

FINAL REPORT

The Role of Phenology and Phenology Change in the Transmission of Arthropod-Borne Diseases: Implications for Management on Military Lands

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14. ABSTRACT Exposure to biting ticks and insects on DoD lands puts military personnel at risk of contracting arthropod-borne diseases, many of which can have debilitating complications. However, because most North American vector-borne diseases are maintained in wildlife reservoirs, disease transmission is often sensitive to environmental conditions, including seasonality and global change. In addition, there is a lack of models that account for the detailed mechanisms and differences among potential control methods. This makes it difficult to predict when and where human disease will appear, and how it should be managed when it does.						
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Abstract

Objectives - Exposure to biting ticks and insects on DoD lands puts military personnel at risk of contracting arthropod-borne diseases, many of which can have debilitating complications. However, because most North American vector-borne diseases are maintained in wildlife reservoirs, disease transmission is often sensitive to environmental conditions, including seasonality and global change. In addition, there is a lack of models that account for the detailed mechanisms and differences among potential control methods. This makes it difficult to predict when and where human disease will appear, and how it should be managed when it does. Climate warming, in particular, can complicate predictive efforts, because it compromises our ability to extrapolate from current conditions or ‘rules-of-thumb’ that have been acquired over years of experience. One of the most important aspects in this regard is phenology change – i.e., the change in the timing of plant and animal lifecycles. Shifting phenologies are not only one of the earliest indicators of climate change. This can then affect disease transmission, fundamentally altering disease dynamics, and impacting everything from disease risk to management options.

Technical Approach - To aid in prediction of human disease risk, and to develop on-the-ground management strategies for reducing disease spread, we *developed modeling frameworks that incorporate phenology and global change impacts on phenology as well as novel model formulations that account for the specifics of different insecticide management strategies*. Our frameworks are broad enough to accommodate a range of different vectors (mosquitos, ticks) and pathogens (virus, bacteria) and are general enough to apply to both well studied diseases, and diseases that have not been as well characterized. For this reason, we focused heavily on the mosquito side of control, where a handful of mosquitoes are responsible for the majority of disease spread, including both common and rare diseases. Using our novel models, we additionally developed a GUI that allows practitioners to input timeseries data on mosquito abundances (e.g. from CDC light traps) and then outputs optimal timing of management strategies. The underlying optimization scheme that we developed for this GUI is broad and flexible, thus management decisions can be made based on the combination of historically observed phenology, cost constraints, and efficacy of the chosen management strategy. In addition, the GUI can be re-run at any point in the season, allowing land managers to update their predictions partway through the year, allowing for incorporation of current year conditions.

Results - Using a range of different modeling approaches, we developed a number of improved models of vector-borne disease management. These models include pertinent mechanisms that differentiate the mode of action of different management strategies, thereby improving all models of vector-borne diseases. We also clearly delineated the difference between approximate, implicit modeling of control, and accurate, mechanistically corrected explicit modeling of control, highlighting when and where the former can be used in place of the latter. Next, we developed models for two diseases – La Crosse Encephalitis and Zika – that have been detected in North America. For the La Crosse Encephalitis model, we began extending results to include phenology, which suggests that some of the observed increase in LAC may be a result of warming conditions. In addition, these results provide a stark warning for the future. Finally, we examined some general models of vector-borne disease systems, including vector and host populations, in the context of

changing phenology due to global change. These models suggest that R_0 will depend on the various perturbations to different vector and host populations, and that effects on dynamics may be complex and non-intuitive, including the appearance of year-to-year cycles and chaos in vector-borne disease outbreaks. Finally, we extended our phenologically explicit modeling to consider specific vectors involved in the most notorious North American vector-borne diseases, including La Crosse, West Nile Virus, and Eastern Equine Encephalitis. We are currently using these models, interfaced to a genetic algorithm, to best predict the timing of management strategies, both under current conditions and in the future. Finally, we capped our work off by developing a GUI that puts our complex mathematical formulations under the cap, allowing management practitioners to input their data on mosquito abundances, as well as their economic and social constraints in order to identify optimal timing of larvicide and adulticide treatments based on their requirements and desires.

Benefits - Predictions from our modeling efforts identify some of the key management mechanisms influencing disease transmission, as well as the relevant ecological processes associated with disease spread. This information allows us to identify the system properties that should be monitored to best predict disease, both now and in the future. Another key contribution from our research is the first ODE epidemiology model for La Crosse Virus. This is an emerging disease that is now one of the most commonly reported arbovirus infections. Finally, application of optimal control to our phenologically explicit models and, in particular, our highly parameterized vector models for *Aedes*, *Culex* and *Culiseta* enables us to predict management strategies that successfully balance the competing needs of vector-borne disease management on military installations. Ultimately we have transitioned our modeling approaches to a GUI interface that can be used by practitioners based on their own data and systems.

Objectives

Although we began this research with the single objective of developing a series of models exploring the role of phenology on vector-borne diseases, in the course of studying these models, we realized that the manner in which control strategies were incorporated had a significant impact on model predictions. For this reason, we arrived at a second objective, which was to better define the modeling of management schemes. This became a pre-goal to our phenology work. Thus, our first objective was to improve model formulation of a variety of different control options available to practitioners. This included models:

1. studying the role of personal protection and waning accessibility;
2. contrasting area-wide ultra low volume (ULV) adulticide sprays, residual adulticide barrier sprays, larval source reduction, and area-wide low volume (LV) larvicide spray
3. selecting optimal combinations of barrier-spraying/larval source reduction and aerial spraying when habitat includes hard to access regions.

For our second objective, specifically focused on disease spread, we had initially planned to target a series of native North American diseases. However, after receiving funding, Zika was introduced into the US. Thus, we spent some time exploring this new disease and its implications for disease transmission in the US. For this reason, we ended up spending less time on some of the anticipated specific native diseases. To counter this we covered a range of broader models that can be applied to specific diseases within the context of phenology and global change, leaving some detailed applications for a future date. In summary, then, our objectives were as follows:

1. understand the spread and dynamics of Zika;
2. explore the role of phenology and phenology change on disease dynamics and the ability of disease to spread (R_0);
3. develop specific predictions for the potential of future disease spread based on detailed physiological or population level data of individual mosquito and host species
4. create a GUI that enables improved practitioner decisions regarding the timing of management actions, including under both current and future conditions.

BACKGROUND

Military personnel, who spend large amounts of time working and training outdoors, routinely risk exposure to biting ticks and insects. Such species are host to a great diversity of arthropod-borne diseases, many of which can have debilitating, long-term, and even life threatening impacts on infected personnel. Consequently, the presence of such diseases, and the interactions of their host arthropods with personnel in training areas, is a significant health concern. For example, infections with tick-borne diseases, have occurred during military training operations in New Jersey and Arkansas. Likewise, Lyme Disease (LD), a particularly widespread tick-borne spirochete, has been increasing among both active and reserve service members. Indeed, LD accounted for 70% of all zoonotic and vector-borne diseases reported by the U.S. Air Force between 2000 and 2011.

Most vector-borne diseases that occur in North America are maintained in wildlife reservoirs with humans as incidental or dead-end hosts. As a consequence, disease transmission pathways are often complex and incompletely characterized. They can involve multiple chains of infection through different host populations, different vector populations and different life-stages, and can vary significantly in space and time as a result of environmental effects on host, vector and disease biology. Even under stationary conditions, this can make it challenging to predict where and when disease will appear in human populations. Under non-stationary conditions, such as those associated with global change, prediction becomes even more difficult. In particular, because different species and different life-stages can respond differently to altered temperature and precipitation patterns, climate change can uncouple certain species or stage interactions while reinforcing others. This is particularly true of phenology change, which is both one of the earliest indicators of climate change, and also a key factor in governing temporal overlap between populations.

Even when it is possible to predict when and where human disease will occur, management of vector-borne diseases can still be difficult. In particular, the timing of intervention strategies should not necessarily occur at the peak of disease risk. Rather, intervention should occur prior to peak disease, at times corresponding to the presence of sensitive targets or opportunities for transmission between key populations (e.g. nymphs and larvae, vectors and hosts). It is often challenging to identify this optimal time for intervention, which can depend strongly on the details of the system, as well as the mechanistic details of the management approaches themselves. For this reason, optimal timing of intervention strategies such that neither diseases nor their management interferes with land-use requirements is a complex task that depends on the interplay between system characteristics and land-use constraints.

PART 1: UNDERSTANDING PERSONAL PROTECTION

This work has been published and can be found at:

Demers, Jeffery, et al. "Dynamic modelling of personal protection control strategies for vector-borne disease limits the role of diversity amplification." *Journal of The Royal Society Interface* 15.145 (2018): 20180166.

Background

The use of epidemiological modelling to study vector-borne diseases has a long history, dating back over 50 years to the classic Ross–MacDonald model [1–3]. Since then, there have been numerous extensions and adaptations [4,5], including spatial dynamics [6], host heterogeneity [7,8], seasonality [9], stochasticity [10] and control [11,12]. There has also been some degree of debate regarding model formulation [13], such as the form of the biting rate and, by extension, disease transmission [14,15]. Unfortunately, different assumptions regarding biting rates can influence predictions for when and where a disease is capable of spreading, as well as estimates of disease controllability.

Model assumptions regarding disease management can also strongly impact estimates of disease controllability. This is particularly true of personal protection. Recently, Milleret al. [16] used a model with two classes of hosts—a protected class and an unprotected class—to show that, in contrast to predictions from simpler models [11,17–21], personal protection use by only sub-portions of the host population can actually worsen an outbreak of a vector-borne disease. This is a result of diversity amplification—an effect in vector-borne disease epidemiology which relates increases in overall disease prevalence to increases in host diversity [22–26]. Amplification is a potential risk whenever vectors preferentially concentrate attacks on sub-populations with high infection susceptibilities [26]. This occurs, for example, when partial personal protection coverage causes mosquitoes to divert from protected individuals and focus bites on unprotected individuals [16,27,28]. Diversion can lead to rapid disease spread within the unprotected sub-population and, consequently, personal protection models which incorporate vector diversion have the potential to display counterintuitive increases in disease severity [16,26,28,29].

Many vector-borne disease models which use multiple host classes and, by extension, potentially exhibit protection-induced diversity amplification (e.g. [16,26,28,29]) suffer from a common shortcoming—assignment of individuals to protected and unprotected classes is assumed static. Some models do allow for hosts who only intermittently apply personal protection (such as hosts who sleep under bed nets only at night), but even in these cases, assignments to sporadically protected and completely unprotected classes typically remain fixed [28,29]. In reality, protection status is dynamic: people forget to apply repellent, run out of repellent, wear down their bed nets, or grow weary of protection efforts and thus falter in accessibility [30,31], and non-accessible individuals can potentially re-acquire protection or re-adopt its use. This is particularly true if rigorous campaign initiatives are mounted in support of personal protection use. Consequently, there exists a flux of hosts into and out of the protected class, and this implies that mosquito focusing on unprotected individuals is actually more diffuse than indicated by static protection class models. Furthermore, static protection classes necessitate that control strategies, for example, the supplying protection or partaking in public service announcements by a health agency, be incorporated into models as direct influences over the

proportions of the two host populations. More realistically, however, distribution constraints and socio-economic factors which deter accessibility [30,31] severely limit controllability over the actual number of protected individuals, and control efforts will instead have a direct influence over the flux between the protected and unprotected classes. That is, the more health agencies do to make available and encourage the use of personal protection, the more likely people are to adopt and re-adopt personal protection.

We developed a methodology for modeling personal protection which accounts for flow between protected and unprotected classes. Specifically, we build a model similar to that in Milleret al.[16], but include movement between classes that we assume to be proportional to control effort. We then studied the impact of movement between the protected and unprotected classes assuming frequency-dependent (gonotrophic-limited) transmission, density-dependent (search-limited) transmission and an intermediate scenario that necessitates a functional response approach. We found that movement between classes and indeed, classes in general, do not matter strongly in the density-dependent limit. However, for the other two scenarios, there is strong divergence between our model, an analogous model with static protected and unprotected classes, and a simpler personal protection model with a homogeneous host population. Whereas our model predicts increased disease spread relative to the model with only a single class of hosts, it predicts decreased disease spread relative to the model with fixed protected and unprotected classes. From this model behaviour, we conclude that hosts' propensity to move between protected and unprotected classes can severely hamper a mosquito's ability to focus bites on anyone group of individuals, thus mitigating the potential for diversity amplification effects. Consequently, our results indicate that, relative to our model, models with static protection classes generally overestimate parameter ranges over which protection-induced disease amplification will be a practical concern. This provides not only a strong theoretical foundation for modelling methodology, but also a partial explanation for the disparity between theoretical prediction of protection-induced diversity amplification and, to the best of our knowledge, its apparent lack of observation in the field

Model Development

We began by carefully examining standard biting rate models. For a population of humans of density N_h homogeneously distributed throughout a unit area, V , we denote by f the average rate at which the human population is bitten by a single mosquito, also located within V . Following Milleret al.[16], Yakob [41] and Antonovicset al.[42], we assume a Holling type-II functional response [43–45] for f :

$$f = \frac{\beta_b A N_h}{1 + \tau_H A N_h} \quad (1.1)$$

where

$$\tau_H = \tau_0 + \beta_b \tau. \quad (1.2)$$

where $1/A$ is defined as the average time taken per unit area by an actively searching mosquito to locate a single human, and β_b denotes the probability that a mosquito will deliver a successful bite to a host once the target has been located and identified. The quantity τ_H denotes the handling time and is defined as the average time taken by a mosquito to identify, engage and process the blood meal from a single human after the human has been located. The handling time is written in terms of a pre- and post-bite handling time, denoted by τ_0 and τ , respectively. The random search rate, A , is associated with the long-range first phase of host location, and depends on the size of the unit area V , the details of the carbon dioxide landscape as determined by both human and non-human sources, and a range of species-specific and environmental factors. The pre-bite handling time, τ_0 , is the average time required to complete the short-ranged second phase of the host seeking process, and should be on the order of minutes or, at most, hours. The post-bite handling time, τ , is the gonotrophic cycle time, and is thus of the order of days [35]. The type-II functional response's capacity to account for gonotrophic, density and behavioural limitations on biting rates allows a spectrum of disease transmission assumptions to be modelled [16,41,42]. We were especially interested in the limits $AN_h\tau_H \gg 1$, and $AN_h\tau_H \ll 1$ corresponding to the so-called frequency-dependent and density-dependent limits, respectively [14,15,42]:

$$f \approx \begin{cases} \frac{\beta_b}{\tau_H}, & AN_h\tau_H \gg 1 \\ \beta_b AN_h, & AN_h\tau_H \ll 1. \end{cases} \quad (1.3)$$

In the frequency-dependent limit, host density is so large that the time spent by mosquitoes in the long-range search phase is negligible compared to the handling time. Mosquitoes bite at a constant rate determined primarily by the gonotrophic cycle time, ultimately resulting in disease transmission assumptions equivalent to those of the Ross–MacDonald model [1–3], which was the first and is arguably the most common framework for modelling vector-borne diseases. In the density-dependent limit, host density is so low that mosquitoes spend the majority of their time in the long-range search phase, and the gonotrophic cycle time is negligible by comparison. Density dependence ultimately leads to mass-action disease transmission, which is another common framework for vector-borne disease modelling [13,14].

Next, we turned our attention to modeling personal protection's influence on biting rates through modified values of the parameters appearing in equations (1.1) and (1.2). Bed nets and DEET primarily influence the short-range, second host-seeking phase and, in particular, the pre-bite handling time, τ_0 , and the bite probability β_b . However, regardless of the protective measure in use, we expect the pre-bite handling time to remain of the order of minutes to hours, thus we expect little change to τ_0 . Rather, the primary effect of personal protection is to alter β_b , reducing this parameter to very small or nearly zero values. In most real disease control scenarios, even when personal protection is made readily available, complete coverage over an entire population is difficult to achieve. Consequently, blood-seeking mosquitoes will likely encounter and attempt to acquire blood from both protected and unprotected humans. Following Milleret al.[16], we define N_u and N_p as distinct unprotected and protected host population densities with associated functional responses:

$$f_u = \frac{\beta_{bu}AN_u}{1 + (\tau_{0u} + \beta_{bu}\tau)AN_u + (\tau_{0p} + \beta_{bp}\tau)AN_p} \quad (1.4)$$

$$f_p = \frac{\beta_{bp}AN_p}{1 + (\tau_{0u} + \beta_{bu}\tau)AN_u + (\tau_{0p} + \beta_{bp}\tau)AN_p} \quad (1.5)$$

where the subscripts ‘u’ and ‘p’ denote quantities associated with the unprotected and protected groups, respectively.

With a fully explicit model for personal protection, our next step was to identify the role of control. In general, control makes protection more available or encourages its continued use. Ultimately, however, personal protection use is a dynamical phenomenon; DEET bottles run dry, bed nets wear down, and accessibility waivers. Thus, individuals continually lose protection. The more DEET and bed nets are made available and the more their use is encouraged, the more people re-acquire access to personal protection and interest in its use. We thus chose to model control as an effect on flow between protected and unprotected classes. Thus, from a control perspective, personal protection acts similar to control schemes used for vaccination [47], albeit with a much faster timescale for return to the unprotected class. We therefore chose to employ the following minimal ODE system as a personal protection control model:

$$\left. \begin{aligned} \dot{N}_u &= \gamma N_p - \kappa N_u \\ \dot{N}_p &= \kappa N_u - \gamma N_p \end{aligned} \right\} \quad (1.6)$$

where $1/\kappa$ is the average time an unprotected individual remains unprotected before acquiring personal protection, and $1/\gamma$ is the average time a protected individual remains protected before running out of DEET, having their bed-net fail, or wavering in accessibility. Increased control effort may increase κ by making additional resources available to unprotected individuals, or may decrease γ by encouraging continued accessibility among protected individuals. For time-independent κ and γ , we found the following equilibrium unprotected and protected population density levels:

$$\left. \begin{aligned} N_u^e &= \frac{\gamma}{\gamma + \kappa} N_h \\ N_p^e &= \frac{\kappa}{\gamma + \kappa} N_h \end{aligned} \right\} \quad (1.7)$$

where N_h is the total density of both protected and unprotected humans. We refer to the model in equation (1.6) as the ‘dynamic two-class model’.

To explore the effects of assuming dynamic personal protection, we next compared three separate models. A ‘one-class model’, a ‘static two-class model’ and our ‘dynamic two-class

model'. Parameters were selected to make all three models as comparable as possible. For the one-class model, we considered the following SIR system:

$$\left. \begin{aligned} \dot{S}_h &= -(1 - \varepsilon)\beta_h f \frac{S_h}{N_h} I_v, \\ \dot{I}_h &= -rI_h + (1 - \varepsilon)\beta_h f \frac{S_h}{N_h} I_v, \\ \dot{R}_h &= rI_h, \\ \dot{S}_v &= \Lambda - \mu S_v - (1 - \varepsilon)\beta_v f \frac{I_h}{N_h} S_v, \\ \dot{I}_v &= -\mu I_v + (1 - \varepsilon)\beta_v f \frac{I_h}{N_h} S_v, \end{aligned} \right\} \quad (1.8)$$

where S_h , I_h and R_h denote the susceptible, infectious and recovered host densities, respectively, while S_v and I_v denote the susceptible and infectious vector densities, respectively. Λ is the mosquito recruitment rate, $1/\mu$ is the average mosquito life-span, r is the rate of host recovery, β_h is the vector to human transmission probability, β_v is the human to vector transmission probability, and ε is the control efficacy, which can vary between zero and one. Following [17–19], we interpreted ε in terms of protection efficacy and the fraction of the population with access to personal protection:

$$\varepsilon = \left(1 - \frac{\beta_{bp}}{\beta_{bu}}\right) \frac{N_p}{N_h}, \quad (1.9)$$

where β_{bu} and β_{bp} are taken from the biting rate formulae equations (1.4) and (1.5) and are defined as the probability for a mosquito to bite an unprotected or protected host, respectively, after locating and identifying the target. The protected human population level, N_p , is a parameter, so for the sake of model comparison, we assumed that $N_p = N_p^e$, and thus can be written in terms of κ and γ as in equation (1.7). Our model assumptions yielded the following basic reproduction number:

$$\mathcal{R}_{01} = \sqrt{\frac{\beta_h \beta_v N_v}{\mu N_h}} \sqrt{\left[1 - \left(1 - \frac{\beta_{bp}}{\beta_{bu}}\right) \frac{\kappa}{\kappa + \gamma}\right]^2 \frac{f^2}{r}}. \quad (1.10)$$

For the static two-class model, we divided the total host population into protected and unprotected classes. The fraction in each class enters as a fixed parameter, with the two classes

summing to N_h . The classes appear both directly in the model and also implicitly through f_p and f_u . The static two-class equivalent to equation (1.8) is as follows:

$$\left. \begin{aligned} \dot{S}_u &= -\beta_h f_u \frac{S_u}{N_u} I_v, \\ \dot{S}_p &= -\beta_h f_p \frac{S_p}{N_p} I_v, \\ \dot{I}_u &= -r I_u + \beta_h f_u \frac{S_u}{N_u} I_v, \\ \dot{I}_p &= -r I_p + \beta_h f_p \frac{S_p}{N_p} I_v, \\ \dot{R}_u &= r I_u, \\ \dot{R}_p &= r I_p, \\ \dot{S}_v &= \Lambda - \mu S_v - \beta_v \left(f_u \frac{I_u}{N_u} + f_p \frac{I_p}{N_p} \right) S_v, \\ \dot{I}_v &= -\mu I_v + \beta_v \left(f_u \frac{I_u}{N_u} + f_p \frac{I_p}{N_p} \right) S_v, \end{aligned} \right\} \quad (1.11)$$

where S_p , I_p and R_p denote densities of protected susceptible, infected and recovered humans, while S_u , I_u and R_u are the equivalent densities of unprotected humans. Again, for the sake of model comparison, we assumed that $N_p = N_p^e$ and $N_u = N_u^e$ so that the protected and unprotected host densities could be written in terms of the parameters κ and γ . The resultant basic reproduction number for the static two-class model is:

$$\mathcal{R}_{02s} = \sqrt{\frac{\beta_h \beta_v N_v}{\mu N_h}} \sqrt{\frac{\kappa + \gamma}{r} \left[\frac{f_p^2}{\kappa} + \frac{f_u^2}{\gamma} \right]}. \quad (1.12)$$

For the dynamic tow-class model, we used the following SIR system:

$$\left. \begin{aligned}
\dot{S}_u &= -\kappa S_u + \gamma S_p - \beta_h f_u \frac{S_u}{N_u} I_v, \\
\dot{S}_p &= \kappa S_u - \gamma S_p - \beta_h f_p \frac{S_p}{N_p} I_v, \\
\dot{I}_u &= -\kappa I_u + \gamma I_p - r I_u + \beta_h f_u \frac{S_u}{N_u} I_v, \\
\dot{I}_p &= \kappa I_u - \gamma I_p - r I_p + \beta_h f_p \frac{S_p}{N_p} I_v, \\
\dot{R}_u &= -\kappa R_u + \gamma R_p + r I_u, \\
\dot{R}_p &= \kappa R_u - \gamma R_p + r I_p, \\
\dot{S}_v &= \Lambda - \mu S_v - \beta_v \left(f_u \frac{I_u}{N_u} + f_p \frac{I_p}{N_p} \right) S_v, \\
\dot{I}_v &= -\mu I_v + \beta_v \left(f_u \frac{I_u}{N_u} + f_p \frac{I_p}{N_p} \right) S_v.
\end{aligned} \right\} \quad (1.13)$$

The resultant basic reproduction number for the dynamic two-class model is:

$$\mathcal{R}_{02_d} = \sqrt{\frac{\beta_h \beta_v N_v}{\mu N_h}} \sqrt{\frac{\kappa + \gamma}{r + \kappa + \gamma} \left[\frac{f_p^2}{\kappa} + \frac{f_u^2}{\gamma} + \frac{(f_p + f_u)^2}{r} \right]}, \quad (1.14)$$

where f_p and f_u are evaluated at the equilibrium protected and unprotected population values. For the sake of comparison, we also considered the limit of no protection, which yields the following basic reproduction number:

$$\mathcal{R}_{00} = \sqrt{\frac{\beta_h \beta_v N_v}{\mu N_h}} \sqrt{\frac{f^2}{r}}. \quad (1.15)$$

Equations (1.10), (1.12) and (1.14) constituted our primary results, which we then interpreted in order to develop an understanding of how dynamism in personal protection might impact predictions of disease spread.

Model Comparisons

Figures 1.1–1.3 show predicted values of R_0 for three different rates of return to the unprotected class ($1/\gamma = 15$ days, 9 months, and 5 years), representing timescales for using up a bottle of DEET (15 days) through to loss/degradation of a bed net (5 years). All three figures show that, relative to both two-class models, the one-class model overestimates disease controllability. One-class models do best and, indeed, are most similar to other curves, in the density-dependent limit (figures 1.1a, 1.2a and 1.3a). Outside of the density-dependent limit, however, the one-class model tends to severely overestimate controllability relative to either two-class model. Specifically, the one-class model always predicts a monotonic decrease in the scaled R_0 as a function of κ , whereas both two-class models become non-monotonic outside of the density-dependent limit. The difference in model behaviour is due to the homogeneous population assumption implicit in the one-class model's formulation—this simplifying assumption prohibits the one-class model from accounting for increases in disease transmission which stem from focused mosquito attacks on unprotected sub-populations [16].

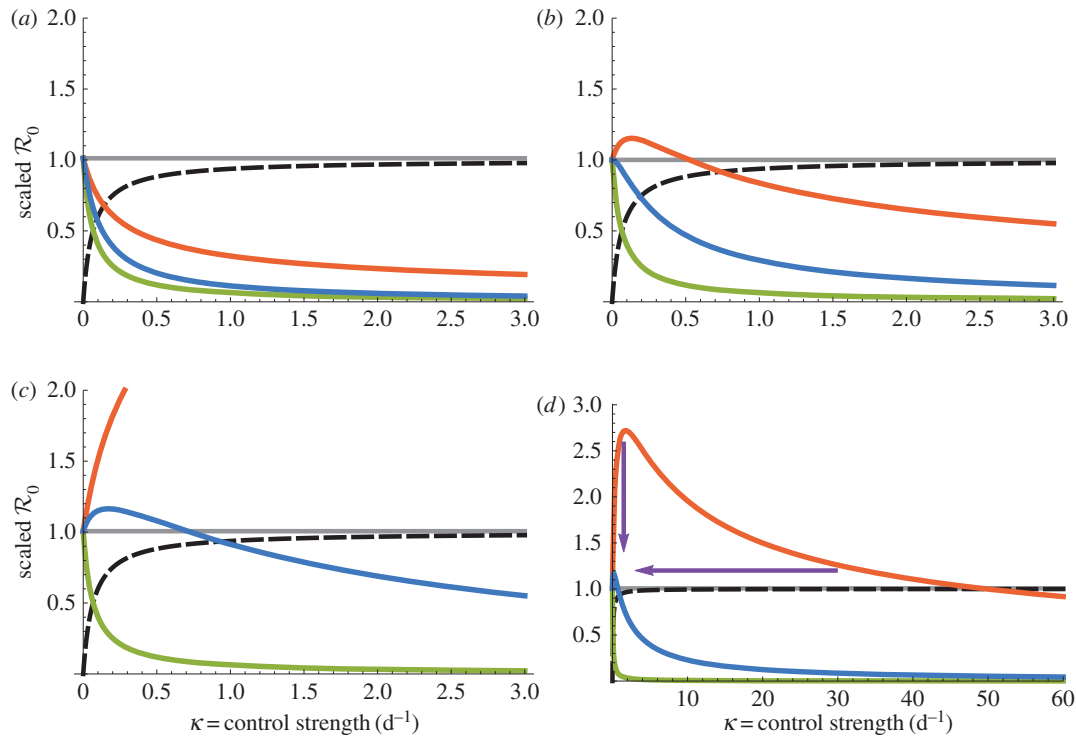


Figure 1.1 Dependencies of R_0 on DEET ($1/\gamma = 15$ days) control strength for the dynamic two-class model (blue), static two-class model (red) and one-class model (green). Corresponding equilibrium proportions of protected hosts are given by the dashed black curve. Two-host models display diversity amplification at control strengths where respective scaled R_0 curves rise above the grey $R_0 = 1$ line. Large suppressions in amplification severity and occurrence range are indicated by vertical and horizontal purple arrows, respectively, in (d). (a) Density-dependent infection $AN_h = 0.1 \text{ d}^{-1}$, (b) moderate infection $AN_h = 1.0 \text{ d}^{-1}$, (c) frequency-dependent infection $AN_h = 10.0 \text{ d}^{-1}$ and (d) frequency-dependent infection (wide view).

Figures 1.1–1.3 also indicate that, relative to our dynamic two-class model, the static two-class model generally underestimates disease controllability and overestimates diversity amplification. More specifically, diversity amplification is indicated whenever scaled R_0 curves exceed unity. Whereas strong amplification is apparent in the static two-class model, particularly under the frequency-dependent limit in figures 1.1d, 1.2d and 1.3d, it is much less severe in the dynamic two-class model, and indeed, even disappears in figure 1.1b. In addition to reduced amplification strength, the dynamic two-class model also predicts large reductions in the parameter ranges over which amplification can occur, particularly under the frequency-dependent limit in figures 1.1d, and 1.2d.

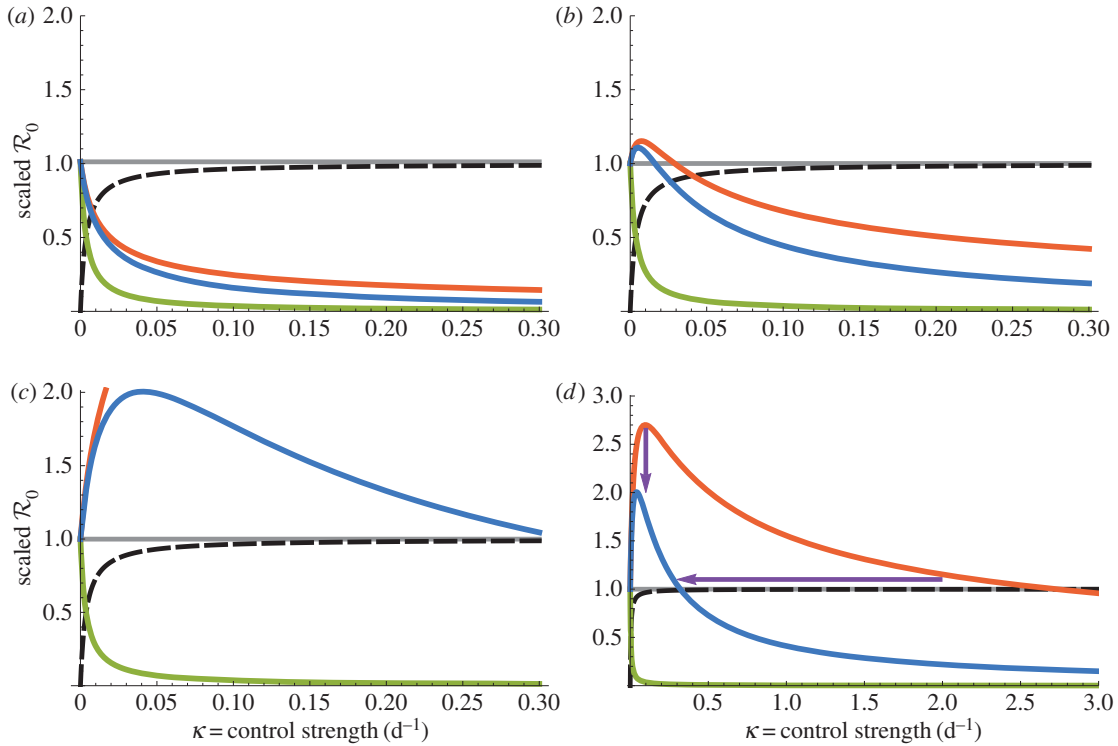


Figure 1.2 Dependencies of R_0 on intermediate protection ($1/\gamma = 9$ months) control strength for the dynamic two-class model (blue), static two-class model (red) and one-class model (green). Corresponding equilibrium proportions of protected hosts are given by the dashed black curve. Large suppressions in amplification severity and occurrence range are indicated by vertical and horizontal purple arrows, respectively, in (d). (a) Density-dependent infection $AN_h = 0.1 \text{ d}^{-1}$, (b) moderate infection $AN_h = 1.0 \text{ d}^{-1}$, (c) frequency-dependent infection $AN_h = 10.0 \text{ d}^{-1}$ and (d) frequency-dependent infection (wide view).

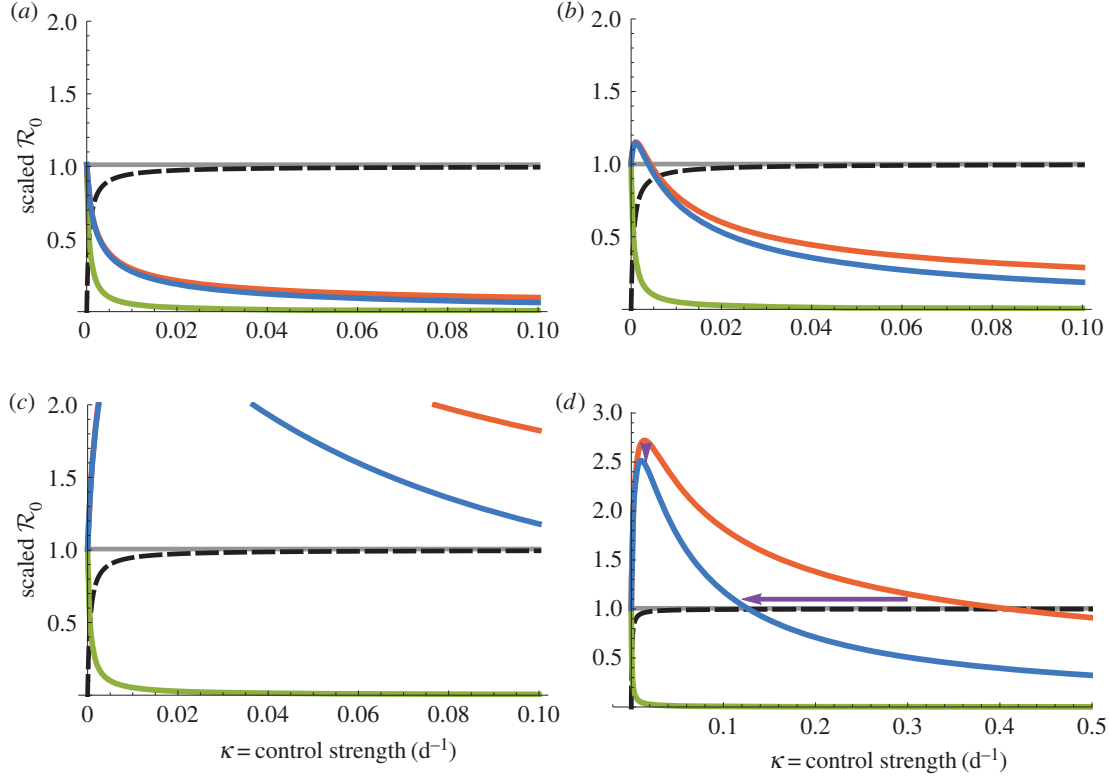


Figure 1.3 Dependencies of R_0 on bed net ($1/\gamma = 5$ years) control strength for the dynamic two-class model (blue), static two-class model (red) and one-class model (green). Corresponding equilibrium proportions of protected hosts are given by the dashed black curve. Large suppressions in amplification severity and occurrence range are indicated by vertical and horizontal purple arrows, respectively, in (d). (a) Density-dependent infection $AN_h = 0.1 \text{ d}^{-1}$, (b) moderate infection $AN_h = 1.0 \text{ d}^{-1}$, (c) frequency-dependent infection $AN_h = 10.0 \text{ d}^{-1}$ and (d) frequency-dependent infection (wide view).

Figure 4 illustrates the reductions in amplification severity and parameter range as explicit functions of AN_h . The decrease in minimum control strength required for amplification suppression in the dynamic two-class model relative to the static two-class model indicates reduction in amplification range, and the decrease in maximum scaled R_0 in the dynamic two-class model relative to the static two-class model indicates reduction in amplification severity. Diversity amplification ultimately results from mosquitoes' propensity to focus bites on preferred hosts [16,26], and so our results in figures 1.1–1.4 indicate that the movement of people between protected and unprotected classes can severely hinder mosquitoes' tendencies to focus attacks on unprotected human sub-populations, even when host population levels are in equilibrium and the flux between classes is rather small. This observation, together with the one-class model's inability to account for diversity amplification, indicates that dynamic protection status will generally result in outbreak characteristics lying somewhere between the one-class and static two-class model behaviour.

