0 dQ_{P_{T_rR_r}}(\sigma) + \int_0^\sigma flux_{T_r}(\tau) dQ_{P_{T_rR_r}}(\sigma - \tau)d\tau \end{aligned} \tag{3.9a}$$

$$\begin{aligned} flux_{S_h}(b) = {} & \Lambda_h(b) - \left[\lambda_s(b) + \lambda_r(b)\right] S_h(b) \\ & + R_s^0 dQ_{P_{R_sS_h}}(b) + \int_0^b flux_{R_s}(\sigma) dQ_{P_{R_sS_h}}(b - \sigma)d\sigma \\ & + R_r^0 dQ_{P_{R_rS_h}}(b) + \int_0^b flux_{R_r}(\sigma) dQ_{P_{R_rS_h}}(b - \sigma)d\sigma. \end{aligned} \tag{3.10a}$$

Equations (3.4b) – (3.10b) give us the survival functions for each human compartment:

$$Q_{I_s}(x) = P_{I_sR_s}(x)P_{I_sT_s}(x)P_{ND}(x)P_{DD_s}(x) \tag{3.4b}$$

$$Q_{T_s}(x) = P_{T_sR_s}(x)P_{ND}(x)P_{DD_s}(x) \tag{3.5b}$$

$$Q_{R_s}(x) = P_{R_sS_h}(x)P_{ND}(x) \tag{3.6b}$$

$$Q_{I_r}(x) = P_{I_rR_r}(x)P_{I_rT_r}(x)P_{ND}(x)P_{DD_r}(x) \tag{3.7b}$$

$$Q_{T_r}(x) = P_{T_rR_r}(x)P_{ND}(x)P_{DD_r}(x) \tag{3.8b}$$

$$Q_{R_r}(x) = P_{R_rS_h}(x)P_{ND}(x) \tag{3.9b}$$

$$Q_{S_h}(x) = P_{ND}(x). \tag{3.10b}$$

We track the initial populations for each human compartment via equations (3.4c) - (3.10c):

$$\tilde{I}_s^0(t) = I_s^0 Q_{I_s}(t) \tag{3.4c}$$

$$\tilde{T}_s^0(t) = T_s^0 Q_{T_s}(t) \tag{3.5c}$$

$$\tilde{R}_s^0(t) = R_s^0 Q_{R_s}(t) \tag{3.6c}$$

$$\tilde{I}_r^0(t) = I_r^0 Q_{I_r}(t) \tag{3.7c}$$

$$\tilde{T}_r^0(t) = T_r^0 Q_{T_r}(t) \tag{3.8c}$$

$$\tilde{R}_r^0(t) = R_r^0 Q_{R_r}(t) \tag{3.9c}$$

$$\tilde{S}_h^0(t) = S_h^0 Q_{S_h}(t). \tag{3.10c}$$

We can take the derivatives of our integrals as in equations (3.4d) - (3.10d):

$$\frac{dI_s}{dt}(t) = \frac{d\tilde{I}_s^0}{dt}(t) + flux_{I_s}(t) + \int_0^t flux_{I_s}(u)\frac{dQ_{I_s}}{dt}(t-u)du, \tag{3.4d}$$

$$\frac{dT_s}{dt}(t) = \frac{d\tilde{T}_s^0}{dt}(t) + flux_{T_s}(t) + \int_0^t flux_{T_s}(u)\frac{dQ_{T_s}}{dt}(t-u)du, \tag{3.5d}$$

$$\frac{dR_s}{dt}(t) = \frac{d\tilde{R}_s^0}{dt}(t) + flux_{R_s}(t) + \int_0^t flux_{R_s}(u)\frac{dQ_{R_s}}{dt}(t-u)du, \tag{3.6d}$$

$$\frac{dI_r}{dt}(t) = \frac{d\tilde{I}_r^0}{dt}(t) + flux_{I_r}(t) + \int_0^t flux_{I_r}(u)\frac{dQ_{I_r}}{dt}(t-u)du, \tag{3.7d}$$

$$\frac{dT_r}{dt}(t) = \frac{d\tilde{T}_r^0}{dt}(t) + flux_{T_r}(t) + \int_0^t flux_{T_r}(u)\frac{dQ_{T_r}}{dt}(t-u)du, \tag{3.8d}$$

$$\frac{dR_r}{dt}(t) = \frac{d\tilde{R}_r^0}{dt}(t) + flux_{R_r}(t) + \int_0^t flux_{R_r}(u)\frac{dQ_{R_r}}{dt}(t-u)du, \tag{3.9d}$$

$$\frac{dS_h}{dt}(t) = \frac{d\tilde{S}_h^0}{dt}(t) + flux_{S_h}(t) + \int_0^t flux_{S_h}(u)\frac{dQ_{S_h}}{dt}(t-u)du, \tag{3.10d}$$

where the derivatives of the product of survival functions for each class are given in Equations (3.4e) - (3.10e):

$$\begin{aligned}\frac{dQ_{I_s}}{dt} = {} & \frac{dP_{I_sR_s}}{dt}P_{I_sT_s}P_{ND}P_{DD_s} + P_{I_sR_s}\frac{dP_{I_sT_s}}{dt}P_{ND}P_{DD_s} \\ & + P_{I_sR_s}P_{I_sT_s}\frac{dP_{ND}}{dt}P_{DD_s} + P_{I_sR_s}P_{I_sT_s}P_{ND}\frac{dP_{DD_s}}{dt}\end{aligned} \tag{3.4e}$$

$$\frac{dQ_{T_s}}{dt} = \frac{dP_{T_sR_s}}{dt}P_{ND}P_{DD_S} + P_{T_sR_s}\frac{dP_{ND}}{dt}P_{DD_s} + P_{T_sR_s}P_{ND}\frac{dP_{DD_s}}{dt} \tag{3.5e}$$

$$\frac{dQ_{R_s}}{dt} = \frac{dP_{R_sS_h}}{dt}P_{ND} + P_{R_sS_h}\frac{dP_{ND}}{dt} \tag{3.6e}$$

$$\begin{aligned}\frac{dQ_{I_r}}{dt} = {} & \frac{dP_{I_rR_r}}{dt}P_{I_rT_r}P_{ND}P_{DD_r} + P_{I_rR_r}\frac{dP_{I_rT_r}}{dt}P_{ND}P_{DD_r} \\ & + P_{I_rR_r}P_{I_rT_r}\frac{dP_{ND}}{dt}P_{DD_r} + P_{I_rR_r}P_{I_rT_r}P_{ND}\frac{dP_{DD_r}}{dt}\end{aligned} \tag{3.7e}$$

$$\frac{dQ_{T_r}}{dt} = \frac{dP_{T_rR_r}}{dt}P_{ND}P_{DD_r} + P_{T_rR_r}\frac{dP_{ND}}{dt}P_{DD_r} + P_{T_rR_r}P_{ND}\frac{dP_{DD_r}}{dt} \tag{3.8e}$$

$$\frac{dQ_{R_r}}{dt} = \frac{dP_{R_rS_h}}{dt}P_{ND} + P_{R_r}\frac{dP_{ND}}{dt} \tag{3.9e}$$

$$\frac{dQ_{S_h}}{dt} = \frac{dP_{ND}}{dt}. \tag{3.10e}$$

We also use definitions (3.4f) - (3.9f) to simplify notation for use in the human model equations:

$$dQ_{P_{I_sR_s}} = -\frac{dP_{I_sR_s}}{dt}P_{I_sT_s}P_{ND}P_{DD_s}, \qquad dQ_{P_{I_sT_s}} = -P_{I_sR_s}\frac{dP_{I_sT_s}}{dt}P_{ND}P_{DD_s} \tag{3.4f}$$

$$dQ_{P_{T_sR_s}} = -\frac{dP_{T_sR_s}}{dt}P_{ND}P_{DD_S} \tag{3.5f}$$

$$dQ_{P_{R_sS_h}} = -\frac{dP_{R_sS_h}}{dt}P_{ND} \tag{3.6f}$$

$$dQ_{P_{I_rR_r}} = -\frac{dP_{I_rR_r}}{dt}P_{I_rT_r}P_{ND}P_{DD_r}, \qquad dQ_{P_{I_rT_r}} = -P_{I_rR_r}\frac{dP_{I_rT_r}}{dt}P_{ND}P_{DD_r} \tag{3.7f}$$

$$dQ_{P_{T_rR_r}} = -\frac{dP_{T_rR_r}}{dt}P_{ND}P_{DD_r} \tag{3.8f}$$

$$dQ_{P_{R_rS_h}} = -\frac{dP_{R_rS_h}}{dt}P_{ND} \tag{3.9f}$$

Now we summarize the mosquito model. Equations (3.11) – (3.13) give the full mosquito model with general distributions:

$$M_s(t) = \tilde{M}_s^0(t) + \int_0^t flux_{M_s}(u)Q_{M_s}(t-u)du \tag{3.11}$$

$$M_r(t) = \tilde{M}_r^0(t) + \int_0^t flux_{M_r}(u)Q_{M_r}(t-u)du \tag{3.12}$$

$$S_v(t) = \tilde{S}_v^0(t) + \int_0^t flux_{S_v}(b)Q_{S_v}(t-b)db. \tag{3.13}$$

Equations (3.11a) - (3.13a) gives us the $flux$ for each vector compartment:

$$flux_{M_s}(u) = \Upsilon_s(u)S_v(u) \tag{3.11a}$$

$$flux_{M_r}(u) = \Upsilon_r(u)S_v(u) \tag{3.12a}$$

$$flux_{S_v}(b) = \Lambda_v(b) - [\Upsilon_s(b) + \Upsilon_r(b)]S_v(b). \tag{3.13a}$$

Equations (3.11b) – (3.13b) give us the survival function for each vector compartment:

$$Q_{M_s}(x) = P_{ND_v}(x) \tag{3.11b}$$

$$Q_{M_r}(x) = P_{ND_v}(x) \tag{3.12b}$$

$$Q_{S_v}(x) = P_{ND_v}(x). \tag{3.13b}$$

We track the initial populations for each vector compartment via equations (3.11c) - (3.13c):

$$\tilde{M}_s^0(t) = M_s^0 Q_{M_s}(t) \tag{3.11c}$$

$$\tilde{M}_r^0(t) = M_r^0 Q_{M_r}(t) \tag{3.12c}$$

$$\tilde{S}_v^0(t) = S_v^0 Q_{S_v}(t). \tag{3.13c}$$

We can take the derivatives of our integrals as in equations (3.11d) - (3.13d):

$$\frac{dM_s}{dt}(t) = \frac{d\tilde{M}_s^0}{dt}(t) + flux_{M_s}(t) + \int_0^t flux_{M_s}(u)\frac{dQ_{M_s}}{dt}(t-u)du \tag{3.11d}$$

$$\frac{dM_r}{dt}(t) = \frac{d\tilde{M}_r^0}{dt}(t) + flux_{M_r}(t) + \int_0^t flux_{M_r}(u)\frac{dQ_{M_r}}{dt}(t-u)du \tag{3.12d}$$

$$\frac{dS_v}{dt}(t) = \frac{d\tilde{S}_v^0}{dt}(t) + flux_{S_v}(t) + \int_0^t flux_{S_v}(b)\frac{dQ_{S_v}}{dt}(t-b)db \tag{3.13d}$$

where the derivatives of the product of survival functions for each class are given in Equations (3.11e) - (3.13e):

$$\frac{dQ_{M_s}}{dt} = \frac{dP_{ND_v}}{dt}. \tag{3.11e}$$

$$\frac{dQ_{M_r}}{dt} = \frac{dP_{ND_v}}{dt}. \tag{3.12e}$$

$$\frac{dQ_{S_v}}{dt} = \frac{dP_{ND_v}}{dt}. \tag{3.13e}$$

In particular, for mosquito-borne disease transmission, we will assume the following standard formulations as in the Ross-Macdonald model for the forces of infection between humans and mosquitoes:

$$\lambda_s(t) = \beta_h M_s(t)/N_h(t) \tag{3.14}$$

$$\lambda_r(t) = \kappa_h \beta_h M_r(t)/N_h(t) \tag{3.15}$$

$$\Upsilon_s(t) = \beta_v(I_s(t) + \psi_s T_s(t))/N_h(t) \tag{3.16}$$

$$\Upsilon_r(t) = \kappa_v \beta_v(I_r(t) + \psi_r T_r(t))/N_h(t) \tag{3.17}$$

where β_h and β_v are transmission terms, κ_h and κ_v are fitness terms that scale the transmission of r-infections, ψ_s and ψ_r scale the transmission of infections for individuals in the treated compartments, and the total human population at time t is

$$N_h(t) = S_h(t) + I_s(t) + I_r(t) + T_s(t) + T_r(t) + R_s(t) + R_r(t).$$

3.4 Reduction of Integral Equations to ODEs

We show the through two examples that if the survival functions are exponential or Erlang (Gamma with integer shape parameter), then it can be reformulated into a system of ODEs. First, we consider the case with all exponential survival functions and derive the corresponding ODE system. Then, we derive the system of ODEs corresponding to Erlang (Gamma)-distributed waiting times in the Infected class for waiting time to Treatment and waiting time to Recovery.