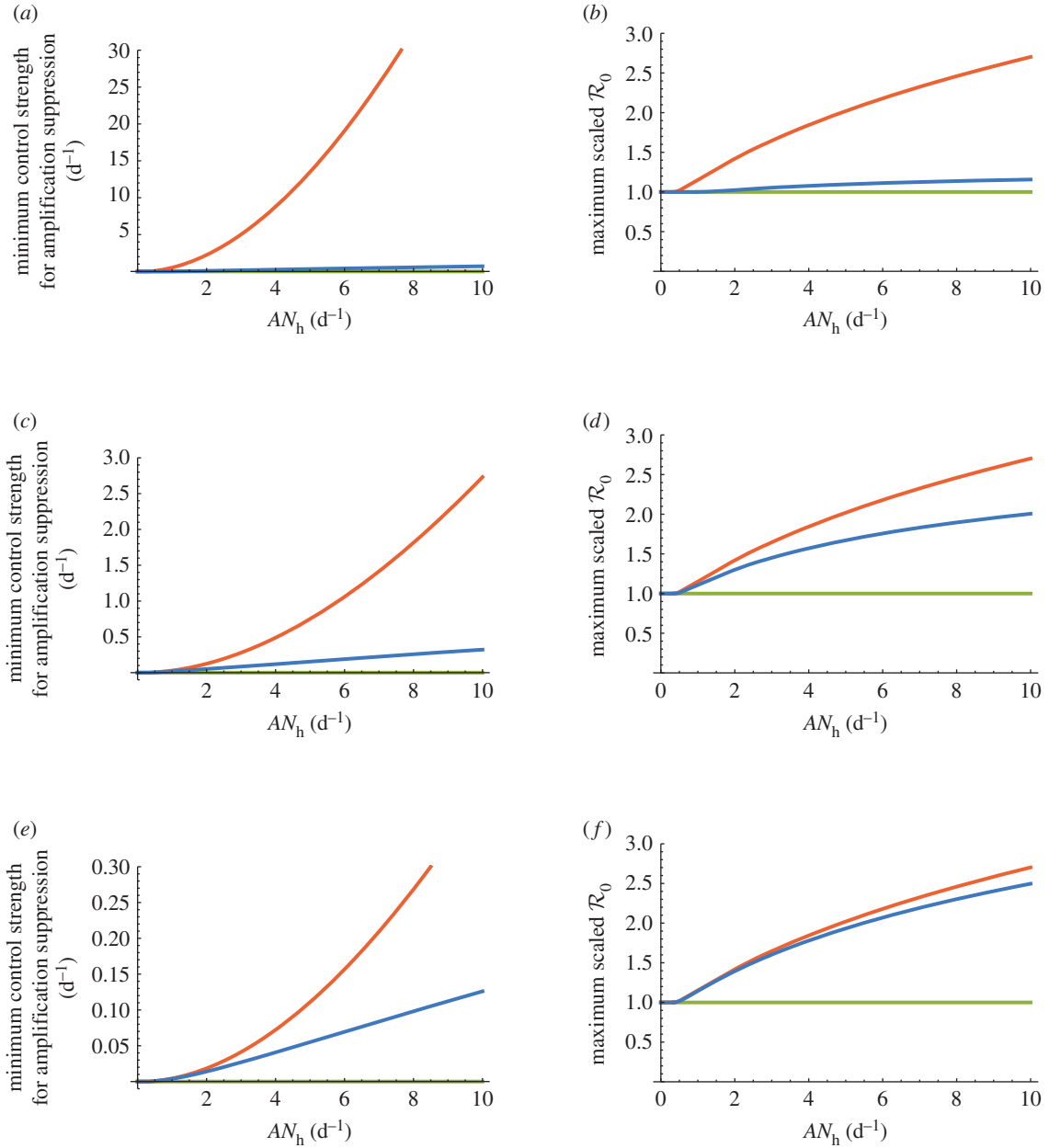


Figure 1.4 Illustrations of amplification range and strength reduction as functions of AN_h using the dynamic two-class model (blue), static two-class model (red) and one-class model (green). The minimum control strength for amplification suppression is the value of control strength κ^* such that scaled R_0 exceeds unity for all control strengths $\kappa \in [0, \kappa^*]$. The maximum scaled R_0 is the value of scaled R_0 at the peak of a model's R_0 versus κ curve for a given value of AN_h . (a) Amplification range reduction $1/\gamma=15$ days, (b) amplification severity reduction $1/\gamma=15$ days, (c) amplification range reduction $1/\gamma=9$ months, (d) amplification severity reduction $1/\gamma=9$ months, (e) amplification range reduction $1/\gamma=5$ years and (f) amplification severity reduction $1/\gamma=5$ years.

Figures 1.1–1.3 differ in their values of $1/\gamma$ —that is, the average amount of time that an individual who transitions into the protected class will remain in the protected class. When $1/\gamma$ is small (figure 1.1), our dynamic two-class model is more similar to the one-class model and less similar to the static two-class model. By contrast, when $1/\gamma$ is large (figure 1.3), our dynamic two-class model is more similar to the static two-class model and less similar to the one-class model. The explanation is relatively straightforward. In the limit of rapid transitions between classes, the distinction between protected and unprotected classes disappears, as people ‘instantaneously’ transition from one class to the other, with no dwell time in either class. In this case, our model behaves very much like the one-class model, where mosquitoes see an average level of protection for any given person, rather than two separate classes of people. At the opposite extreme, in the limit of slow class transitions, the flux between classes becomes insignificant. In this case, an average person remains protected or unprotected for such a long time that, at least on the timescale of disease dynamics, there are, in essence, two distinct host sub-populations, which is the assumption of the static two-class model. To the extent that κ and γ are finite and non-zero, our model is important in providing estimates for disease spread and controllability at intermediate scenarios between the one- and static two-class models.

Summary and Conclusions

We introduced a dynamic two-class model to describe vector-borne disease systems incorporating hosts who use personal protection measures. The effects of personal protection usage at the level of individual hosts are captured by functional response biting rates, and the effects of large-scale personal protection campaigns at the community level are captured through flows between protected and unprotected classes. Class flow can severely reduce amplification in both severity and range of occurrence, relative to predictions from existing static two-class models. This, along with the natural propensity of humans to discontinue and re-adopt protection use, offers potential explanation for the lack of observed protection-induced amplification in the field, despite predictions implied by existing models. Static two-class models can fail because they do not acknowledge the fundamental difference between genuinely distinct host species and protected versus unprotected individuals: species type is fixed, while protection status is not. Our dynamic two-class model combines the desirable features of one-class models (dynamic control) and static two-class models (host variability) to provide an ecologically sound methodology for modelling personal protection distribution as a community-wide dynamic control strategy in vector-borne disease systems.

PART 2: UNDERSTANDING DIFFERENT MANAGEMENT STRATEGIES

This work has been submitted, and can be found at: Demers, Jeffery, et al. "Implicit versus explicit control strategies in models for vector-borne disease epidemiology." *bioRxiv* (2019): 753475.

Background

Health and government agencies throughout the world regularly implement large-scale mosquito management strategies, such as area-wide adulticide and larvicide spray programs. These programs form an important line of defense against the proliferation of vector-borne diseases like malaria, dengue, and ZIKA [1]. Unfortunately, they also come with monetary costs, potential environmental impacts, and societal concerns. Given these constraints, mathematical models can serve as important tools for predicting the effects of control efforts and optimizing control efficacies and costs. Indeed, the efficacies of adult and larval control measures have been assessed and optimized using both simple, deterministic epidemic models[2, 3, 4, 5] and complex disease models with features such as stochasticity [6,7], seasonality[8,9,10,11], host heterogeneity [11,12,13,14], and spatial structure [6,7,13].

To assess the effects and efficacy of real-world vector management strategies using a mathematical model, a modeler must first select a scheme by which the control's influence will be incorporated into the model's structure or behavior. One common choice is to simply infer the effects of control by analyzing changes in model behavior under variations in model parameters relative to their natural values [2,4,5,6,9,12,13,14,15,16,17,18,19]. For example, in many vector-borne disease models, the effects of adulticide on outbreak severity are inferred through the responses of important threshold quantities like the basic reproduction number [20, 21] to increases in vector death rates, while the effects of larvicides are inferred through the analogous responses to increases in larval death rates or decreases in vector emergence rates [14, 15,17,18]. Models of this class incorporate control only implicitly through it's overall gross effects on model parameters. A second, more complicated method for incorporating control into vector-borne disease models is to directly model the effects of control on vector populations or environmental parameters [3,7,8,9,10,11,22]. For example, an area-wide adulticide spray could be modeled as a sudden, direct decrease in the adult vector population at the time of application. Likewise, larval habitat reduction could be modeled as a sudden, direct decrease and subsequent recovery in larval carrying capacity. Models of this class incorporate control explicitly through it's specific and direct effects on the vector population.

Explicit and implicit control models complement one another in their strengths and weaknesses. Explicit controls translate directly into real-world actions, thus can better capture the specifics of different management schemes on mechanisms of vector control. This approach, however, requires knowledge of the biological interactions between disease vectors and control measures, and often introduces non-autonomous dynamics as a result of a real-world control's time-dependent efficacy and discontinuous actuation. Consequently, explicit controls increase model complexity. The inherent time-dependence of explicit control is particularly problematic for model analysis, as non-autonomous dynamics severely obfuscate definition and calculation of the basic reproduction number [22, 23, 24]. Implicit controls, on the other hand, introduce no additional complexity into underlying disease models. The greater analytical tractability of

implicit control facilitates model analysis, including the use of optimal control theory to predict potentially time-dependent variations in model parameters which optimally balance disease severity with control costs [2,4,5,12,14,25]. However, these models cannot incorporate the details of different management strategies. This makes them less relevant to on-the-ground management decision-making. These deficits obstruct researchers' ability to systematically and reliably apply modeling results as guides for designing real-world disease management strategies, thus defeating one of the motivating purposes for incorporating control into disease models.

To overcome issues with standard implicit control models, we formally defined the notion of implicit control as an approximation for the average effects of explicit control. Working within the framework of a simple ordinary differential equation (ODE) population model, we proposed mathematical formulations for the implicit control approximations of common adult and larval population control techniques in terms of their measurable, real-world explicit control properties. Specifically, we focused on mosquitoes as disease vectors and considered control strategies for area-wide ultra low volume (ULV) adulticide sprays, residual adulticide barrier sprays, larval source reduction, and area-wide low volume (LV) larvicide spray. Although our proposed framework is intuitive and straightforward, our work highlights the subtle biological and mathematical consequences which can emerge when implicit control is formally defined as an approximation of more realistic, explicit controls. In particular, our work clarifies, biologically and mathematically, the conditions under which implicit control can accurately capture the average effects of explicit control. Our work represents a step towards making epidemiological modeling a more readily applicable tool for guiding real-world disease management decisions.

Model Development

We began with the following, basic ODE model for a well-mixed adult vector population evolving under natural, uncontrolled conditions within some spatially and temporally homogeneous area:

$$\dot{X}^0(t) = -\mu^0 X^0(t) + \Lambda^0, \quad (2.1)$$

where $X^0(t)$ denotes the size of the vector population under natural conditions at time t , Λ^0 denotes the natural vector emergence rate, and μ^0 denotes the natural per capita vector death rate. Given an initial population $X^0(t')$ at time t' , Eq. (1) implies the following population at a later time t :

$$\begin{aligned} X^0(t) &= X^0(t')e^{-\mu^0(t-t')} + \frac{\Lambda^0}{\mu^0} \left(1 - e^{-\mu^0(t-t')}\right) \\ &\underset{t \rightarrow \infty}{=} \frac{\Lambda^0}{\mu^0}. \end{aligned} \quad (2.2)$$

where the second line indicates relaxation to the natural equilibrium value Λ^0/μ^0 in the longtime limit.

Implicit control is typically incorporated into disease models through variations in model parameters, specifically the vector emergence and death rates in the case of Eq. (2.1). In most implicit control modeling studies which use Eq. (2.1), adulticide control measures are incorporated as an increase in vector death rate, and various larval control measures like larvicide sprays and larval source reduction are incorporated as a decrease in vector emergence rate [2,5, 12,15]. We chose to follow this standard and seemingly reasonable convention, with a key goal being to clarify its conditions of validity and its degree of accuracy. Letting $\mu^I(t)$ denote the modified death rate under the action of implicitly modeled adulticide:

$$\begin{aligned}\mu^I(t) &= \mu^0 (1 + \gamma^I(t)) \\ &= \frac{\mu^0}{1 - \rho^I(t)},\end{aligned}\tag{2.3}$$

where $\gamma^I(t) \in [0, \infty)$ is the possibly time-dependent fractional increase in vector death rate, and $\rho^I(t) \in [0, 1)$ is defined by

$$\rho^I(t) = \frac{\gamma^I(t)}{1 + \gamma^I(t)}.\tag{2.4}$$

The modified emergence rate under the action of larval control is then $\Lambda^I(t)$, where

$$\Lambda^I(t) = \Lambda^0(1 - \sigma^I(t)),\tag{2.5}$$

where $\sigma^I(t) \in [0, 1]$ is the possibly time-dependent fractional decrease in vector emergence rate due to the action larval control measures. Letting $X^I(t)$ denote the vector population modeled at the implicit level, adulticide and larval control modify Eq. (2.1) as follows:

$$\dot{X}^I(t) = -\mu^I(t)X^I(t) + \Lambda^I(t).\tag{2.6}$$

Importantly, the time-dependencies in $\gamma^I(t)$, $\rho^I(t)$, and $\sigma^I(t)$ are solely reflections of time-dependent variations in implementation strategies. For our analysis, we focused on the simplest case - constant control strengths which correspond to fixed implementation strategies. By fixed implementation strategy, we mean real-world control protocols whose defining properties, such as application schedule and volume of pesticide released per application, do not vary over time. At constant control strengths γ^I , ρ^I , and σ^I , the vector population under adulticide control relaxes to the following equilibrium:

$$\begin{aligned}X^I(t) &\underset{t \rightarrow \infty}{=} \frac{\Lambda^0}{\mu^0(1 + \gamma^I)} (1 - \sigma^I) \\ &= \frac{\Lambda^0}{\mu^0} (1 - \rho^I) (1 - \sigma^I).\end{aligned}\tag{2.7}$$

To model explicit control strategies, we focused on four different control methods: area-wide ultra low volume (ULV) adulticide sprays, residual adulticide barrier sprays, larval source reduction, and area-wide low volume (LV) larvicide spray. For ULV, spray remains in the air and actively kills over a negligible timeperiod in comparison to natural mosquito average life-times (which are typically on the order of weeks [1]). Since the natural mosquito life-time is the characteristic time-scale over which the ODE population model in Eq. (2.1) responds to changes, we therefore chose to model ULV adulticide spray as an instantaneous impulsive fractional decrease in mosquito population at the time of application. For an impulse applied at time t , we let $X^E(t-)$ be the population level just before the impulse, $X^E(t+)$ be the population level just after the impulse, and $\rho^E \in [0,1]$ be the percent population knockdown per application, such that

$$X^E(t^+) = X^E(t^-)(1 - \rho^E). \quad (2.8)$$

After the impulse, the vector population recovers according to Eq. (2.2)

$$X^E(t+s) = X^E(t^-)(1 - \rho^E)e^{-\mu^0 s} + \frac{\Lambda^0}{\mu^0} (1 - e^{-\mu^0 s}), \quad (2.9)$$

where $s > 0$.

By contrast to ULV adulticide, residual barrier sprays have a long-lasting killing effect. To model this within the context of the dynamics of Eq. (2.1), we assumed that residual barrier sprays instantaneously increase the death rate by a fraction $\gamma^E \in [0, \infty)$ above the natural mosquito death rate, which then decays exponentially at rate $\eta^E \in (0, \infty)$. For an impulse applied at time t , we thus have

$$\mu^E(t^+) = \mu^0 (1 + \gamma^E), \quad (2.10)$$

$$\mu^E(t+s) = \mu^0 (1 + \gamma^E e^{-\eta^E s}), \quad (2.11)$$

where, again, $s > 0$. The term $\mu^0 \gamma^E$ is the average rate at which a mosquito will contact and die from a pesticide treated surface just after application, and the exponential decay $\exp[-\eta^E t]$ models the natural evaporation, breakdown and, consequently, decreasing concentration of poison on the landing surfaces. Assuming a single impulse applied at time t , an initial population $X^E(t)$, evolves according to the following population dynamics

$$\frac{d}{ds} X^E(t+s) = -\mu^E(t+s) X^E(t+s) + \Lambda^0, \quad (2.12)$$

with corresponding solution

$$X^E(t+s) = X^E(t) \exp \left[-\mu^0 s - \gamma^E \frac{\mu^0}{\eta^E} (1 - e^{-\eta^E s}) \right]$$

$$\begin{aligned}
& + \exp \left[-\mu^0 s - \gamma^E \frac{\mu^0}{\eta^E} \left(1 - e^{-\eta^E s} \right) \right] \Lambda^0 \int_0^s ds' \exp \left[\mu^0 s' + \gamma^E \frac{\mu^0}{\eta^E} \left(1 - e^{-\eta^E s'} \right) \right] \\
& = X^E(t)g(s) + \frac{\Lambda^0}{\mu^0} g(s)I(s),
\end{aligned} \tag{2.13}$$

where

$$g(s) = \exp \left[-\mu^0 s - \gamma^E \frac{\mu^0}{\eta^E} \left(1 - e^{-\eta^E s} \right) \right], \tag{2.14}$$

$$I(s) = \int_0^s ds' \mu^0 \exp \left[\mu^0 s' + \gamma^E \frac{\mu^0}{\eta^E} \left(1 - e^{-\eta^E s'} \right) \right] \tag{2.15}$$

$$= \frac{\mu^0}{\eta^E} \exp \left[\gamma^E \frac{\mu^0}{\eta^E} \right] \left(\gamma^E \frac{\mu^0}{\eta^E} \right)^{\frac{\mu^0}{\eta^E}} \Gamma \left[-\frac{\mu^0}{\eta^E}, \gamma^E \frac{\mu^0}{\eta^E} e^{-\eta^E s}, \gamma^E \frac{\mu^0}{\eta^E} \right], \tag{2.16}$$

where $s > 0$ and Γ denotes the doubly incomplete gamma function

$$\Gamma[a, z_0, z_1] = \int_{z_0}^{z_1} dt t^{a-1} e^{-t}. \tag{2.17}$$

Larval source reduction causes a decrease in the larval carrying capacity. In our simple population model in Eq. (2.1), the mosquito emergence rate is interpreted as proportional to the larval carrying capacity, so we chose to model the effects of larval source reduction by assuming an impulsive reduction in the mosquito emergence rate, which we denote by $\Lambda^E(t)$. Specifically, we assumed that larval source reduction occurs instantaneously and decreases the emergence rate by a fraction $\sigma^E \in [0, 1]$. We then assumed that this effect decays exponentially at a rate $\nu^E \in (0, \infty)$. For an impulse applied at time t , we have

$$\Lambda^E(t+) = \Lambda^0 (1 - \sigma^E), \tag{2.18}$$

$$\Lambda^E(t+s) = \Lambda^0 \left(1 - \sigma^E e^{-\nu^E s} \right), \tag{2.19}$$

where $s > 0$. The term σ^E represents the fraction of larval carrying capacity eliminated, and the exponential decay factor models a spontaneous reappearance of available receptacles (due to residents' non-accessibility, rainfall into containers like bromeliads that are non-removable, etc.). The numerical values of σ^E and ν^E can vary widely depending on the specifics of the area being modeled and are difficult to determine via field studies [30]. However, we generally expect $1/\nu^E$ to be on the order of days to weeks in residential areas with sufficient levels of rainfall and varying levels of accessibility. Applying Eqs. (2.18) and (2.19) to a population of mosquitoes $X^E(t)$, we have

$$\frac{d}{ds}X^E(t+s) = -\mu^0 X^E(t+s) + \Lambda^E(t+s), \quad (2.20)$$

with solution

$$X^E(t+s) = X^E(t)e^{-\mu^0 s} + \frac{\Lambda^0}{\mu^0} \left(1 - e^{-\mu^0 s}\right) - \sigma^E \frac{\Lambda^0}{\nu^E - \mu^0} \left(e^{-\mu^0 s} - e^{-\nu^E s}\right). \quad (2.21)$$

For LV larvicide control, we proposed a simple step function model. Though admittedly more of an approximation than our other models, this was the best approach within the context of the study, and it facilitated analytical calculations, which were critical for model interpretation. Specifically, we set $\sigma^E \in [0,1]$ to be the fraction of larval habitat containers able to be reached by LV larvicide spray during an area-wide application, and we approximated the larvicide's effect by assuming that the treated containers become uninhabitable and support no larvae for the efficacy time $1/\nu^E \in (0,\infty)$, effectively reducing the larval carrying capacity by a factor $1-\sigma^E$. Experimental data suggest $1/\nu^E$ to be on the order of several weeks, while σ^E will vary based on the specific environmental features of the area being modeled [30,34]. After the efficacy time $1/\nu^E$, the larval carrying capacity is assumed to return to its natural value. For a single impulse of control applied at time t , our LV larvicide model gives the following functional form for Λ^E

$$\Lambda^E(t+s) = \begin{cases} \Lambda^0(1 - \sigma^E) & s \leq \frac{1}{\nu^E} \\ \Lambda^0 & \frac{1}{\nu^E} < s. \end{cases} \quad (2.22)$$

The resulting population dynamics are given by the following solution:

$$X^E(t+s) = \begin{cases} X^E(t)e^{-\mu^0 s} + \frac{\Lambda^0}{\mu^0}(1 - \sigma^E) \left(1 - e^{-\mu^0 s}\right) & s \leq \frac{1}{\nu^E} \\ X^E(t)e^{-\mu^0 s} + \frac{\Lambda^0}{\mu^0} \left(1 - e^{-\mu^0 s} - \sigma^E e^{-\mu^0 s} \left(e^{-\frac{\mu^0}{\nu^E}} - 1\right)\right) & \frac{1}{\nu^E} < s. \end{cases} \quad (2.23)$$

To relate implicit control strategies to explicit control strategies that capture more mechanistic detail, we specifically focused on periodic control schemes. Within this type of system, we defined ‘overall average’ reduction to mean the reduction in vector population size averaged over time, and we demanded that an explicit protocols’ application schedule yield constant time-averaged populations when the averaging sample time approaches infinity. Formally, this allowed us to define the time-independent implicit adulticide control strength as

$$\rho^I(\gamma^E, \eta^E, \tau_\mu) = 1 - \lim_{T \rightarrow \infty} \frac{1}{\Lambda^0/\mu^0} \frac{1}{T} \int_{t_0}^T ds X^E(s), \quad (2.24)$$

where $X^E(t)$ evolves under the action of either ULV adulticide spray or residual barrier adulticide spray, τ_μ is the period of the application protocol, and t_0 is an arbitrary constant. Likewise, our definition of ‘overall average’ allowed us to define the time-independent larvicide control strength as

$$\sigma^I(\sigma^E, \nu^E, \tau_\Lambda) = 1 - \lim_{T \rightarrow \infty} \frac{1}{\Lambda^0/\mu^0} \frac{1}{T} \int_{t_0}^T ds X^E(s), \quad (2.25)$$

where $X^E(t)$ evolves under the action of either larval source reduction or LV larvicide spray, τ_A is the period of the application protocol, and t_0 is an arbitrary constant. Equation 2.24 defines a manifold in $\rho^I - \rho^E - \eta^E - \tau_\mu$ space (as does Eq. (25) analogously). If the defining properties ρ^E , η^E , and τ_μ are assumed to be time-dependent in reflection of a time-dependent implementation strategy, there will exist a corresponding trajectory traced on the $\rho^I - \rho^E - \eta^E - \tau_\mu$ manifold, and this trajectory will endow a time-dependence to ρ^I . Thus, time-dependent implicit controls inherit their time-dependencies from the time-dependencies in the defining properties of the underlying explicit controls.

In addition to single control mechanisms, we also considered joint control strategies involving two or more methods. To define joint control strategies involving only adulticide, we considered ULV adulticide spray and residual barrier spray applied with parameters $\gamma^E_1, \eta^E_1, \tau_{\mu 1}$ and γ^E_2, η^E_2 , and $\tau_{\mu 2}$, respectively. This yielded a vector population $X^E(t)$ with the joint implicit control strength given by

$$\rho^I(\gamma^E_1, \eta^E_1, \tau_{\mu 1}, \gamma^E_2, \eta^E_2, \tau_{\mu 2}) = 1 - \lim_{T \rightarrow \infty} \frac{1}{\Lambda^0/\mu^0} \frac{1}{T} \int_{t_0}^T ds X^E(s). \quad (2.26)$$

Similarly, for combinations of larvicide controls, we were able to express the joint implicit control strength by

$$\sigma^I(\sigma^E_1, \nu^E_1, \tau_{\Lambda 1}, \sigma^E_2, \nu^E_2, \tau_{\Lambda 2}) = 1 - \lim_{T \rightarrow \infty} \frac{1}{\Lambda^0/\mu^0} \frac{1}{T} \int_{t_0}^T ds X^E(s). \quad (2.27)$$

The potential for synergistic effects, however, became problematic when both adulticide and larval control protocols were considered simultaneously. This synergy called into question the validity of implicit modeling in general. To deal with this, we derived a general expression to demonstrate synergistic effects in combining adulticide and larvicide and to demonstrate their contribution to the average population reduction. Our approach involved a combination of Floquet and Fourier analysis.

Specifically, we considered the simple vector dynamics model from Eq. (2.1), subject to multiple explicit adulticide and larvicide control schemes.

$$\dot{X}^E(t) = -\mu^E(t)X^E(t) + \Lambda^E(t), \quad (2.28)$$

This allowed us to write the following general expressions

$$\mu^E(t) = \mu^0 (1 + f_\mu(t)) \quad (2.29)$$

$$\Lambda^E(t) = \Lambda^0 (1 - f_\Lambda(t)), \quad (2.30)$$

where $f_\mu(t) \in [0, \infty)$ results from some combination of periodically applied residual barrier spray and ULV spray, and where $f_\Lambda(t) \in [0, 1]$ results from some combination of larval source reduction and LV larvicide spray. We assumed that $f_\mu(t)$ and $f_\Lambda(t)$ have periods τ_μ and τ_Λ , respectively, and that the periods were commensurable, meaning that

$$m_\mu \tau_\mu = m_\Lambda \tau_\Lambda = \tau_c, \quad (2.31)$$

where τ_c is a larger combined period and m_μ and m_Λ are positive integers with greatest common divisor unity, implying that $X^E(t)$ evolves periodically with period τ_c in the long-time limit.

Applying a Floquet transform to the periodically driven linear ODE with periodic coefficients in Eq. (2.28), followed by a Fourier transform and then an inverse Floquet transform, yielded a set of closed form expressions for the Fourier modes of the periodic solution, with the zeroth mode giving the time-averaged solution. From this, we defined the following pertinent terms.

$$\begin{aligned} M &= \frac{1}{\tau_\mu} \int_0^{\tau_\mu} dt \mu^E(t) \\ &= \mu^0 (1 + \langle f_\mu \rangle_{\tau_\mu}), \end{aligned} \quad (2.32)$$

$$\begin{aligned} P(t) &= \exp \left[Mt - \int_0^t dt' \mu^E(t') \right] \\ &= \exp \left[\mu^0 \langle f_\mu \rangle_{\tau_\mu} t - \mu^0 \int_0^t dt' f_\mu(t') \right]. \end{aligned} \quad (2.33)$$

$$\begin{aligned} Q(t) &= P(t)^{-1} \\ &= \exp \left[-\mu^0 \langle f_\mu \rangle_{\tau_\mu} t + \mu^0 \int_0^t dt' f_\mu(t') \right]. \end{aligned} \quad (2.34)$$

where M is the time-averaged death rate, $P(t)$ is the Floquet operator, and $Q(t)$ is the reverse Floquet operator. Once $X^E(t)$ has relaxed into its long-time periodic orbit, we can define the following Fourier decompositions

$$\begin{aligned}
X^E(t) &= \sum_{n=-\infty}^{\infty} X_n e^{2\pi i n \frac{t}{\tau_c}} \\
P(t) &= \sum_{n=-\infty}^{\infty} P_n e^{2\pi i n \frac{t}{\tau_\mu}} \\
Q(t) &= \sum_{n=-\infty}^{\infty} Q_n e^{2\pi i n \frac{t}{\tau_\mu}} \\
\Lambda^E(t) &= \sum_{n=-\infty}^{\infty} \Lambda_n e^{2\pi i n \frac{t}{\tau_\Lambda}},
\end{aligned} \tag{2.35-2.38}$$

where i denotes the imaginary unit and the summations are over all positive and negative integers. The long-time average of $X^E(t)$ is given by its zeroth order Fourier mode:

$$X_0 = \sum_{j,k=-\infty}^{\infty} \frac{P_k Q_{-k-m_\Lambda j}}{M - \frac{2\pi i k}{\tau_\mu}} \Lambda_{m_\mu j}. \tag{2.39}$$

Through examination of several limits, we were able to decompose the actions of adulticide and larvicide in Eq. (2.39) into distinct synergistic and non-synergistic contributions.

$$X_0 = \frac{\Lambda^0}{\mu^0} (1 - \sigma^I) (1 - \rho^I) + \sum_{\substack{j,k=-\infty \\ i \neq 0}}^{\infty} \frac{P_k Q_{-k-m_\Lambda j}}{M - \frac{2\pi i k}{\tau_\mu}} \Lambda_{m_\mu j}, \tag{2.40}$$

where

$$\begin{aligned}
\sigma^I &= \langle f_\Lambda \rangle_{\tau_\Lambda} \\
&= 1 - \frac{\Lambda_0}{\Lambda^0}.
\end{aligned} \tag{2.41}$$

is the implicit larval control strength as defined in Eqs. (2.25) and (2.27), written in terms of the zero Fourier mode of the corresponding explicit larval protocol, while

$$\rho^I = 1 - \sum_{k=-\infty}^{\infty} \frac{P_k Q_{-k}}{\frac{M}{\mu^0} - \frac{2\pi i k}{\mu^0 \tau_\mu}}. \tag{2.42}$$

is the implicit adulticide strength defined in Eqs. (2.24) and (2.26), written in terms of the adulticide Floquet-Fourier modes. Eq. (4.40) to the implicitly controlled equilibrium population reduction in Eq. (4.7), we were able to determine that implicit control modeling accounts for precisely the non-synergistic effects between larval controls and adulticides, and that implicit control accurately describes the average effects of explicit control when the synergistic term in Eq. (4.40) are negligible. To determine the importance of synergistic effects, we then examined

their magnitude as a function of relative timing shifts between adulticide and larval controls or phenological emergence rate oscillations by calculating the synergy factor S , defined as

$$S = \frac{\sum_{\substack{j,k=-\infty \\ j \neq 0}}^{\infty} \frac{P_k Q_{-k-m_\Lambda j}}{M - \frac{2\pi i k}{\tau_\mu}} \Lambda_{m_\mu j} e^{-2\pi i m_\mu j \frac{z}{\tau_\Lambda}}}{\frac{\Lambda^0}{\mu^0} (1 - \sigma^I) (1 - \rho^I)}, \quad (2.43)$$

where z denotes the lag of the larval protocol relative to the adulticide protocol. The synergy factor S can take on both positive and negative values; negative S values indicate beneficial synergistic effects which reduce the average vector population below the level suggested by implicitly modeled controls, while positive values indicate counter productive synergistic effects which increase the average vector population.

Model Analysis

We first considered the relationship between explicitly modeled ULV and implicit control models. Repeated use of Eq. (2.9), averaged over a period, gives the following expression for the explicit vector population

$$\langle X^E \rangle_{\tau_\mu} \xrightarrow{t \rightarrow \infty} \frac{\Lambda^0}{\mu^0} \left(1 - \frac{\rho^E}{1 - (1 - \rho^E) e^{-\mu^0 \tau_\mu}} \frac{1 - e^{-\mu^0 \tau_\mu}}{\mu^0 \tau_\mu} \right) \quad (2.44)$$

Relating this to the corresponding implicit control scheme gives the following

$$\rho^I = \frac{\rho^E}{1 - (1 - \rho^E) e^{-\mu^0 \tau_\mu}} \frac{1 - e^{-\mu^0 \tau_\mu}}{\mu^0 \tau_\mu}. \quad (2.45)$$

Figure 2.1 shows a density plot indicating the strength of ρ^I as a function of ρ^E and τ_μ . Comparison of the explicit control dynamics with corresponding implicit control dynamics is additional when in Fig. 2.2. Figure 1 indicates that strong implicit control strength occurs only for short periods τ_μ and high percent knockdowns ρ^E . From Fig. 2, we see that the implicit control dynamics more closely match the explicit control dynamics for short application periods and low percent knockdowns. The Floquet quantities for ULV are additionally found as

$$M = \mu^0 - \frac{\ln(1 - \rho^E)}{\tau_\mu}, \quad (2.46)$$

$$P(t) = (1 - \rho^E)^{1 - \frac{(t \bmod \tau_\mu)}{\tau_\mu}}, \quad (2.47)$$

$$Q(t) = (1 - \rho^E)^{-1 + \frac{(t \bmod \tau_\mu)}{\tau_\mu}}. \quad (2.48)$$

with the Fourier modes given by

$$\begin{aligned} P_n &= \frac{1}{\tau_\mu} \int_0^{\tau_\mu} dt e^{-2\pi i n \frac{t}{\tau}} P(t) \\ &= \rho^E \frac{1}{\ln \left[\frac{1}{1-\rho^E} \right] - 2\pi i n}, \end{aligned} \quad (2.49)$$

$$\begin{aligned} Q_n &= \frac{1}{\tau_\mu} \int_0^{\tau_\mu} dt e^{-2\pi i n \frac{t}{\tau}} Q(t) \\ &= \frac{\rho^E}{1 - \rho^E} \frac{1}{\ln \left[\frac{1}{1-\rho^E} \right] + 2\pi i n}. \end{aligned} \quad (2.50)$$

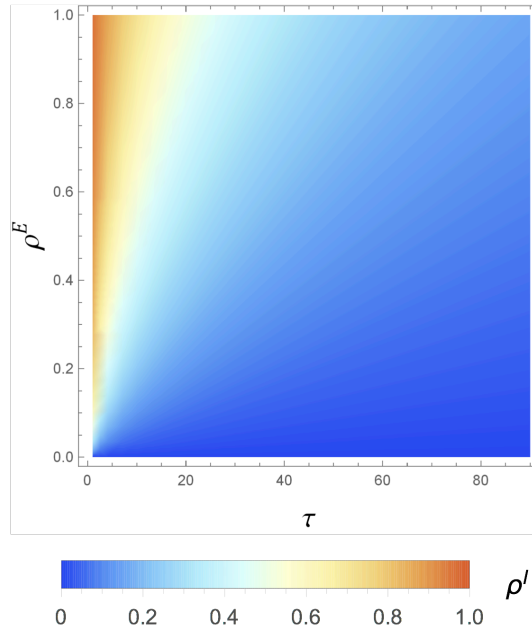


Figure 2.1 Density plot indicating the magnitude of the implicit control strength ρ^I as a function of the explicit control parameters ρ^E and τ_μ , where $1/\mu_0 = 2$ weeks. The color scale indicates the value of ρ^I .