3.4.1 Exponential Distributions for All Classes

First, we assume that all survival functions are exponentially-distributed as in column 'EXP' in Table 3.4. We also take their corresponding derivatives with respect to system time:

$$\begin{aligned}
P_{I_sR_s}(t) = \exp(-\sigma_s t) \quad &\Longrightarrow \quad \frac{dP_{I_sR_s}}{dt}(t) = -\sigma_s \exp(-\sigma_s t) = -\sigma_s P_{I_sR_s}(t) \\
P_{I_rR_r}(t) = \exp(-\sigma_r t) \quad &\Longrightarrow \quad \frac{dP_{I_rR_r}}{dt}(t) = -\sigma_r \exp(-\sigma_r t) = -\sigma_r P_{I_rR_r}(t) \\
P_{I_sT_s}(t) = \exp(-a t) \quad &\Longrightarrow \quad \frac{dP_{I_sT_s}}{dt}(t) = -a \exp(-a t) = -a P_{I_sT_s}(t) \\
P_{I_rT_r}(t) = \exp(-a t) \quad &\Longrightarrow \quad \frac{dP_{I_rT_r}}{dt}(t) = -a \exp(-a t) = -a P_{I_rT_r}(t) \\
P_{T_sR_s}(t) = \exp(-\alpha_s t) \quad &\Longrightarrow \quad \frac{dP_{T_sR_s}}{dt}(t) = -\alpha_s \exp(-\alpha_s t) = -\alpha_s P_{T_sR_s}(t) \\
P_{T_rR_r}(t) = \exp(-\alpha_r t) \quad &\Longrightarrow \quad \frac{dP_{T_rR_r}}{dt}(t) = -\alpha_r \exp(-\alpha_r t) = -\alpha_r P_{T_rR_r}(t) \\
P_{R_sS_h}(t) = \exp(-\omega_s t) \quad &\Longrightarrow \quad \frac{dP_{R_sS_h}}{dt}(t) = -\omega_s \exp(-\omega_s t) = -\omega_s P_{R_sS_h}(t) \\
P_{R_rS_h}(t) = \exp(-\omega_r t) \quad &\Longrightarrow \quad \frac{dP_{R_rS_h}}{dt}(t) = -\omega_r \exp(-\omega_r t) = -\omega_r P_{R_rS_h}(t)
\end{aligned}$$

$$
\begin{aligned}
P_{DD_s}(t) = \exp(-\delta_s t) \quad &\Longrightarrow \quad \frac{dP_{DD_s}}{dt}(t) = -\delta_s \exp(-\delta_s t) = -\delta_s P_{DD_s}(t) \\
P_{DD_r}(t) = \exp(-\delta_r t) \quad &\Longrightarrow \quad \frac{dP_{DD_r}}{dt}(t) = -\delta_r \exp(-\delta_r t) = -\delta_r P_{DD_r}(t) \\
P_{ND}(t) = \exp(-\mu_h t) \quad &\Longrightarrow \quad \frac{dP_{ND}}{dt}(t) = -\mu_h \exp(-\mu_h t) = -\mu_h P_{ND}(t) \\
P_{ND_v}(t) = \exp(-\mu_v t) \quad &\Longrightarrow \quad \frac{dP_{ND_v}}{dt}(t) = -\mu_v \exp(-\mu_v t) = -\mu_v P_{ND_v}(t).
\end{aligned}
$$

Substituting these survival functions and their derivatives into Equations (3.4e) - (3.10e) and (3.11e) - (3.13e) gives us

$$
\begin{aligned}
\frac{dQ_{I_s}}{dt} &= \frac{dP_{I_sR_s}}{dt} P_{I_sT_s} P_{ND} P_{DD_s} + P_{I_sR_s} \frac{dP_{I_sT_s}}{dt} P_{ND} P_{DD_s} \\
&\qquad + P_{I_sR_s} P_{I_sT_s} \frac{dP_{ND}}{dt} P_{DD_s} + P_{I_sR_s} P_{I_sT_s} P_{ND} \frac{dP_{DD_s}}{dt} \\
&= -\sigma_s P_{I_sR_s} P_{I_sT_s} P_{ND} P_{DD_s} - a P_{I_sR_s} P_{I_sT_s} P_{ND} P_{DD_s} \\
&\qquad - \mu_h P_{I_sR_s} P_{I_sT_s} P_{ND} P_{DD_s} - \delta_s P_{I_sR_s} P_{I_sT_s} P_{ND} P_{DD_s} \\
&= -\sigma_s Q_{I_s} - a Q_{I_s} - \mu_h Q_{I_s} - \delta_s Q_{I_s} = -(\sigma_s + a + \mu_h + \delta_s) Q_{I_s} \qquad \text{(3.4e, EXP)} \\
\frac{dQ_{T_s}}{dt} &= -\alpha_s P_{T_sR_s} P_{ND} P_{DD_S} - \mu_h P_{T_sR_s} P_{ND} P_{DD_s} - \delta_s P_{T_sR_s} P_{ND} P_{DD_s} \\
&= -\alpha_s Q_{T_s} - \mu_h Q_{T_s} - \delta_s Q_{T_s} = -(\alpha_s + \mu_h + \delta_s) Q_{T_s} \qquad \text{(3.5e, EXP)} \\
\frac{dQ_{R_s}}{dt} &= \frac{dP_{R_sS_h}}{dt} P_{ND} + P_{R_sS_h} \frac{dP_{ND}}{dt} = -\omega_s P_{R_sS_h} P_{ND} - \mu_h P_{R_sS_h} P_{ND} \\
&= -\omega_s Q_{R_s} - \mu_h Q_{R_s} = -(\omega_s + \mu_h) Q_{R_s} \qquad \text{(3.6e, EXP)} \\
\frac{dQ_{I_r}}{dt} &= \frac{dP_{I_rR_r}}{dt} P_{I_rT_r} P_{ND} P_{DD_r} + P_{I_rR_r} \frac{dP_{I_rT_r}}{dt} P_{ND} P_{DD_r} \\
&\qquad + P_{I_rR_r} P_{I_rT_r} \frac{dP_{ND}}{dt} P_{DD_r} + P_{I_rR_r} P_{I_rT_r} P_{ND} \frac{dP_{DD_r}}{dt} \\
&= -\sigma_r P_{I_rR_r} P_{I_rT_r} P_{ND} P_{DD_r} - a P_{I_rR_r} P_{I_rT_r} P_{ND} P_{DD_r} \\
&\qquad - \mu_h P_{I_rR_r} P_{I_rT_r} P_{ND} P_{DD_r} - \delta_r P_{I_rR_r} P_{I_rT_r} P_{ND} P_{DD_r} \\
&= -\sigma_r Q_{I_r} - a Q_{I_r} - \mu_h Q_{I_r} - \delta_r Q_{I_r} = -(\sigma_r + a + \mu_h + \delta_r) Q_{I_r} \qquad \text{(3.7e, EXP)} \\
\frac{dQ_{T_r}}{dt} &= \frac{dP_{T_rR_r}}{dt} P_{ND} P_{DD_r} + P_{T_rR_r} \frac{dP_{ND}}{dt} P_{DD_r} + P_{T_rR_r} P_{ND} \frac{dP_{DD_r}}{dt} \\
&= -\alpha_r P_{T_rR_r} P_{ND} P_{DD_r} - \mu_h P_{T_rR_r} P_{ND} P_{DD_r} - \delta_r P_{T_rR_r} P_{ND} P_{DD_r} \\
&= -\alpha_r Q_{T_r} - \mu_h Q_{T_r} - \delta_r Q_{T_r} = -(\alpha_r + \mu_h + \delta_r) Q_{T_r} \qquad \text{(3.8e, EXP)}
\end{aligned}
$$

$$\frac{dQ_{R_r}}{dt} = \frac{dP_{R_rS_h}}{dt}P_{ND} + P_{R_r}\frac{dP_{ND}}{dt} = -\omega_r P_{R_rS_h}P_{ND} - \mu_h P_{R_r}P_{ND}$$
$$= -\omega_r Q_{R_s} - \mu_h Q_{R_s} = -(\omega_r + \mu_h)Q_{R_s} \quad \text{(3.9e, EXP)}$$
$$\frac{dQ_{S_h}}{dt} = \frac{dP_{ND}}{dt} = -\mu_h P_{ND} = -\mu_h Q_{S_h} \quad \text{(3.10e, EXP)}$$
$$\frac{dQ_{M_s}}{dt} = \frac{dP_{ND_v}}{dt} = -\mu_v P_{ND_v} = -\mu_v Q_{M_s} \quad \text{(3.11e, EXP)}$$
$$\frac{dQ_{M_r}}{dt} = \frac{dP_{ND_v}}{dt} = -\mu_v P_{ND_v} = -\mu_v Q_{M_r} \quad \text{(3.12e, EXP)}$$
$$\frac{dQ_{S_v}}{dt} = \frac{dP_{ND_v}}{dt} = -\mu_v P_{ND_v} = -\mu_v Q_{S_h}. \quad \text{(3.13e, EXP)}$$

Substituting these survival functions and their derivatives into the definitions in Equations (3.4f) - (3.9f), we get

$$dQ_{P_{I_sR_s}} = \sigma_s P_{I_sR_s}P_{I_sT_s}P_{ND}P_{DD_s} = \sigma_s Q_{I_s}, \qquad dQ_{P_{I_sT_s}} = aP_{I_sR_s}P_{I_sT_s}P_{ND}P_{DD_s} = aQ_{I_s}$$
(3.4f, EXP)

$$dQ_{P_{T_sR_s}} = \alpha_s P_{T_sR_s}P_{ND}P_{DD_S} = \alpha_s Q_{T_s} \quad \text{(3.5f, EXP)}$$
$$dQ_{P_{R_sS_h}} = \omega_s P_{R_sS_h}P_{ND} = \omega_s Q_{R_s} \quad \text{(3.6f, EXP)}$$
$$dQ_{P_{I_rR_r}} = \sigma_r P_{I_rR_r}P_{I_rT_r}P_{ND}P_{DD_r} = \sigma_r Q_{I_r}, \qquad dQ_{P_{I_rT_r}} = aP_{I_rR_r}P_{I_rT_r}P_{ND}P_{DD_r} = aQ_{I_r}$$
(3.7f, EXP)

$$dQ_{P_{T_rR_r}} = \alpha_r P_{T_rR_r}P_{ND}P_{DD_r} = \alpha_r Q_{T_r} \quad \text{(3.8f, EXP)}$$
$$dQ_{P_{R_rS_h}} = \omega_r P_{R_rS_h}P_{ND} = \omega_r Q_{R_r}. \quad \text{(3.9f, EXP)}$$

We can substitute these survival functions and derivatives into our $flux$ expressions from Equations (3.4a) - (3.10a) and (3.11a) - (3.13a):

$$flux_{I_s}(u) = \lambda_s(u)S_h(u) - \lambda_r(u)I_s(u) \quad \text{(3.4a, EXP)}$$
$$flux_{T_s}(\tau) = aI_s^0 Q_{I_s}(\tau) + a\int_0^\tau flux_{I_s}(u)Q_{I_s}(\tau - u)du - \varphi\lambda_r(\tau)T_s(\tau)$$
$$= aI_s(\tau) - \varphi\lambda_r(\tau)T_s(\tau) \quad \text{(3.5a, EXP)}$$
$$flux_{R_s}(\sigma) = \sigma_s I_s^0 Q_{I_s}(\sigma) + \sigma_s\int_0^\sigma flux_{I_s}(u)Q_{I_s}(\sigma - u)du$$
$$+ \alpha_s T_s^0 Q_{T_s}(\sigma) + \alpha_s\int_0^\sigma flux_{T_s}(\tau)Q_{T_s}(\sigma - \tau)d\tau - \lambda_r(\sigma)R_s(\sigma)$$

$$= \sigma_s I_s(\sigma) + \alpha_s T_s(\sigma) - \lambda_r(\sigma) R_s(\sigma) \quad \text{(3.6a, EXP)}$$

$$flux_{I_r}(u) = \lambda_r(u)\left[S_h(u) + I_s(u) + T_s(u) + R_s(u)\right] \quad \text{(3.7a, EXP)}$$

$$flux_{T_r}(\tau) = aI_r^0 Q_{I_r}(\tau) + a\int_0^\tau flux_{I_r}(u) Q_{I_r}(\tau - u)du = aI_r(\tau) \quad \text{(3.8a, EXP)}$$

$$\begin{aligned} flux_{R_r}(\sigma) &= \sigma_r I_r^0 Q_{I_r}(\sigma) + \sigma_r \int_0^\sigma flux_{I_r}(u) Q_{I_r}(\sigma - u)du \\ &\quad + \alpha_r T_r^0 Q_{T_r}(\sigma) + \alpha_r \int_0^\sigma flux_{T_r}(\tau) Q_{T_r}(\sigma - \tau)d\tau \\ &= \sigma_r I_r(\sigma) + \alpha_r T_r(\sigma) \end{aligned} \quad \text{(3.9a, EXP)}$$

$$\begin{aligned} flux_{S_h}(b) &= \Lambda_h(b) - \left[\lambda_s(b) + \lambda_r(b)\right] S_h(b) \\ &\quad + \sigma_s R_s^0 Q_{R_s}(b) + \sigma_s \int_0^b flux_{R_s}(\sigma) Q_{R_s}(b - \sigma)d\sigma \\ &\quad + \sigma_r R_r^0 Q_{R_r}(b) + \sigma_r \int_0^b flux_{R_r}(\sigma) Q_{R_s}(b - \sigma)d\sigma \\ &= \Lambda_h(b) - \left[\lambda_s(b) + \lambda_r(b)\right] S_h(b) + \sigma_s R_s(b) + \sigma_r R_r(b). \end{aligned} \quad \text{(3.10a, EXP)}$$

$$flux_{M_s}(u) = \Upsilon_s(u) S_v(u) \quad \text{(3.11a, EXP)}$$

$$flux_{M_r}(u) = \Upsilon_r(u) S_v(u) \quad \text{(3.12a, EXP)}$$

$$flux_{S_v}(b) = \Lambda_v(b) - \left[\Upsilon_s(b) + \Upsilon_r(b)\right] S_v(b). \quad \text{(3.13a, EXP)}$$

Now we substitute the $flux$es and survival function derivatives into our integral equation derivatives from Equations (3.4d) - (3.10d) and (3.11d)-(3.13d). We note that the derivative structure for the initial conditions follows the same structure as what is computed below as a result of the product rule for derivatives. Hence, each term in the derivatives for the initial conditions can be added to its corresponding term that results from the derivative of the integral for each class. For ease of notation, we omit the initial conditions for each class in the following computation, but one can add them with the same resulting system:

$$\begin{aligned} \frac{dI_s}{dt}(t) &= flux_{I_s}(t) + \int_0^t flux_{I_s}(u) \frac{dQ_{I_s}}{dt}(t - u)du \\ &= \lambda_s(t) S_h(t) - \lambda_r(t) I_s(t) - (\sigma_s + a + \mu_h + \delta_s) \int_0^t flux_{I_s}(u) \frac{Q_{I_s}}{dt}(t - u)du \\ &= \lambda_s(t) S_h(t) - \lambda_r(t) I_s(t) - (\sigma_s + a + \mu_h + \delta_s) I_s(t) \end{aligned} \quad \text{(3.4d, EXP)}$$

$$\frac{dT_s}{dt}(t) = aI_s(t) - \varphi\lambda_r(t)T_s(t) - (\alpha_s + \mu_h + \delta_s)\int_0^t flux_{T_s}(u)Q_{T_s}(t-u)du$$

$$= aI_s(t) - \varphi\lambda_r T_s(t) - (\alpha_s + \mu_h + \delta_s)T_s(t) \qquad \text{(3.5d, EXP)}$$

$$\frac{dR_s}{dt}(t) = flux_{R_s}(t) + \int_0^t flux_{R_s}(u)\frac{dQ_{R_s}}{dt}(t-u)du$$

$$= \sigma_s I_s(t) + \alpha_s T_s(t) - \lambda_r(t)R_s(t) - (\omega_s + \mu_h)\int_0^t flux_{R_s}(u)Q_{R_s}(t-u)du$$

$$= \sigma_s I_s(t) + \alpha_s T_s(t) - \lambda_r(t)R_s(t) - (\omega_s + \mu_h)R_s(t) \qquad \text{(3.6d, EXP)}$$

$$\frac{dI_r}{dt}(t) = flux_{I_r}(t) + \int_0^t flux_{I_r}(u)\frac{dQ_{I_r}}{dt}(t-u)du$$

$$= \lambda_r(t)[S_h(t) + I_s(t) + T_s(t) + R_s(t)] - (\sigma_r + a + \mu_h + \delta_r)\int_0^t flux_{I_r}(u)Q_{I_r}(t-u)du$$

$$= \lambda_r(t)[S_h(t) + I_s(t) + T_s(t) + R_s(t)] - (\sigma_r + a + \mu_h + \delta_r)I_r(t) \qquad \text{(3.7d, EXP)}$$

$$\frac{dT_r}{dt}(t) = flux_{T_r}(t) + \int_0^t flux_{T_r}(u)\frac{dQ_{T_r}}{dt}(t-u)du$$

$$= aI_r(t) - (\alpha_r + \mu_h + \delta_r)\int_0^t flux_{T_r}(u)Q_{T_r}(t-u)du$$

$$= aI_r(t) - (\alpha_r + \mu_h + \delta_r)T_r(t) \qquad \text{(3.8d, EXP)}$$

$$\frac{dR_r}{dt}(t) = flux_{R_r}(t) + \int_0^t flux_{R_r}(u)\frac{dQ_{R_r}}{dt}(t-u)du$$

$$= \sigma_r I_r(t) + \alpha_r T_r(t) - (\omega_r + \mu_h)\int_0^t flux_{R_r}(u)Q_{R_r}(t-u)du$$

$$= \sigma_r I_r(t) + \alpha_r T_r(t) - (\omega_r + \mu_h)R_r(t) \qquad \text{(3.9d, EXP)}$$

$$\frac{dS_h}{dt}(t) = flux_{S_h}(t) + \int_0^t flux_{S_h}(u)\frac{dQ_{S_h}}{dt}(t-u)du$$

$$= \Lambda_h(t) - [\lambda_s(t) + \lambda_r(t)]S_h(t) + \sigma_s R_s(t) + \sigma_r R_r(t) - \mu_h\int_0^t flux_{S_h}(u)Q_{S_h}(t-u)du$$

$$= \Lambda_h(t) - [\lambda_s(t) + \lambda_r(t)]S_h(t) + \sigma_s R_s(t) + \sigma_r R_r(t) - \mu_h S_h(t) \qquad \text{(3.10d, EXP)}$$

$$\frac{dM_s}{dt}(t) = flux_{M_s}(t) + \int_0^t flux_{M_s}(u)\frac{dQ_{M_s}}{dt}(t-u)du$$

$$= \Upsilon_s(t)S_v(t) - \mu_v\int_0^t flux_{M_s}(u)Q_{M_s}(t-u)du$$

$$= \Upsilon_s(t)S_v(t) - \mu_v M_s(t) \qquad \text{(3.11d, EXP)}$$

$$\frac{dM_r}{dt}(t) = flux_{M_r}(t) + \int_0^t flux_{M_r}(u)\frac{dQ_{M_r}}{dt}(t-u)du$$

$$
\begin{aligned}
&= \Upsilon_r(t)S_v(t) - \mu_v \int_0^t flux_{M_r}(u)Q_{M_r}(t-u)du \\
&= \Upsilon_r(t)S_v(t) - \mu_v M_r(t) && \text{(3.12d, EXP)} \\
\frac{dS_v}{dt}(t) &= flux_{S_v}(t) + \int_0^t flux_{S_v}(b)\frac{dQ_{S_v}}{dt}(t-b)db \\
&= \Lambda_v(t) - [\Upsilon_s(t) + \Upsilon_r(t)]S_v(t) - \mu_v \int_0^t flux_{S_v}(b)Q_{S_v}(t-b)db \\
&= \Lambda_v(t) - [\Upsilon_s(t) + \Upsilon_r(t)]S_v(t) - \mu_v S_v(t) && \text{(3.13d, EXP)}
\end{aligned}
$$

Thus, we get the ODE system in Equations (3.4d, EXP) - (3.13d, EXP) corresponding to our human and mosquito diagrams in Figures 3.1 and 3.2 where the rates between compartments are the the inverse of the means for the corresponding survival functions.

3.4.2 Gamma Distributions for Infectious Classes

Suppose instead that $P_{I_sR_s}$, $P_{I_sT_s}$, $P_{I_rR_r}$, and $P_{I_rT_r}$ are Gamma-distributed while all other survival scenarios are exponential. In this case, the Integral Equations reduce to a system of ODEs corresponding to the human transfer diagram in Figure 3.8 and the mosquito transfer diagram in 3.2 from Chapter 2. Note the grid structure that emerges for the I_s and I_r classes, which is not straightforward, as a result of two Gamma-distributed survival scenarios associated with the infected classes. First, we define all survival functions as in column 'IT+IR' in Table 3.4. We also take their corresponding derivatives with respect to system time:

$$
\begin{aligned}
P_{I_sR_s}(t) &= \exp(-N_{\sigma_s}\sigma_s t)\sum_{n=1}^{N_{\sigma_s}} \frac{(N_{\sigma_s}\sigma_s t)^{n-1}}{(n-1)!} \\
\implies \frac{dP_{I_sR_s}}{dt}(t) &= N_{\sigma_s}\sigma_s \exp(-N_{\sigma_s}\sigma_s t)\sum_{n=1}^{N_{\sigma_s}-1} \frac{(N_{\sigma_s}\sigma_s t)^{n-1}}{(n-1)!} \\
&\quad - N_{\sigma_s}\sigma_s \exp(-N_{\sigma_s}\sigma_s t)\sum_{n=1}^{N_{\sigma_s}} \frac{(N_{\sigma_s}\sigma_s t)^{n-1}}{(n-1)!} \\
&= -N_{\sigma_s}\sigma_s \exp(-N_{\sigma_s}\sigma_s t)\frac{(N_{\sigma_s}\sigma_s t)^{N_{\sigma_s}-1}}{(N_{\sigma_s}-1)!}
\end{aligned}
$$

$$P_{I_rR_r}(t) = \exp(-N_{\sigma_r}\sigma_r t)\sum_{n=1}^{N_{\sigma_r}} \frac{(N_{\sigma_r}\sigma_r t)^{n-1}}{(n-1)!}$$

$$\implies \frac{dP_{I_rR_r}}{dt}(t) = N_{\sigma_r}\sigma_r \exp(-N_{\sigma_r}\sigma_r t)\sum_{n=1}^{N_{\sigma_r}-1} \frac{(N_{\sigma_r}\sigma_r t)^{n-1}}{(n-1)!}$$

$$- N_{\sigma_r}\sigma_r \exp(-N_{\sigma_r}\sigma_r t)\sum_{n=1}^{N_{\sigma_r}} \frac{(N_{\sigma_r}\sigma_r t)^{n-1}}{(n-1)!}$$

$$= -N_{\sigma_r}\sigma_r \exp(-N_{\sigma_r}\sigma_r t)\frac{(N_{\sigma_r}\sigma_r t)^{N_{\sigma_r}-1}}{(N_{\sigma_r}-1)!}$$

$$P_{I_sTs}(t) = \exp(-N_{a_s}at)\sum_{n=1}^{N_{a_s}} \frac{(N_{a_s}at)^{n-1}}{(n-1)!}$$

$$\implies \frac{dP_{I_sT_s}}{dt}(t) = N_{a_s}a \exp(-N_{a_s}at)\sum_{n=1}^{N_{a_s}-1} \frac{(N_{a_s}at)^{n-1}}{(n-1)!}$$

$$- N_{a_s}a \exp(-N_{a_s}at)\sum_{n=1}^{N_{a_s}} \frac{(N_{a_s}at)^{n-1}}{(n-1)!}$$

$$= -N_{a_s}a \exp(-N_{a_s}at)\frac{(N_{a_s}at)^{N_{a_s}-1}}{(N_{a_s}-1)!}$$

$$P_{I_rTr}(t) = \exp(-N_{a_r}at)\sum_{n=1}^{N_{a_r}} \frac{(N_{a_r}at)^{n-1}}{(n-1)!}$$

$$\implies \frac{dP_{I_rT_r}}{dt}(t) = N_{a_r}a \exp(-N_{a_r}at)\sum_{n=1}^{N_{a_r}-1} \frac{(N_{a_r}at)^{n-1}}{(n-1)!}$$

$$- N_{a_r}a \exp(-N_{a_r}at)\sum_{n=1}^{N_{a_r}} \frac{(N_{a_r}at)^{n-1}}{(n-1)!}$$