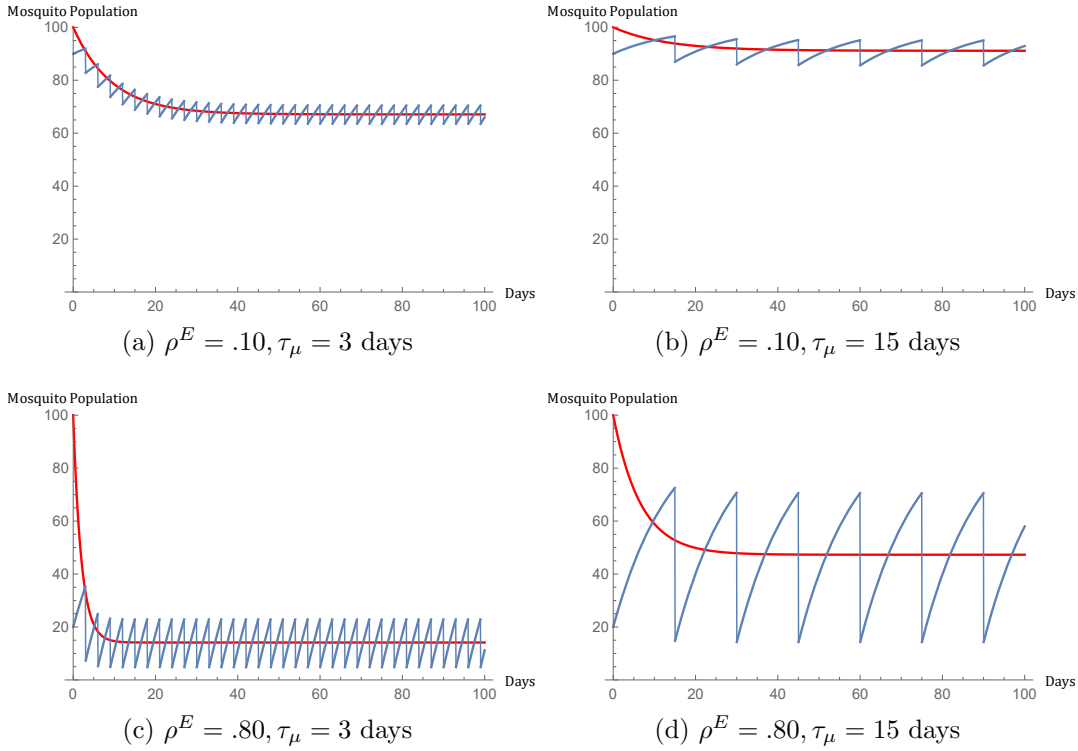


Figure 2.2 Time evolution of a population of 100 mosquitoes under ULV adulticide spray applied beginning at $t=0$, where $1/\mu_0 = 2$ weeks and $X^E(0) = \Lambda_0/\mu_0 = 100$. Explicit control dynamics are represented by the blue curves, and the red curves give the corresponding implicit control approximation.

Second, we considered the relationship between explicitly modeled residual barrier spray and implicit control models. Repeated use of Eq. (2.13), averaged over a period, gives the following expression for the explicit vector population

$$\langle X^E \rangle_{\tau_\mu} \underset{t \rightarrow \infty}{=} \frac{\Lambda_0}{\mu_0} \frac{1}{\tau_\mu} \int_0^{\tau_\mu} ds \left[g(s)I(s) + g(s) \frac{g(\tau_\mu)I(\tau_\mu)}{1 - g(\tau_\mu)} \right]. \quad (2.51)$$

Again, relating this result to the implicit control model gives

$$\rho^I = 1 - \frac{1}{\tau_\mu} \int_0^{\tau_\mu} ds \left[g(s)I(s) + g(s) \frac{g(\tau_\mu)I(\tau_\mu)}{1 - g(\tau_\mu)} \right]. \quad (2.52)$$

Eq. (2.52) does not simplify to a closed form analytic expression and must be evaluated numerically. Density plots indicating values for ρ^I are given in Fig. 2.3, and a comparison of explicitly controlled dynamics and the corresponding implicitly controlled dynamics under residual barrier spray is given in Fig. 2.4. From Fig. 2.3, it is clear that weak implicit control

strength occurs only for very small explicit control efficacies γ^E and long application periods τ_μ . Comparing to Fig. 2.1, it is also clear that residual barrier spray has weak implicit control strengths ρ^I over a much smaller parameter range than does ULV adulticide spray. Figure 2.4 indicates that the implicit control approximation most closely matches explicit control dynamics for shorter application periods. The Floquet quantities for residual barrier spray are additionally found as

$$M = \mu^0 \left(1 + \gamma^E \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu} \right), \quad (2.53)$$

$$P(t) = \exp \left[-\gamma^E \mu^0 (t \bmod \tau_\mu) \left(\frac{1 - e^{-\eta^E (t \bmod \tau_\mu)}}{\eta^E (t \bmod \tau_\mu)} - \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu} \right) \right], \quad (2.54)$$

$$Q(t) = \exp \left[\gamma^E \mu^0 (t \bmod \tau_\mu) \left(\frac{1 - e^{-\eta^E (t \bmod \tau_\mu)}}{\eta^E (t \bmod \tau_\mu)} - \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu} \right) \right], \quad (2.55)$$

with the Fourier modes given by

$$\begin{aligned} P_n &= \frac{1}{\tau_\mu} \int_0^{\tau_\mu} dt e^{-2\pi i n \frac{t}{\tau_\mu}} P(t) \\ &= \frac{e^{-\gamma^E \frac{\mu^0}{\eta^E}}}{\eta^E \tau_\mu} \left(\gamma^E \frac{\mu^0}{\eta^E} \right)^{-\frac{2\pi i n}{\eta^E \tau_\mu} + \gamma^E \frac{\mu^0}{\eta^E} \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu}} \\ &\quad \times \exp \left[i\pi \left(1 + \gamma^E \frac{\mu^0}{\eta^E} \right) + \frac{2\pi^2 n}{\eta^E \tau_\mu} \right] \Gamma \left[\frac{2\pi i n}{\eta^E \tau_\mu} - \gamma^E \frac{\mu^0}{\eta^E} \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu}, -\gamma^E \frac{\mu^0}{\eta^E}, -\gamma^E \frac{\mu^0}{\eta^E} e^{-\eta^E \tau_\mu} \right], \end{aligned} \quad (2.56)$$

$$\begin{aligned} Q_n &= \frac{1}{\tau_\mu} \int_0^{\tau_\mu} dt e^{-2\pi i n \frac{t}{\tau_\mu}} Q(t) \\ &= \frac{e^{\gamma^E \frac{\mu^0}{\eta^E}}}{\eta^E \tau_\mu} \left(\gamma^E \frac{\mu^0}{\eta^E} \right)^{-\frac{2\pi i n}{\eta^E \tau_\mu} - \gamma^E \frac{\mu^0}{\eta^E} \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu}} \Gamma \left[\frac{2\pi i n}{\eta^E \tau_\mu} + \gamma^E \frac{\mu^0}{\eta^E} \frac{1 - e^{-\eta^E \tau_\mu}}{\eta^E \tau_\mu}, \gamma^E \frac{\mu^0}{\eta^E} e^{-\eta^E \tau_\mu}, \gamma^E \frac{\mu^0}{\eta^E} \right], \end{aligned} \quad (2.57)$$

where Γ is the doubly incomplete gamma function, and we adopt the convention that complex numbers are written with their phase angles within the interval $(-\pi, \pi]$.

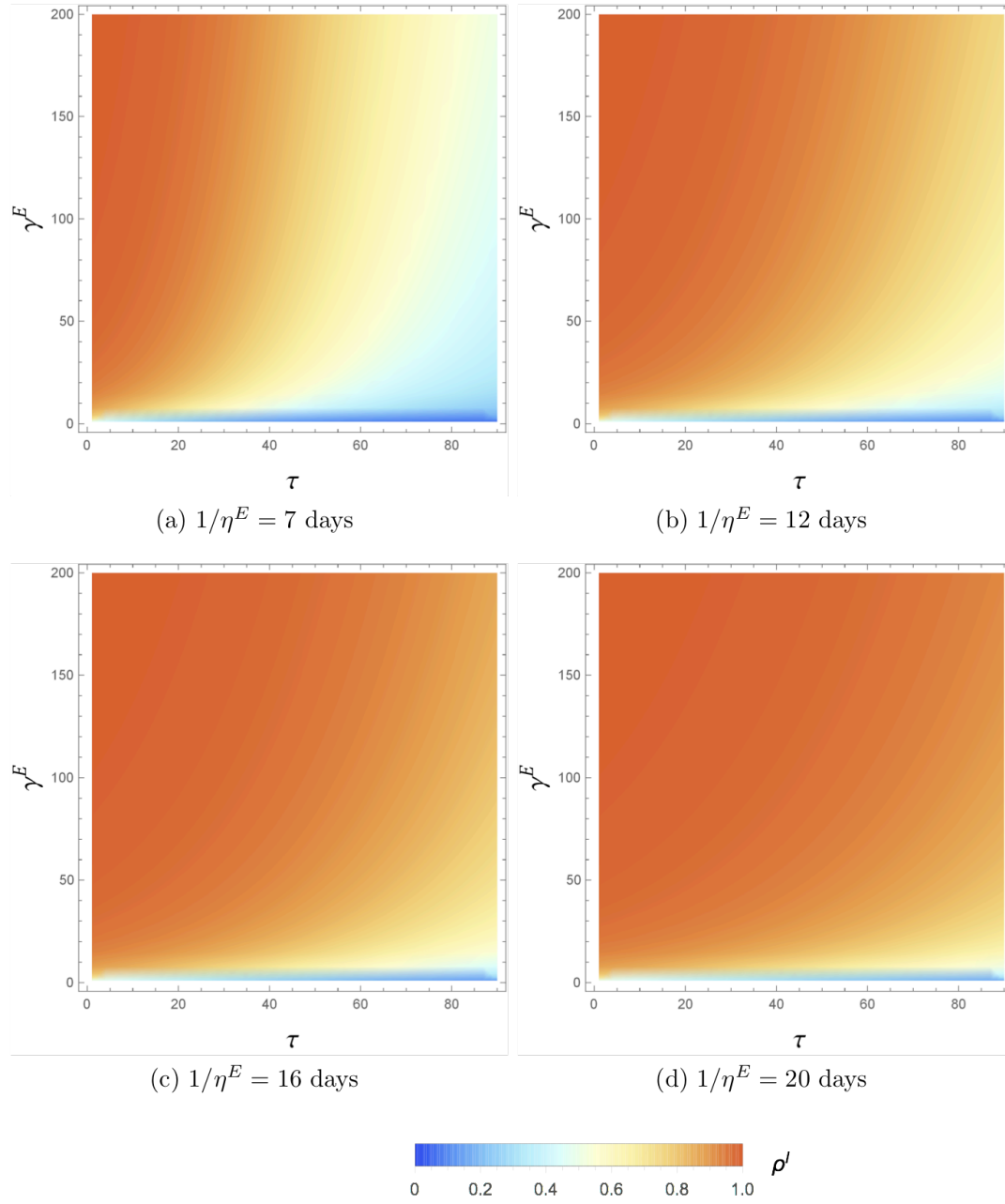


Figure 2.3 Density plots indicating the magnitude of implicit residual barrier spray control strength ρ^I as a function of the explicit control parameters γ^E , η^E , and τ_μ , where $1/\mu_0 = 2$ weeks. The color scale indicates the value of ρ^I .

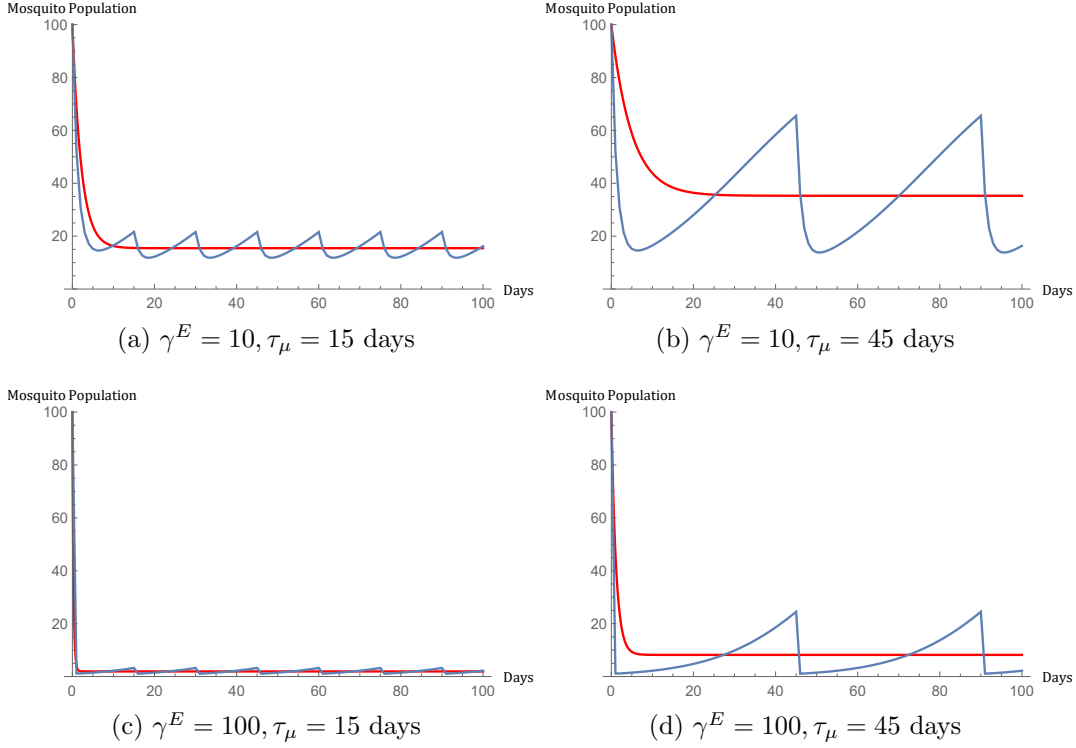


Figure 2.4 Time evolution of a population of 100 mosquitoes under residual barrier spray/adulticide applied at $t=0$, where $1/\mu_0=2$ weeks, $X^E(0)=A_0/\mu_0=100$, and $1/\eta^E=12$ days. Explicit control dynamics are represented by the blue curve, and the red curve gives the corresponding implicit control approximation.

We next considered the combined effect of both adulticide strategies. When both residual barrier spray and ULV adulticide spray are applied with periods $\tau_{\mu 1}$ and $\tau_{\mu 2}$, respectively, with an overall combined period τ_μ such that

$$m_1 \tau_{\mu 1} = m_2 \tau_{\mu 2} = \tau_\mu, \quad (2.58)$$

then the overall implicit control can be written in terms of the Floquet-Fourier modes as follows

$$\begin{aligned} \rho^I = & 1 - \sum_{n=-\infty}^{\infty} \sum_{\substack{k=-\infty \\ m_1 k_1 + m_2 k_2 = n}}^{\infty} \frac{P_{k_1}^1 Q_{-k_1}^1 P_{k_2}^2 Q_{-k_2}^2}{1 + \frac{\langle f_1 \rangle_{\tau_1}}{\mu^0} + \frac{\langle f_2 \rangle_{\tau_2}}{\mu^0} - \frac{2\pi i n}{\mu^0 \tau_\mu}} \\ & - \sum_{n=-\infty}^{\infty} \sum_{\substack{k_1, k_2, j_1, j_2 = -\infty \\ m_1 k_1 + m_2 k_2 = n \\ m_1 j_1 + m_2 j_2 = -n \\ j_1 \neq -k_1, j_2 \neq -k_2}}^{\infty} \frac{P_{k_1}^1 Q_{j_1}^1 P_{k_2}^2 Q_{j_2}^2}{1 + \frac{\langle f_1 \rangle_{\tau_1}}{\mu^0} + \frac{\langle f_2 \rangle_{\tau_2}}{\mu^0} - \frac{2\pi i n}{\mu^0 \tau_\mu}} e^{-2\pi i (k_2 + j_2) \frac{z}{\tau_{\mu 2}}}. \end{aligned} \quad (2.59)$$

Unfortunately, we were unable to reduce either the synergistic or non-synergistic components of Eq. (2.59) to simple analytical expressions. To overcome this challenge, we hypothesized the

following relationship between joint and individual implicit controls, and then examined deviations from this simple combination model

$$\rho^{IH} = 1 - \frac{(1 - \rho_1^I)(1 - \rho_2^I)}{1 - \rho_1^I \rho_2^I}, \quad (2.60)$$

Fig. 2.5 shows values of ρ^I as a function of ULV percent knockdown and timing offset between ULV and residual barrier spray. Figure 2.6 shows the relative differences between ρ^I and ρ^{IH} . In general, we found that ρ^I is most sensitive to variances in z when τ_2 is an integer multiple of τ_1 , which is indicative of a resonance phenomenon. For all application periods considered, we found the magnitude of $(\rho^{IH} - \rho^I)/\rho^I$ to be at most a little over .01, thus our simple additive model in Eq. (2.60) was quite accurate.

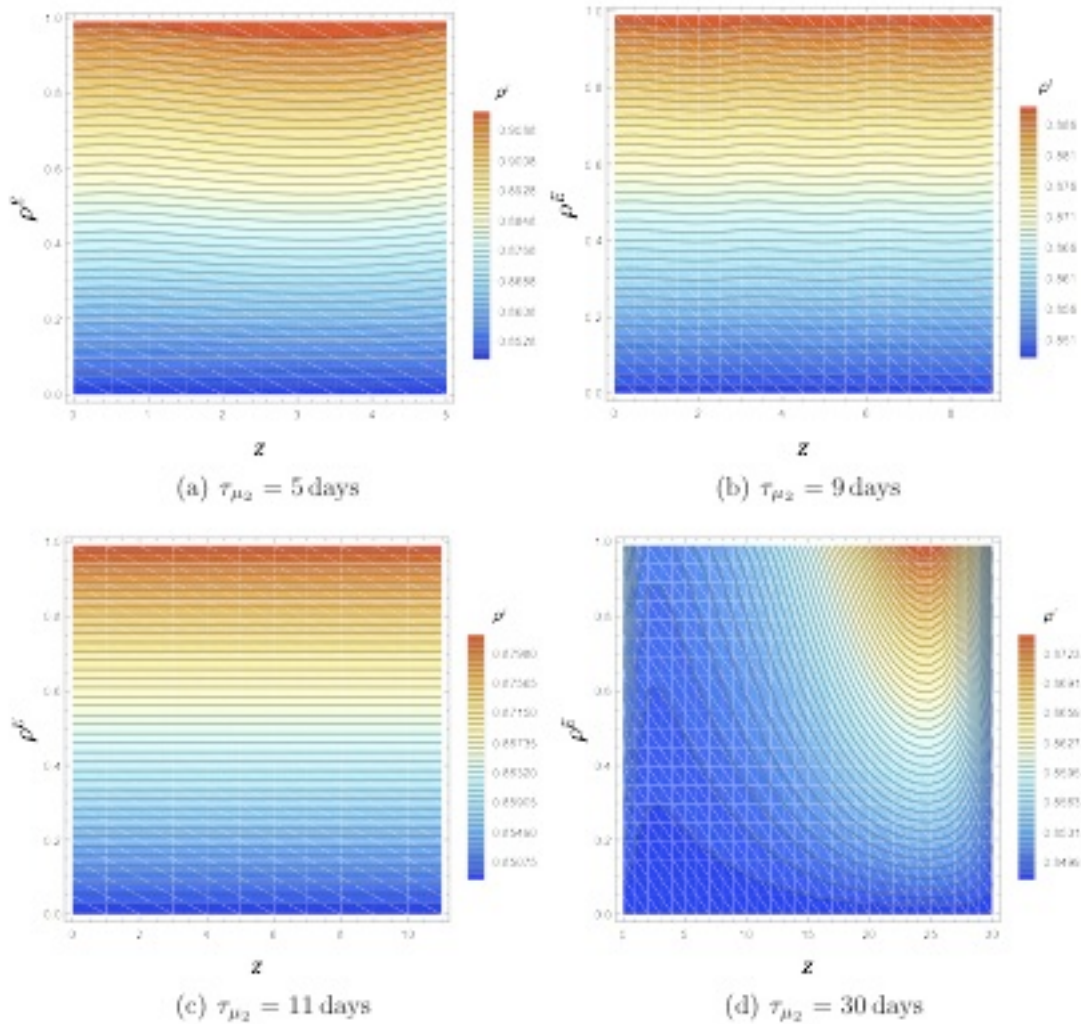


Figure 2.5 Contour plots indicating the implicit population reduction ρ^I for combined ULV adulticide and residual barrier spray as a function of the explicit ULV fractional knockdown ρ^E and timing offset z for various values of the ULV period $\tau_{\mu 1}$, assuming a natural vector lifetime of 14 days. Residual barrier spray is applied with a period $\tau_{\mu 2} = 30$ days, assuming $\gamma^E = 20$ and $1/\eta^E = 12$ days.

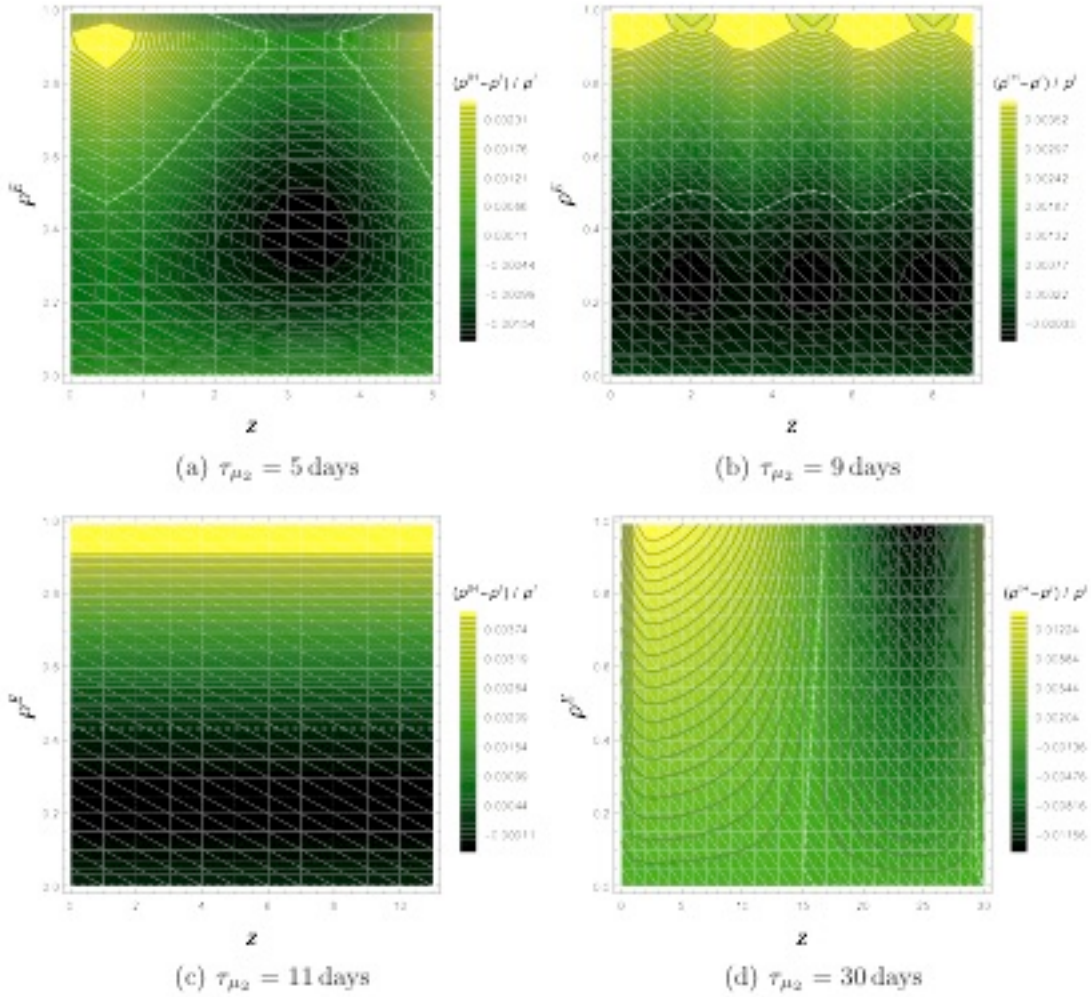


Figure 2.6 Contour plots indicating the relative difference between ρ^I and ρ^{IH} for combined ULV adulticide and weakly efficacious residual barrier spray as a function of the explicit ULV fractional knockdown ρ^E and timing offset z for various values of the ULV period τ_{μ_2} , assuming a natural vector lifetime of 14 days. Residual barrier spray is applied with a period $\tau_{\mu_1} = 30$ days, assuming $\gamma^E = 20$ and $1/\eta^E = 12$ days. The white dashed line indicates the contour $\rho^I = \rho^{IH}$.

We next focused on larval source reduction. For periodic controls applied continuously with period τ_A beginning at time $t = 0$, the larval emergence rate is given by

$$\Lambda^E(t) = \Lambda^0 \left(1 - \sigma^E e^{-\nu^E(t \bmod \tau_A)} \right), \quad (2.61)$$

with Fourier modes

$$\Lambda_n = \frac{1}{\tau_A} \int_0^{\tau_A} dt \Lambda^E(t), \quad (2.62)$$

which gives

$$\Lambda_n = \begin{cases} \Lambda^0 \left(1 - \sigma^E \frac{1 - e^{\nu^E \tau_\Lambda}}{\nu^E \tau_\Lambda} \right) & n = 0 \\ -\Lambda^0 \sigma^E \frac{1 - e^{\nu^E \tau_\Lambda}}{\nu^E \tau_\Lambda + 2\pi i n} & n \neq 0. \end{cases} \quad (2.63)$$

Ultimately, this yields the following expression for implicit larval control:

$$\sigma^I = \sigma^E \frac{1 - e^{\nu^E \tau_\Lambda}}{\nu^E \tau_\Lambda}. \quad (2.64)$$

Density plots indicating the values of σ^E are shown in Fig. 2.7, and a comparison of the explicitly controlled dynamics to the corresponding implicitly controlled dynamics are given in Fig. 2.8. Overall, we found that larval source reduction had strong implicit control strength σ^I only for application periods τ_A shorter than the decay time $1/\nu^E$, and that the implicit dynamics better approximate the explicit dynamics for shorter application periods and smaller explicit efficacies σ^E .

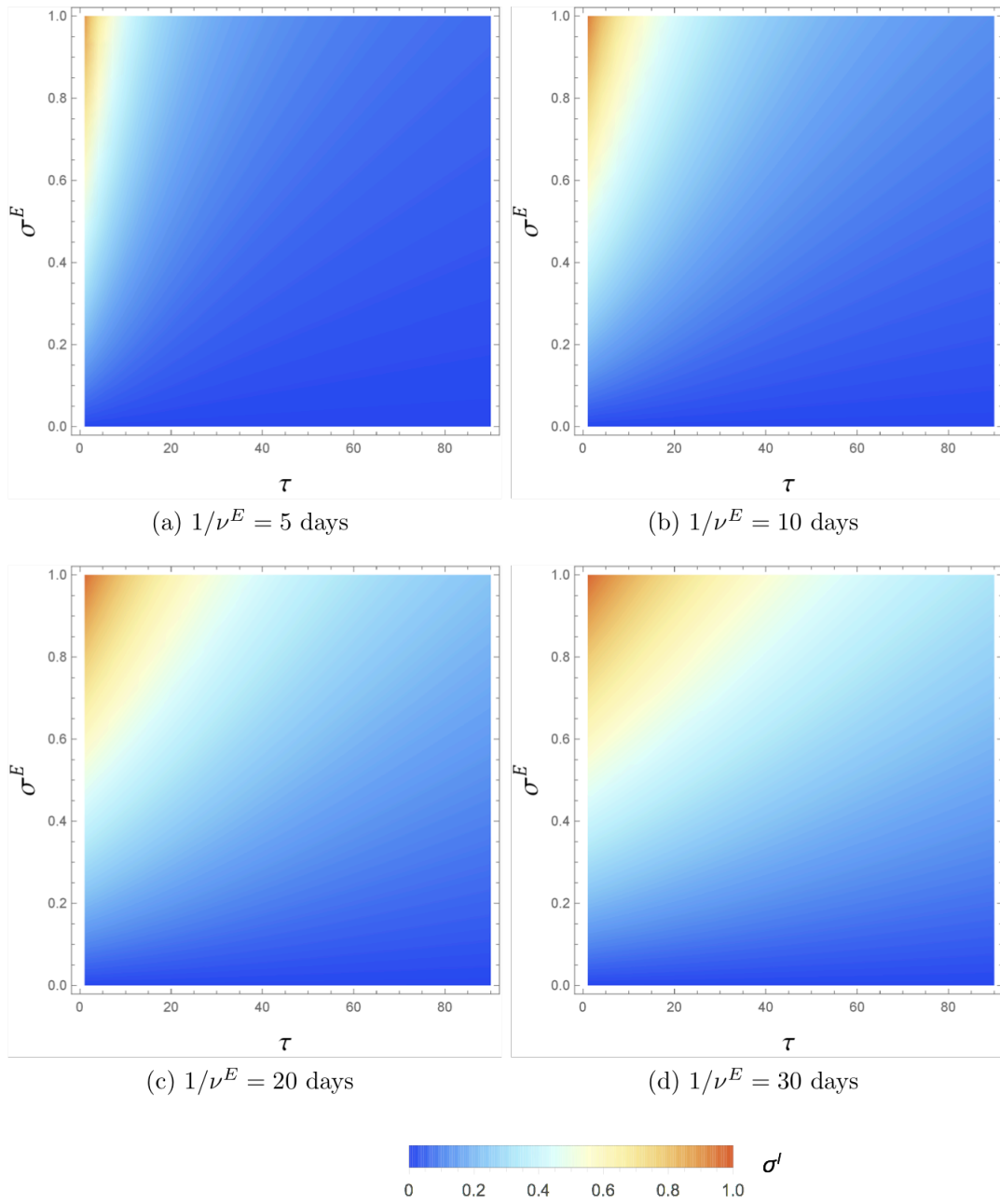


Figure 2.7 Density plots indicating the magnitude of implicit larval source reduction control strength σ' as a function of the explicit control parameters σ^E , ν^E , and τ_A . The color scale indicates the value of σ' .

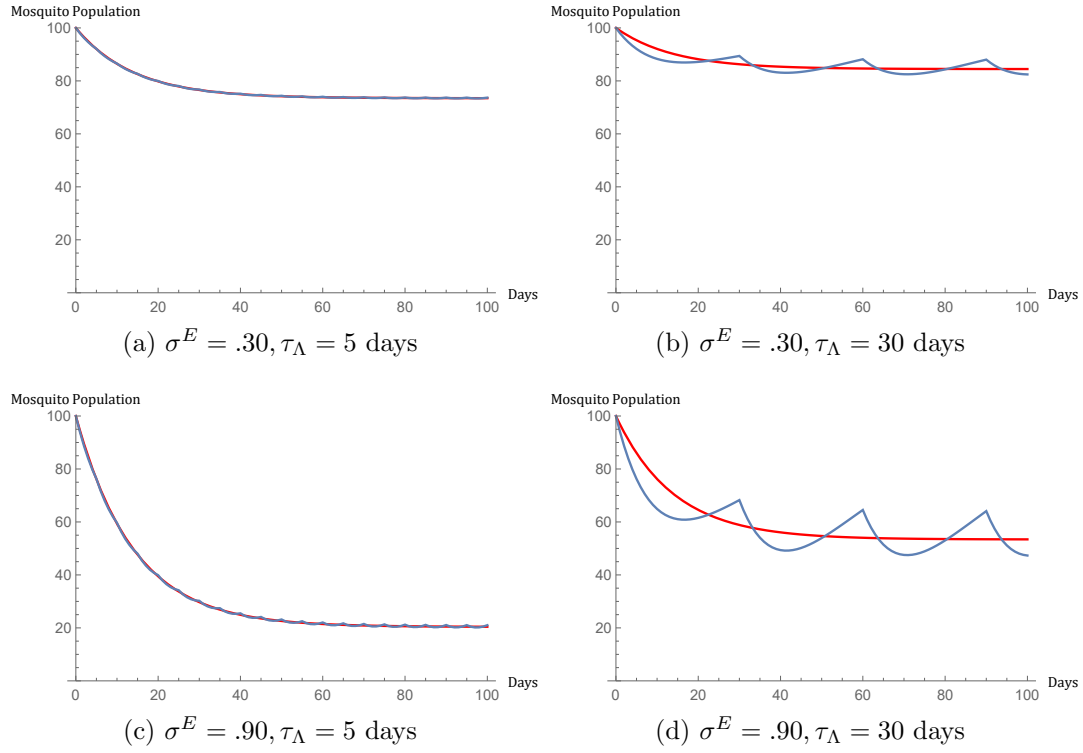


Figure 2.8 Time evolution of a population 100 mosquitoes under larval source reduction control applied at $t=0$, where $1/\mu_0=2$ weeks, $X^E(0)=\Lambda_0/\mu_0=100$, and $1/\nu^E=20$ days. Explicit control dynamics are represented by the blue curve, and the red curve gives the corresponding implicit control approximation.

The final single control that we considered was LV larvicide spray. For LV larvicide spray applied periodically with period τ_Λ beginning at time $t=0$, the larval emergence rate is given by

$$\Lambda^E(t) = \begin{cases} \Lambda^0(1 - \sigma^E) & \tau_\Lambda \leq \frac{1}{\nu^E} \\ \Lambda^0(1 - \sigma^E) & \tau_\Lambda > \frac{1}{\nu^E}, t \bmod \tau_\Lambda \leq \frac{1}{\nu^E} \\ \Lambda^0 & \tau_\Lambda > \frac{1}{\nu^E}, t \bmod \tau_\Lambda > \frac{1}{\nu^E}. \end{cases} \quad (2.65)$$

The corresponding Fourier modes are given by

$$\begin{aligned}
\Lambda_n &= \frac{1}{\tau_\Lambda} \int_0^{\tau_\Lambda} dt \Lambda^E(t) \\
&= \begin{cases} \Lambda^0(1 - \sigma^E) & \tau_\Lambda \leq \frac{1}{\nu^E}, n = 0 \\ 0 & \tau_\Lambda \leq \frac{1}{\nu^E}, n \neq 0 \\ \Lambda^0 \left(1 - \frac{\sigma^E}{\nu^E \tau_\Lambda}\right) & \tau_\Lambda > \frac{1}{\nu^E}, n = 0 \\ -\Lambda^0 \sigma^E \frac{1 - e^{-\frac{2\pi i n}{\nu^E \tau_\Lambda}}}{2\pi i n} & \tau_\Lambda > \frac{1}{\nu^E}, n \neq 0, \end{cases}
\end{aligned} \tag{2.66}$$

While the expression for implicit control is given by

$$\sigma^I = \begin{cases} \sigma^E & \tau_\Lambda \leq \frac{1}{\nu^E} \\ \frac{\sigma^E}{\nu^E \tau_\Lambda} & \tau_\Lambda > \frac{1}{\nu^E}. \end{cases} \tag{2.67}$$

Thus, for application periods shorter than the efficacy time $1/\nu^E$, the implicit and explicit control descriptions of periodic LV larvicide spray are equivalent, and all Fourier modes Λ_n vanish for $n \neq 0$. Figure 2.9 shows density plots indicating the values of σ^E , and a comparison of the explicitly controlled dynamics to the corresponding implicitly controlled dynamics is given in Fig. 2.10. We find the parameter range over which LV larvicide spray has strong implicit control strength to be larger than the parameter range over which larval source reduction has strong implicit control strength. As well, we find that strong LV larvicide implicit control strength requires at least moderate σ^E and an application period not much greater than the efficacy time $1/\nu^E$. Finally, we find that the implicit dynamics most closely match the explicit dynamics for small σ^E and small application periods.