$$= -N_{a_r}a \exp(-N_{a_r}at)\frac{(N_{a_r}at)^{N_{a_r}-1}}{(N_{a_r}-1)!}$$

$$P_{T_sR_s}(t) = \exp(-\alpha_s t) \implies \frac{dP_{T_sR_s}}{dt}(t) = -\alpha_s \exp(-\alpha_s t) = -\alpha_s P_{T_sR_s}(t)$$

$$P_{T_rR_r}(t) = \exp(-\alpha_r t) \implies \frac{dP_{T_rR_r}}{dt}(t) = -\alpha_r \exp(-\alpha_r t) = -\alpha_r P_{T_rR_r}(t)$$

$$P_{R_sS_h}(t) = \exp(-\omega_s t) \implies \frac{dP_{R_sS_h}}{dt}(t) = -\omega_s \exp(-\omega_s t) = -\omega_s P_{R_sS_h}(t)$$

$$P_{R_rS_h}(t) = \exp(-\omega_r t) \implies \frac{dP_{R_rS_h}}{dt}(t) = -\omega_r \exp(-\omega_r t) = -\omega_r P_{R_rS_h}(t)$$

$$P_{DD_s}(t) = \exp(-\delta_s t) \implies \frac{dP_{DD_s}}{dt}(t) = -\delta_s \exp(-\delta_s t) = -\delta_s P_{DD_s}(t)$$

$$P_{DD_r}(t) = \exp(-\delta_r t) \implies \frac{dP_{DD_r}}{dt}(t) = -\delta_r \exp(-\delta_r t) = -\delta_r P_{DD_r}(t)$$

$$P_{ND}(t) = \exp(-\mu_h t) \qquad \Longrightarrow \qquad \frac{dP_{ND}}{dt}(t) = -\mu_h \exp(-\mu_h t) = -\mu_h P_{ND}(t)$$
$$P_{ND_v}(t) = \exp(-\mu_v t) \qquad \Longrightarrow \qquad \frac{dP_{ND_v}}{dt}(t) = -\mu_v \exp(-\mu_v t) = -\mu_v P_{ND_v}(t).$$

We then substitute these survival functions into our Integral Equation in (3.4) - (3.13). For integrals with the Gamma survival functions, we define

$$I_s(t) = \sum_{j=1}^{N_{a_s}} \sum_{k=1}^{N_{\sigma_s}} I_s^{(j,k)} \qquad \text{and} \qquad I_r(t) = \sum_{l=1}^{N_{a_r}} \sum_{m=1}^{N_{\sigma_r}} I_r^{(l,m)}$$

where

$$\begin{aligned} I_s^{(j,k)} = \int_0^t & flux_{I_s}(u) \exp(-N_{\mu_h}\mu_h(t-u)) \exp(-N_{\delta_s}\delta_s(t-u)) \\ & \times \exp(-N_{a_s}a(t-u)) \frac{(N_{a_s}a(t-u))^{j-1}}{(j-1)!} \exp(-N_{\sigma_s}\sigma_s(t-u)) \frac{(N_{\sigma_s}\sigma_s(t-u))^{k-1}}{(k-1)!}\, du \\ I_r^{(l,m)} = \int_0^t & flux_{I_r}(u) \exp(-N_{\mu_h}\mu_h(t-u)) \exp(-N_{\delta_r}\delta_r(t-u)) \\ & \times \exp(-N_{a_r}a(t-u)) \frac{(N_{a_r}a(t-u))^{l-1}}{(l-1)!} \exp(-N_{\sigma_r}\sigma_r(t-u)) \frac{(N_{\sigma_r}\sigma_r(t-u))^{m-1}}{(m-1)!}\, du. \end{aligned}$$

We also define

$$T_s(t) = \sum_{k=1}^{N_{\sigma_s}} T_s^{(k)}(t) \qquad \text{and} \qquad T_r(t) = \sum_{m=1}^{N_{\sigma_r}} T_r^{(m)}(t)$$

where

$$\begin{aligned} T_s^{(k)} &= \int_0^t \left[N_{a_s} a I_s^{(N_{a_s},k)}(u) - \varphi\lambda_r(u) T_s^{(k)}(u) \right] Q_{T_s}(t-u)du \\ T_r^{(m)} &= \int_0^t \left[N_{a_r} a I_r^{(N_{a_s},k)}(u) \right] Q_{T_s}(t-u)du. \end{aligned}$$

Now we substitute the $flux$es and survival function derivatives into our integral equation derivatives from Equations (3.4d) - (3.13d). The Integral Equation system then reduces to

the following system of ODEs:

$$\frac{dI_s^{(j,k)}}{dt} = \begin{cases} \lambda_s S_h - \lambda_r I_s^{(1,1)} - (N_{a_s} a + \mu_h + \delta_s) I_s^{(1,1)}, & j = k = 1 \\ N_{a_s} a I_s^{(j-1,1)} - \lambda_r I_s^{(j,1)} - (N_{a_s} a + \mu_h + \delta_s) I_s^{(j,1)}, & 1 < j \leq N_{a_s},\ k = 1 \\ N_{\sigma_s} \sigma_s I_s^{(1,k-1)} - \lambda_r I_s^{(1,k)} - (N_{\sigma_s} \sigma_s + \mu_h + \delta_s) I_s^{(1,k)}, & j = 1,\ 1 < k \leq N_{\sigma_s} \\ N_{a_s} a I_s^{(j-1,k)} + N_{\sigma_s} \sigma_s I_s^{(j,k-1)} - \lambda_r I_s^{(j,k)} & \\ \qquad -(N_{\sigma_s} \sigma_s + \mu_h + \delta_s) I_s^{(j,k)}, & 1 < j \leq N_{a_s}, 1 < k \leq N_{\sigma_s} \end{cases} \tag{3.4d, IT+IR}$$

$$\frac{dT_s^{(k)}}{dt} = \begin{cases} N_{a_s} a I_s^{(N_{a_s},k)} - \varphi \lambda_r T_s^{(k)} - (\alpha_s + \mu_h + \delta_s) T_s^{(k)}, & 1 \leq k \leq N_{\sigma_s} \end{cases} \tag{3.5d, IT+IR}$$

$$\frac{dR_s}{dt} = \sigma_s I_s + \alpha_s \sum_{k=1}^{N_{\sigma_s}} T_s^{(k)} - \lambda_r R_s - (\omega_s + \mu_h) R_s \tag{3.6d, IT+IR}$$

$$\frac{dI_r^{(l,m)}}{dt} = \begin{cases} \lambda_r \left(S_h + \sum_{j=1}^{N_{a_s}} \sum_{k=1}^{N_{\sigma_s}} I_s^{(j,k)} + \varphi \sum_{k=1}^{N_{\sigma_s}} T_s^{(k)} + R_s \right) & \\ \qquad -(N_{a_r} a + \mu_h + \delta_r) I_r^{(1,1)}, & l = m = 1 \\ N_{a_r} a I_r^{(l-1,1)} - (N_{a_r} a + \mu_h + \delta_r) I_r^{(l,1)}, & 1 < l \leq N_{a_r},\ m = 1 \\ N_{\sigma_r} \sigma_r I_r^{(1,m-1)} - (N_{\sigma_r} \sigma_r + \mu_h + \delta_r) I_r^{(1,m)}, & l = 1,\ 1 < m \leq N_{\sigma_r} \\ N_{a_r} a I_r^{(l-1,m)} + N_{\sigma_r} \sigma_r I_r^{(l,m-1)} & \\ \qquad -(N_{\sigma_r} \sigma_r + \mu_h + \delta_r) I_r^{(l,m)}, & 1 < l \leq N_{a_r}, 1 < m \leq N_{\sigma_r} \end{cases} \tag{3.7d, IT+IR}$$

$$\frac{dT_r^{(m)}}{dt} = \begin{cases} N_{a_r} a I_r^{(N_{a_r},m)} - (\alpha_r + \mu_h + \delta_r) T_r^{(m)}, & 1 \leq l \leq N_{\sigma_r} \end{cases} \tag{3.8d, IT+IR}$$

$$\frac{dR_r}{dt} = \sigma_r I_r + \alpha_r T_r - (\omega_r + \mu_h) R_r \tag{3.9d, IT+IR}$$

$$\frac{dS_h}{dt} = \Lambda_h - [\lambda_s + \lambda_r] S_h + \sigma_s R_s + \sigma_r R_r - \mu_h S_h \tag{3.10d, IT+IR}$$

$$\frac{dM_s}{dt} = \Upsilon_s S_v - \mu_v M_s \tag{3.11d, IT+IR}$$

$$\frac{dM_r}{dt} = \Upsilon_r S_v - \mu_v M_r \tag{3.12d, IT+IR}$$

$$\frac{dS_v}{dt} = \Lambda_v - [\Upsilon_s + \Upsilon_r] S_v - \mu_v S_v \tag{3.13d, IT+IR}$$

Table 3.4: Scenarios for choice of survival function in Integral Equation model. We set the mean for each distribution to remain constant across scenarios. We focus on varying the choice of survival function for infected and treated classes. We use a shape parameter of $N = 3$ when we simulate with a Gamma or Weibull distribution in Section 3.5. We use general shape parameters, N_{σ_s}, N_{σ_r}, N_{a_s}, and N_{a_r} in Section 3.4.2.

Function \ Scenario	EXP	IT3	IR3	IT+IR	TR3	IR3 + TR3	GAMMA3	WEIBULL3
$P_{I_sR_s}(x)$ mean $= 1/\sigma_s$	Exponential	Exponential	Gamma shape $= 3$	Gamma shape $= N_{\sigma_s}$	Exponential	Gamma shape $= 3$	Gamma shape $= 3$	Weibull shape $= 3$
$P_{I_rR_r}(x)$ mean $= 1/\sigma_r$	Exponential	Exponential	Gamma shape $= 3$	Gamma shape $= N_{\sigma_r}$	Exponential	Gamma shape $= 3$	Gamma shape $= 3$	Weibull shape $= 3$
$P_{I_sT_s}(x)$ mean $= 1/a$	Exponential	Gamma shape $= 3$	Exponential	Gamma shape $= N_{a_s}$	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{I_rT_r}(x)$ mean $= 1/a$	Exponential	Gamma shape $= 3$	Exponential	Gamma shape $= N_{a_r}$	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{T_sR_s}(x)$ mean $= 1/\alpha_s$	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Gamma shape $= 3$	Gamma shape $= 3$	Weibull shape $= 3$
$P_{T_rR_r}(x)$ mean $= 1/\alpha_r$	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Gamma shape $= 3$	Gamma shape $= 3$	Weibull shape $= 3$
$P_{R_sS_h}(x)$ mean $= 1/\omega_s$	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{R_rS_h}(x)$ mean $= 1/\omega_r$	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{DD_s}(x)$ mean $= 1/\delta_s$	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{DD_r}(x)$ mean $= 1/\delta_r$	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{ND}(x)$ mean $= 1/\mu_h$	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$
$P_{ND_v}(x)$ mean $= 1/\mu_v$	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Gamma shape $= 3$	Weibull shape $= 3$

Thus, we get an ODE system in Equations (3.4d, IT+IR) - (3.13d, IT+IR). We use $N_{\sigma_s} = 3$, $N_{\sigma_r} = 4$, $N_{a_s} = 3$, and $N_{a_r} = 4$ as an example in the flow diagram for the human population in Figure 3.8, where the rates between compartments are the inverse of the means for the corresponding survival functions. Because mosquito survival functions were all exponential, we get the same diagram for the mosquito population here as in Figure 3.2 from Chapter 2. Recall that the forces of infection, $\lambda_s, \lambda_r, \Upsilon_s$, and Υ_r are still functions of population size as defined in Equations (3.14) - (3.17).

Note the unconventional grid compartments for I_s and I_r that arise from the assumption of two Gamma-distributed waiting times to recovery and treatment in those classes. We also note that although the treatment classes are exponentially distributed for all survival scenarios, they are still broken up as a result of entering T_s or T_r from different stages of natural progression to recovery in the corresponding infection classes. We also note that if we have three Gamma-distributed waiting times in I_s (or I_r), perhaps disease or natural mortality, then this I_s grid would become 3-dimensional in order to account for survival from three different scenarios.

3.5 Model Analysis, Simulations, and Discussion

In this section, we will compute the reproduction and invasion numbers associated with our system, simulate our integral system with a numerical scheme we developed using MATLAB, and discuss effects and results of varying the choice of survival functions for each class.

3.5.1 Reproduction and Invasion Numbers

For calculating the reproduction numbers for each strain, as well as to calculate the invasion numbers for one strain to invade the other, we will use the following notation. The mean residence time, $\mathcal{D}_X$, in class $X \in \{I_s, T_s, R_s, I_r, T_r, R_r, S_h, M_s, M_r, S_v\}$ can be calculated by integrating the survival function for scenario X, $Q_X(t)$, over all time as follows:

$$\mathcal{D}_X = \int_0^\infty Q_X(t)dt. \tag{3.18}$$

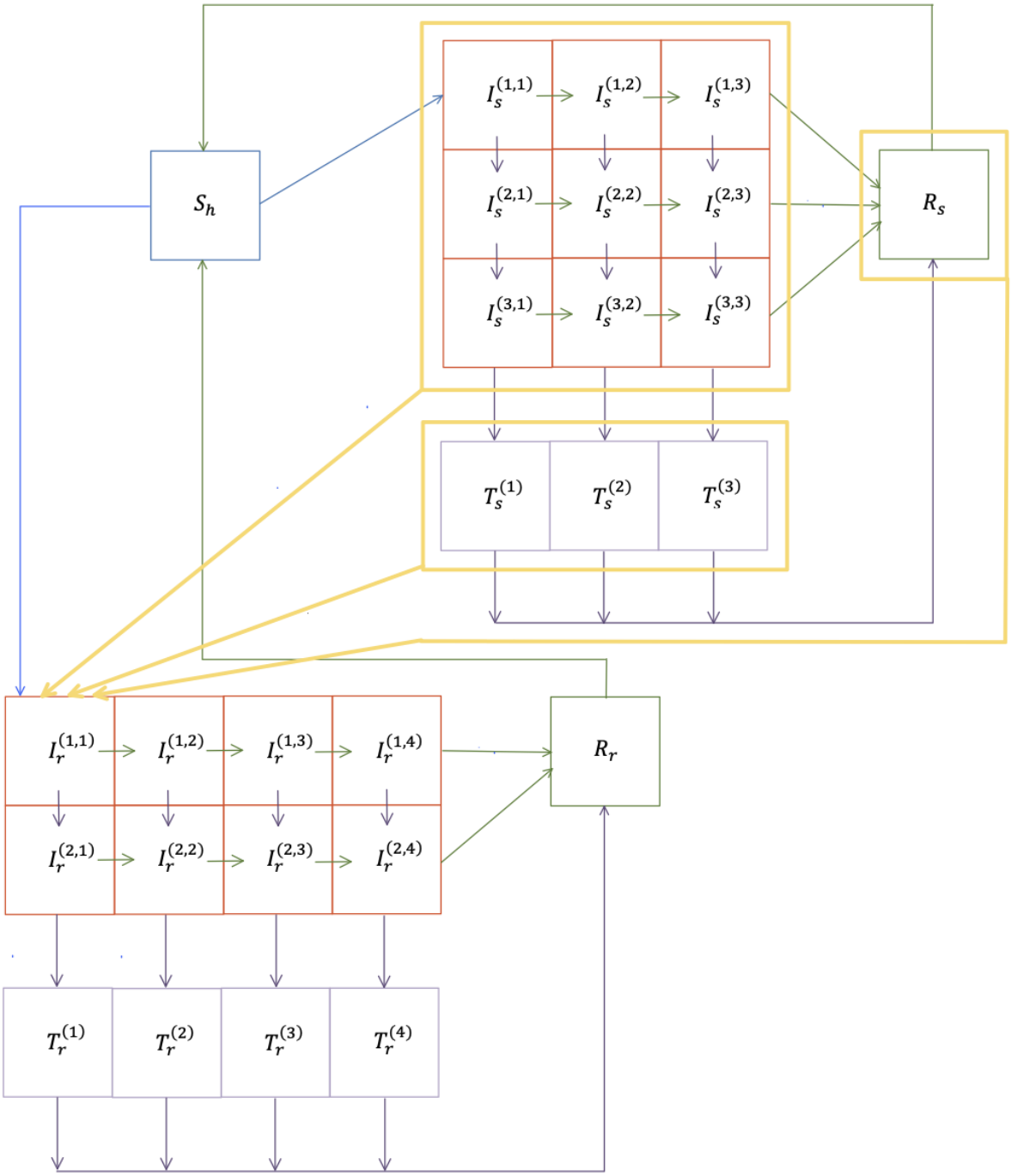


Figure 3.8: Flow diagram for human populations resulting from survival scenario IT+IR in Table 3.4 for the ODE system in Equations (3.4d, IT+IR) - (3.13d, IT+IR). We use $N_{\sigma_s} = 3$, $N_{\sigma_r} = 4$, $N_{a_s} = 3$, and $N_{a_r} = 2$. We omit birth and death rates from the diagram. The rate from $I_s^{(j,k)}$ to $I_s^{(j,k+1)}$ is $N_{\sigma_s}\sigma_s$. The rate from $I_s^{(j,k)}$ to $I_s^{(j+1,k)}$ is $N_{a_s}a$. The rate from $I_r^{(l,m)}$ to $I_r^{(l,m+1)}$ is $N_{\sigma_r}\sigma_r$. The rate from $I_r^{(l,m)}$ to $I_r^{(l+1,m)}$ is $N_{a_r}a$. The compartments surrounded by yellow boxes indicates s-infected/treated/recovered individuals who become infected with the resistant strain and move to I_r.

Probabilities, $\mathcal{T}_Y$, of scenarios $Y \in \{I_sR_s, I_sT_s, T_sR_s, R_sS_h, I_rR_r, I_rT_r, T_rR_r, R_rS_h\}$ in the model can be calculated as follows:

$$\mathcal{T}_Y = \int_0^\infty dQ_Y(t)dt. \tag{3.19}$$

The scenario $Y = KL$ represents adjusted survival probabilities for moving from class K to class L. The reproduction numbers for the two strains can be calculated as follows:

$$\mathscr{R}_s^2 = \beta_v \left(\mathcal{D}_{I_s} + \psi_s \mathcal{T}_{I_sT_s}\mathcal{D}_{T_s}\right) \cdot \beta_h \left(\frac{N_v^*}{N_h^*}\right)(\mathcal{D}_{M_s}) \tag{3.20}$$

$$\mathscr{R}_r^2 = \kappa_v\beta_v \left(\mathcal{D}_{I_r} + \psi_r \mathcal{T}_{I_rT_r}\mathcal{D}_{T_r}\right) \cdot \kappa_h\beta_h \left(\frac{N_v^*}{N_h^*}\right)(\mathcal{D}_{M_r}). \tag{3.21}$$

Where N_h^* and N_v^* represent the total human and vector populations, respectively, at the disease-free equilibrium (DFE). Note that at the DFE we have

$$0 = \frac{dN_h}{dt} \qquad \Longrightarrow \qquad 0 = \Lambda_h - \mu_h N_h^* \qquad \Longrightarrow \qquad N_h^* = \frac{\Lambda_h}{\mu_h}$$

and

$$0 = \frac{dN_v}{dt} \qquad \Longrightarrow \qquad 0 = \Lambda_v - \mu_v N_v^* \qquad \Longrightarrow \qquad N_v^* = \frac{\Lambda_v}{\mu_v}.$$

Hence,

$$\mathscr{R}_s^2 = \beta_v \left(\mathcal{D}_{I_s} + \psi_s \mathcal{T}_{I_sT_s}\mathcal{D}_{T_s}\right) \cdot \beta_h \left(\frac{\Lambda_v\mu_h}{\Lambda_h\mu_v}\right)(\mathcal{D}_{M_s}) \tag{3.22}$$

$$\mathscr{R}_r^2 = \kappa_v\beta_v \left(\mathcal{D}_{I_r} + \psi_r \mathcal{T}_{I_rT_r}\mathcal{D}_{T_r}\right) \cdot \kappa_h\beta_h \left(\frac{\Lambda_v\mu_h}{\Lambda_h\mu_v}\right)(\mathcal{D}_{M_r}). \tag{3.23}$$

We can also compute the invasion number for our model. Because of the structure of our model and the invasion number, we need only replace the DFE with the corresponding SSE and RSE. The invasion number for the sensitive strain invading the resistant strain

Table 3.5: MATLAB files developed to simulate Integral Equation model.

Filename	Description
main.m	Main file to run the algorithm; Defines time-vector and parameter/distribution sets; Calls all required scripts;
load_params_distr_initials.m	Loads parameter set; Defines name for data and figure storage; Defines survival function distributions and shapes; Defines initial conditions;
compute_ODE.m	Stores parameters into object storage; Computes ODE solution with ode45; Uses ShIsIrTsTrRsRrSvMsMr_func.m for ODE; Used to compare solution to Integral Equation model with exponential distributions;
load_survival_func_2strains.m	Creates survival functions using Survival_Func.m; Creates survival function derivatives using Survival_Func_Deriv.m; Evaluates and stores survival functions and derivatives at all timepoints; Multiplies survival function values for a given class; Multiplies survival function products with relevant initial conditions;
initialize_storage.m	Initializes storage for all classes in model; Stores initial conditions into first storage slot; Initializes important quantities (birth rates, forces of infection, transmission terms, other flux terms, integrated flux terms);
calculate_second_timepoint.m	Calculates integrals at second timepoints using left rectangles;
calculate_other_timepoints.m	Calculates integrals at all other timepoints using integral_func.m (combination of trapz and left rectangles); Uses two nested for loops: inner loop computes flux for a given class; outer loop multiplies flux by survival functions and integrates to time t;
compute_R_invasion_nums.m	Computes the reproduction numbers and invasion numbers for each strain

equilibrium (RSE) is calculated as

$$(\mathscr{R}_s^r)^2 = \beta_v \left(\frac{S_v^+}{N_v^+}\right)(\mathcal{D}_{I_s} + \psi_s \mathcal{T}_{I_s T_s} \mathcal{D}_{T_s}) \cdot \beta_h \left(\frac{S_h^+}{N_h^+}\right)\left(\frac{N_v^+}{N_h^+}\right)(\mathcal{D}_{M_s}) \tag{3.24}$$

where S_h^+, S_v^+, and N_v^+ correspond to RSE values. The invasion number for the resistant strain invading the sensitive strain equilibrium (SSE) is calculated as

$$\begin{aligned}(\mathscr{R}_r^s)^2 = \kappa_v \beta_v \left(\frac{S_v^{++}}{N_v^{++}}\right)(\mathcal{D}_{I_r} + \psi_r \mathcal{T}_{I_r T_r} \mathcal{D}_{T_r}) \\ \times \kappa_h \beta_h \left(\frac{S_h^{++} + I_s^{++} + \varphi T_s^{++} + R_s^{++}}{N_h^{++}}\right)\left(\frac{N_v^{++}}{N_h^{++}}\right)(\mathcal{D}_{M_r})\,.\end{aligned} \tag{3.25}$$

where $S_h^{++}, I_s^{++} S_v^{++}, T_s^{++}, R_s^{++}, N_v^{++}$, and N_v^{++} correspond to SSE values.

3.5.2 Numerical Methods

We utilize MATLAB to simulate this model. Because of the complexity of the system of integral equations, we had to develop a new numerical scheme using MATLAB's trapz as the numerical integrator. Since the integral equations are interdependent, we employ trapz at each timestep in order to calculate the next timestep up to the current time t. For example, the solution for I_s at time t depends on the values of I_s at all timepoints before t. The MATLAB code developed in order to simulate our integral equation model can be found in the GitHub repository listed in Appendix B. The code includes several scripts and functions in order to simulate and plot our model solutions. Below is a list of files used in running the numerical algorithm and model simulation. Table 3.5 provides a description of what each file does. Notice the numerical algorithm is implemented in scripts 5 and 6, while the other scripts are for set-up and initializing storage:

- `main.m`

  Calls the following scripts in this order:

  1. `load_params_distr_initials.m`
  2. `compute_ODE.m`

3. `load_survival_func_2strains.m`
4. `initialize_storage.m`
5. `calculate_second_timepoint.m`
6. `calculate_other_timepoints.m`
7. `compute_R_invasion_nums.m`

These scripts call the functions:

(a) `ShIsIrTsTrRsRrSvMsMr_func.m`

(b) `Survival_Func.m`

(c) `Survival_Func_Deriv.m`

(d) `integral_func.m`

In the next section, we implement this code to simulate and plot our Integral Equation model.

3.5.3 Simulations and Discussion

First, we tested the accuracy of our method by simulating the integral equation model with all exponential survival functions via our numerical scheme and comparing with the numerical solution for the corresponding ODE system using MATLAB's ode45 solver.