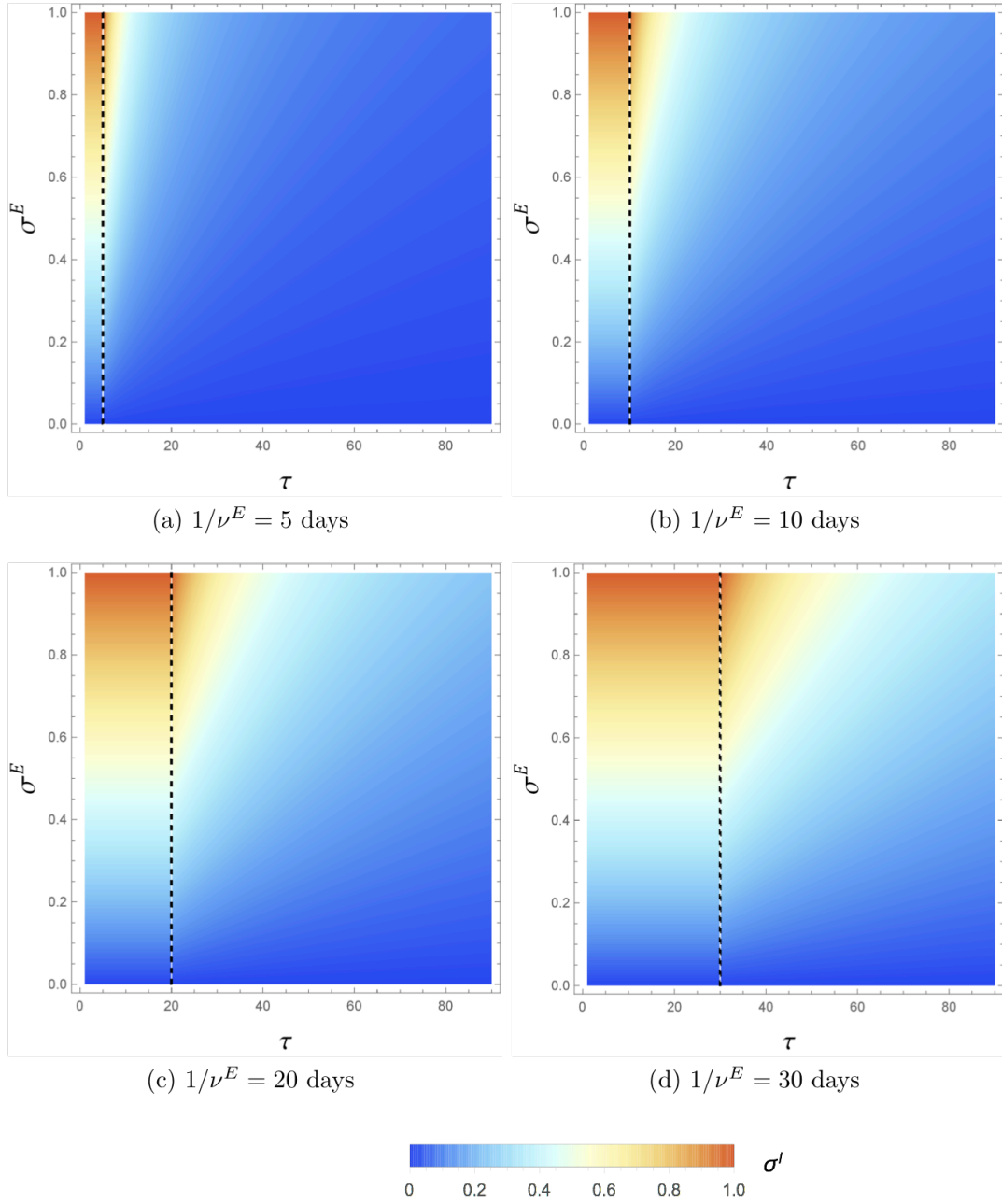


Figure 2.9 Density plots indicating the magnitude of implicit LV larvicide spray control strength σ^I as a function of the explicit control parameters σ^E , ν^E , and τ_A . The color scale indicates the value of σ^I , and the dashed lines mark $\tau = 1/\nu^E$.

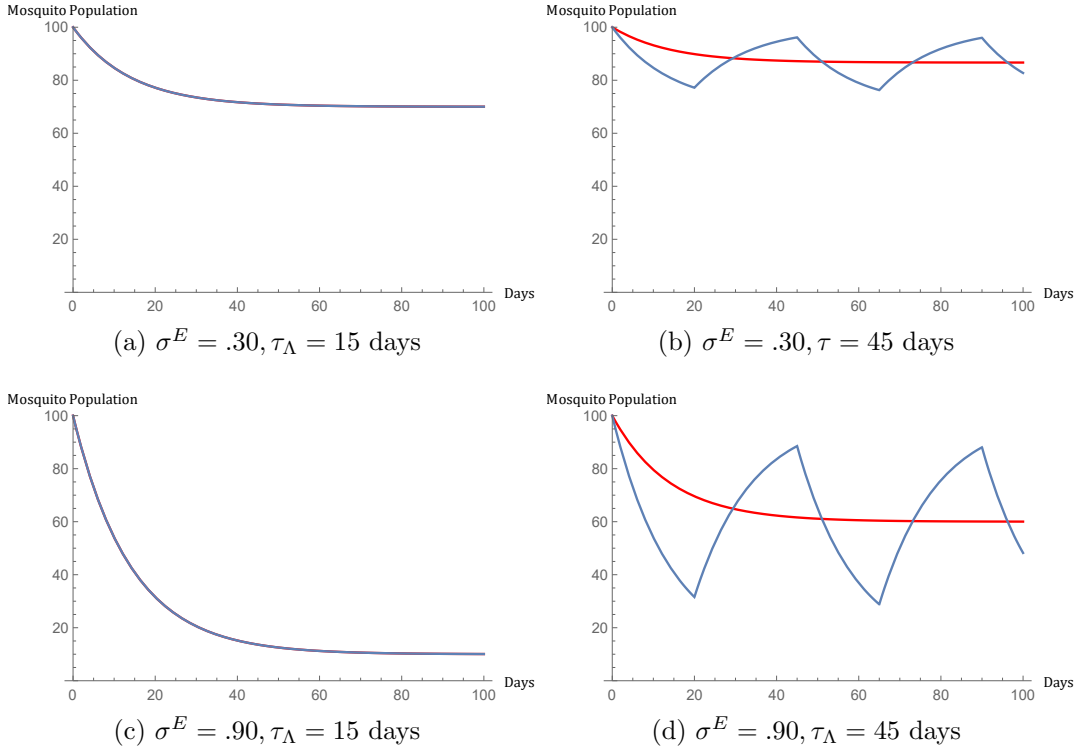


Figure 2.10 Time evolution of a population of 100 mosquitoes under larval source reduction control applied at $t=0$, where $1/\mu_0 = 2$ weeks, $X^E(0) = \Lambda_0/\mu_0 = 100$, and $1/\nu^E = 20$ days. Explicit control dynamics are represented by the blue curve, and the red curve gives the corresponding implicit control approximation.

Because of model formulation, combination of larvicide controls was only possible for systems where the two larvicide strategies operate on independent components of larval habitat. In this case, the resulting model is fully additive, and requires no further analysis.

For combined adulticide and larvicide controls, the controls enter the population dynamics independently at the implicit level, and Eq. (2.45) shows that the average vector population level under the corresponding joint explicit controls is given by the implicit control population level plus a synergistic correction term. To determine the importance of the synergistic correction, as well as the effects of relative shifts in application timings, we considered explicit adulticide protocols applied in conjunction with explicit larval control protocols, where we assumed a time lag of z days in the larval protocols relative to the adulticide protocols. Contour plots indicating the values of S for ULV adulticide with larval source reduction and residual barrier spray with larval source reduction are shown in Figs. 2.11 and 2.12 respectively.

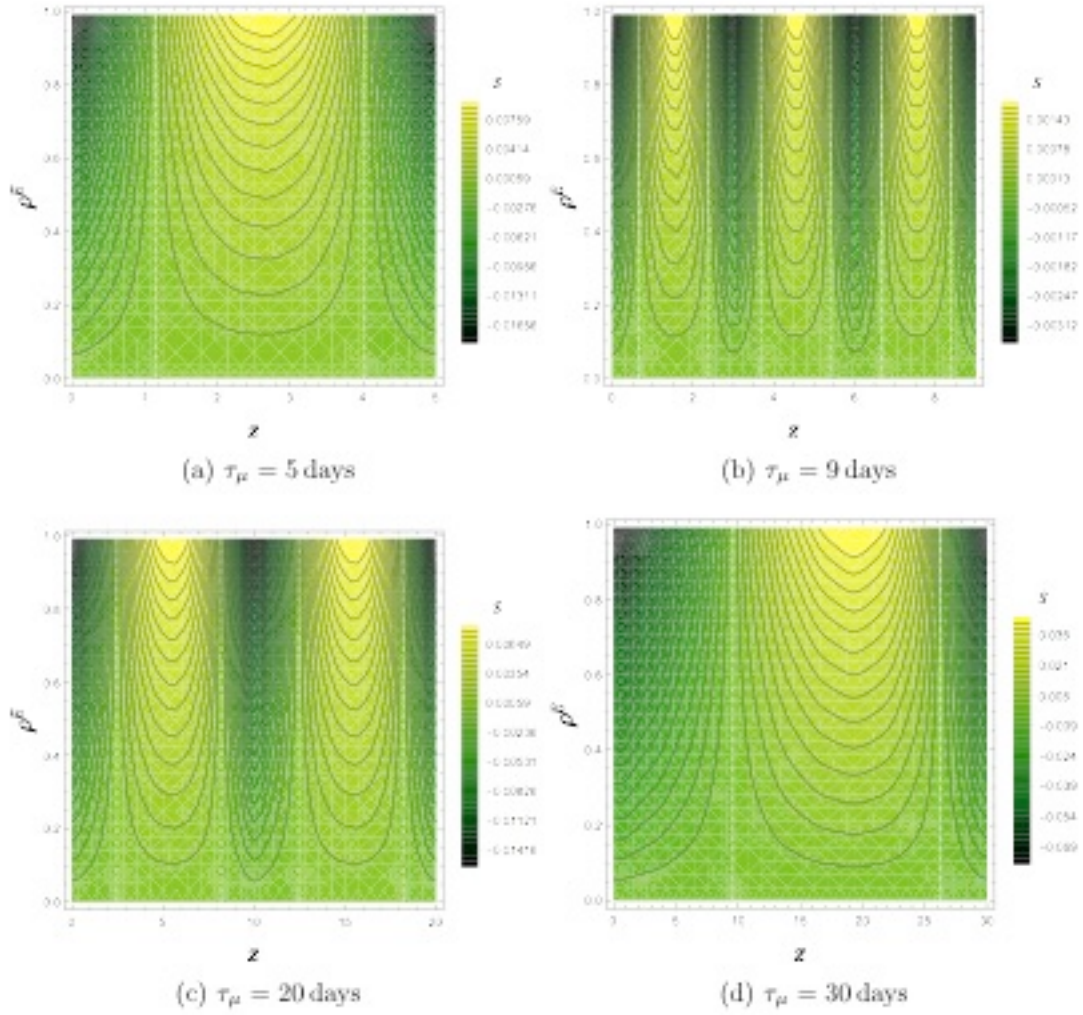


Figure 2.11 Contour plots indicating the value of synergy factor S for combined ULV adulticide and larval source reduction as a function of the explicit ULV fractional knockdown ρ^E and timing offset z for various values of the adulticide period τ_μ , assuming a natural vector lifetime of 14 days. Larval source reduction is applied with a period $\tau_L = 30$ days and $1/v^E = 20$ days. The white dashed lines indicate no synergy $S = 0$.

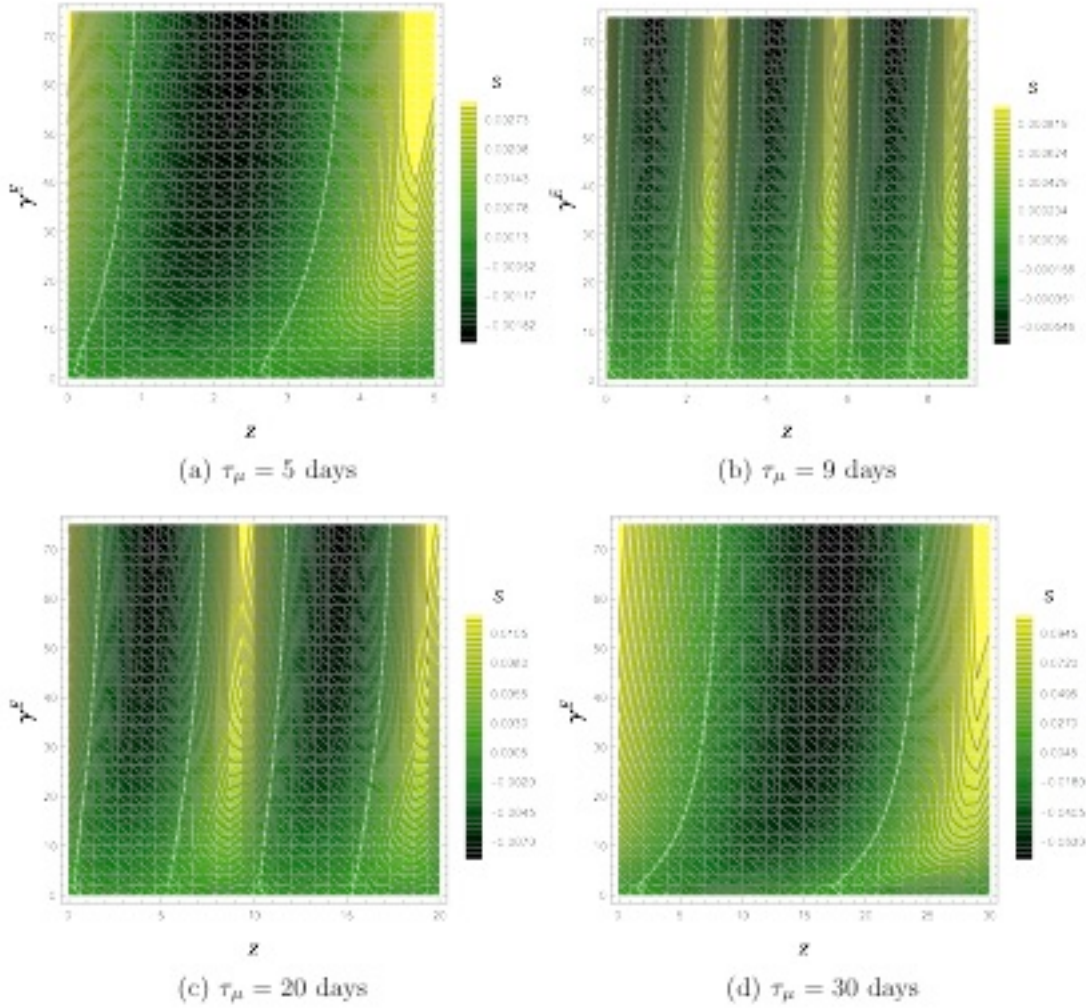


Figure 2.12 Contour plots indicating the value of synergy factor S for combined residual barrier spray larval source reduction as a function of the explicit residual barrier strength knockdown γ^E and timing offset z for various values of the adulticide period τ_μ , assuming a natural vector lifetime of 14 days and $1/\eta^E = 12$. Larval source reduction is applied with a period $\tau_A = 30$ days and $1/\nu^E = 20$ days. The white dashed lines indicate no synergy $S = 0$.

In keeping with the second objective of our work, and the primary objective of our initial proposal, we also used our models to explore synergy between management and natural variation in the mosquito population that results from phenology. Specifically, the value of S can be used to determine under what conditions it is worthwhile to adjust the timing of regular adulticide applications relative to seasonal oscillations to maximize beneficial synergy. As a specific, illustrative example, we considered a sinusoidally oscillating vector emergence rate as a basic model for seasonal or monthly fluctuations in rainfall or temperature. Letting A_0 represent the average emergence rate and τ_A represent the oscillation period, we obtained the time-dependent emergence rate $A^E(t)$ as

$$\Lambda^E(t) = \Lambda^0 \left[1 + \sigma^E \sin \left(\frac{2\pi(t - z)}{\tau_\Lambda} \right) \right], \quad (2.68)$$

where z is a timing offset which sets the peak emergence rate to occur every $z + (k + 1/4)\tau_\Lambda$ days, where k is any integer. Under a sinusoidal emergence rate and constant vector death rate μ_0 , an analytic expression for the periodic vector population can be found, and one can show that the peak periodic vector population lags the peak emergence oscillation by a time $(\tau_\Lambda/2\pi)\arctan(2\pi/(\mu_0\tau_\Lambda))$. The Fourier modes of the sinusoidal emergence rate are

$$\Lambda_n = \begin{cases} \Lambda^0, & n = 0 \\ -\frac{1}{2}i\Lambda^0\sigma^E e^{-\frac{2\pi iz}{\tau_\Lambda}}, & n = 1 \\ \frac{1}{2}i\Lambda^0\sigma^E e^{\frac{2\pi iz}{\tau_\Lambda}}, & n = -1 \\ 0, & n \neq 0, 1, -1. \end{cases} \quad (2.69)$$

If an adulticide is now applied with period τ_μ beginning at time $t = 0$ such that the combined adulticide and emergence rate period is given by τ_c , the emergence rate oscillations will have non-zero Fourier modes only for $n = 0, \pm 1$, thus to have possible non-zero values of the synergy factor S , we must have $m_\mu = 1$, which implies that the adulticide application period must be greater than or equal to τ_Λ :

$$\tau_\mu = m_\Lambda \tau_\Lambda = \tau_c, \quad (2.70)$$

where the integer m_Λ gives the number of complete emergence rate oscillations occurring over an adulticide application period. This result provides the following useful information for planning control strategies: in order to leverage beneficial synergy between a sinusoidal emergence rate and multiple adulticide impulses of the same type applied over an oscillation period, the impulse timings are required to be spaced non-uniformly in time. Figure 2.13 shows contour plots for the values S under various parameters for ULV adulticide spray and various offsets z from seasonal timing. Similar results can be derived for other management strategies. Figure 2.13 indicates that for the short emergence oscillation period of 5 days, synergistic effects between ULV adulticide and the oscillating emergence rate give a maximal population reduction when the adulticide impulse is applied about 1.75 days after the peak emergence rate oscillation. At an emergence oscillation period of 60 days, the maximally beneficial synergy occurs when the adulticide impulse is applied about 10 days after the peak emergence oscillation. Synergistic effects can provide beneficial increases at 10% to 20% reductions in the population relative to the average population for both short and long application periods.

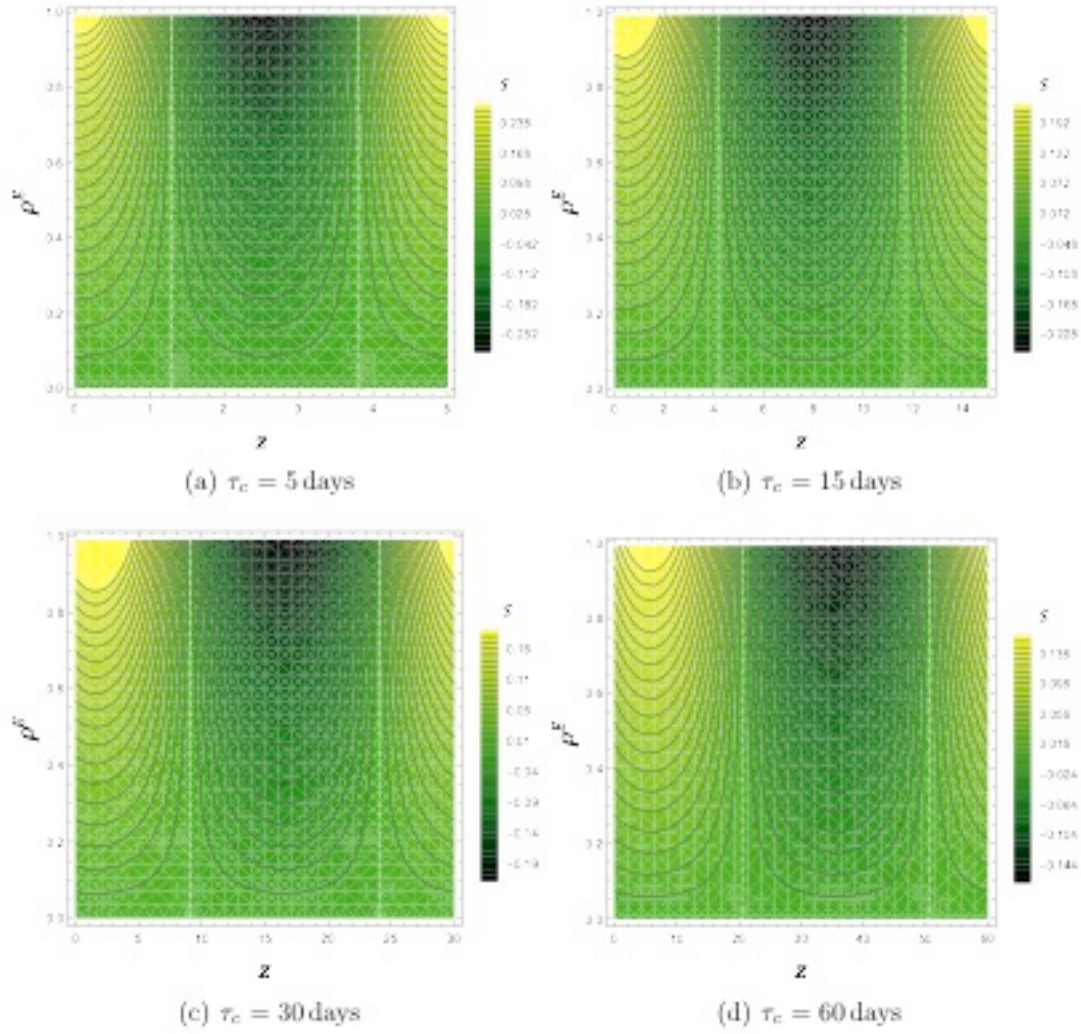
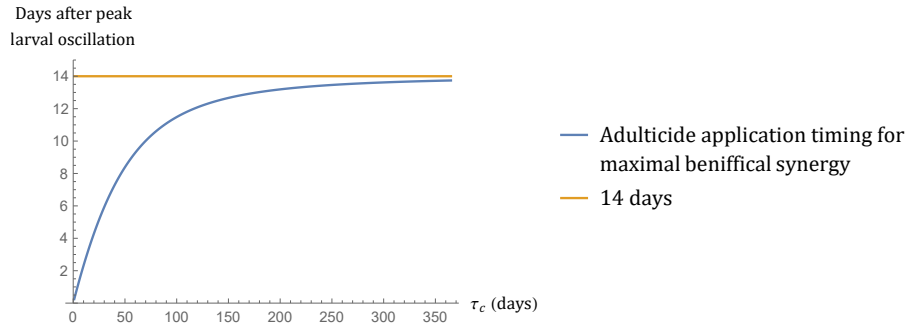
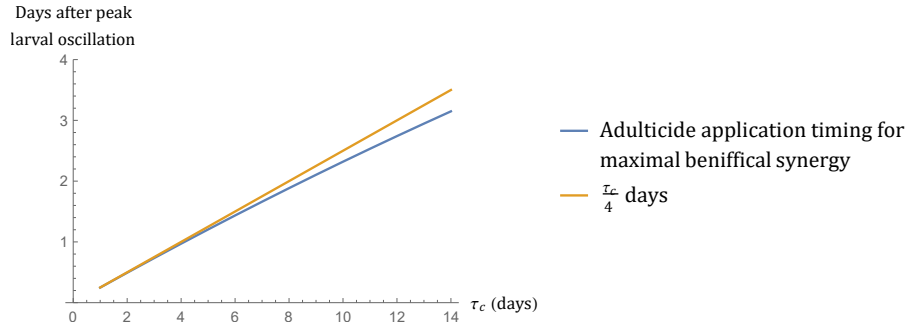


Figure 2.13 Contour plots indicating the value of synergy factor S for ULV adulticide with phenological oscillations as a function of the explicit ULV fractional knockdown ρ^E and timing offset z , assuming a natural vector lifetime of 14 days and $\sigma^E = 1$. The white dashed lines indicate no synergy $S=0$.

Figure 2.14 shows extensions to larger oscillations, including 365 day oscillations typical of seasonal phenology.



(a) Oscillation periods up to a year



(b) Short oscillation periods

Figure 2.15 Plots indicating the timing of ULV adulticide application required for maximum beneficial synergistic effects with phenological emergence rate oscillations, assuming a natural vector lifetime of 14 days.

The central results of this section are thus stated as the following vector management recommendations: to achieve maximally beneficial synergy between a ULV adulticide protocol and a sinusoidal emergence rate, for a single application over an emergence period, apply the impulse at time of the uncontrolled peak vector oscillation, and for multiple applications over an emergence period, the optimal impulse timings will be spaced non-uniformly in time.

Summary and Conclusions

Optimal control theory provides a set of mathematical tools which, when applied to vector-borne disease models, can be used to find control protocols for achieving a control objective, such as $R_0 < 1$, which minimizes a cost of control, or to find control protocols which optimally balance a disease cost with a cost of control. Due to the mathematical complexities inherent to optimal control theory, optimal control problems for vector-borne disease models are often formulated at the implicit level, where simplified numerical techniques are often possible and analytical results are sometimes within reach. Unfortunately, real-world monetary costs of control are defined in terms of explicit control properties like application frequency, so defining realistic control costs in terms of implicit control strengths alone is a difficult task. Essentially, to define a realistic cost function for implicit control strengths, one must determine the relationship between implicit control strengths and explicit control properties. For this reason, we set a goal to relate implicit and explicit control models.

Specifically, we have clarified the previously vague relationship between implicit and explicit control, and have shown that implicit control is an approximation representing the overall average effects of infinitely repeated fixed-strategy explicit control protocols (such as periodic application schedules), where over-all average means an average over time. Strong synergistic effects between explicit adulticide and larval controls can invalidate implicit control as a self-consistent modeling scheme, but we have shown synergistic effects to be negligible precisely when implicit control can be considered an accurate approximation. Thus, the accuracy and biological meaningfulness of implicit control go hand-in-hand.

PART 3: UNDERSTANDING HETEROGENEITY IN CONTROL ACCESS

Background

The increased worldwide emergence and re-emergence of vector-borne diseases seen in recent decades demands increasingly efficacious responses from health and government agencies for the prevention of public health crises [1, 2, 3]. Strategies for managing these diseases typically consist of regular, large-scale larvicide and adulticide application by airplanes and/or trucks, combined with on-the-ground control efforts that require officials obtain access to areas where mosquitoes are actively breeding in order to eliminate sources of standing water susceptible to oviposition, as well as to applying larvicide and adulticide precisely and thoroughly.

Both aerial/truck and on-the-ground strategies have advantages and disadvantages. Aerial spraying can quickly provide blanket coverage to an entire region. However, adulticide aerial spray is only effective against active mosquitoes who come into contact with short-lived airborne insecticide plumes, so repeated frequent applications may be required to achieve sufficient levels of control [15]. Repeated application of aerial adulticide can become costly and promote insecticide resistance, and residents may be uncomfortable with planes flying overhead frequently. Therefore, aerial spraying alone may not always be a viable strategy [3, 16]. With on-the-ground control, a longer lasting, more effective residual barrier adulticide spray can be applied to vegetation and other mosquito landing surfaces, and potential larval habitats (e.g. receptacles for standing water) can be identified and removed. This approach, however, is reported to be costly and time-consuming, and access to certain locations may be restricted by vegetation (e.g., in forested areas, these may represent regions of thick underbrush or dense swamp) or by resident accessibility (e.g., home owners may not allow officials into their yard, or may not be home). This makes coverage of large-scale regions potentially difficult to achieve [15]. The inaccessible locations within a broader region may be randomly dispersed or highly clustered, for example due to social influences in urban settings, or larger extents of specific habitats in natural settings, and the clustering of control access can influence overall control efficacy [17]. Further, although accessible and inaccessible locations are spatially localized to individual sites or clusters of sites, mosquito motion allows localized heterogeneous levels of vector control to produce effects over larger, potentially regional, spatial scales [17, 18].

Aerial spraying and on-the-ground control strategies provide a trade-off between small-scale localized control efficacy and ease in achieving efficient large-scale region-wide control coverage [15]. This trade-off, together with local social, political, and economic concerns, makes the design and implementation of effective integrated vector management strategies a logistical challenge [3, 16]. Given the complexities inherent to designing integrated vector management programs, mathematical models are useful tools for analyzing and predicting the efficacy of interventions strategies. Previous studies often incorporating additional controls such as vaccination and personal protection, have used metapopulation models to incorporate individual homogeneous patches of vector and host populations connected via a network structures allowing host and/or vector movement between connected patches, and are natural candidates for modelling disease systems with spatial heterogeneities at both large and small spatial scales. Results from metapopulation models have shown that network connectivity generally allows disease levels to persist in patches where they would otherwise face rapid extinction, which has important implications for designing vector management strategies.

Model Development

We chose to model a larger region with variable accessibility as a two-dimensional lattice of $N \times N$ square patches indexed by integers i , where $i \in \{1, 2, \dots, N^2 - 1, N^2\}$, laid out as in Fig. 3.1. Each patch represents a physical area of size $l \times l$, and we assume N_{ih} hosts reside in within patch i . We posit that while present in the area, hosts spend the majority of their time in and around their home patch (e.g., territory), and that the time spent traveling throughout the region is negligible by comparison. Mosquitoes, on the other hand, move continually in a somewhat random manner, and they may pass through many patches over the course of a lifetime depending on the physical patch size; *Aedes aegypti*, for example, will disperse hundreds to thousands of meters from their emergence site over the course of a lifetime [20]. Based on this observation, we consider a simplified model in which mosquitoes are able to move between neighboring patches while hosts remain fixed at their home patch.

1	2	3		$N-1$	N
$N+1$	$N+2$	$N+3$		$2N-1$	$2N$
$2N+1$	$2N+2$	$2N+3$		$3N-1$	$3N$
$\vdots$	$\vdots$	$\vdots$		$\vdots$	$\vdots$
$(N-2)N+1$	$(N-2)N+2$	$(N-2)N+3$		$(N-1)N-1$	$(N-1)N$
$(N-1)N+1$	$(N-1)N+2$	$(N-1)N+3$		N^2-1	N^2

Figure 3.1 Site indices and corresponding locations within the larger region

To capture mosquito movement, we let $N_i^v(t)$ denote the distribution of mosquitoes at patch i at a time t , and then modeled mosquito motion with a nearest neighbor random walk between patches, assuming the following population dynamics

$$\dot{N}_i^v(t) = \Lambda_i - \mu_i N_i^v(t) + \sum_{\substack{j=1 \\ j \neq i}}^{N^2} (\omega_{ij} N_j^v(t) - \omega_{ji} N_i^v(t)), \quad (3.1)$$

where Λ_i denotes the mosquito emergence rate in patch i , μ_i denotes the per-capita mosquito death rate in patch i , and ω_{ij} denotes the transition probability per unit time for an individual mosquito to hop from patch j to patch i . We assumed that parameters can vary across the network

due to control efforts. The probability per unit time for a mosquito to transition out of patch i , denoted by ω_{ii} is then defined by

$$\omega_{ii} = - \sum_{\substack{j=1 \\ j \neq i}}^{\mathcal{N}^2} \omega_{ji}, \quad (3.2)$$

and can be used to simplify the summation in Eq. (3.1)

$$\dot{N}_i^v(t) = \Lambda_i - \mu_i N_i^v + \sum_{j=1}^{\mathcal{N}^2} \omega_{ij} N_j^v(t). \quad (3.3)$$

Assuming unbiased nearest neighbor hopping with hopping rate ω , we can write ω_{ij} as

$$\omega_{ij} = -\omega \mathcal{L}_{ij}, \quad (3.4)$$

where $\mathcal{L}_{ij}$ denotes the elements of an $\mathcal{N}^2 \times \mathcal{N}^2$ Laplacian matrix associated with nearest neighbor connectivity of our network. The equilibrium mosquito population distribution, whose value in patch i we denote by N_i^{ve} , is given by the stationary solution to Eq. (3.3). This solution can be written compactly in vector-matrix notation as

$$\mathbf{N}^{ve} = (\mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} \mathbf{\Lambda}. \quad (3.4)$$

where $\mathbf{N}_v$ and $\mathbf{\Lambda}$ denote $\mathcal{N}^2$ - dimensional column vectors with components N_{iv} and Λ_{vi} , respectively, and $\mu_{\mathcal{N}^2}$ is the $\mathcal{N}^2 \times \mathcal{N}^2$ diagonal matrix with entries along the diagonal given by μ_i .

To capture system dynamics, we selected the following SEIR model

$$\begin{aligned}
\dot{S}_i^v(t) &= \Lambda_i - \mu_i S_i^v(t) - \omega \sum_{j=1}^{N^2} \mathcal{L}_{ij} S_j^v(t) - \beta^v b \frac{I_i^h(t)}{N^h} S_i^v(t) \\
\dot{E}_i^v(t) &= -\mu_i E_i^v(t) - \omega \sum_{j=1}^{N^2} \mathcal{L}_{ij} E_j^v(t) + \beta^v b \frac{I_i^h(t)}{N^h} S_i^v(t) - p^v E_i^v(t) \\
\dot{I}_i^v(t) &= -\mu_i I_i^v(t) - \omega \sum_{j=1}^{N^2} \mathcal{L}_{ij} I_j^v(t) + p^v E_i^v(t) \\
\dot{S}_i^h(t) &= -\beta^h b \frac{S_i^h(t)}{N^h} I_i^v(t) \\
\dot{E}_i^h(t) &= \beta^h b \frac{S_i^h(t)}{N^h} I_i^v(t) - p^h E_i^h(t) \\
\dot{I}_i^h(t) &= p^h E_i^h(t) - r I_i^h(t) \\
\dot{R}_i^h(t) &= r I_i^h(t),
\end{aligned} \tag{3.5}$$

where $S_{iv}(t)$, $E_{iv}(t)$, and $I_{iv}(t)$ are the number of susceptible, exposed and infected vectors in patch i at time t and $S_{ih}(t)$, $E_{ih}(t)$, $I_{ih}(t)$ and $R_{ih}(t)$ are the number of susceptible, exposed, infected and recovered hosts in patch i at time t . As we were primarily interested in the heterogeneities introduced by access variability, we assumed the total number of hosts in each patch was a fixed constant N^h . Similarly, the per-bite host-to-vector and vector-to-host transmission probabilities, β^v and β^h , respectively, the extrinsic and intrinsic incubation periods, $1/p_v$ and $1/p_h$, respectively, and the average host recovery time, $1/r$, were all assumed to be patch-independent. We assumed host birth and death rates were negligible over the time scale of interest and that all infectious mosquitoes die before recovering.

To incorporate on-the-ground and adulticide aerial spray control strategies into this model, we included patch-dependent, time-independent reductions and increases in vector emergence and death rates, respectively. Controls incorporated in this manner are simple but effective models for describing the effects of regularly repeated fixed strategy real-world controls[21]. Under this modeling methodology, the optimal control protocols for reducing the basic reproduction number are naturally phrased in terms of actionable control advice based on real-world control parameters (see PART 2 above).

In the absence of control, we assumed homogeneous natural death and emergence rates, denoted by μ_0 and Λ_0 , respectively, in each patch throughout the region. Adulticide aerial spray is an area-wide control assumed to cover the entire region equally, so we modeled this strategy as a uniform increase in vector death rates at every site. On-the-ground control affects only the ‘accessible’ sites. We modeled this strategy as a uniform increase in vector death rate and decrease in vector emergence rate in accessible/accessible sites only. We thus have three possible assignments for the vector death rate in patch i :

$$\mu_i = \begin{cases} \mu_0, & \text{No controls applied to system} \\ \mu_N, & \text{Controlled system, patch } i \text{ non-compliant} \\ \mu_C, & \text{Controlled system, patch } i \text{ compliant} \end{cases}$$

And similarly, three possible assignments for vector birth rate in patch i

$$\Lambda_i = \begin{cases} \Lambda_0, & \text{No controls applied to system} \\ \Lambda_N, & \text{Controlled system, patch } i \text{ non-compliant} \\ \Lambda_C, & \text{Controlled system, patch } i \text{ compliant} \end{cases}$$

Using the above model, we focused on predicting the basic reproduction number, R_0 . Following [23], the next generation matrix FV^{-1} for our disease system in Eq. (3.5) can be written as the following $4N^2 \times 4N^2$ matrix:

$$\mathcal{FV}^{-1} = \begin{pmatrix} 0_{2N^2} & 0_{2N^2} \\ FV_{21}^{-1} & FV_{22}^{-1} \end{pmatrix}, \quad (3.6)$$

where

$$FV_{21}^{-1} = \begin{pmatrix} p^v (p^v 1_{N^2} + \mu_{N^2} + \omega \mathcal{L})^{-1} & 0_{N^2} \\ 0_{N^2} & 1_{N^2} \end{pmatrix}, \quad (3.7)$$

$$FV_{22}^{-1} = \begin{pmatrix} 0_{N^2} & \beta^v \frac{b}{r} p^v (p^v 1_{N^2} + \mu_{N^2} + \omega \mathcal{L})^{-1} (N^h)^{-1} N_{N^2}^{ve} \\ \beta^h b (\mu_{N^2} + \omega \mathcal{L})^{-1} & 0_{N^2} \end{pmatrix}. \quad (3.8)$$

If E_v, E_h, I_v , and I_h exposed and infectious vectors and hosts are introduced as a perturbation to a completely susceptible disease-free equilibrium state, the distribution of newly generated exposed and infectious vectors is given by the next generation matrix's action on the $4N^2$ dimensional column matrix $((E_v)^T, (E_h)^T, (I_v)^T, (I_h)^T)^T$ as follows:

$$\mathcal{FV}^{-1} \begin{pmatrix} \mathbf{E}^v \\ \mathbf{E}^h \\ \mathbf{I}^v \\ \mathbf{I}^h \end{pmatrix} = \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ p^v (p^v 1_{\mathcal{N}^2} + \mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} \mathbf{E}^v + \beta^v \frac{b}{r} p^v (p^v 1_{\mathcal{N}^2} + \mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (N^h)^{-1} N_{\mathcal{N}^2}^{ve} \mathbf{I}^h \\ \mathbf{E}^h + \beta^h b (\mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} \mathbf{I}^v \end{pmatrix} \quad (3.9)$$

The eigenvalues λ of the next generation matrix can be found by solving the following characteristic equation:

$$\begin{aligned} 0 &= \text{Det} [\lambda 1_{4\mathcal{N}^2} - \mathcal{FV}^{-1}] \\ &= \lambda^{2\mathcal{N}^2} \text{Det} \left[\lambda^2 1_{\mathcal{N}^2} - \beta^v b \beta^h \frac{b}{r} p^v (\mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (p^v 1_{\mathcal{N}^2} + \mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (N^h)^{-1} N_{\mathcal{N}^2}^{ve} \right]. \end{aligned} \quad (3.10)$$

Letting $\mathcal{M}$ denote the following matrix

$$\mathcal{M} = \beta^v b \beta^h \frac{b}{r} p^v (\mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (p^v 1_{\mathcal{N}^2} + \mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (N^h)^{-1} N_{\mathcal{N}^2}^{ve}, \quad (3.11)$$

the above characteristic equation can be written as

$$0 = \lambda^{2\mathcal{N}^2} \text{Det} [\lambda^2 1_{\mathcal{N}^2} - \mathcal{M}]. \quad (3.12)$$

The corresponding eigenvectors of $\mathcal{FV}^{-1}$ are determined by the relation

$$\lambda \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \mathbf{I}^v \\ \mathbf{I}^h \end{pmatrix} = \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \beta^v \frac{b}{r} p^v (p^v 1_{\mathcal{N}^2} + \mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (N^h)^{-1} N_{\mathcal{N}^2}^{ve} \mathbf{I}^h \\ \beta^h b (\mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} \mathbf{I}^v \end{pmatrix}. \quad (3.13)$$

while the eigenvalues of $(\mathcal{FV}^{-1})^2$ are given by the set $\{\lambda^2 | \lambda \text{ an eigenvalue of } \mathcal{FV}^{-1}\}$, with corresponding eigenvectors determined by

$$\lambda^2 \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \mathbf{I}^v \\ \mathbf{I}^h \end{pmatrix} = \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \underline{\mathcal{M}}\mathbf{I}^v \\ \mathcal{M}\mathbf{I}^h \end{pmatrix}, \quad (3.14)$$

where

$$\underline{\mathcal{M}} = \beta^v b \beta^h \frac{b}{r} p^v (p^v 1_{\mathcal{N}^2} + \mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1} (N^h)^{-1} N_{\mathcal{N}^2}^{ve} (\mu_{\mathcal{N}^2} + \omega \mathcal{L})^{-1}. \quad (3.15)$$

The matrices M and $\underline{M}$ have identical spectra, and we refer to them as the “second generation” matrices. If a completely susceptible disease-free equilibrium state is perturbed by the introduction of $\mathbf{I}^v$ infectious vectors, the disease will first travel through the susceptible host population, and those hosts who become infectious will pass the disease to the susceptible vector population, ultimately resulting in a distribution $\underline{M}\mathbf{I}^v$ of newly infectious vectors. Likewise, if $\mathbf{I}^h$ infectious hosts are introduced as a perturbation to a 100% susceptible disease-free equilibrium state, a distribution $M\mathbf{I}^h$ of newly infectious hosts will be generated as the disease passes through the susceptible vector population. We use these second generation matrices to determine R_0 by finding the largest non-negative solutions to Eq. (3.12) and the corresponding worst case scenario spatial distributions of infectious host and vectors by solving the following eigenvector equations:

$$\begin{aligned} \mathcal{R}_0^2 \mathbf{I}^h &= \mathcal{M} \mathbf{I}^h \\ \mathcal{R}_0^2 \mathbf{I}^v &= \underline{\mathcal{M}} \mathbf{I}^v. \end{aligned} \quad (3.16)$$

We first considered the simplest scenario – a single, isolated patch. In this case, the SEIR model in Eq. (3.5) reduces to a single-patch SEIR, making the characteristic equation trivial to solve. For the single uncontrolled, non-accessible and accessible patches, R_0 is given, respectively, by

$$\begin{aligned} \mathcal{R}_{00} &= \sqrt{\beta^v \frac{b}{r} \beta^h \frac{b}{\mu_0} \frac{p_v}{p_v + \mu_0} \frac{1}{N^h} \frac{\Lambda_0}{\mu_0}} \\ \mathcal{R}_{0N} &= \sqrt{\beta^v \frac{b}{r} \beta^h \frac{b}{\mu_N} \frac{p_v}{p_v + \mu_N} \frac{1}{N^h} \frac{\Lambda_N}{\mu_N}} \\ \mathcal{R}_{0C} &= \sqrt{\beta^v \frac{b}{r} \beta^h \frac{b}{\mu_C} \frac{p_v}{p_v + \mu_C} \frac{1}{N^h} \frac{\Lambda_C}{\mu_C}}. \end{aligned} \quad (3.17)$$

Further analysis showed that these are also the values of R_0 for the special case of a region with

multiple patches where all patches are identical (e.g., all uncontrolled, all non-accessible or all accessible).

Next, we considered what we termed the ‘infinitely fast hopping limit’, wherein $\omega \rightarrow \infty$. For this, we utilized the methods of Tien et al. outlined in [25]. This allowed us to obtain the following expression for R_0

$$\mathcal{R}_0 \underset{\omega \rightarrow \infty}{=} \sqrt{\beta^v \frac{b}{r} \beta^h \frac{b}{\langle \mu \rangle} \frac{p^v}{p^v + \langle \mu \rangle} \frac{1}{N^h} \frac{\langle \Lambda \rangle}{\langle \mu \rangle}}. \quad (3.18)$$

Finally, we considered the other extreme, which we termed the ‘infinitely slow hopping limit’, with $\omega = 0$. In this case, all patches decouple, meaning that R_0 is given by the worst possible scenario of any single patch, and thus

$$\begin{aligned} \mathcal{R}_{0(0)} &= \max_i \left\{ \sqrt{\beta^h \frac{b}{\mu_i} \beta^v \frac{b}{r} \frac{p^v}{p^v + \mu_i} \frac{1}{N^h} \frac{\Lambda_i}{\mu_i}} \right\} \\ &= \begin{cases} \mathcal{R}_{00}, & \text{Uncontrolled system} \\ \mathcal{R}_{0N}, & \text{Less than 100\% compliant} \\ \mathcal{R}_{0C}, & \text{100\% compliant.} \end{cases} \end{aligned} \quad (3.19)$$

From the limits above, we next considered finite hopping rates. For the case of slow but non-zero hopping, we analyzed our system using degenerate perturbation theory. Although perturbation results for R_0 were complicated, they indicated that, for a given set of accessible and non-accessible control efficacies and a given neighborhood accessibility structure, the reduction in R_0 induced by small non-zero mosquito hopping (e.g. the value of δR_0) is determined by the larger and most tightly clustered non-accessible patches.

To model control within our heterogeneous patch system, we used the results from PART 2 (see above). This involves repeated application at a fixed rate. When this is the case, it is reasonable to expect the associated cost of control to be roughly proportional to the application frequency. On-the-ground control requires small teams of government or health agency employees to visit every site in the region so that they may access the location and implement residual barrier spray and larval source reduction. This requires a greater numbers of man-hours to deliver in regions with high rates of access. We therefore assume the following daily cost of control C which depends linearly on the application frequencies f_A and f_D :

$$C = c_A f_A + (c_{DC} f + c_{DN}(1 - f)) f_D. \quad (3.20)$$

In the above equation, c_A is the cost per application of adulticide aerial spray applied to the entire region, c_{DC} is the cost for applying on-the-ground control to a 100-patch region at 100% accessibility, c_{DN} is the labor cost for applying on-the-ground control to a 100-patch neighborhood at 0% accessibility, and f is the fraction of accessible sites in the region.

We consider the following control problem: for combined aerial spray and on-the-ground control strategies, aerial spray only, and on-the-ground control only, find the application frequencies f_A and f_D which suppress outbreak potential by reducing R_0 to unity while

minimizing the cost of control C , subject to $f_A, f_D \in [0, 1 \text{ day}^{-1}]$. The bounds $0 \leq f_A, f_D \leq 1 \text{ day}^{-1}$ limit control applications to occur at a rate of at most once per day. Even if unlimited resources were available, societal and logistical concerns would likely prohibit government or health agency employees from applying pesticides and invading yards more than once per day.

Model Analysis

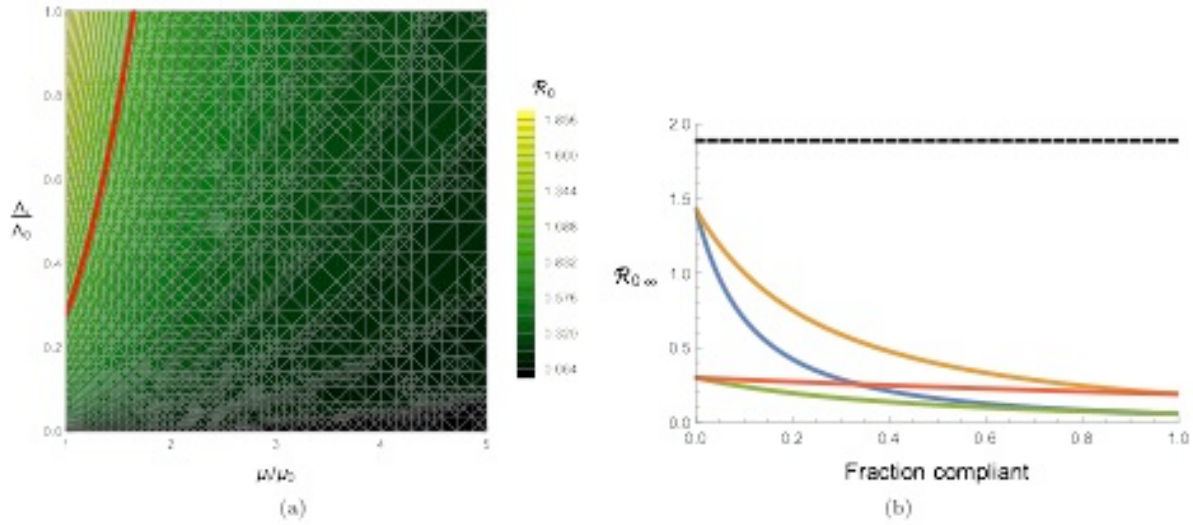


Figure 3.1 (a) Single-site basic reproduction number values as a function of the relative controlled death rate μ_i/μ_0 and relative controlled emergence rate Λ_i/Λ_0 . These values also represent the homogeneous system basic reproduction numbers when μ_i and Λ_i are uniform across the neighborhood, as well as the no-hopping basic reproduction numbers when μ_i and Λ_i are the non-accessible death and emergence rates. Control efficacy increases along the μ_i/μ_0 axis and decreases along the Λ_i/Λ_0 axis. The case of no control is represented by the upper left corner where $R_0 = 1.89$, and the red line indicates $R_0 = 1$. Control efficacy for non-accessible sites is represented along the top of the plot where $\Lambda_i = \Lambda_0$. (b) Infinitely fast hopping basic reproduction number values as a function of percent accessibility. The dotted black line represents the uncontrolled value $R_{0\infty} = 1.89$, and the different color curves represent varying degrees of control efficacy in accessible and non-accessible sites. **Blue** represents strong accessible efficacy and weak non-accessible efficacy, **orange** represents moderate accessible efficacy and weak non-accessible efficacy, **green** represents strong accessible efficacy and moderate non-accessible efficacy, and **red** represents moderate accessible efficacy and moderate non-accessible efficacy.

Fig. 3.1 shows numerical simulation results for the analytic expressions for R_0 derived for infinitely slow hopping, infinitely fast hopping, and homogeneous systems. Figure 3.1a represents the single-site, homogeneous system, and no-hopping R_0 values as a function of relative adulticide efficacy μ_i/μ_0 and relative larval source reduction efficacy Λ_i/Λ_0 . For the case of a single site, μ_i and Λ_i represent the site's controlled death and emergence rates, and for the case of a homogeneous system, μ_i and Λ_i represent the controlled death and emergence rates,

which are uniform over the entire system. For an inhomogeneous system, Fig. 3.1a represents the

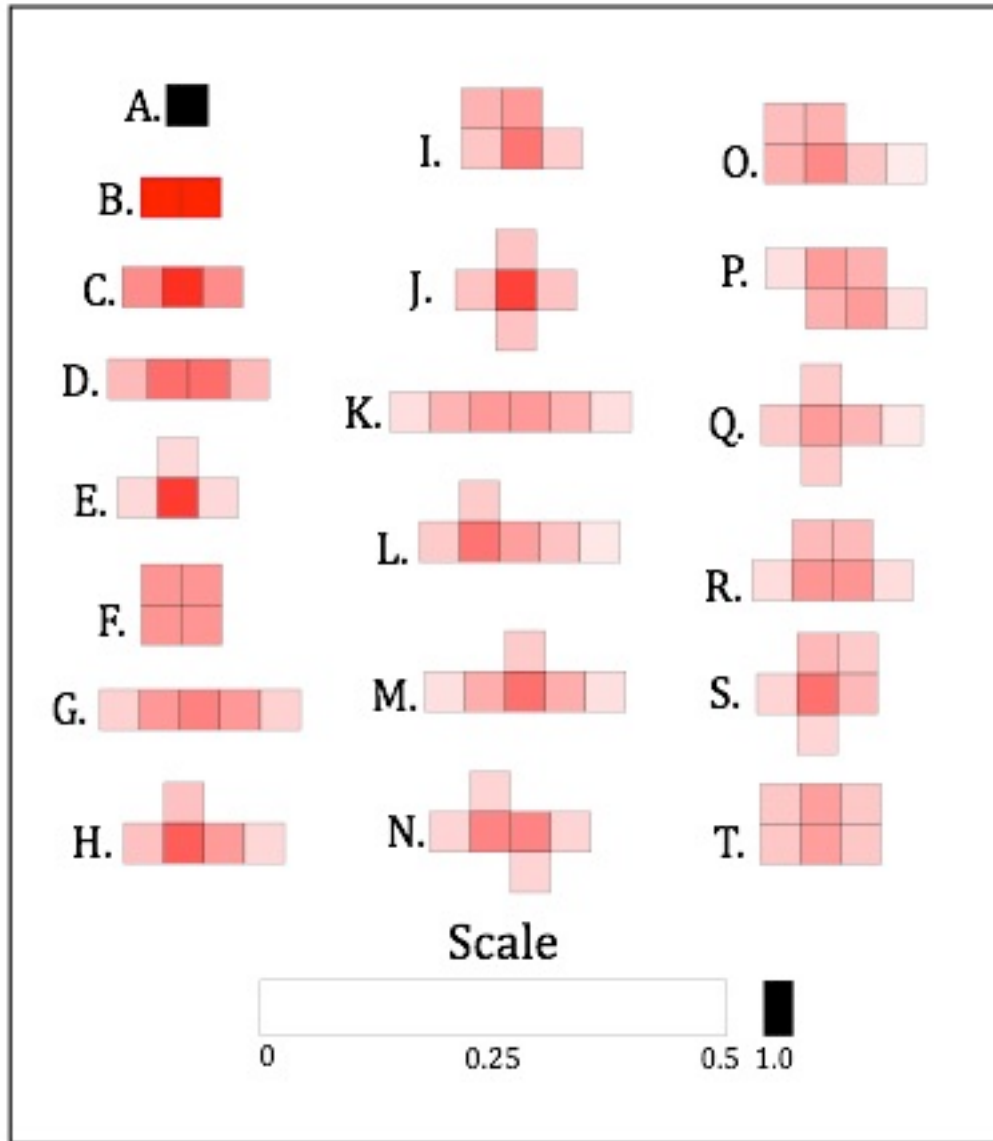


Figure 3.2 Various possible arrangements of varying sizes of non-compliant blocks. The shading within a particular configuration indicates the distributions of the unperturbed eigenvectors $I^h(0)$ and $I^v(0)$ as determined by first order perturbation analysis when that configuration is the unique configuration which determines $\delta R(0)$ in a region. Any configuration of size one through six can be obtained from one of the pictured configurations through a number of bending symmetry operations.

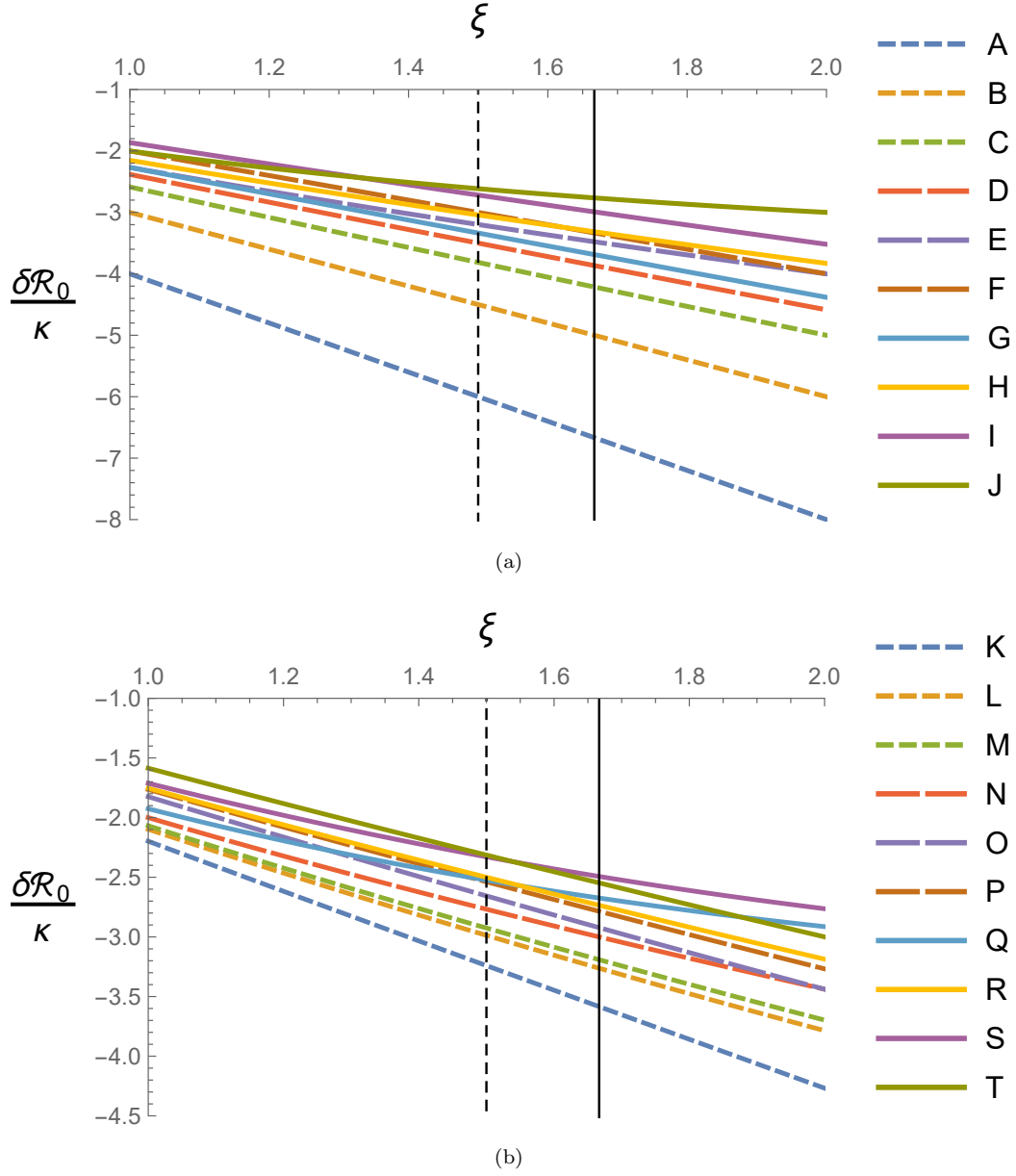


Figure 3.3 Basic reproduction number perturbation (scaled by κ) as functions of ξ induced by the non-accessible blocks pictured in Fig. 3.2. In Fig. 3.3a, line A represents a single non-compliant site, line B represents a block of two non-compliant sites, line C represents a block of three non-compliant sites, lines D, E, and F represent different configurations of blocks of four non-compliant sites, and lines G, H, I, and J represent different blocks of five non-compliant sites. All lines in Fig. 3.3b represent different blocks of six non-compliant sites. In both plots, the solid black vertical line $\xi = 5/3$ is the largest value of ξ achievable when $p^V = \mu_0$, and corresponds to the case of no control in non-accessible sites and strongly efficacious control control in accessible sites. The dotted vertical line $\xi = 1.5$ corresponds to the maximum possible value of ξ in the limit of strongly efficacious non-compliant control $\mu_N / p^V \rightarrow \infty$

no-hopping basic reproduction number when μ_i and λ_i represent non-accessible death and emergence rates. We assume that non-accessible sites are only subject to an adulticide spray which does not decrease vector emergence rates below their natural value, so the relevant values of R_0 are given along the top of Fig. 3.1a. In general we see that R_0 decreases as μ_i/μ_0 increases from zero to infinity, and that R_0 increases as λ_i/λ_0 increases from zero to one, thus implying that R_0 generally decreases with increasing control efficacy. The red line in Fig. 3.1a represents $R_0 = 1$ so parameter values to the right of and below this line will effectively suppress outbreak potential for our model parameters in a single-site system, homogeneous system, or no-hopping system. The case of no control is given in the upper left-hand corner of Fig. 3.1a, where $R_0 = 1.89$. Figure 3.1b shows the infinite hopping basic reproduction number $R_{0\infty}$ as a function of percent accessible patches, assuming various accessible and non-accessible control efficacies. At zero percent accessible, on-the-ground control has no effect on the system, so the corresponding $R_{0\infty}$ values in Fig. 3.1b represent aerial control only and are equivalent to the homogeneous system R_0 values. In general, $R_{0\infty}$ decreases as a function of percent accessible, and it decreases more rapidly when the relative efficacy of accessible control to non-accessible control is larger.

Figures 3.2 and 3.3 summarize our results for the perturbation analysis for small non-zero hopping rates. Specifically, Fig. 3.2 shows a number of clustering arrangements for non-accessible blocks of sizes one through six sites. In Fig. 3.3, we plot the corresponding values of $\delta R_0/\alpha$ induced by those non-accessible blocks as a function of ξ (the relative efficacy of accessible versus non-accessible control), assuming that the blocks pictured are completely surrounded by accessible sites. If more than one non-accessible configuration in Fig. 3.2 is present in a region, the corresponding values of δR_0 indicated by Fig. 3.3 will represent candidate δR_0 values, and the actual value of δR_0 will be determined by the block with the largest candidate. The shading within any one particular configuration in Fig. 3.2 shows the distributions of the unperturbed eigenvectors $I_h(0)$ and $I_v(0)$ as determined by first order perturbation analysis when that configuration gives the unique largest candidate δR_0 value in a region. For a given configuration, we see that $I_h(0)$ and $I_v(0)$ tend to peak and decay away from the sites with the fewest number of connections to the configuration border.

Fig. 3.4 shows optimized control results for the cases of no mosquito hopping, infinitely fast mosquito hopping, and homogeneous systems (at any hopping rate). These correspond to the special cases where we can find analytic expressions for R_0 that do not depend on the spatial distribution of accessible plots. In the no hopping limit, we find that, unless the system is 100% accessible, the optimal control action is to apply only aerial spray about once every 4.80 days at a cost of about \$5.02 per day on average. At 100% accessibility, the optimal control action is to apply only on-the-ground control about once every 4.5 months at a cost of about \$3.08 per day on average. Finding that on-the-ground control is never recommended below 100% accessibility reflects the fact that, at a hopping rate of zero, the basic reproduction number is determined solely by the non-accessible sites. For homogeneous systems, R_0 is independent of hopping rate, and therefore for any ω , the optimal control action for a 100% accessible system is on-the-ground only control applied about once every 4.5 months, while the optimal control action for a 100% non-accessible system is aerial spray only control applied about once every 4.80 days. In the infinitely fast hopping limit, we find that below about 4.58% accessibility, the optimal control action is aerial spray only control applied about once every 4.80 days. Above about 4.80% accessibility, the optimal control action is on-the-ground only control, with optimal application frequencies decreasing as accessibility increases. At about 4.80% accessibility, on-

the-ground control must be applied about once every 19.5 days at a cost of about \$4.74 per day on average. The on-the-ground only daily cost and application frequency reduce to \$3.08 per day and about once every 4.5 months, respectively, as percent accessibility approaches 100%. We thus see that only within a narrow accessibility interval (4.58%, 4.80%) does optimal control require combined aerial spray and on-the-door strategies. In this interval, the combined controls are applied less frequently than they would be if they were used on their own.

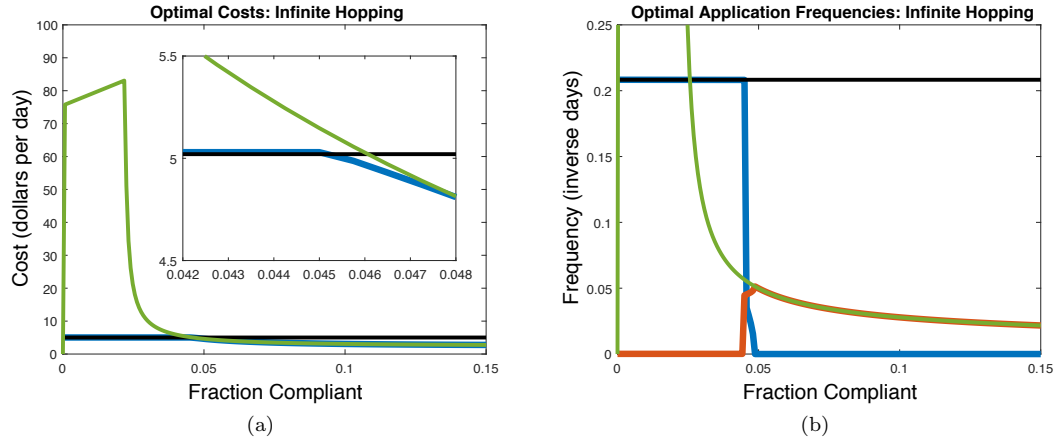


Figure 3.4 Optimal costs and application frequencies in the infinite hopping $\omega \rightarrow \infty$ limit as functions of percent accessibility. For the special cases of 100% and 0% accessibility, the above optimal costs and application frequencies are equivalent to the optimal costs and application frequencies for a homogeneous region at any hopping rate. In Fig. 3.4a, the blue curve is the optimal costs for combined aerial spray and on-the-ground strategies, while the green and black curves are the optimal costs for on-the-ground only control and aerial only control, respectively. The crossover points in the zoomed-in inset show the cut-off accessibility levels, beyond which combined control strategies or on-the-ground only control becomes more cost effective than aerial only control. In Fig.3.4b, the blue and the red curves are the optimal aerial and on-the-ground application frequencies, respectively, for combined control strategies, while the green and black curves are the optimal application frequencies for on-the-ground only control and aerial only control, respectively. The optimal on-the-ground only costs increase linearly between 0% and about 2.1% accessibility in Fig. 3.4a, and the optimal on-the-ground only frequencies are equal to 1 day⁻¹.

Figures 3.5 and 3.6 show the effects of finite hopping rates on optimal control. Specifically, they show optimized costs and applications frequencies as functions of hopping rate for specific clustered and dispersed 20% and 60% accessible distributions under both periodic and reflecting boundary conditions. for a given accessibility level, the different boundary conditions yield negligible differences in optimized cost and frequency curves for the clustered configurations, and yield qualitatively and numerically similar curves for the dispersed configurations. Generally, the periodic boundary systems are slightly cheaper to control than the corresponding reflecting boundary systems, and require slightly less frequent control applications. Figures 3.5 and 3.6 also show that, unlike boundary conditions, accessibility clustering can have a strong effect on optimal controls. Clustered systems are much more expensive to control than the corresponding dispersed systems, and they require much more

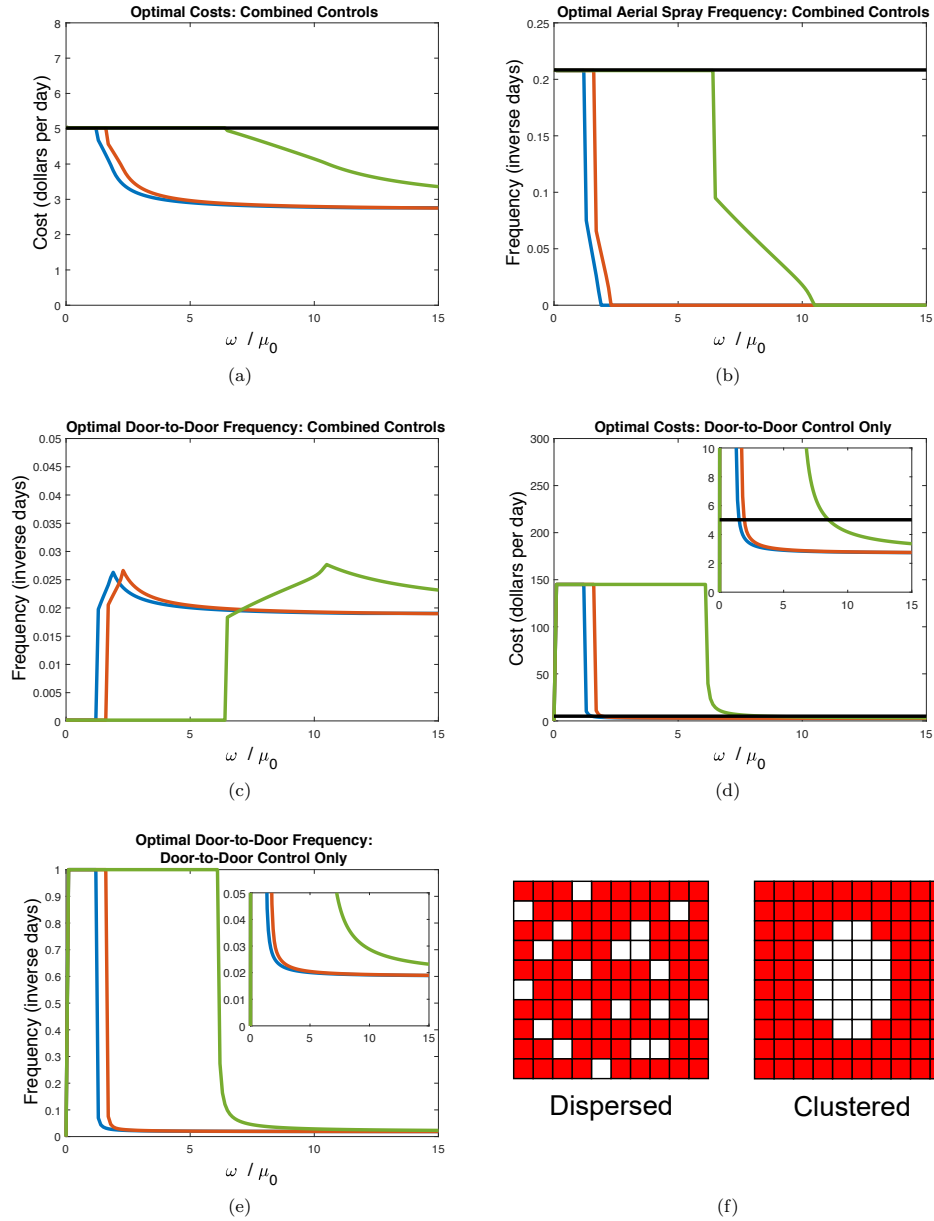


Figure 3.5 Optimal controls and application frequencies for the 20% accessibility dispersed and clustered distributions in Fig. 3.5f, where white squares indicate compliant sites, and red squares indicate non-compliant sites. Blue and red curves correspond to the dispersed distribution under periodic and reflecting boundary conditions, respectively. The differences in costs and frequencies between reflecting and periodic boundary conditions is negligible for the clustered distributions, and the green curves in the figures correspond to the clustered distribution under either reflecting or periodic boundaries (these curves coincide). The black line in Figs. 3.5a, 3.5b, and 3.5d corresponds to aerial spray control only (e.g. used without on-the-ground control). The crossover points in the zoomed-in inset in Fig. 3.5d are the cut-off hopping rates beyond which on-the-ground control alone becomes more cost-effective than aerial spraying alone.

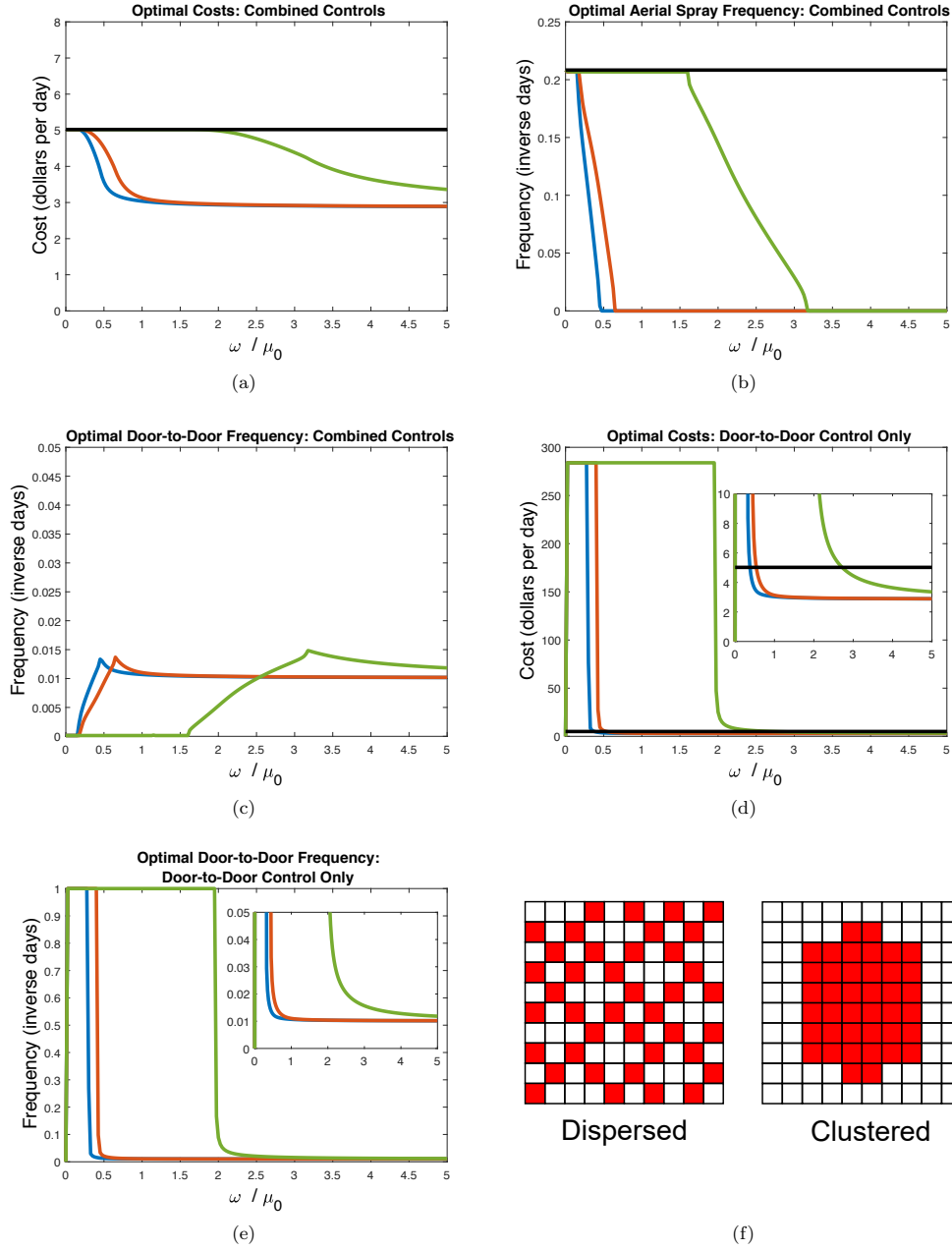


Figure 3.6 Optimal controls and application frequencies for the 60% accessibility dispersed and clustered distributions in Fig. 3.6f, where white squares indicate compliant sites, and red squares indicate non-compliant sites. Blue and red curves correspond to the dispersed distribution under periodic and reflecting boundary conditions, respectively. The differences in costs and frequencies between reflecting and periodic boundary conditions is negligible for the clustered distributions, and the green curves in the figures correspond to the clustered distribution under either reflecting or periodic boundaries (these curves coincide). The black line in Figs. 3.6a, 3.6b and 3.6d corresponds to aerial spray control only (e.g. used without on-the-ground control). The crossover points in the zoomed-in inset in Fig. 3.6d are the cut-off hopping rates beyond which on-the-ground only control becomes more cost-effective than aerial spray only control.

frequent control applications. Further, Figs. 3.5 and 3.6 show that as hopping rates increase, optimized control becomes cheaper and needs to be applied less often, and that for small hopping rates, the optimal control action is to apply aerial only control about once every 4.80 days. Focusing on any one configuration and boundary condition, we see that as the hopping rate increases away from zero, there exists a threshold hopping rate where the optimal control action transitions from an aerial spray only strategy to a combined aerial spray and on-the-ground strategy. At even larger hopping rates, we find a second threshold where the optimal control action transitions from a combined control strategy to an on-the-ground only control strategy. For the clustered 20% accessibility distribution in Fig. 3.5, under either boundary condition, optimal control action calls for combined strategies for hopping rates $\omega \in (6.20\mu_0, 10.5\mu_0)$. For hopping rates below and above this interval, optimal control action calls for aerial spray only and on-the-ground only, respectively. The corresponding intervals for the dispersed 20% accessibility distribution are given by $(1.30\mu_0, 1.90\mu_0)$ under periodic boundary conditions and $(1.70\mu_0, 2.30\mu_0)$ under reflecting boundary conditions. For the 60% accessibility distributions in Fig. 3.6, the corresponding intervals are given by $(1.65\mu_0, 3.18\mu_0)$ for the clustered distribution under either boundary condition, $(0.175\mu_0, 0.475\mu_0)$ for the dispersed distribution under periodic boundary conditions, and $(0.200\mu_0, 0.650\mu_0)$ for the dispersed distribution under reflecting boundary conditions.