In Figure 3.9, we simulate our system of integral equations using a parameter set that leads to the disease dying out and the populations settling into a disease-free equilibrium (DFE) with all survival probabilities set to an exponential distribution. See Table 2 for parameter values used. Note that the recovery rate is slow, but the infected, treated, and recovered populations in this simulation do eventually go to zero as everyone returns to a state of susceptibility. In row 1, we simulate our integrals using our MATLAB code. In row 2, we utilize MATLAB's ode45 solver to simulate the corresponding ODEs. Lastly, row 3 plots the percent difference between the first two rows in order to compare accuracy for the integrals in row 1. Notice that the differences are small, and hence lead us to conclude that our integral code runs with relatively high accuracy for tracking the population sizes over a

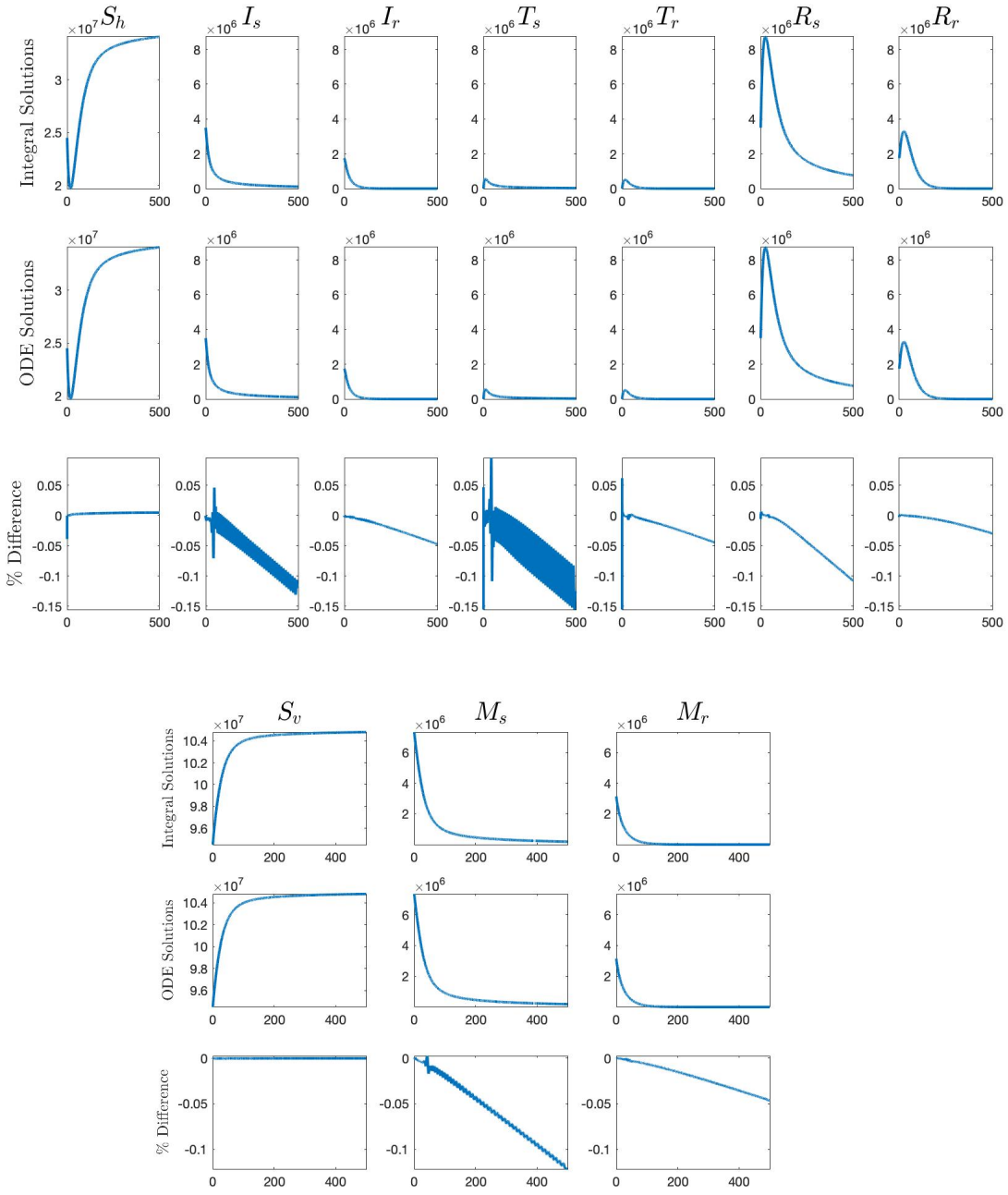


Figure 3.9: Simulations of Integral Equations (row 1) compared to ODEs (row 2) reaching the disease-free equilibrium (DFE) with exponential distributions for all survival scenarios. We compare the percent difference between corresponding integrals and ODEs in row 3.

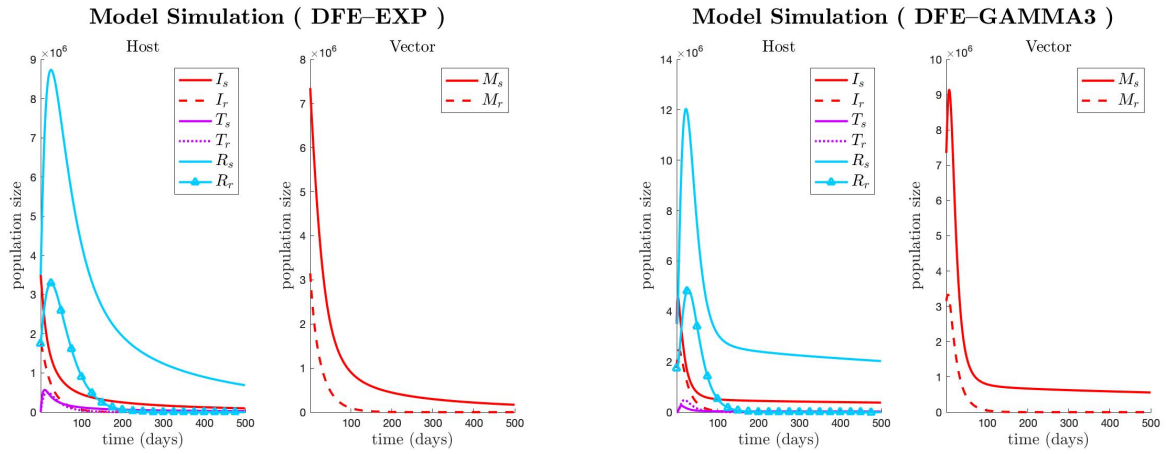


Figure 3.10: Simulations of Integral Equations reaching the DFE with exponential distributions for all survival scenarios (*left*) and with the GAMMA3 survival scenario set (*right*). We note that the EXP set runs to zero eventually whereas teh GAMMA3 case settles to a positive endemic SSE. We see that the change in survival function alone caused our system to shift from the DFE to a long-term low-disease state where the sensitive strain eventually out-competes the resistant strain in the GAMMA3. Note that $\mathscr{R}_s < 1$ and $\mathscr{R}_r < 1$ in the EXP case for this parameter set while $\mathscr{R}_s > 1$ and $\mathscr{R}_r < 1$ in the GAMMA3 case for this parameter set. We omit the S_h and S_v classes.

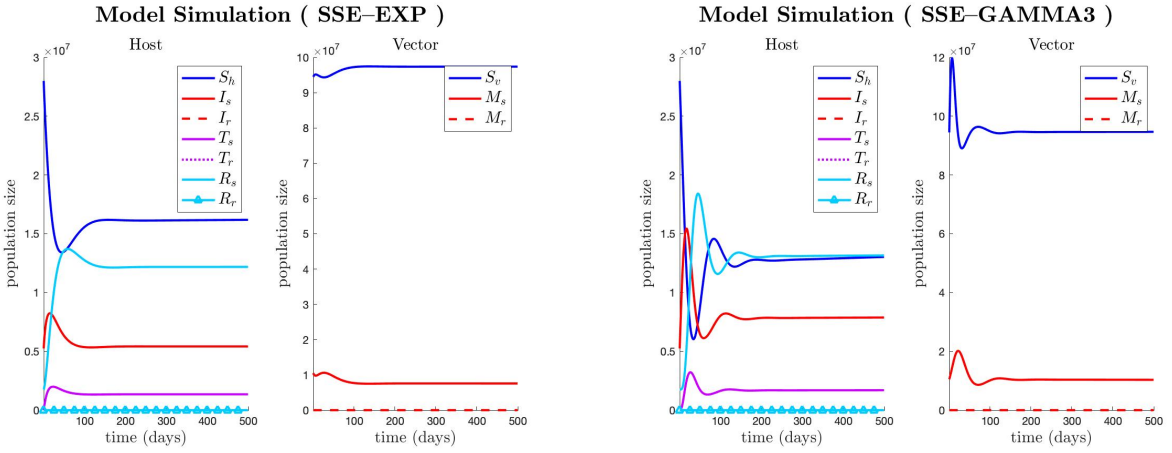


Figure 3.11: Simulations of Integral Equations reaching the SSE (with the resistant strain turned off) with exponential distributions for all survival scenarios (*left*) and with the GAMMA3 survival scenario set (*right*). We see that a change of survival function causes our system to settle with a higher number of infectious individuals in the GAMMA3 case compared to the EXP case. Note that $\mathscr{R}_s > 1$ in both cases for this parameter set.

period of 500 days. We also tested our numerical scheme with smaller population sizes and found the difference to decrease to the order of 1×10^{-3}. We now vary the choice of survival functions for the same baseline parameter set to compare differences in disease persistence.

Now that we have established the reliability of our MATLAB code for simulating the integral equation model, we investigate the disease equilibrium. First, we make slight parameter changes (see Table 2 in Appendix A) to achieve a sensitive-strain only equilibrium (SSE) with exponential distributions as seen in Figure 3.11 (*left).* We then increase κ_h (see Table 2 in Appendix A) to achieve a resistant-strain only equilibrium (RSE) with exponential distributions as seen in Figure 3.12 (*right).* Notice that the resistant strain simulation settles to a lower equilibrium than the sensitive strain due to the fitness parameter κ_h that incorporates a biological trade-off for drug-resistance.

Now we consider three parameter sets: DFE, SSE, RSE. The DFE is the parameter set that results in a disease-free state in the EXP case with both strains initially present. The SSE is the parameter set that results in a sensitive-strain-only state in the EXP case with only the sensitive strain initially present. Lastly, the RSE is the parameter set that results in a resistant-strain-only state in the EXP case with only the resistant strain initially present. We consider several sets of survival functions, which can be found in Table 3.4. Assume that every survival scenario for each class is Gamma-distributed with a shape parameter of $N = 3$ while the mean remains the same as in the case with exponentially-distributed survival scenarios (scenario GAMMA3 in Table 3.4).

We see that in Figure 3.10 (*right*), the populations approach a (small) sensitive strain equilibrium (SSE) with no other changes in the baseline parameter set instead of the DFE as in Figure 3.10 (*left*). That is, when we change the implied shape of our data, the disease outcome has changed from a disease-free equilibrium to a sensitive-strain equilibrium. Hence using the correct shape of our data will drastically affect our model results. Note that in Figure 3.15, $\mathscr{R}_s < 1$ and $\mathscr{R}_s < 1$ for the EXP case, as expected with the DFE. However, $\mathscr{R}_s > 1$ with $\mathscr{R}_r < 1$ in the GAMMA3 case and thus we approach a SSE. We also note that in the WEIBULL3 case, $\mathscr{R}_s$ and $\mathscr{R}_r$ is smaller than in the EXP case. Hence, we should remain at the DFE in that case.

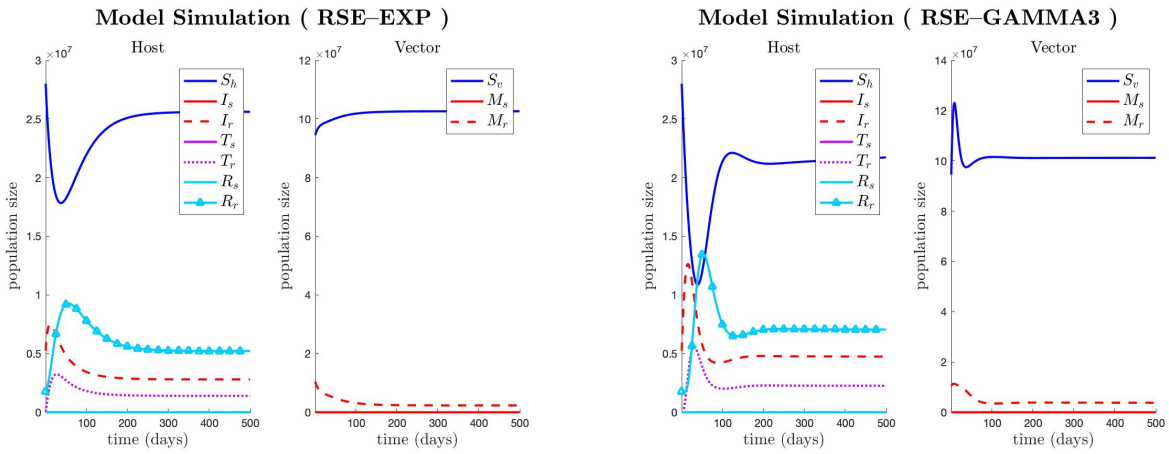


Figure 3.12: Simulations of Integral Equations reaching the RSE (with the sensitive strain turned off) with exponential distributions for all survival scenarios (*left*) and with the GAMMA3 survival scenario set (*right*). We see that a change of survival function causes our system to settle with a higher number of infectious individuals in the GAMMA3 case compared to the EXP case. Note that $\mathscr{R}_r > 1$ in both cases for this parameter set.