Figures 3.7 and 3.8 show the results of our randomized on-the-ground only control analysis. Generally, we see that for a given level of clustering, controllability increases with hopping rate, and that control costs and application frequencies decrease on average. Likewise, for a given hopping rate, the more dispersed distributions tend to be more controllable and cheaper to control than the clustered distribution. In Fig. 3.7, we see that for a given hopping rate and level of clustering, there exists a region of low accessibility where average costs increase linearly with percent accessible and the corresponding average application frequencies are equal to 1day^{-1} . This accessible region corresponds to the region in 3.8 where nearly all generated configurations for that hopping rate and clustering level are uncontrollable. As accessibility levels increase beyond this region, average costs and average frequencies quickly drop as more and more of the generated configurations become controllable. For each hopping rate and clustering level in Fig. 3.8, we note the existence of an accessible controllability interval. At accessibility levels below the controllability interval, no generated configurations are controllable, and at accessibility above the interval, all generated configurations are controllable. Within the interval, a non-zero fraction of the generated configurations are controllable. We also note the existence of a accessibility cost-effectiveness interval. At accessibility levels below the cost-effectiveness interval, no generated configurations are cheaper to control than with aerial spray only control, and at accessibility levels above the interval, all generated configurations are cheaper to control than with aerial spray only control. The controllability and cost-effectiveness intervals are given, respectively, by $(7\%, 12\%)$ and $(10\%, 16\%)$ for $\omega = 5.0\mu_0$ dispersed, $(13\%, 26\%)$ and $(17\%, 37\%)$ for $\omega = 5.0\mu_0$ clustered, $(23\%, 49\%)$ and $(29\%, 62\%)$ for $\omega = 1.0\mu_0$ dispersed, $(56\%, 81\%)$ and $(60\%, 89\%)$ for $\omega = 1.0\mu_0$ clustered, $(42\%, 81\%)$ and $(52\%, 89\%)$ for $\omega = 0.5\mu_0$ dispersed, and $(79\%, 92\%)$ and $(92\%, 95\%)$ for $\omega = 0.5\mu_0$ clustered.

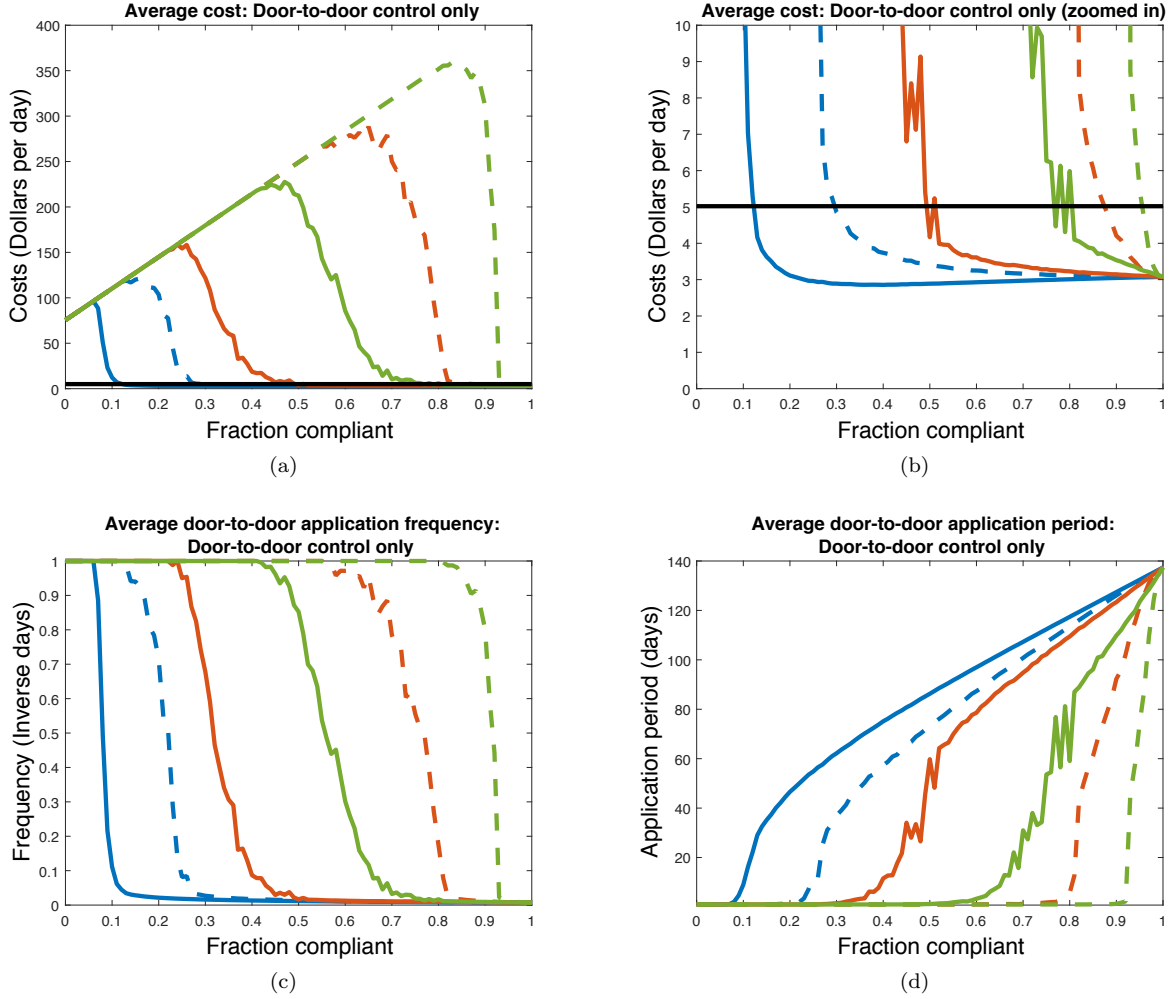


Figure 3.7 On-the-ground only control costs, application frequencies, and application periods required to bring R_0 to unity (or as low as possible when the system is uncontrollable) as a function of percent accessibility. Blue, red, and green curves correspond to the hopping rates $\omega = 5\mu_0$, $\omega = \mu_0$, and $\omega = 0.5\mu_0$, respectively. For each value of percent accessibility and hopping rate, we average over 200 random neighborhood accessibility configurations that are either highly clustered (dashed curves) or randomly dispersed (solid curves), assuming periodic boundary conditions. The crossover points in the zoomed-in plot in Fig. 3.7b indicate cut-off accessibility levels beyond which on-the-ground only control becomes more cost-effective than aerial only control on average. Figures 3.7c and 13.7d represent the same information; we display both application period and application frequency for visual clarity.

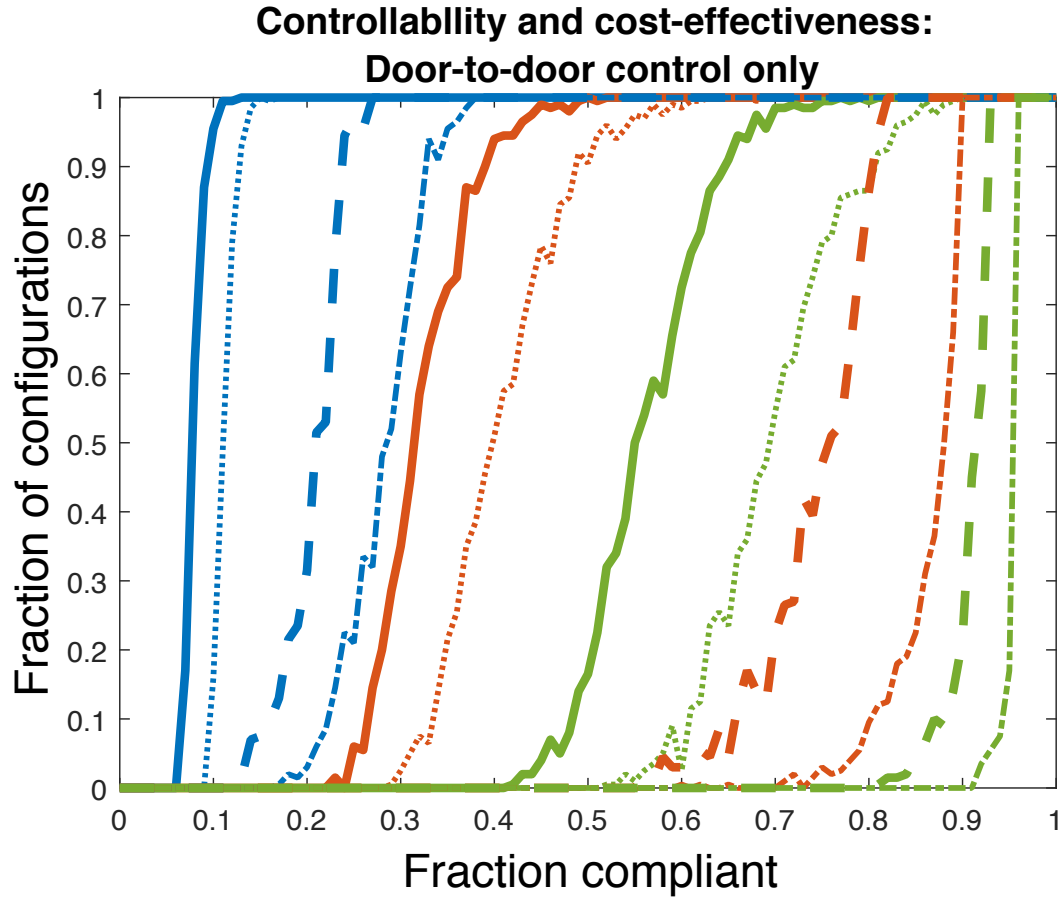


Figure 3.8 Shown here are the fraction of neighborhood configurations that can be controlled with on-the-ground control alone as a function of percent accessibility, as well as the fraction of configurations that are more cost-effective to be controlled with on-the-ground control compared to aerial spraying. Results are shown for three values of the vector hopping rate: Blue, red, and green curves correspond to the hopping rates $\omega = 5\mu_0$, $\omega = \mu_0$, and $\omega = 0.5\mu_0$, respectively. For each value of percent accessibility and hopping rate, we average over 200 random regional accessibility configurations which are either highly clustered or randomly dispersed, assuming periodic boundary conditions. Solid curves represent the fractions of randomly dispersed configurations that are controllable with on-the-ground control, and the neighboring dotted curves represent the fractions of randomly dispersed configurations that are both controllable and cost-effective (e.g. those that are both controllable and cheaper to control with on-the-ground control than with aerial spray). The dashed curves represent the fractions of highly clustered configurations that are controllable, and the neighboring dashed-dotted curves represent the fractions of highly clustered configurations that are both controllable and cost-effective.

Overall, our findings indicate that the cost-optimal on-the-ground and area-wide aerial spray application frequencies required for reducing R_0 to unity are influenced by the rate of mosquito motion, the level of on-the-ground accessibility, as well as the degree of accessibility clustering. The manner in which these factors influence the optimal choice between on-the-ground control only, aerial spray control only, and a combined integrated vector management

strategy is a central result of this work. At low levels of accessibility, on-the-ground control alone can not control the system unless the mosquito hopping rate is sufficiently large. Mathematically, this effect arises from the fact that the system-wide R_0 is determined by an infectious vector population which is distributed in and around the larger more clustered non-accessible blocks of sites. In this sense, on-the-ground control can only reduce the system-wide R_0 when the infectious vectors originating in the non-compliant blocks have sufficient mobility such that they spend enough time in accessible sites to feel the effects of strong accessible control. This explains why a greater level of clustering of non-accessible sites is more difficult to control than a dispersed distribution of non-accessible sites; vectors existing in an extremely deep block of non-accessibility require an extreme amount of mobility in order to feel the effects of on-the-ground control in accessible sites. However, even at infinitely fast mosquito motion, under our model and control parameters, the system is uncontrollable under on-the-ground control at accessibility levels below about 2%, regardless of accessibility clustering. Simply put, even if the vector population is able to be essentially eliminated in accessible sites, such sites must comprise about 2% of the total area, at minimum, in order to have any hope of on-the-ground control alone preventing an epidemic outbreak. More realistically, at finite (potentially small) hopping rates, much greater levels of accessibility are required for on-the-ground controllability, especially if the accessibility distribution is highly clustered.

When a system is uncontrollable with on-the-ground control alone, control efforts must be supplemented by area-wide spraying, and the combined action of on-the-ground control and aerial spraying can potentially be more cost-effective than either strategy used alone. For a given distribution of compliant sites, when hopping rates are far too slow for the system to be controllable with on-the-ground control alone, the optimal action is to use only area-wide spraying. In such cases, an inability to spray frequently due to societal concerns, budgetary constraints, or resistance concerns is detrimental to disease control, and no amount of on-the-ground control can make up for the deficit. As hopping rates approach the on-the-ground controllability threshold from below, the optimal control action becomes to supplement aerial spraying with on-the-ground control. Here, the disease is still uncontrollable under on-the-ground only, so an inability to conduct frequent area-wide spraying is still detrimental to outbreak prevention. However, mosquito motion is fast enough such that a non-trivial fraction of infectious vectors originating in non-accessible sites will travel to accessible sites where they experience the effects of on-the-ground control. As hopping rates continue to increase past the on-the-ground controllability threshold, aerial spray is optimally applied less frequently, and on-the-ground control is optimally applied more frequently. At these hopping rates, an inability to conduct aerial spraying will not be detrimental to outbreak prevention, but will require sub-optimal spending on on-the-ground efforts in order to control the system. At large enough hopping rates, the system will not only be controllable under on-the-ground efforts alone, but will also be much more cost effective under on-the-ground control alone than under aerial spray alone. Here, the optimal control action is to apply only on-the-ground control.

Generally speaking, systems with lower levels of accessibility and greater levels of clustering will have larger intervals of hopping rates where optimal control actions call for using aerial spray, either alone or combined with on-the-ground efforts. Likewise, systems with smaller hopping rates will have greater numbers of accessibility levels and randomly dispersed distributions of compliant sites for which the optimal control action is to apply aerial spray only in comparison to systems with faster hopping rates. For a given hopping rate, there will be a greater number of highly clustered accessibility distributions for which the optimal control action

is only aerial spray in comparison to more randomly dispersed accessibility distributions. As shown in Fig. 3.8, the effects of accessibility clustering is diminished at larger hopping rates. This follows from the notion that highly mobile vectors experience the effects of accessible and non-accessible sites in a more averaged sense in correspondence to the fraction accessibility in the region, where the actual spatial distributions of accessibility and non-accessibility become increasingly irrelevant as $\omega \rightarrow \infty$.

It is important to note that even when a system is controllable under on-the-ground control alone, using only on-the-ground control may not be more cost-effective than aerial spray alone, despite on-the-ground's higher control strength and lasting effects in accessible sites relative to aerial spray. Specifically, Fig. 3.8 indicates that for a given hopping rate, the number of accessibility configurations which are controllable under on-the-ground alone is smaller than the number of configurations which are cost-effective under on-the-ground alone. The differences between the number of configurations which are controllable and the number of configurations which are cost-effective, however, tends to be small outside of the narrow accessibility ranges where systems transition from always uncontrollable to always controllable. On the other hand, Figs. 3.5 and 3.6 show that, for a given accessibility configuration, the range of hopping rates over which the system is controllable is greater than the range of hopping rates which are cost-effective, and that the differences between the two ranges are rather small. In any event, we obtain the following 'rules of thumb' - when a system is in the range of uncontrollable to almost controllable, the optimal control action is to apply only aerial spray; when a system is in the range of almost controllable to controllable and slightly more cost-effective, the optimal control action is to apply a combined aerial spray on-the-ground strategy; when a system is controllable and in the range of slightly more to much more cost-effective, the optimal control action is to apply on-the-ground control only.

Summary and Conclusions

Mosquito motion, door-to-door control compliance levels, and spatial clustering of accessible sites play an important role in determining whether or not vector-borne disease can be controlled by area-wide aerial spraying and/or on-the-ground control, as well as the most cost-effective strategies for control in a regional scale system. We find that, in general, increased mosquito motion, increased accessibility levels, and decreased accessibility clustering are all beneficial for the efficacy of on-the-ground control efforts. We note the numerical results presented here are all based on a disease-related parameter set representative of typical values associated with vector-borne diseases such as Zika or dengue in North America. Our intent here is not to provide specific control advice which can be responsibly applied directly in the field. Rather, we have focused on providing mechanistic insight into the biological factors which should, in conjunction with additional practical considerations that can not be reliably modeled, be considered when designing a real-world integrated vector management strategy. Our specific numerical results are most appropriate for use as a simplified baseline example case from which one can build some mathematical intuition for control efficacy on regional scales.

PART 4: LA CROSSE ENCEPHALITIS

This work has been published, and can be found at: Bewick, Sharon, et al. "Epidemiology of La Crosse virus emergence, Appalachia Region, United States." *Emerging infectious diseases* 22.11 (2016): 1921.

Background

In recent years, several vector-borne diseases have re-emerged either at new locations or to new levels in historic ranges. Commonly cited factors for re-emergence include evolution of novel vector or pathogen strains (1), increased human mobility or disease spread by infected travelers, decreased herd immunity (2), landscape change (3), climate change (4), and invasion of new regions by competent disease vectors (5). Although continent-scale disease translocations are almost always a result of human transport, pathogens that exhibit novel regional spread and/or increased transmission in pre-existing locations are more difficult to explain. Such is the case with La Crosse encephalitis (LAC), a mosquito-borne viral disease currently emerging in Tennessee, North Carolina, Virginia, and West Virginia. With 30-180 cases of severe LAC reported annually (6), and an estimated total disease incidence as high as 300,000 cases per year, LAC is rapidly becoming a leading cause of encephalitis in the United States (7, 8). In severe cases, LAC has lifelong neurologic consequences (6) and carries an estimated fatality rate of 0.5-1.9% (6, 9).

Previously, most LAC cases were associated with forested areas in the Midwest (10). However, since the mid-1990s, the Appalachian region has emerged as a new and important focus for the disease (8, 11-13). One potential explanation is the introduction of the invasive Asian tiger mosquito (*Aedes albopictus*, henceforth the 'tiger mosquito') (14). Historically, LAC was maintained through a cycle involving the eastern tree-hole mosquito (*Ochlerotatus triseriatus*, henceforth the 'tree-hole mosquito') and three mammal species – eastern chipmunks (*Tamias striatus*), grey squirrels (*Sciurus carolinensis*) and fox squirrels (*Sciurus niger*) (10, 15). However, demonstrated laboratory competence (16, 17), isolation of LAC virus from field-collected tiger mosquito pools (18), observation of LAC-positive tiger mosquitoes at sites with human LAC infections (19), and the coincidental link between tiger mosquito invasion and the emergence of LAC in Appalachia (11) indicate that the tiger mosquito may now be aiding in LAC spread. Unfortunately, while these observations demonstrate the potential of the tiger mosquito to influence LAC dynamics, this mosquito's contribution to observed increases in LAC transmission remains unclear.

One obstacle to identifying the role of the tiger mosquito in LAC emergence is our limited understanding of how invasive species interact with native disease cycles and how this affects disease transmission, both within natural reservoirs and to human hosts. Epidemiological modeling is a powerful tool that has proven useful for understanding the outcomes of different transmission pathways in other disease systems. To our knowledge, however, there are no dynamic models for LAC, even for the case where the tree-hole mosquito is the only disease vector. Here we develop a compartmental model (see Figure 4.1) for LAC. We use this model to explore LAC dynamics in both the native and invaded systems and to assess the likelihood that the Asian tiger mosquito is responsible for the emergence of LAC in Appalachia.

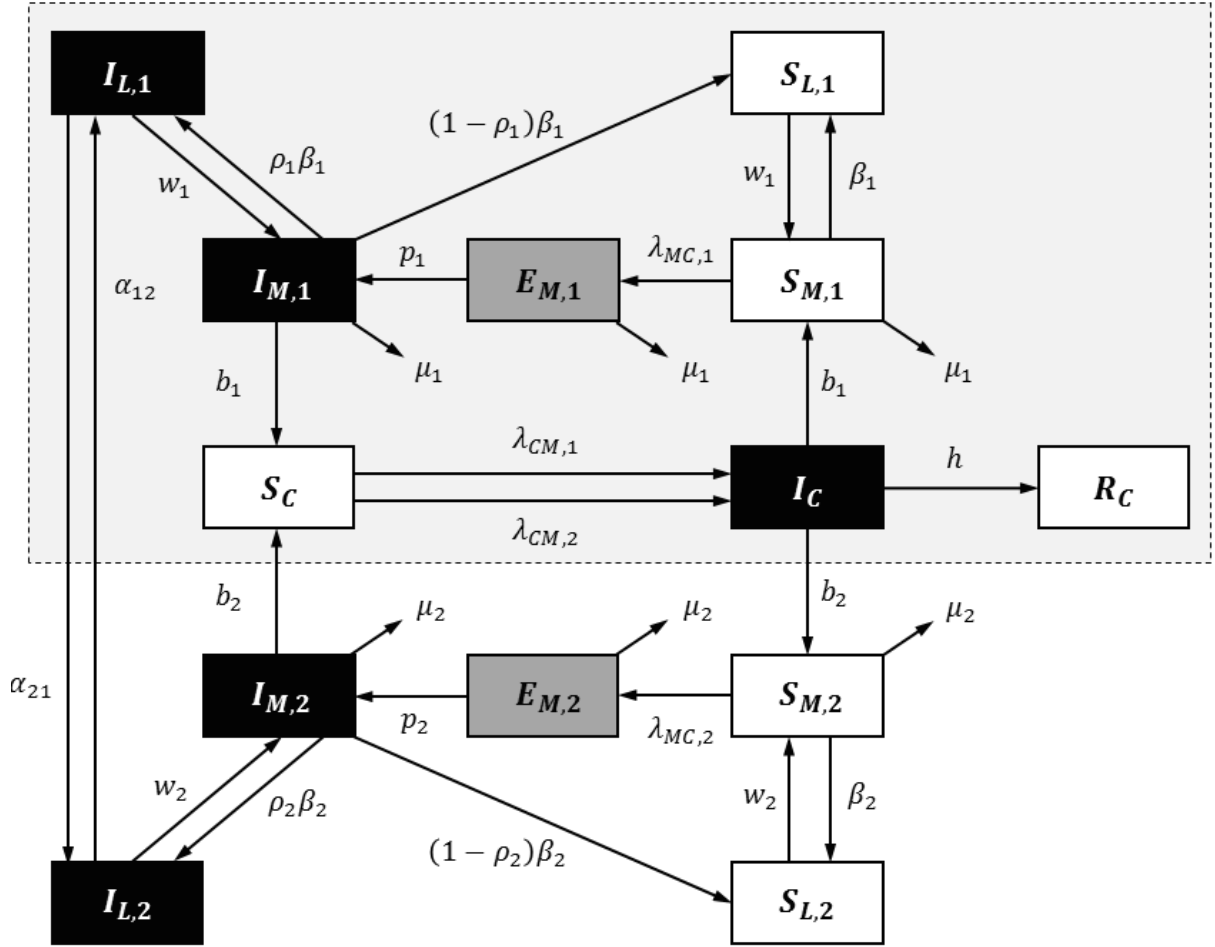


Figure 4.1 Schematic illustrating transitions/interactions in our compartmental model. Subscripts ‘1’, ‘2’ and ‘C’ are used to denote parameters and state variables for the tree-hole mosquito, tiger mosquito and host populations. S , I , E and R are used for susceptible, infected, exposed and recovered classes. A discussion of parameters can be found at (science.umd.edu/biology/faganlab/disease-ecology.html). Black boxes are used for infected classes, grey boxes for exposed classes, and white boxes for susceptible/recovered classes. A dotted line and grey shadow demarcate the subset of transitions/interactions that define the native system prior to tiger mosquito invasion.

Model Development

We built three separate models: (i) a model where the tree-hole mosquito is the only LAC vector, (the ‘Tree-hole Model’), (ii) a model where the tiger mosquito is the only LAC vector, (the ‘Tiger Model’) and (iii) a model where both tree-hole and tiger mosquitoes simultaneously serve as LAC vectors, (the ‘Tree-hole & Tiger Model’). (In model iii, either mosquito species may be driven extinct through competitive exclusion; thus while both vectors are potentially present, it is possible that only one persists). For all models, we assumed that the vertebrate host was the eastern chipmunk. The basic dynamical system (see Figure 1) is as follows:

Host(s):

$$\frac{dS_C}{dt} = -\frac{S_C}{N_C} \sum_{j=1}^V \lambda_{CM,j} b_j I_{M,j} \quad (4.1.a)$$

$$\frac{dI_C}{dt} = \frac{S_C}{N_C} \sum_{j=1}^V \lambda_{CM,j} b_j I_{M,j} - h I_C \quad (4.1.b)$$

$$\frac{dR_C}{dt} = h I_C \quad (4.1.c)$$

Vector(s):

$$\frac{dS_{L,j}}{dt} = \frac{\beta_j}{K_j} (S_{M,j} + (1 - \rho_j) I_{M,j}) (K_j - N_{L,j} - \sum_{k=1, k \neq i}^V \alpha_{jk} N_{L,k}) - w_j S_{L,j} \quad (4.1.d)$$

$$\frac{dI_{L,j}}{dt} = \frac{\beta_j}{K_j} \rho_j I_{M,j} (K_j - N_{L,j} - \sum_{k=1, k \neq i}^V \alpha_{jk} N_{L,k}) - w_j I_{L,j} \quad (4.1.e)$$

$$\frac{dS_{M,j}}{dt} = w_j S_{L,j} - \lambda_{MC,j} b_j S_{M,j} \frac{I_C}{N_C} - \mu_j S_{M,j} \quad (4.1.f)$$

$$\frac{dE_{M,j}}{dt} = \lambda_{MC,j} b_j S_{M,j} \frac{I_C}{N_C} - \mu_j E_{M,j} - p_j E_{M,j} \quad (4.1.g)$$

$$\frac{dI_{M,j}}{dt} = w_j I_{L,j} + p_j E_{M,j} - \mu_j I_{M,j} \quad (4.1.h)$$

where for vector population $j = 1$ (tree-hole mosquitoes) or 2 (tiger mosquitoes) we consider susceptible ($S_{L,j}$) and infected ($I_{L,j}$) female larvae (where the ‘larval stage’ includes both the egg stage and the true larval stage), as well as susceptible ($S_{M,j}$), exposed ($E_{M,j}$) and infected ($I_{M,j}$) female adults. The total larval population of mosquito species j is given by $N_{L,j} = S_{L,j} + I_{L,j}$, while the total adult population is given by $N_{M,j} = S_{M,j} + E_{M,j} + I_{M,j}$. For hosts, we consider susceptible (S_C), infected (I_C) and recovered (R_C) classes. The total population of the host species is given by $N_C = S_C + I_C + R_C$, where N_C is defined as a model parameter.

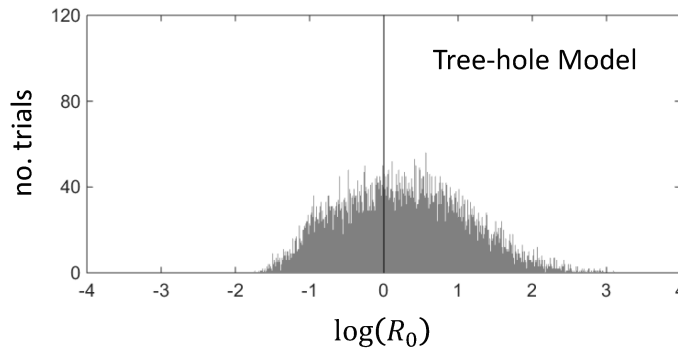
Model Analysis

Figure 2 presents a Latin Hypercube Sampling analysis of R_0 for each of our three models. Interestingly, we find that sustained LAC transmission can occur in the majority of Tree-hole Model scenarios (60%), but only in a small fraction of Tiger Model scenarios (3%). This is surprising, because the average tiger mosquito population has approximately twice as many biting females per hectare as does the average tree-hole mosquito population— a feature that reflects both the higher larval carrying capacity and the faster larval maturation rate of tiger mosquitoes versus tree-hole mosquitoes. Clearly, the numerical abundance of the tiger mosquito does not compensate for its lower horizontal and vertical LAC transmission rates and its lower biting rates on key host species.

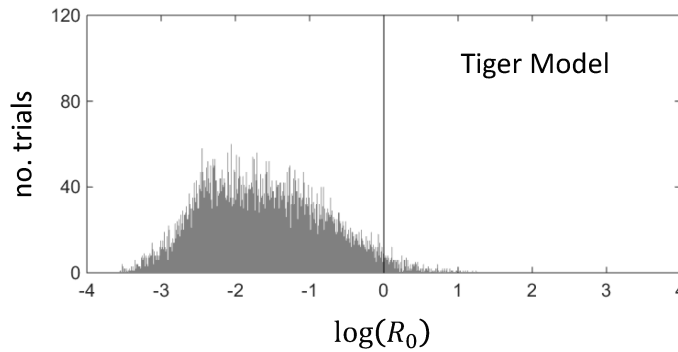
Moving to the two-vector system, our results for the Tiger & Tree-hole Model indicate a similar outcome – that the invasion of tiger mosquitoes into tree-hole mosquito populations should reduce the fraction of scenarios (from 60% to 37%) where LAC transmission is viable. Thus, instead of causing the emergence of new LAC foci, the invasion by tiger mosquitoes should instead drive LAC out of regions where it could previously persist. This is again a function of the poor intrinsic capability of tiger mosquitoes to serve as LAC vectors. It also depends on asymmetric competition between tiger and tree-hole mosquitoes. For example,

whereas 14% of parameter combinations yield tiger mosquitoes competitively excluding tree-hole mosquitoes, the converse is true for only 0.03% of parameter combinations. Moreover, even when tree-hole and tiger mosquitoes coexist, the tree-hole mosquito population suffers an average 63% population reduction through interspecific competition. By contrast, interspecific competition only reduces the tiger mosquito population by an average of 16%. Not surprisingly, then, when both mosquito species are present, the vast majority (on average 78%) are tiger mosquitoes. Because the tiger mosquito is the poorer of the two LAC vectors, its invasion actually reduces the likelihood of LAC transmission.

a.



b.



c.

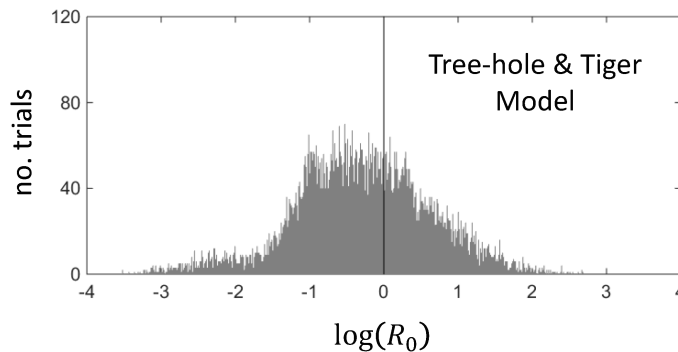
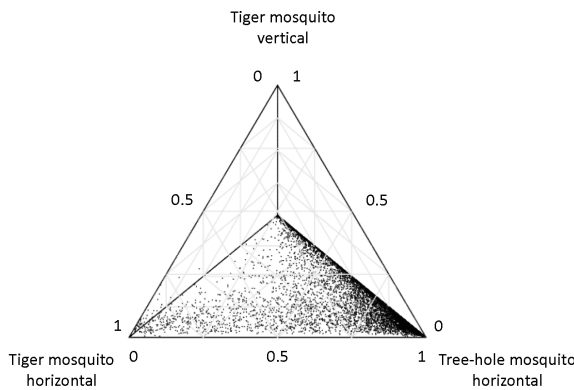


Figure 4.2 Histograms of R_0 values based on LHS analyses with 10,000 randomly selected parameter sets. In each panel, the black vertical line at $\log(R_0) = 0$ corresponds to the general breakpoint between growing and shrinking infection rates, and thus represents the threshold for LAC persistence. (a) the Tree-hole Model, (b) the Tiger Model, and (c) the Tree-hole & Tiger Model.

Figure 4.3 illustrates LHS results for an elasticity analysis of the four viral transmission pathways in the Tree-hole & Tiger Model. In the majority of scenarios, the pathway that is most important for disease spread is horizontal transmission by tree-hole mosquitoes. Vertical transmission by tree-hole mosquitoes can also be important, but usually only in cases where the role of tiger mosquitoes is minimal. For scenarios where tiger mosquitoes contribute to spread, the important pathway is horizontal transmission either by tiger mosquitoes alone or else in combination with horizontal transmission by tree-hole mosquitoes. By contrast, vertical transmission by tiger mosquitoes is rarely important, and only matters in systems where horizontal transmission by tiger mosquitoes is already the major mode of disease spread.

a.



b.

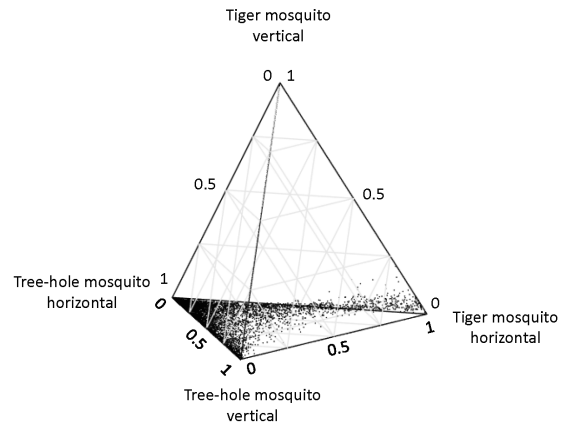


Figure 4.3 Two views of a quaternary plot showing the relative contributions to R_0 from (i) horizontal transmission by tree-hole mosquitoes, (ii) vertical transmission by tree-hole mosquitoes, (iii) horizontal transmission by tiger mosquitoes, and (iv) vertical transmission by tiger mosquitoes. This figure plots only the 8602 replicates (out of 10000) wherein tiger and tree-hole mosquitoes coexisted.

Table 1 outlines summary statistics for our dynamic analyses. Importantly, predictions from dynamic models are similar to predictions for R_0 (LAC transmission in 46% of scenarios) and match many expectations from LAC systems. First, in both the native system (i.e., the Tree-hole Model) and the invaded system (i.e., the Tree-hole & Tiger Model) host seroprevalence rates should be remarkably high, approaching 100% towards the end of the season (mean [median] end-of-season host seroprevalence rates of 89% [99%] in the Tree-hole Model and 84% [97%] in the Tree-hole & Tiger Model). This is consistent with findings from Wisconsin where, at least in high quality habitat, multiple surveys have demonstrated that antibody prevalence rates in chipmunks can be well over 50%, often nearing 100% late in the season (15, 22). At the same time, our model predicts very low numbers of LAC-positive mosquitoes, even in the native system (mean [median] yearly averages of 2.0% [1.6%] for the Tree-hole Model). Again, this is highly consistent with observed minimum field infection rates (MFIR) that range from 0.26/1000 to 12.5/1000 (13, 23-26). Interestingly, predicted infection rates in overwintering eggs are even lower than rates of infection in adult populations (mean [median] end-of-season infection rates of 0.63% [0.49%] respectively for the Tree-hole Model.) This reflects the fact that transovarial

Table 1. Summary statistics* for epidemiological metrics based on LHS analysis of the full dynamic model; all metrics beyond the first row are only calculated for the subset of simulations that gave infected mosquitoes.

	Tree-hole Model	Tiger Model	Tree-hole and Tiger Model*
Parameter Sets with LAC Persistence	46%	0.20%	24%
End of Season Host Seroprevalence Rate			
Mean	89%	79%	84%
Median	99%	88%	97%
Maximum	100%	100%	100%
Mid-Season Host Seroprevalence Rate			
Mean	65%	12%	18%
Median	74%	8.9%	12%
Maximum	100%	38%	98%
Peak No. Infected Mosquitoes (ha⁻¹)			
Mean	32	58	23
Median	22	50	16
Maximum	331	200	222
Peak Mosquito Infection Rate			
Mean	4.5%	1.6%	1.9%
Median	3.5%	1.5%	1.3%
Maximum	27%	5.3%	15%
Average Mosquito Infection Rate			
Mean	2.0%	0.44%	0.80%
Median	1.6%	0.33%	0.57%
Maximum	13%	1.8%	6.8%
Max. Human Transmission (mo⁻¹person⁻¹ha⁻¹)			
Mean	15	59	14
Median	8.6	40	7.9
Maximum	251	247	221
Timing of Peak Human Transmission			
Mean	8/14	9/21	8/23
Median	8/10	9/28	8/21
Earliest	6/21	8/26	6/26
Latest	9/30**	9/30**	9/30**
End of Season Egg Infection Rates			
Mean	0.63%	0.08%	0.28%
Median	0.49%	0.07%	0.20%
Maximum	5.0%	0.32%	2.2%

* We avoid reporting minimum values since these are likely to depend on the threshold that we selected for determining disease persistence (see Appendix IV).

**In these systems, the abundance of infected mosquitoes was still increasing at the end of the season. This indicates that infection rates do not slow prior to the decline in mosquitoes at the end of the summer.

transmission is less than 100% and that overwintering eggs are laid later in the season, sometimes after peak LAC transmission has subsided. Again, predicted rates of egg infection strongly agree with field data indicating that 0.29-0.6% of overwintering eggs from LAC endemic sites yield LAC-positive larvae (26, 27). Finally, our predicted timing of peak human disease risk is broadly consistent with observed human LAC cases that tend to occur in late summer and early fall (8, 12).

What our dynamic model does not predict is any increase in LAC prevalence in the invaded system (i.e., Tree-hole & Tiger Model) as compared to the native system (i.e., Tree-hole Model). In fact, even in systems where LAC survives introduction of the tiger mosquito, the tiger mosquito tends to dampen LAC transmission. In Table 1, for example, both the absolute number of infected mosquitoes and the rate of mosquito infection are lower in the Tree-hole & Tiger Model as compared to the Tree-hole Model. Consistent with mosquito infection rates, we find that host seroprevalence rates are also lower when tiger mosquitoes are present. Although the tiger mosquito is a poor amplifying vector for LAC, it may still increase human LAC cases. Indeed, because this species is an aggressive human biter, it has the potential to intensify the rate of disease transfer to human populations, albeit while simultaneously reducing disease spread in wildlife reservoirs (i.e., it may act as a bridge vector). Table 1, however, shows that this is not the case. Although tiger mosquito biting rates on humans (not shown) partially compensate for lower rates of LAC transmission in wildlife reservoirs, this compensation is not complete. Thus, human infections are still predicted to occur more commonly in the uninvaded versus the invaded system.

Figure 4.4 summarizes our PRCC results for model parameters. In single-vector models – i.e., the Tree-hole Model (white) and the Tiger Model (black) – transmission rates, biting rates, mosquito survival rates, mosquito population growth rates, mosquito maturation rates, mosquito carrying capacity, and rates of LAC dissemination in mosquitoes are all positively correlated with R_0 . In contrast, rates of host recovery are negatively correlated with R_0 , as is host population size. Though this latter result is somewhat counterintuitive, it is well known for systems with a saturating functional response (28).

In the two-vector model, most PRCC values are reduced, but maintain the same sign. This reflects the similar effect but lower importance of either mosquito species individually when both species are present. Not surprisingly, PRCC reductions are more severe for the tiger mosquito, which is the less competent and thus less important vector in the two-vector system. Although the majority of PRCC values merely exhibit reductions in the two-vector model, several undergo more striking changes. First, both the tiger mosquito population growth rate and the tiger mosquito carrying capacity switch from being positively correlated with R_0 (strongly so in the case of carrying capacity) in the Tiger Model to being negatively correlated with R_0 in the Tree-hole & Tiger Model. This is because tiger mosquitoes are generally detrimental to LAC spread in systems where the native vector is also present. Importantly, this conclusion accords with our general finding that tiger mosquitoes should, if anything, reduce LAC transmission. Second, the population growth rate of the tree-hole mosquito actually becomes more important when tiger mosquitoes are present. This parameter is particularly important in the Tree-hole & Tiger Model because it helps to influence the outcome of interspecific competition. Specifically, high tree-hole mosquito growth rates give this species a fighting chance against the more aggressive, generally more fecund tiger mosquito population.

While PRCC analysis can identify correlations between model parameters and disease outcomes, large PRCC values additionally indicate model parameters that contribute a high

degree of uncertainty to model predictions. In the Tree-hole & Tiger Model, the largest sources of uncertainty in R_0 are the survival rate of tree-hole mosquitoes, the biting rate of tree-hole mosquitoes, and interspecific competition of tiger mosquitoes on tree-hole mosquitoes. In the Tree-hole Model and the Tiger Model, the largest contributions to uncertainty are again survival and biting rates, but also vector carrying capacities.

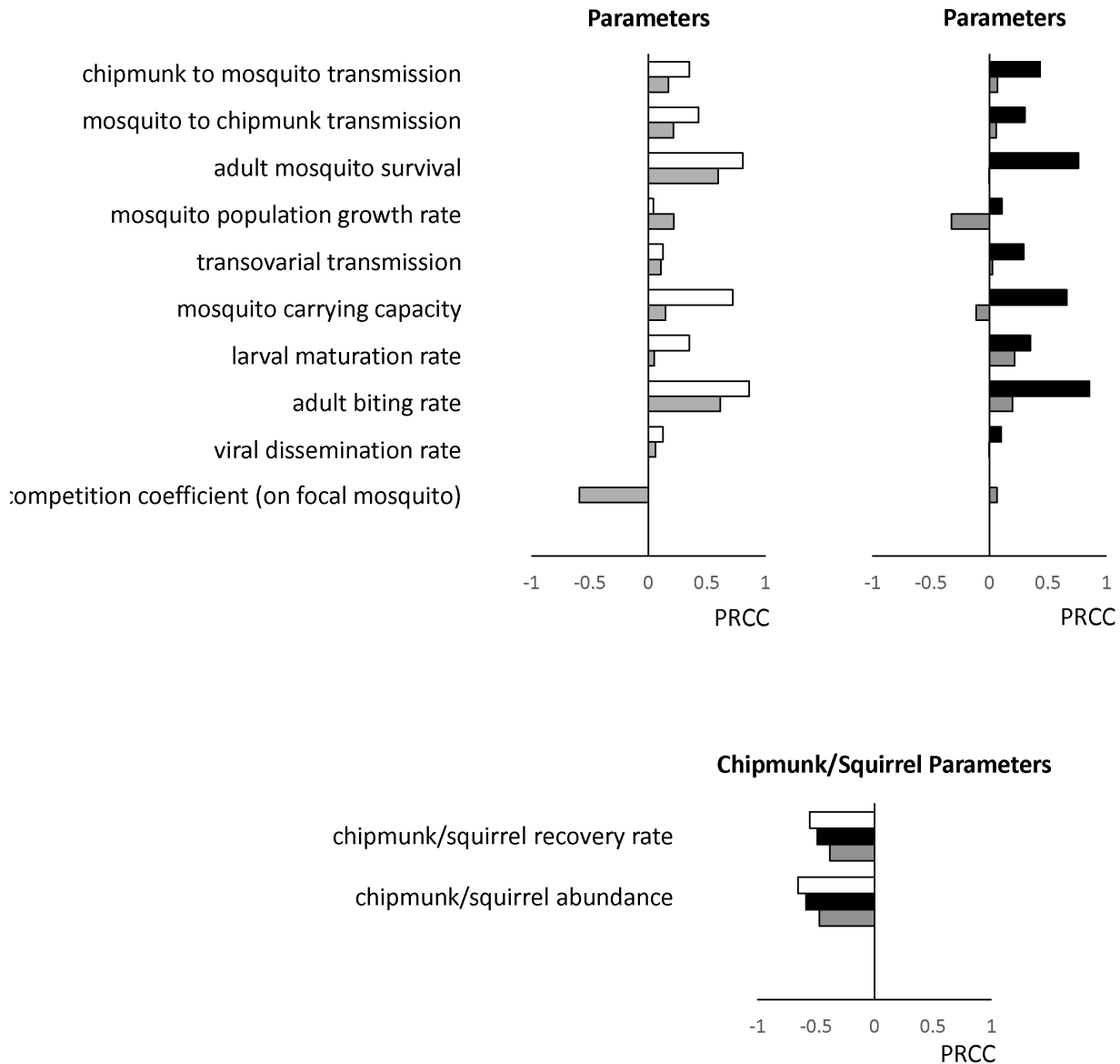


Figure 4.4 Partial Rank Correlation Coefficients (PRCCs) for the effect of each model parameter on the basic reproduction number, R_0 , in the Tree-hole Model (white), the Tiger Model (black) and the Tree-hole & Tiger Model (grey). Positive PRCC values indicate that R_0 is positively correlated with a specific parameter, whereas negative PRCC values indicate the opposite.

Recently, we have begun to extend our La Crosse model to consider temperature dependent effects associated with seasonality, and the impact that this has on control. Figure 4.5 shows preliminary results assuming variable mosquito demographic parameters as a function of average

seasonal temperatures in the state of Ohio, along with optimal control results for the best timing of larvicide and adulticide.

Optimal control of La Crosse Virus under a temperature variable environment

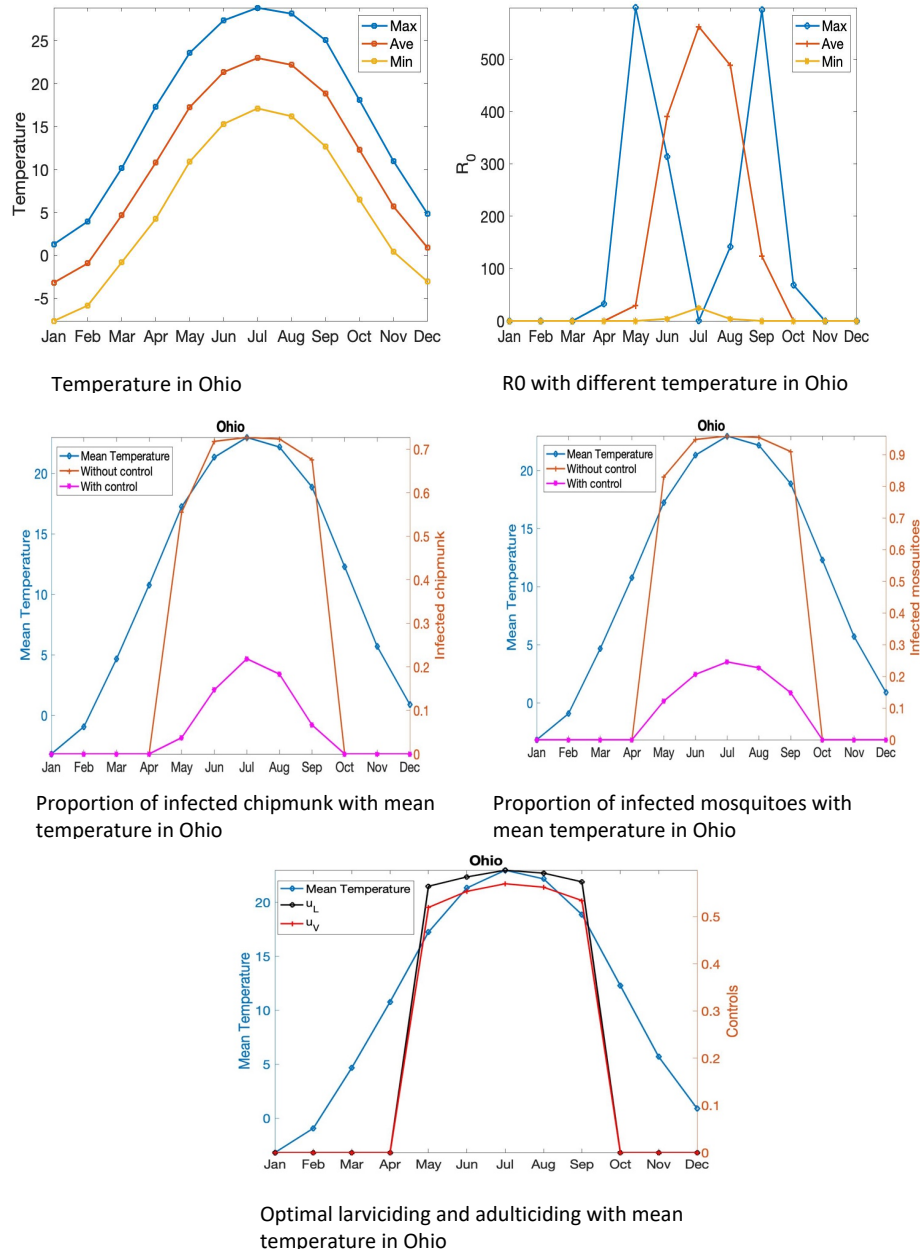


Figure 4.5 Preliminary results for temperature dependent proportions of infected hosts and vectors, along with instantaneous R_0 as a function of season, and optimal larvicide and adulticide treatment over the course of one year.

Figure 4.6 shows the potential effects of optimally timed control depending on yearly temperatures over a 10°C range. Specifically, we find that less control is required at lower

tempeartures, and that significantly greater reductions, particularly in infected hosts, can be realized at lower temperatures.

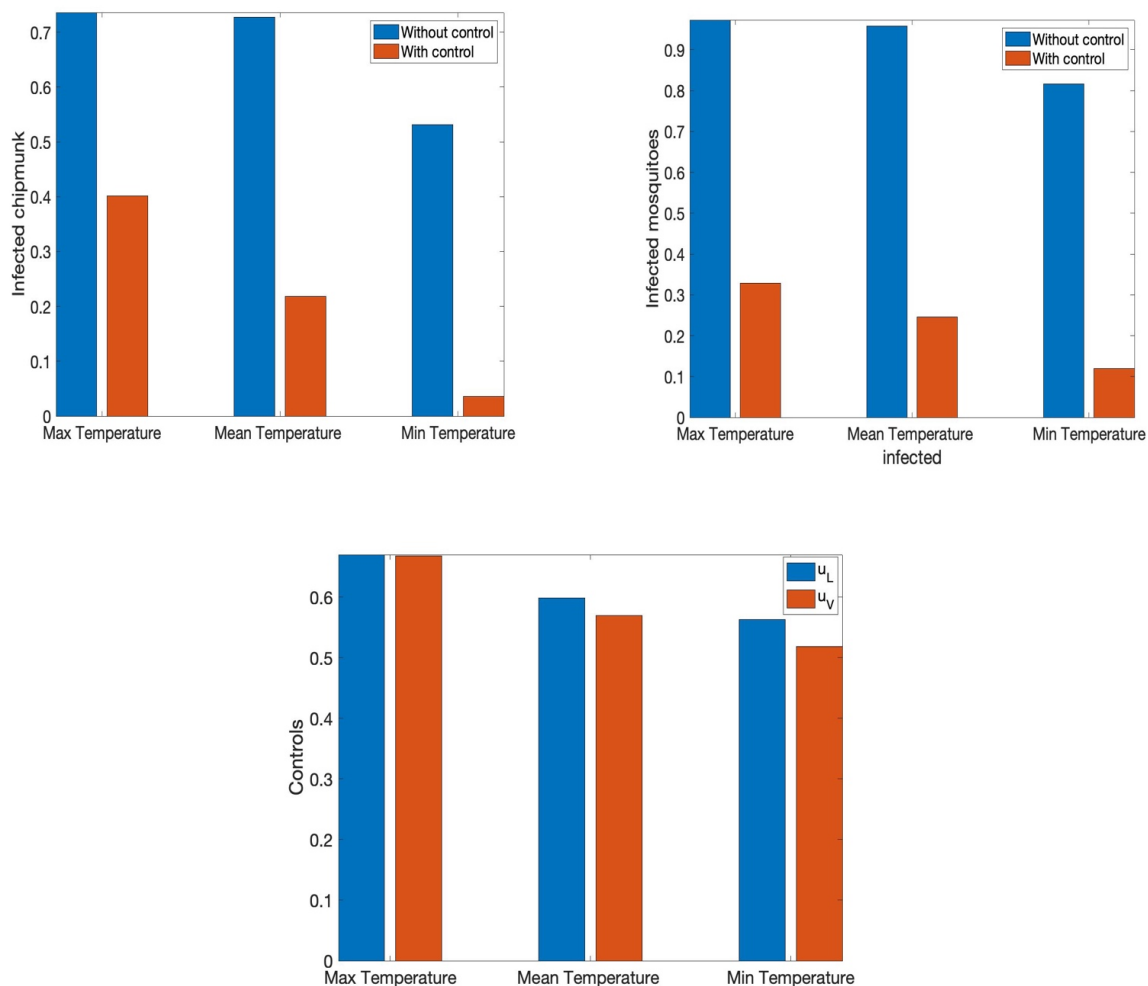


Figure 4.6 Preliminary results showing the number of infected hosts and vectors, as well as total controls implemented at three different mean yearly temperatures. These results suggest that La Crosse Encephalitis will become more costly and more difficult to control with increasing global temperatures.

Conclusions and Summary

We developed what appears to be the first dynamic model for LAC. In contrast to previous conclusions (29), our model suggests that LAC should be sustainable in 46-60% of scenarios where the tree-hole mosquito serves as the sole vector. Interestingly, this still indicates a sizeable number of scenarios where LAC transmission should not occur. One interpretation is that LAC spread is only marginally favorable, and that small changes in system characteristics, for example different mosquito or viral strains or environmental conditions, are sufficient to initiate or suppress disease transmission. This could explain the patchy detection of LAC across its native range (9), as well as the sudden appearance of LAC at sites where the disease was previously absent.

One factor that does not explain the emergence of novel LAC foci is the invasion of tiger mosquitoes. In fact, we predict that the invasive tiger mosquito should actually reduce disease transmission in both wildlife reservoirs and human populations (even accounting for the fact that tiger mosquitoes are aggressive human biters). Thus the presence of the invasive tiger mosquito is not sufficient to explain the dramatic increase in LAC cases observed in Appalachia (8, 11-13, 30, 31). Interestingly, the Midwest has not seen any increase in LAC prevalence since the tiger mosquito's arrival. Indeed, reported cases in the region have decreased (11) (see Appendix VII), which is consistent with predictions from our model.

Increased warming temperatures, on the other hand, do appear to be detrimental in terms of both the degree of LAC spread, as well as the cost of LAC control. This suggests that the increasing prevalence of LAC in Appalachia may be driven by ongoing global change, and suggests that further emphasis be placed on LAC control in the future.

PART 5: ZIKA

This work has been published, and can be found at:

Agusto, Folashade B., S. Bewick, and W. F. Fagan. "Mathematical model of Zika virus with vertical transmission." *Infectious Disease Modelling* 2.2 (2017): 244-267.

Agusto, F. B., S. Bewick, and W. F. Fagan. "Mathematical model for Zika virus dynamics with sexual transmission route." *Ecological Complexity* 29 (2017): 61-81.

Bewick, Sharon, et al. "Zika virus: endemic versus epidemic dynamics and implications for disease spread in the Americas." *BioRxiv* (2016): 041897.

Background

After being discovered in Ugandan forests in 1947 (1), Zika virus (ZIKV) remained a relatively minor arboviral disease for 60 years (2). In 2007, however, an outbreak of ZIKV on Yap Island (3) in the Pacific Ocean signaled spread of the virus beyond its historic range (2-4). From Yap Island, ZIKV was transported to French Polynesia in 2013 (5) and then on to Brazil in 2014 (6-8). Once in Brazil, the virus took off, 'spreading explosively' (9) throughout both South and Central America. By early 2016, for example, local transmission of ZIKV had been reported in 20 countries and territories in the Americas (10). Initially, ZIKV was not viewed as a significant public health threat. Indeed, with a negligible mortality rate and symptoms resembling a mild form of dengue (DENV) (2), the ZIKV outbreak appeared to be more of a nuisance than a public health emergency. In November 2015, however, alarms were raised about a potential connection between ZIKV transmission and increasing rates of newborn microcephaly (11).

In 2017, confirmation of the link between ZIKV and microcephaly was made. This, and the >20-fold increase in microcephaly in regions of Brazil where ZIKV was spreading (12) caused countries to take drastic precautionary action. The United States Centers for Disease Control (CDC), for example, posted a travel alert recommending that pregnant women avoid regions in the Caribbean and Latin America where ZIKV transmission is ongoing (13). Meanwhile, public health officials in El Salvador and Colombia have suggested that women delay pregnancy up to two years until ZIKV outbreaks can be controlled (14).

Like other viruses in the genus *Flavivirus*, for example DENV, West Nile Virus (WNV) and Yellow Fever Virus (YFV), ZIKV is primarily spread by mosquitoes. For ZIKV, the main vectors appear to be members of the genus *Aedes* (15), including the notorious *Ae. aegypti*. This is of concern because *Aedes* species are widespread in warmer temperate and tropical regions (16, 17). In addition, although chemical larvicides and adulticides are somewhat effective at reducing certain *Aedes* populations, these mosquitoes can reproduce in very small containers of standing water. This makes complete eradication difficult (18).

We considered three interesting features of ZIKV dynamics. First, we asked why a correlation only recently emerging between prenatal exposure to ZIKV and microcephaly. Second, we asked about the role of vertical transmission in ZIKV dynamics. Third, we asked about the role of sexual transmission in ZIKV dynamics. This final question is interesting, because ZIKV is relatively unique among vector-borne diseases in terms of its ability for sexual transmission.

Model Development

To examine the question of the recent connection between ZIKV and microcephaly, we considered the following age, sex and reproductive status model:

Humans (S-I-R):

Pre-reproductive females and males:

$$\begin{aligned}
 \frac{dS_j}{dt} &= \overbrace{\delta(S_p + I_p + R_p)}^{\text{birth}} - \overbrace{\eta_j S_j}^{\text{maturation}} - \overbrace{\frac{\beta_h b}{N_h} S_j I_v}^{\text{infection}} \\
 \frac{dI_j}{dt} &= \overbrace{-\eta_j I_j}^{\text{maturation}} + \overbrace{\frac{\beta_h b}{N_h} S_j I_v}^{\text{infection}} - \overbrace{r I_j}^{\text{recovery}} \\
 \frac{dR_j}{dt} &= \overbrace{-\eta_j R_j}^{\text{maturation}} + \overbrace{r I_j}^{\text{recovery}}
 \end{aligned} \tag{5.1}$$

Reproductive females (not pregnant):

$$\begin{aligned}
 \frac{dS_x}{dt} &= \overbrace{\frac{\eta_j}{2} S_j}^{\text{maturation}} - \overbrace{\eta_{xy} S_x}^{\text{maturation}} - \overbrace{p S_x}^{\text{pregnancy}} + \overbrace{\delta S_p}^{\text{delivery}} - \overbrace{\frac{\beta_h b}{N_h} S_x I_v}^{\text{infection}} \\
 \frac{dI_x}{dt} &= \overbrace{\frac{\eta_j}{2} I_j}^{\text{maturation}} - \overbrace{\eta_{xy} I_x}^{\text{maturation}} - \overbrace{p I_x}^{\text{pregnancy}} + \overbrace{\delta I_p}^{\text{delivery}} + \overbrace{\frac{\beta_h b}{N_h} S_x I_v}^{\text{infection}} - \overbrace{r I_x}^{\text{recovery}} \\
 \frac{dR_x}{dt} &= \overbrace{\frac{\eta_j}{2} R_j}^{\text{maturation}} - \overbrace{\eta_{xy} R_x}^{\text{maturation}} - \overbrace{p R_x}^{\text{pregnancy}} + \overbrace{\delta R_p}^{\text{delivery}} + \overbrace{r I_x}^{\text{recovery}}
 \end{aligned} \tag{S1.2.c}$$

Reproductive females (pregnant):

$$\begin{aligned}
 \frac{dS_p}{dt} &= \overbrace{p S_x}^{\text{pregnancy}} - \overbrace{\delta S_p}^{\text{delivery}} - \overbrace{\frac{\beta_h b}{N_h} S_p I_v}^{\text{infection}} \\
 \frac{dI_p}{dt} &= \overbrace{p I_x}^{\text{pregnancy}} - \overbrace{\delta I_p}^{\text{delivery}} + \overbrace{\frac{\beta_h b}{N_h} S_p I_v}^{\text{infection}} - \overbrace{r I_p}^{\text{recovery}} \\
 \frac{dR_p}{dt} &= \overbrace{p R_x}^{\text{pregnancy}} - \overbrace{\delta R_p}^{\text{delivery}} + \overbrace{r I_p}^{\text{recovery}}
 \end{aligned}$$

Reproductive males:

$$\begin{aligned}
 \frac{dS_y}{dt} &= \overbrace{\frac{\eta_j}{2} S_j}^{\text{maturation}} - \overbrace{\eta_{xy} S_y}^{\text{maturation}} - \overbrace{\frac{\beta_h b}{N_h} S_y I_v}^{\text{infection}} \\
 \frac{dI_y}{dt} &= \overbrace{\frac{\eta_j}{2} I_j}^{\text{maturation}} - \overbrace{\eta_{xy} I_y}^{\text{maturation}} + \overbrace{\frac{\beta_h b}{N_h} S_y I_v}^{\text{infection}} - \overbrace{r I_y}^{\text{recovery}} \\
 \frac{dR_y}{dt} &= \overbrace{\frac{\eta_j}{2} R_j}^{\text{maturation}} - \overbrace{\eta_{xy} R_y}^{\text{maturation}} + \overbrace{r I_y}^{\text{recovery}}
 \end{aligned}$$

Post-reproductive females and males:

$$\begin{aligned}\frac{dS_m}{dt} &= \overbrace{\eta_{xy}(S_x + S_y)}^{\text{maturation}} - \overbrace{\eta_m S_m}^{\text{death}} - \overbrace{\frac{\beta_{hb}}{N_h} S_m I_v}^{\text{infection}} \\ \frac{dI_m}{dt} &= \overbrace{\eta_{xy}(I_x + I_y)}^{\text{maturation}} - \overbrace{\eta_m I_m}^{\text{death}} + \overbrace{\frac{\beta_{hb}}{N_h} S_m I_v}^{\text{infection}} - \overbrace{r I_m}^{\text{recovery}} \\ \frac{dR_m}{dt} &= \overbrace{\eta_{xy}(R_x + R_y)}^{\text{maturation}} - \overbrace{\eta_m R_m}^{\text{death}} + \overbrace{r I_m}^{\text{recovery}}\end{aligned}$$

where S , I and R are populations that are susceptible to, infected with, and recovered from (and thus immune to) ZIKV, respectively, and subscripts on the state variables are: j for children, x for reproductive-aged females that are not pregnant, p for reproductive-aged females that are pregnant, y for males within the age range of reproductive females, and m for adults beyond reproductive age (as based on female reproduction).

To examine the role of vertical transmission, we considered the following, somewhat more simplified model:

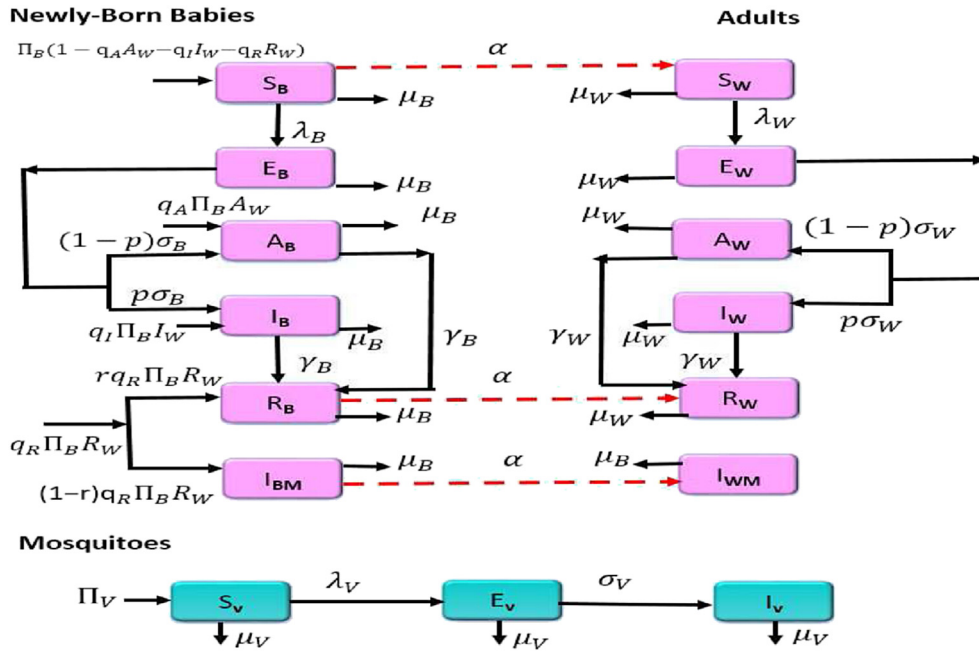


Figure 5.1 Flow diagram for our vertical transmission model

with associated equations

$$\begin{aligned}
S'_B(t) &= \pi_B - q_A \pi_B A_W(t) - q_I \pi_B I_W(t) - q_R \pi_B R_W(t) - \lambda_B(I_V, N_B) S_B(t) - (\alpha + \mu_B) S_B(t) \\
E'_B(t) &= \lambda_B(I_V, N_B) S_B(t) - (\alpha + \sigma_B + \mu_B) E_B(t) \\
A'_B(t) &= q_A \pi_B A_W(t) + (1 - p) \sigma_B E_B(t) - (\alpha + \gamma_B + \mu_B) A_B(t) \\
I'_B(t) &= q_I \pi_B I_W(t) + p \sigma_B E_B(t) - (\alpha + \gamma_B + \mu_B) I_B(t) \\
I'_{BM}(t) &= r q_R \pi_B R_W(t) - (\alpha + \mu_B) I_{BM}(t) \\
R'_B(t) &= (1 - r) q_R \pi_B R_W(t) + \gamma_B A_B(t) + \gamma_B I_B(t) - (\alpha + \mu_B) R_B(t) \\
S'_W(t) &= \alpha S_B(t) - \lambda_W(I_V, N_W) S_W(t) - \mu_W S_W(t) \\
E'_W(t) &= \lambda_W(I_V, N_W) S_W(t) - (\sigma_W + \mu_W) E_W(t) \\
A'_W(t) &= (1 - p) \sigma_W E_W(t) - (\gamma_W + \mu_W) A_W(t) \\
I'_W(t) &= p \sigma_W E_W(t) - (\gamma_W + \mu_W) I_W(t) \\
I'_{WM}(t) &= \alpha I_{BM}(t) - \mu_W I_{WM}(t) \\
R'_W(t) &= \alpha R_B(t) + \gamma_W A_W(t) + \gamma_W I_W(t) - \mu_W R_W(t) \\
S'_V(t) &= \pi_V - \lambda_V(A_B, I_B, A_W, I_W, N_B, N_W) S_V(t) - \mu_V S_V(t) \\
E'_V(t) &= \lambda_V(A_B, I_B, A_W, I_W, N_B, N_W) S_V(t) - (\mu_V + \sigma_V) E_V(t) \\
I'_V(t) &= \sigma_V E_V(t) - \mu_V I_V(t).
\end{aligned}$$

(5.2)

with state variables defined as follows:

Description of the state variables and parameters of the Zika model (2.1).

Variable	Description
$S_B(t), S_W(t)$	Susceptible newly born babies and adults
$E_B(t), E_W(t)$	Exposed newly born babies and adults
$A_B(t), A_W(t)$	Asymptomatic newly born babies and adults
$I_B(t), I_W(t)$	Symptomatic newly born without microcephaly and adults
$I_{BM}(t), I_{WM}(t)$	Microcephalic newly born babies and adults
$R_B(t), R_W(t)$	Recovered newly born babies and adults
$S_V(t)$	Susceptible female mosquitoes
$E_V(t)$	Exposed female mosquitoes
$I_V(t)$	Infected female mosquitoes
Parameter	Description
π_B	Birth rate newly born babies
p	Fraction of adults and newly born babies who are asymptomatic
$1 - p$	Remaining fraction of adults and newly born babies who are infectious
α	Maturation rate
r, q_A, q_I, q_R	Fractions of newly born babies who are infected and have microcephaly
$1 - r$	Remaining fraction of newly born babies who have microcephaly
η	Modification parameter
β_W, β_B	Transmission probability <i>per</i> contact of adults and newly born babies
ρ_W, ρ_B	Infectivity modification parameters in asymptomatic adults and newly born babies
σ_W, σ_B	Progression rate of exposed adults and newly born babies
γ_W, γ_B	Recovery rate of asymptomatic and symptomatic adults and newly born babies
μ_W, μ_B	Natural death rate of adults and newly born babies
π_V	Recruitment rate of mosquitoes
β_V	Transmission probability <i>per</i> contact of susceptible mosquitoes
b_V	Mosquito biting rate
σ_V	Progression rate of exposed mosquitoes
μ_V	Natural death rate of mosquitoes

To examine the role of sexual transmission, we again considered a somewhat simplified model, as follows:

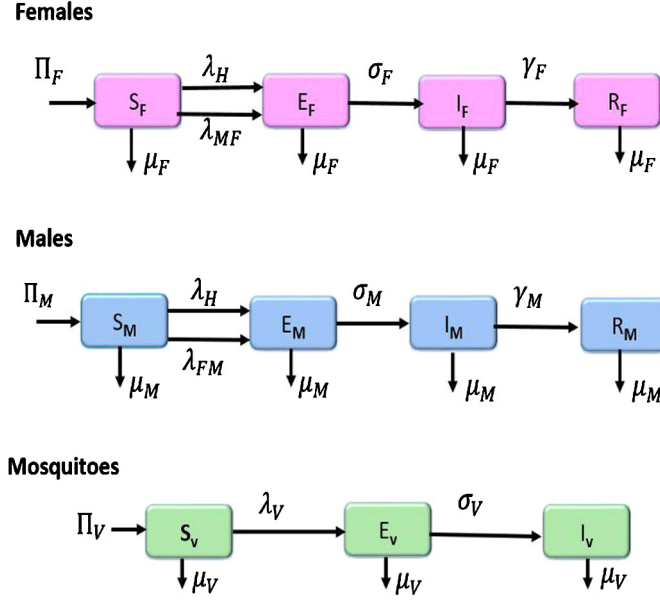


Figure 5.2 Flow diagram for our sexual transmission model

$$\begin{aligned}
 \frac{dS_F}{dt} &= \Pi_F - \frac{b_V \beta_H I_V S_F}{N_H} - \frac{C_{M_1} \beta_M I_M S_F}{N_F} - \mu_F S_F \\
 \frac{dE_F}{dt} &= \frac{b_V \beta_H I_V S_F}{N_H} + \frac{C_{M_1} \beta_M I_M S_F}{N_F} - (\sigma_F + \mu_F) E_F \\
 \frac{dI_F}{dt} &= \sigma_F E_F - (\gamma_F + \mu_F) I_F \\
 \frac{dR_F}{dt} &= \gamma_F I_F - \mu_F R_F \\
 \frac{dS_M}{dt} &= \Pi_M - \frac{b_V \beta_H I_V S_M}{N_H} - \frac{C_F \beta_F I_F S_M}{N_M} - \frac{C_{M_2} \beta_M I_M S_M}{N_M} - \mu_M S_M \\
 \frac{dE_M}{dt} &= \frac{b_V \beta_H I_V S_M}{N_H} + \frac{C_F \beta_F I_F S_M}{N_M} + \frac{C_{M_2} \beta_M I_M S_M}{N_M} - (\sigma_M + \mu_M) E_M \\
 \frac{dI_M}{dt} &= \sigma_M E_M - (\gamma_M + \mu_M) I_M \\
 \frac{dR_M}{dt} &= \gamma_M I_M - \mu_M R_M \\
 \frac{dS_V}{dt} &= \Pi_V - \frac{b_V \beta_V (I_F + I_M) S_V}{N_H} - \mu_V S_V \\
 \frac{dE_V}{dt} &= \frac{b_V \beta_V (I_F + I_M) S_V}{N_H} - (\sigma_V + \mu_V) E_V \\
 \frac{dI_V}{dt} &= \sigma_V E_V - \mu_V I_V,
 \end{aligned}$$

(5.3)

	Description
Variable	
$S_F(t), S_M(t)$	Susceptible females and males
$E_F(t), E_M(t)$	Exposed females and males
$I_F(t), I_M(t)$	Infected females and males
$R_F(t), R_M(t)$	Recovered females and males
$S_V(t)$	Susceptible mosquitoes
$E_V(t)$	Exposed mosquitoes
$I_V(t)$	Infected mosquitoes
Parameter	
Π_H	Recruitment rate of females and males
C_F, C_{M_1}	Heterosexual contact rate between females and males
C_{M_2}	Homosexual contact rate between males
β_H	Transmission probability <i>per</i> contact of susceptible humans with infected mosquitoes
σ_F, σ_M	Progression rate of exposed females and males
γ_F, γ_M	Recovery rate of females and males
μ_F, μ_M	Natural death rate of females and males
π_V	Recruitment rate of mosquitoes
β_F, β_M	Transmission probability <i>per</i> contact of females and males
b_V	Mosquito biting rate
β_V	Transmission probability <i>per</i> contact of susceptible mosquitoes with infected humans
σ_V	Progression rate of exposed mosquitoes
μ_V	Natural death rate of mosquitoes

Model Analysis

Figure 5.3 shows the predicted number of women who will experience a ZIKV infection during pregnancy as a function of the number of years since ZIKV arrival in a region based on the dynamics in Eq. (5.1). Similar dynamics are observed for all but the most conservative estimates of ZIKV transmission, suggesting that one third to one half of women who are or become pregnant during the first year of a ZIKV outbreak will experience a ZIKV infection at some point during their pregnancy. These results immediately explain the dramatic increase in microcephaly rates in Brazil. Indeed, even if ZIKV crosses the placenta in only a small fraction of infections, or only affects the fetus during the early stages of pregnancy, there will still be a sizeable fraction of babies born with ZIKV complications.