In Figure 3.11 (*right*), the populations approach a sensitive strain equilibrium (SSE) with no other changes in the baseline parameter set. Notice that the GAMMA3 survival set causes an increase in the I_s population compared to Figure 3.11 (*left*). That is, when we change the implied shape of our data, the disease outcome has increased the number of total s-infections at the SSE.

Similarly, in Figure 3.12 (*right*), the populations approach a resistant strain equilibrium (RSE) with no other changes in the baseline parameter set. Notice that the GAMMA3 survival set causes an increase in the I_r and T_r populations compared to Figure 3.12 (*left*). That is, when we change the implied shape of our data, the disease outcome has increased the number of total r-infections at the RSE.

Now we use the RSE parameter set and turn on s-infections in Figure 3.13, which we label as the RSE_S simulation. We see that in both survival function cases, the sensitive strain invades the RSE, where the populations in infectious compartments are higher in the GAMMA3 case. Note that in Figure 3.16, $\mathscr{R}_s^r > 1$ for both the EXP case and GAMMA3 case (as well as all other cases). Hence we have an unstable RSE. We also note that the WEIBULL3 case has the highest $\mathscr{R}_s^r$ value in this scenario. We note that in this scenario $\mathscr{R}_r^s > 1$ and $\mathscr{R}_r > 1$. Hence, we reach coexistence in this case.

Lastly, we use the SSE parameter set and turn on r-infections in Figures 3.14, which we label as the SSE_R simulation. We see that in both survival function cases, the resistant strain is unable to invade the SSE, and the populations settle to the original SSE as seen in Figure 3.11, though it takes longer to reach equilibrium after the resistant strain dies off. Note that in Figure 3.16, $\mathscr{R}_r^s < 1$ for both the EXP case and GAMMA3 case (as well as all other cases). Hence we do not have a stable coexistence equilibrium. We also note that the WEIBULL3 case again has the lowest $\mathscr{R}_r^s$ value in this scenario. Overall, the low $\mathscr{R}_r^s$ values for all scenarios is most likely related to the fact that the resistant strain has the fitness parameters κ_h and κ_v that scale the transmission rate for r-infection and hence it is harder for the resistant strain to persist in the presence of other strains.

Overall, we see that the choice of survival function in our model can impact the results of our dynamical system in terms of disease persistence. The Gamma distributions seem to lengthen the time an individual can spend in an infectious class so that the reproduction

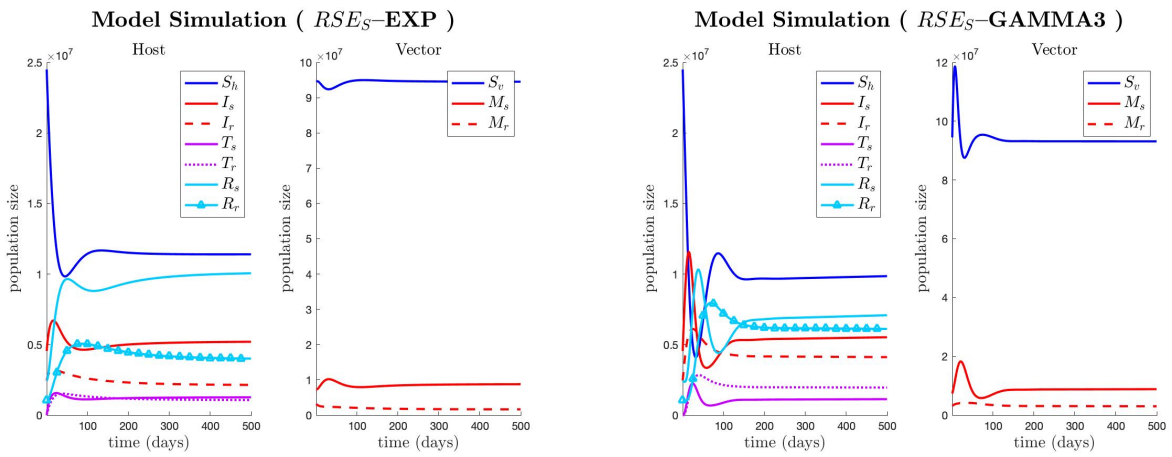


Figure 3.13: Simulations of Integral Equations using the RSE parameter set with all exponential distributions (*left*) and with GAMMA3 distributions (*right*) after turning on s-infections. Note that the sensitive strain was able to invade the RSE in the EXP case, corresponding with $\mathscr{R}_s^r > 1$ for the EXP case in Figure 3.16. Also, the sensitive strain was able to invade the RSE in the GAMMA3 case, corresponding with $\mathscr{R}_s^r > 1$ for the GAMMA3 case in Figure 3.16. In both cases, using the RSE parameter set, we can calculate $\mathscr{R}_r > 1$, $\mathscr{R}_s^r > 1$, $\mathscr{R}_s > 1$, and $\mathscr{R}_r^s > 1$ so that we have coexistence.

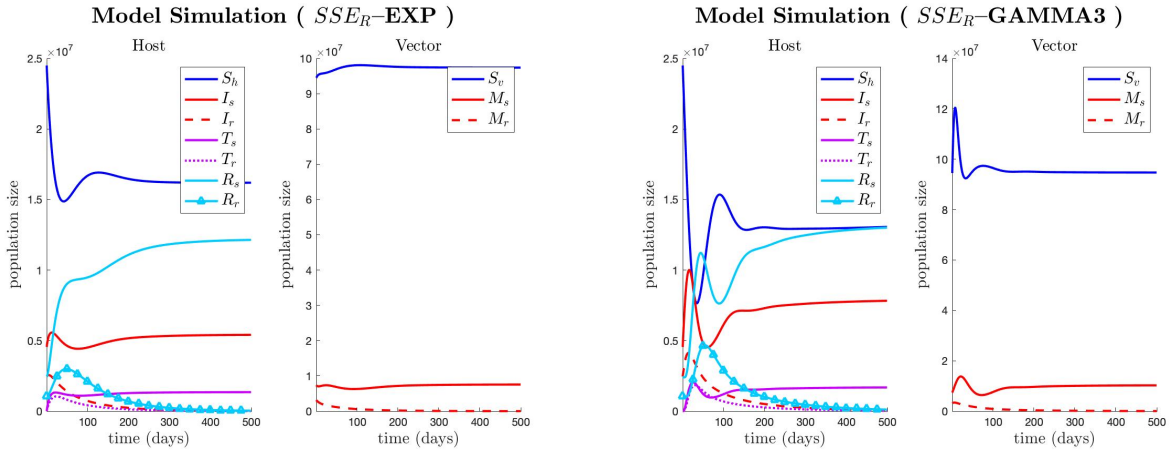


Figure 3.14: Simulations of Integral Equations using the SSE parameter set with all exponential distributions (*left*) and with GAMMA3 distributions (*right*) after turning on r-infections. Note that the resistant strain was unable to invade the SSE in the EXP case, corresponding to $\mathscr{R}_r^s < 1$ for the EXP case in Figure 3.16. Similarly, resistant strain was unable to invade the SSE in the GAMMA3 case, corresponding to $\mathscr{R}_r^s < 1$ for the GAMMA3 case in Figure 3.16. In both cases, using the SSE parameter set, we can calculate $\mathscr{R}_r < 1$, $\mathscr{R}_s > 1$, $\mathscr{R}_s^r > 1$, and $\mathscr{R}_r^s < 1$.

numbers rise above 1. Other distributions (like Weibull) seems to lower the amount of time an individual is infectious and hence contributes to less infections overall so that the reproduction number lowers below 1. Note that the TR3 case results in similar reproduction and invasion numbers as the EXP case and the IR3 + TR3 case results in similar reproduction numbers to the IR3 cases. This indicates that the change in treatment to recovery survival shape does not have much impact on the disease outcomes.

3.6 Conclusion

In summary, we use survival functions in order to generalize waiting time distributions for each population class in our $SITRS$-SI model framework. This allows us to adjust our waiting times based on data related to a wide range of scenarios including natural and disease mortality, symptom onset, treatment progression, and recovery rates. Depending on the survival functions that best fit data, our integrals may not reduce to a system of ODEs as in the case of exponential and gamma-distributed survival functions. Hence this derivation allows us to model systems that may not be accurately represented by ordinary differential equations.

We develop a novel numerical algorithm in order to simulate our Integral Equation model. This method allows users to choose the distributions that best fit their data and is adaptable to a variety of biological systems. The interdependence of our integral equations created a challenge in simulating them, hence the need for a new algorithm. With this algorithm, we can now simulate these integral equations that incorporate general survival probabilities for waiting times in each class of the system.

This general framework is important because changing the shape of our survival functions can significantly change the outcome of disease persistence as seen in our numerically computed reproduction numbers, even when the mean of the corresponding probability density function is the same. In particular, model-informed control policies could be misleading if the appropriate distributions are not considered for each class. In order to accurately inform public health policy, we can use data for distributions of quantities like the infectious period, time to symptom onset, human lifespan, etc. These distributions can be

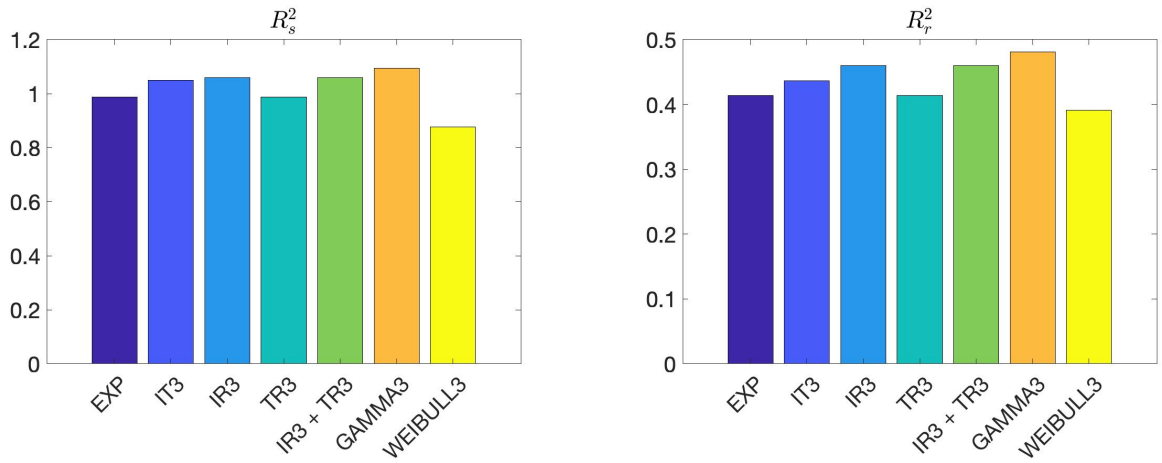


Figure 3.15: Reproductions numbers for the sensitive strain invading the DFE (*left*) and the resistant strain invading the DFE (*right*) for survival function groupings: EXP, IT3, IR3, TR3, IR3+TR3, GAMMA3, WEIBULL3 from Table 3.4.

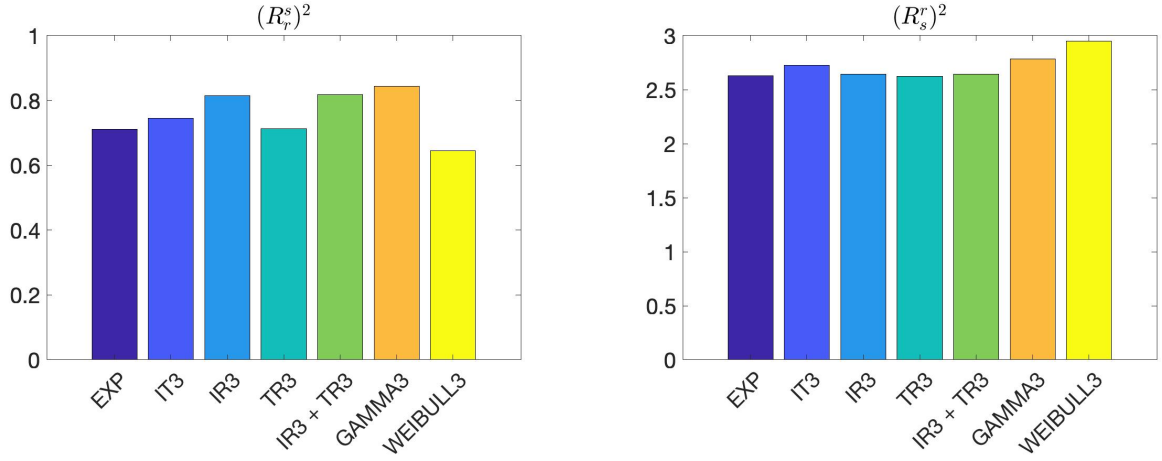


Figure 3.16: Invasion numbers for the sensitive strain invading the RSE (*left*, $\mathscr{R}_r > 1$) and the resistant strain invading the SSE (*right*, $\mathscr{R}_s > 1$) for survival function groupings: EXP, IT3, IR3, TR3, IR3+TR3, GAMMA3, WEIBULL3 from Table 3.4.

fitted by an appropriate survival function, whose parameters can then be readily implemented into our numerical algorithm for simulation. These simulations allow health experts to make well-informed pubic health policies. In terms of malaria, we can now better understand the progression of the disease and the effects of treatment dynamics on a population so as to combat the emergence of drug-resistant malaria.

Chapter 4

Conclusion

4.1 Summary

We began our work in Chapter 2 by attempting to incorporate parameters that could link pharmacodynamics and pharmacokinetics (PKPD) into a 2-strain $SITRS$-SI ODE mosquito-borne disease model with a sensitive strains (s-) and resistant strain (r-). We were motivated by malaria, which has seen the emergence of parasite drug-resistance. In order to study the effects of treatment and drug-resistance on a population, we incorporate parameters φ, which scales r-infected mosquito to s-treated human transmission based on drug concentration in the human bloodstream, along with Ψ_s and Ψ_r, which scales the s- and r-infectious human-to-mosquito transmission, respectively. Our analysis of reproduction numbers, invasion numbers, and equilibria indicated that the PKPD parameters Ψ_s and Ψ_r could be the subject of control measures that focus on drug-treatments that quickly reduce parasite load so as to decrease total population infections, specifically r-infections.

The model we developed in Chapter 2 had treatment populations broken up into n classes. We considered breaking up these treatment classes using parasite density or drug-concentration data, but the structure we should use was not immediately clear to us. Hence, we considered using general distributions for survival scenarios in each class and developed an $SITRS$-SI Integral Equation model in Chapter 3. We considered different survival scenarios in each class and realized that the choice of survival function could influence the disease outcome of our model. That is, some choices of survival functions lead to elimination

of both sensitive and resistant strains, while others, with the same parameter set and means, cause a shift to an endemic equilibrium.

4.2 Next Steps

We incorporated our PKPD parameters φ, Ψ_s, and Ψ_r as constants in our Integral Equation model. However, we would like to make the parameters dependent on time since treatment onset (i.e. treatment age). In other words we wish to make φ, Ψ_s, and Ψ_r functions of time-since-treatment onset that are fitted to PKPD data. The work in Chapter 3 establishes the framework within which we can embed these PKPD parameters that are treatment-age dependent.

We consider the following $T_s(t)$ equation (omitting initial conditions) that is e a candidate for the integral form we would need in order to incorporate the time-since-treatment dependent parameter φ, depends on drug concentration in the s-treated human:

$$T_s(t) = \int_0^t \left(\int_0^\tau flux_{I_s}(u) dQ_{I_s T_s}(\tau - u) du \right.$$
$$\left. - \int_0^\tau \varphi(\tau - \tau_0) \lambda_r(\tau) T_s(\tau) \left(-dQ_{T_s}(\tau - \tau_0)\right) d\tau_0 \right) Q_{T_s}(t - \tau) d\tau \tag{4.1}$$

where the term

$$\int_0^\tau \varphi(\tau - \tau_0) \lambda_r(\tau) T_s(\tau) \left(-dQ_{T_s}(\tau - \tau_0)\right) d\tau_0$$

records individuals who are r-infected at time τ with transmission scaled by

$$\int_0^\tau \varphi(\tau - \tau_0) \left(-dQ_{T_s}(\tau - \tau_0)\right) d\tau_0,$$

where $\tau - \tau_0$ is the time since entering the treated class at infection time τ. These individuals then leave and move to I_r. However, more work must be done in order to verify this is the correct incorporation of φ.

We consider the following $M_s(t)$ equation (omitting initial conditions) that is a candidate for the integral form we would need in order to incorporate the time-since-treatment

dependent parameter Ψ_s, which depends on parasite density in the bitten, infected human:

$$M_s(t) = \int_0^t \beta_v \left(\frac{I_s(u)}{N_h(u)} + \int_0^u \Psi_s(u-\tau_0) \left(-dQ_{T_s}(u-\tau_0)\right) \frac{T_s(u)}{N_h(u)} S_v(u) d\tau_0 \right) Q_{M_s}(t-u) du \tag{4.2}$$

where the term

$$\int_0^u \Psi_s(u-\tau_0) \left(-dQ_{T_s}(u-\tau_0)\right) \frac{T_s(u)}{N_h(u)} S_v(u) d\tau_0$$

records mosquitoes who are s-infected at time u with transmission scaled by

$$\int_0^u \Psi_s(u-\tau_0) \left(-dQ_{T_s}(u-\tau_0)\right) d\tau_0$$

where $u-\tau_0$ is the time since a human entered the s-treated class at infection time u. Again, more work must be done in order to verify this is the correct incorporation of Ψ_s. We would incorporate Ψ_r into the M_r equation in a similar manner.

We would also like to investigate and determine the assumptions that are required in the structure of φ, Ψ_s, and Ψ_r for the integral equations with Gamma-distributions to reduce to ODEs.

By incorporating a time-dependent φ and Ψ, we could more accurately link the within-host and between host dynamics of disease. We note that this system could be applied to other biological systems. Hence, we have created a general model that can be applied to a variety of contexts.

We would also like to do more work in optimizing our numerical algorithm in MATLAB for solving this system of Integral Equations. By doing so, we would be able to run a sensitivity analysis on our model and determine parameters of interest for controlling disease persistence.

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Appendices

A Parameters

A.1 Modeling Malaria with Treatment Using Ordinary Differential Equations (Parameters)

Table 1: Parameter values for ODE model in Chapter 2. Units for time-related parameters are in days.

Parameter	Baseline	Lower Bound	Upper Bound	Reference
Λ_h	3.55×10^3	2.24×10^3	5.08×10^3	Chitnis [33]
Λ_v	$3 \times \mu_v(\Lambda_h/\mu_h)$	$1 \times \mu_v(\Lambda_h/\mu_h)$	$10 \times \mu_v(\Lambda_h/\mu_h)$	Chitnis [33]
μ_h	4.43×10^{-5}	4.25×10^{-5}	4.791×10^{-5}	Manore [12]
μ_v	$1/14$	$1/21$	$1/7$	Manore [12]
δ_s	$0.4/(1000 \times 365)$	$0.3/(1000 \times 365)$	$0.6/(1000 \times 365)$	Desai [34]
δ_r	$0.4/(1000 \times 365)$	$0.3/(1000 \times 365)$	$0.6/(1000 \times 365)$	Desai [34]
β_h	0.5561	0.18	0.9	Chitnis [33]
β_v	0.0927	0.03	0.2	Chitnis [33]
κ_h	0.6	0.001	0.999	Assumed
κ_v	0.6	0.001	0.999	Assumed
a	$1/5$	$1/10$	$1/3$	Assumed
α_k	$1/(52/n)$	$1/(100/n)$	$1/(1/n)$	Assumed
ω_s	$1/370$	$1/400$	$1/10$	O'Meara [11]
ω_r	$1/370$	$1/400$	$1/10$	O'Meara [11]
σ_s	$1/33$	$1/365$	$1/28$	Filipe [35]
σ_r	$1/33$	$1/365$	$1/28$	Filipe [35]
φ_k	$0.000001 + k/(n+1)$	$0.000001 + k/n$	$0.000001 + (k+1)/n$	Assumed
$\Psi_{s,k}$	$1 - k/(n+1)$	$1 - k/n$	$1 - (k+1)/n$	Assumed
$\Psi_{r,k}$	$1 - k/(n+1)$	$1 - k/n$	$1 - (k+1)/n$	Assumed

A.2 Modeling Malaria with Treatment Using Integral Equations (Parameters)

Table 2: Parameter values for Integral Equation model in Chapter 3. Units for time-related parameters are in days.

Parameter	Symbol	Value		Reference
$P_{I_sR_s}(x)$ mean	$1/\sigma_s$	$1/(6 \times (1/33))$	(DFE)	Filipe [35] (base)
		$1/(1 \times (1/33))$	(SSE)	Filipe [35] (base)
		$1/(1 \times (1/33))$	(RSE)	Filipe [35] (base)
$P_{I_rR_r}(x)$ mean	$1/\sigma_r$	$1/(6 \times (1/60))$	(DFE)	Filipe [35] (base)
		$1/(1 \times (1/60))$	(SSE)	Filipe [35] (base)
		$1/(1 \times (1/60))$	(RSE)	Filipe [35] (base)
$P_{I_sT_s}(x)$ mean	$1/a$	$1/0.05$		Assumed
$P_{I_rT_r}(x)$ mean	$1/a$	$1/0.05$		Assumed
$P_{T_sR_s}(x)$ mean	$1/\alpha_s$	$1/(1/5)$		Assumed
$P_{T_rR_r}(x)$ mean	$1/\alpha_r$	$1/(1/5)$		Assumed
$P_{R_sS_h}(x)$ mean	$1/\omega_s$	$1/(1/28)$		O'Meara [11]
$P_{R_rS_h}(x)$ mean	$1/\omega_r$	$1/(1/28)$		O'Meara [11]
$P_{DD_s}(x)$ mean	$1/\delta_s$	$1/(0.4/(1000 \times 365))$		Desai [34]
$P_{DD_r}(x)$ mean	$1/\delta_r$	$1/(0.8/(1000 \times 365))$		Desai [34]
$P_{ND}(x)$ mean	$1/\mu_h$	$1/(4.43 \times 10^{-5}))$		Manore [12]
$P_{ND_v}(x)$ mean	$1/\mu_v$	$1/(1/14))$		Manore [12]
human to mosquito transmission	β_h	$1.1 \times (0.1251)$	(DFE)	Chitnis [33] (base)
		$1 \times (0.1251)$	(SSE)	Chitnis [33] (base)
		$1.25 \times (0.1251)$	(RSE)	Chitnis [33] (base)
mosquito to human transmission	β_v	$1.1 \times (0.0313)$	(DFE)	Chitnis [33] (base)
		$1 \times (0.0313)$	(SSE)	Chitnis [33] (base)
		$1.25 \times (0.0313)$	(RSE)	Chitnis [33] (base)
r-infection scale (r-infected human to mosquito)	κ_h	0.6	(DFE)	Assumed
		0.6	(SSE)	Assumed
		0.7	(RSE)	Assumed
r-infection scale (r-infected mosquito to human)	κ_v	0.4		Assumed
s-infection scale (s-treated human to mosquito)	Ψ_s	0.6		Assumed
r-infection scale (r-treated human to mosquito)	Ψ_r	0.6		Assumed
r-infection scale (r-infected mosquito to s-treated human)	φ	1		Assumed
human birth rate	Λ_h	$\mu_h \times N_h^0$		Chitnis [33]
mosquito birth rate	Λ_v	$\mu_v \times N_v^0$		Chitnis [33]

B GitHub

Visit https://github.com/mgrogan1/grogan-dissertation.git for code developed to analyze and simulate models in Chapters 2 and 3.

Vita

Margaret Ann Grogan was born in Madison, Wisconsin. At the age of 2, her family moved to LaGrange, Kentucky where she grew up loving school and competing in many sports including Cross Country, Track and Field, and Swimming. Margaret attended Samford University on academic and NCAA Division I athletic scholarships where she received a B.S. in Mathematics along with a minor in Sports and Recreation Ministry in the Spring of 2016. She began graduate school at the University of Kentucky with the intent of working towards a PhD in Mathematics. Margaret received her M.A. in Mathematics in the Fall of 2018 and then transferred to the University of Tennessee at the beginning of the Fall of 2019 to finish her dissertation with her research advisor, Olivia Prosper. Throughout her graduate schooling, Margaret worked as a Graduate Teaching Assistant and taught a variety of classes while working on research in Mathematical Biology.