Figure 4 shows yearly prenatal exposures to ZIKV that would be expected in regions where the virus has been endemic for many years (i.e., equilibrium exposure rates). Compared to the 30-40% of pregnant women infected during the first year of a ZIKV epidemic (see Figure 5.3), predicted yearly exposures in regions where the disease is endemic are dramatically lower, typically below 5 infections per 1000 births. This is slightly higher than the approximately 0.1 cases of microcephaly per 1000 live birth reported in most countries without ZIKV transmission (28). However, 5 cases per 1000 births is our highest estimate, and further assumes that all infected pregnancies suffer microcephaly complications. If ZIKV crosses the placenta in only a fraction of these cases, or only affects the baby during certain stages of pregnancy, rates would be much lower. Thus, based on our model predictions, it seems highly likely that ZIKV related microcephaly could easily go undetected in systems with endemic ZIKV – even assuming high surveillance rates. Together, Figures 3 and 4 explain why the relationship between ZIKV and microcephaly was only detected once ZIKV emerged in new regions where it had not occurred previously.

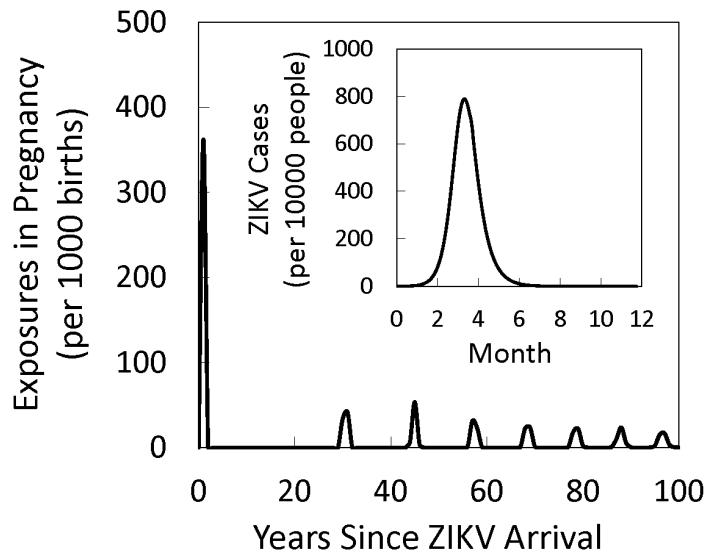


Figure 5.3 Predicted ZIKV dynamics, showing the number of women who experience a ZIKV infection during pregnancy as a function of the number of years since ZIKV arrival in the country or region. The inset shows the total number of ZIKV cases during the first year of the epidemic.

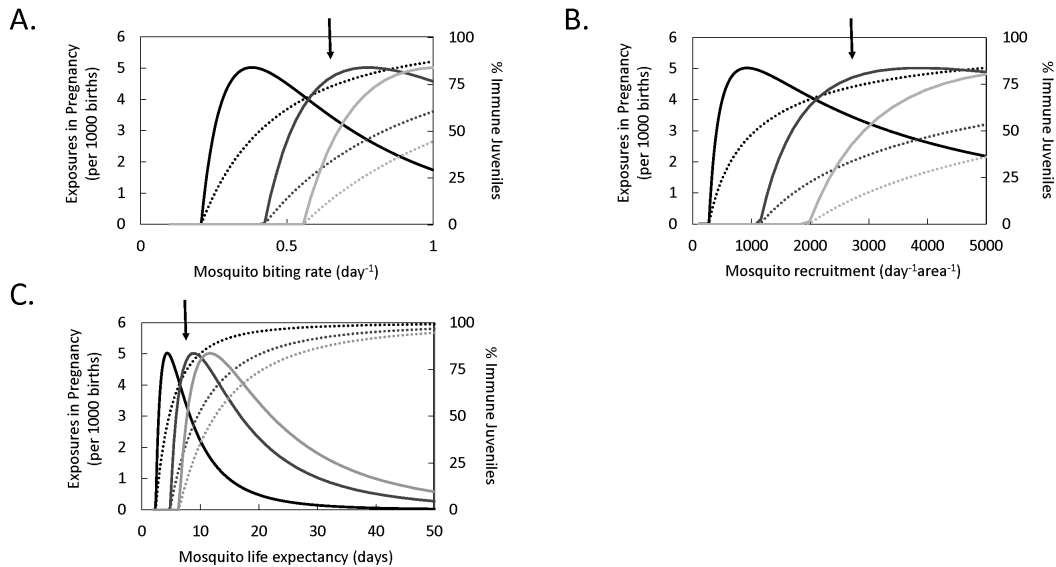


Figure 5.4 Number of women who experience an active ZIKV infection at any point during pregnancy (solid lines) and percentage of children (below reproductive age) that have acquired ZIKV immunity (dotted lines) as a function of (A) mosquito biting rates, (B) mosquito recruitment rates, and (C) mosquito life expectancy in a region with endemic disease (i.e., a system at equilibrium). Results are shown for high (black), intermediate (dark grey), and low (light grey) ZIKV transmission scenarios. Curves cross the x-axis at the threshold for disease persistence ($R_0 = 1$). The black arrows show the average values of the parameters under consideration, and thus can be thought of as starting points for control.

Figure 5.5 shows PRCC analysis of the ZIKV model with vertical transmission. Notably, vertical transmission does not have a huge effect on the ability of ZIKV to spread. However, this does not negate the importance of vertical transmission in driving microcephaly rates across infants born during a ZIKV outbreak.

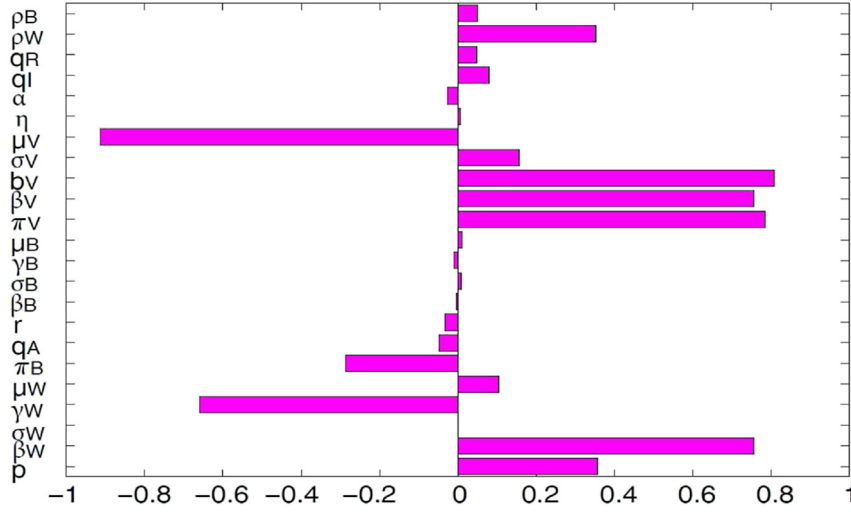


Figure 5.5 PRCC values for the Zika model (5.2), using as response functions the basic reproduction number R_0 .

Using our ZIKV model with vertical transmission, we thus considered a variety of control schemes. Figure 5.6 shows the number of adult ZIKV cases, infant ZIKV cases and infant cases of microcephaly for three different levels of mosquito control.

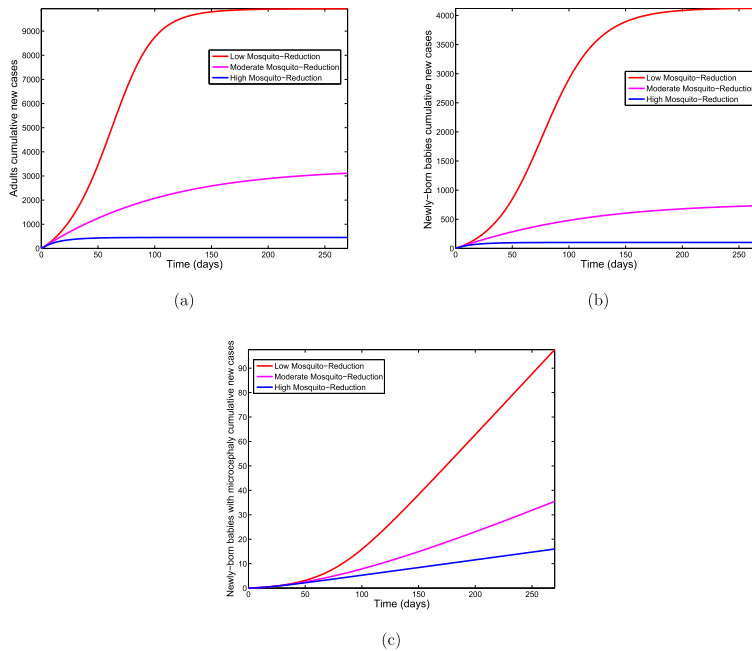


Figure 5.6 Simulation of the Zika model (5.2) for various control levels of the mosquito reduction control strategy. (a). The cumulative number of new Zika cases in adults. (b). The cumulative number of new Zika cases in newly born babies. (c). The cumulative number of new cases of newly born babies with microcephaly.

Figure 5.7 shows the number of adult ZIKV cases, infant ZIKV cases and infant cases of microcephaly for three different levels of personal protection use.

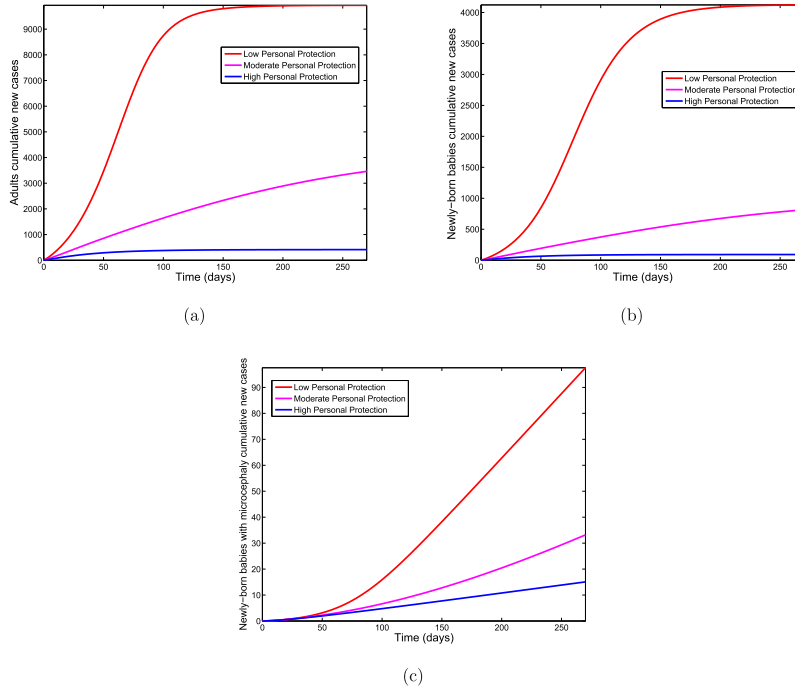


Figure 5.7 Simulation of the Zika model (5.2) for various levels of personal protection use. (a). The cumulative number of new Zika cases in adults. (b). The cumulative number of new Zika cases in newly born babies. (c). The cumulative number of new cases of newly born babies with microcephaly.

Figure 5.8 shows the number of adult ZIKV cases, infant ZIKV cases and infant cases of microcephaly for three different levels of delayed pregnancy.

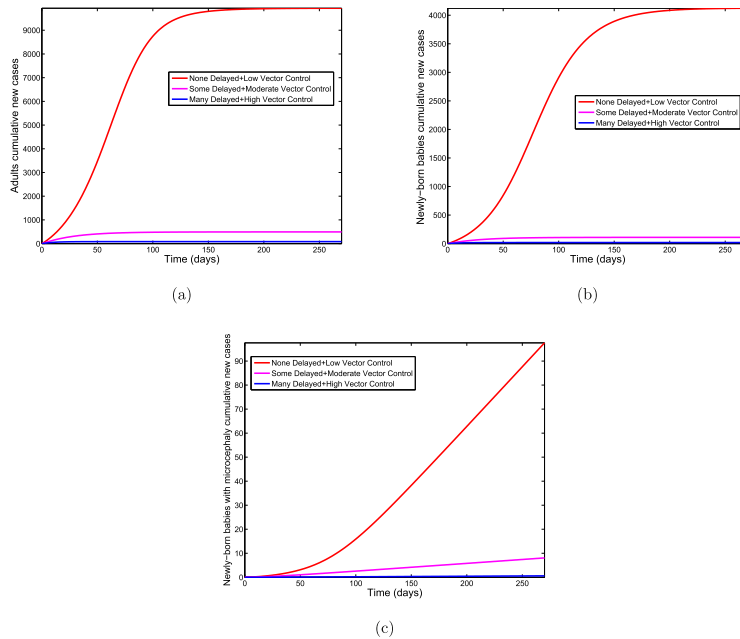


Figure 5.8 Simulation of the Zika model (5.2) for various levels of delayed pregnancy. (a). The cumulative number of new Zika cases in adults. (b). The cumulative number of new Zika cases in newly born babies. (c). The cumulative number of new cases of newly born babies with microcephaly.

Recognizing that delayed pregnancy is not always an option, this appears to be one of the best mechanisms for preventing ZIKV associated microcephaly during an outbreak. This result is consistent with our previous findings regarding microcephaly rates during the initial outbreak versus subsequent outbreaks in a country where ZIKV has become endemic.

Using our ZIKV model with sexual transmission, we explore the role of risky sexual behavior on ZIKV transmission and prevalence in male and female populations. Figure 5.9 shows how ZIKV is more prevalent in the female population versus the male population when heterosexual men have multiple female partners while homosexual males are monogamous. The reverse, however, is true when heterosexual men are more likely to be monogamous versus homosexual men.

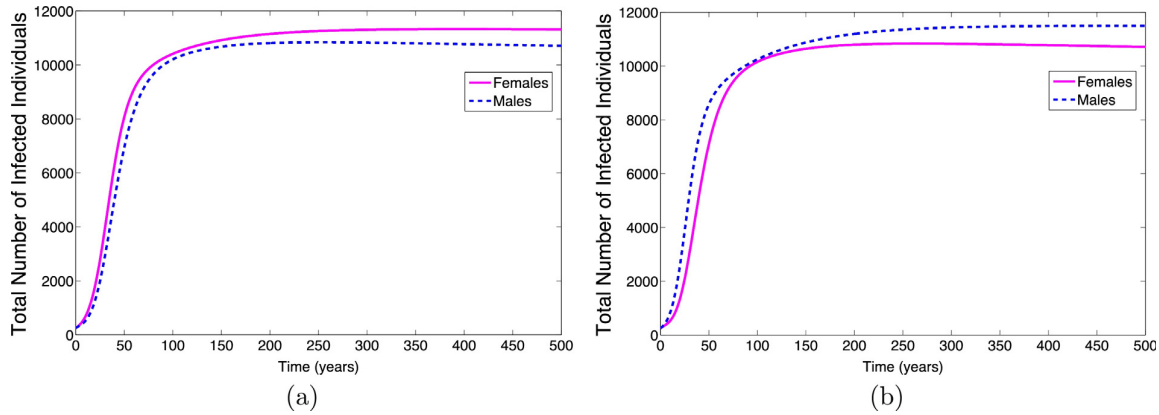


Figure 5.9 Simulation of the Zika model (5.3) as a function of time with different sexual contact rates. (a) Setting the sexual contact rate $C_F=0$, $C_{M1}=50$, $C_{M2}=2$. (b) Setting the sexual contact rate $C_F=0$, $C_{M1}=2$, $C_{M2}=80$.

Summary and Conclusions

By exploring Zika using three different models, we found an explanation for observed increases in microcephaly in regions where ZIKV has recently been introduced. We also identified strategies for combatting ZIKV microcephaly, and characterized the degree to which sexual behavior might impact the dynamics of ZIKV spread.

PART 6: PHENOLOGY MODELS

Background

Phenology – the seasonal timing of plant and animal life-cycles – governs temporal interactions of species across ecosystems. As such, it is an important driver of ecological processes. With respect to pathogen exposure pathways, phenology can affect whether or not a particular disease persists, the severity of disease spread and the timing of disease appearance in susceptible populations. These factors, in turn, inform management decisions regarding the best intervention strategies and when these should occur to optimally reduce disease risk. Unfortunately, species phenologies are shifting as a result of climate change. Furthermore, shifts in phenology, both across life-stages and among species, are occurring at different rates, altering intra- and interspecific interactions. Because these interactions are critical to disease transmission, disease dynamics may be particularly sensitive to phenology change. Although there is a long history of vector-borne disease models in epidemiology, few account for species phenology, and even fewer do so in the context of complex, multi-species interaction networks.

Several modeling papers have considered seasonality or phenology. Ding (11) used a hybrid model with discrete ‘summer’ and ‘winter’ seasons to study the temporal dynamics of ticks, mice and Lyme disease and the optimal timing of acaricide application for disease management. Although two discrete seasons can only capture phenology in the broadest sense, Ding’s work was a first step towards integrating multi-species interaction networks and management strategies in a seasonal environment. In a more recent study, Thomas, et al. (12) applied a similar, two season model to understand the impact of insecticide use to control WNV. Their model included a temperature dependent delay-differential equation, and predicted that spraying in the fall would be more effective than spraying in warmer months. Again, however, the model did not include explicit phenology.

Even fewer modeling papers have considered the role of seasonality on the basic reproduction number R_0 – a quantity that is often the focus of epidemiological models. In particular extension of R_0 to seasonal systems is relatively recently, having only been developed within the past few years. Thus, while R_0 has been studied for systems with periodic vector populations, the broader influences of phenology on persistence of vector-borne diseases remain poorly known. A better understanding of the fundamental relationships between model parameters, phenology and disease persistence could provide valuable insight into disease ecology. This is particularly true for rare diseases that have not been extensively studied, but is also true for more common diseases that are strongly affected by seasonality and therefore may not be fully described by existing qualitative models that do not consider phenology.

Model Development

To explore the effect of seasonality in multi-species host and vector populations on the basic reproduction number, R_0 , we model a disease whose dynamics are described using a prototypical SI, SIR, or SIRS-type compartmental ordinary differential equation (ODE) model, where $I_{iv}(t)$ and $S_{iv}(t)$, denote the infectious and susceptible population densities of the i th vector species, respectively, and likewise for $I_{ih}(t)$ and $S_{ih}(t)$ are the i th host species. Recovered classes, if present, will be irrelevant in our mathematical analysis. The time evolution of the infectious compartments are given by the following ODE’s:

$$\begin{aligned}
\frac{dI_i^v(t)}{dt} &= -\alpha(t)_i^v I_i^v + \sum_{j=1}^{N^h} \beta_{ij}^v \frac{f_{ij}}{N_j^h(t)} S_i^v(t) I_j^h(t) \\
\frac{dI_i^h(t)}{dt} &= -\alpha(t)_i^h I_i^h + \sum_{j=1}^{N^v} \beta_{ij}^h \frac{f_{ji}}{N_j^v(t)} I_h^v(t) S_j^h(t).
\end{aligned}
\tag{6.1}$$

In Eq. (6.1), β_{ij}^v denotes the probability of transmission from host type j to vector type i , and β_{ij}^h denotes the probability of transmission from vector type j to host type i . The terms $\alpha(t)_i^v$ and $\alpha(t)_i^h$ denote the rates at which infectious vectors and hosts exit the infectious classes. These rates are expected to vary seasonally in conjunction with the host and vector populations. Specifically, when population are “in-season” (meaning a times of large population density), infectious individuals experience favorable environmental conditions and remain in the area for the duration of the infection, so the corresponding exit rates are expected to be given by the natural recovery rates (or the natural death rates when recovery times are much larger than the average lifespans). When populations are “out-of-season” (meaning a times of negligible population density), individuals quickly exit the area due to either migration or rapid death caused by unfavorable environmental conditions, so the corresponding exit rates are expected to be much larger than the in-season values.

To enable calculation of multi-species seasonal R_0 values, we assume simple pulsed population models where population values are a fixed non-zero constant when in-season, and are zero when out of season. Specifically:

$$\begin{aligned}
N_i^v(t) &= \begin{cases} N_i^v, & (t - z_i^v) \bmod T < \tau_i^v \\ 0, & \text{otherwise} \end{cases} \\
N_i^h(t) &= \begin{cases} N_i^h, & (t - z_i^h) \bmod T < \tau_i^h \\ 0, & \text{otherwise} \end{cases}
\end{aligned}
\tag{6.2}$$

In Eq. (6.2), T is the length of the year, τ_{iv} is the length of the on-season for vector species i , z_{iv} is the time of year at the on-season of which vector species i begins, and N_{iv} is the population level reached by vector species i during the on-season. The corresponding terms for host populations are defined analogously. Although biologically simplistic, these pulsed population models are able to capture basic effects related to the relative timings of vector/host presence and absence. Further, pulsed populations will require mathematics for calculating the periodic basic reproduction number that are far more tractable than the mathematics under more realistic population models.

The exit rates out of the infections classes are assumed to have the same timings as the corresponding pulsed populations. When vector species i is in-season, the infectious recovery time is assumed to be much larger the natural species lifetime, so the exit rate out of the infectious class is assumed to be given by the natural death rate denoted by μ_{vi} . Out-of-season, the exit rate of vector species i is denoted by γ_{iv} , where $\gamma_{iv} \geq \mu_{vi}$. We thus have

$$\alpha_i^v(t) = \begin{cases} \mu_{vi}^v, & (t - z_i^v) \bmod T < \tau_i^v \\ \gamma_{iv}^v, & \text{otherwise.} \end{cases}
\tag{6.3}$$

The host species are assumed to recover from infection over time scales much shorter than their average lifetimes, so the in-season exit rates are taken to be natural recovery rates, denoted by r_i^h for host species i . The out-of-season exit rate is denoted γ_i^h for host species i , where $\gamma_i^h \geq r_i^h$, and we thus have

$$\alpha_i^h(t) = \begin{cases} r_i^h, & (t - z_i^h) \bmod T < \tau_i^h \\ \gamma_i^h, & \text{otherwise.} \end{cases} \quad (6.4)$$

Model Analysis

From the model defined in Eqs. (6.1-6.4), it is possible to explore the effect of seasonality on the basic reproduction R_0 in multispecies seasonal models. Figure 6.1 shows the predicted value of R_0 as a function of the relative timing of host phenology to vector phenology for a disease system involving a single vector and a single host for a range of different host and vector exit rates. Importantly, we find that a slight offset results in a larger R_0 , which is counterintuitive. Indeed, one would inherently expect that perfectly aligned phenologies would be most conducive to disease spread.

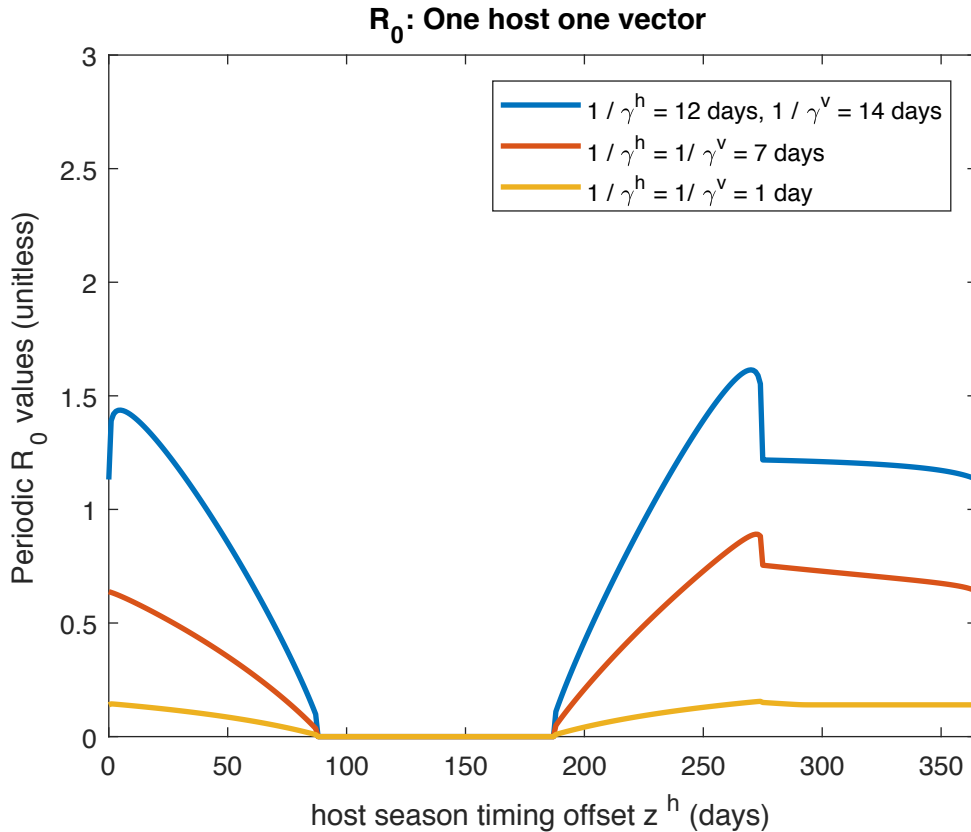


Figure 6.1 Calculated values of R_0 as a function of the phenology difference between host and vector species

Figure 6.2 extends Figure 6.1 by considering a system with 2 hosts and a single vector. Again, the slight mismatch in phenology between host and vector species at the maximum value of R_0 is apparent in this somewhat more complex system.

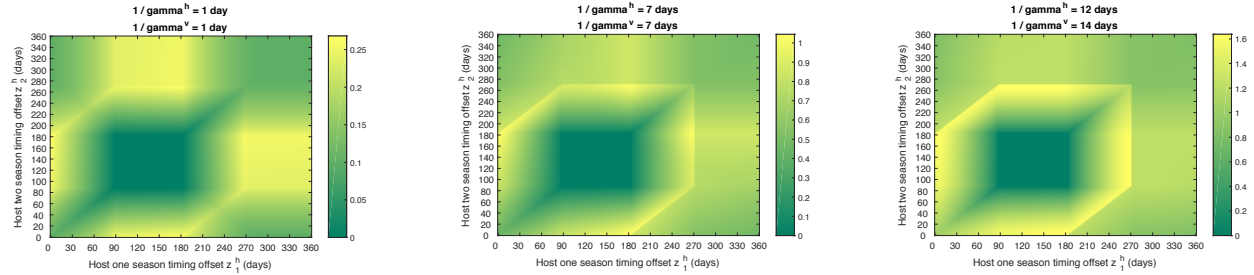


Figure 6.2 Calculated values of R_0 as a function of the phenology difference between two hosts and vector species

Figure 6.3 extends Figure 6.1 by considering a system with a single host and 2 vectors. As in Figures 6.1 and 6.2, the mismatch in phenology between host and vector species at the maximum value of R_0 is apparent in this system as well.

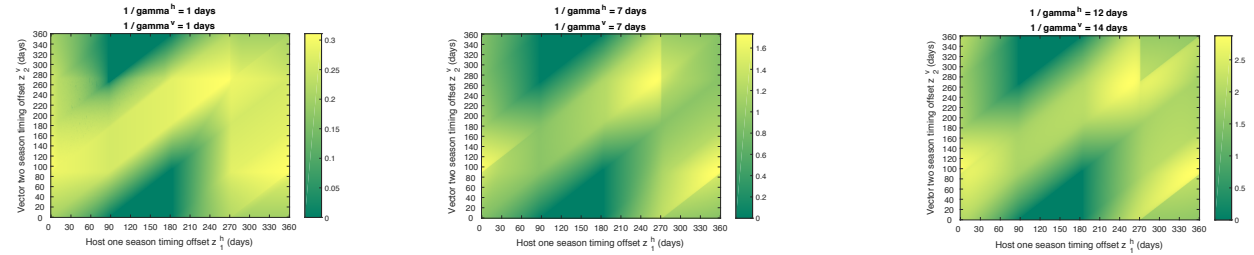


Figure 6.3 Calculated values of R_0 as a function of the phenology difference between a host and two vector species

In addition to an R_0 analysis, we used numerical simulations to explore the dynamics of a similarly pulsed phenological model with a single host and vector species. This model is shown in Figure 6.4, along with results for infected hosts as a function of phenological mismatch. Interestingly, we found clear evidence of a bifurcation as a function of the mismatch in timing between host and vector seasonal timing. In particular, changes in this mismatch can drive disease from an endemic equilibrium to year-to-year oscillations in disease severity and even into a chaotic regime, where there is no way to predict the level of disease from one year to the next. This finding of changes in qualitative dynamics of a simple SIR type model based on the seasonality of the host relative to the vector suggests that climate change may have a negative and unpredictable effect on disease dynamics.

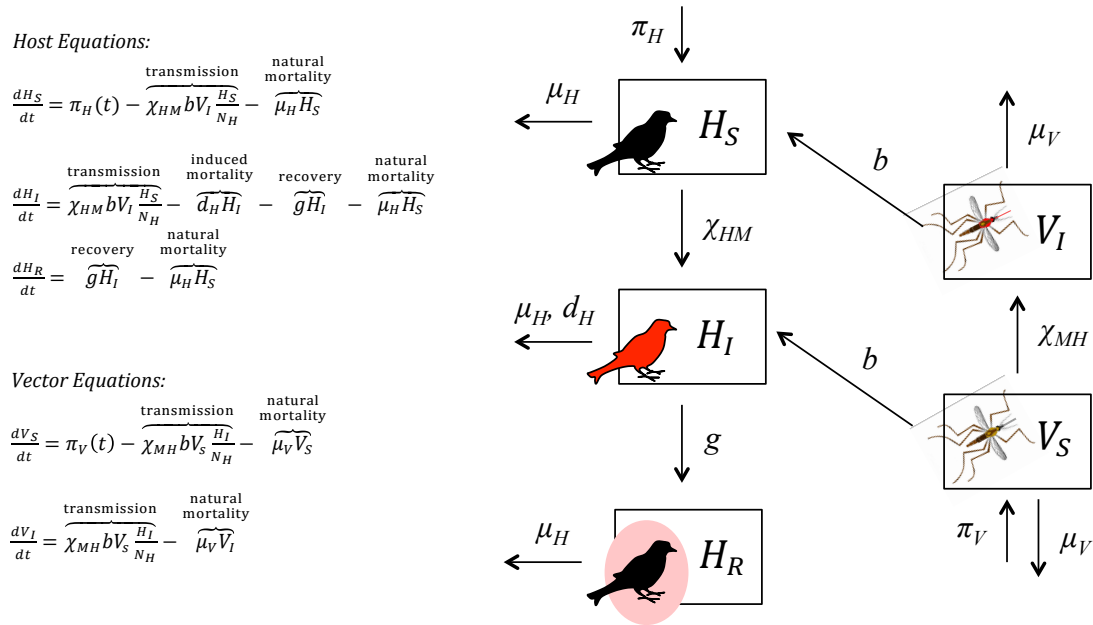


Figure 6.4 Simple single vector single host model to explore the role of phenology on disease dynamics.

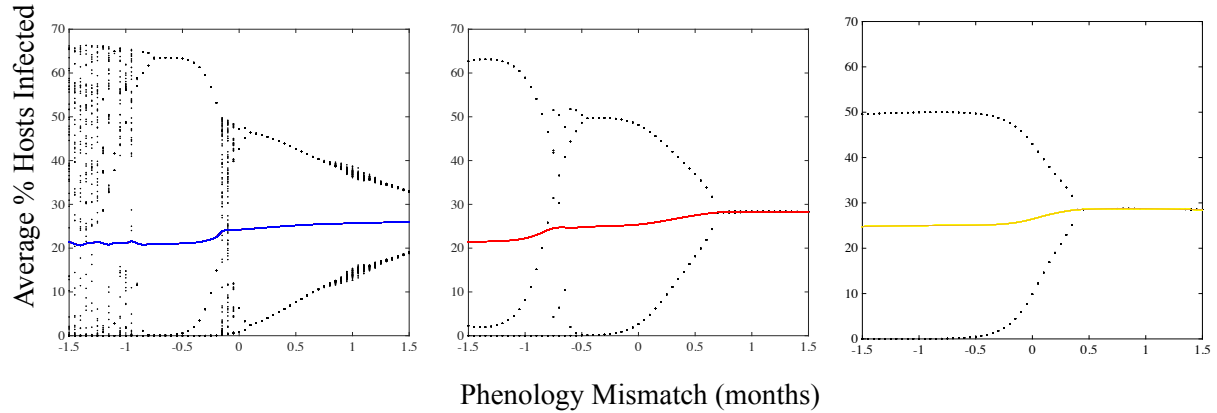


Figure 6.5 Orbit plots showing the average percent of hosts infected as a function of phenology mismatch between the host and vector populations.

The above models are simple and generic, aiming to capture the effect of phenology without becoming mired in the details of any specific system. However, we also explored more specific models carefully parameterized to capture the temperature dependent life-histories of three different genera of mosquito – *Aedes*, *Culex* and *Culiseta*. These three genera are responsible for the majority of disease spread of North American mosquito-borne disease systems, for example La Crosse Encephalitis, West Nile Virus and Eastern Equine Encephalitis respectively. For these

species, we used data on larval development rates over five instars, along with estimates of adult mortality as a function of temperature, and fecundity as a function of temperature to predict changes in mosquito population dynamics throughout a season and also in the context of overall global warming. Next, we interfaced these models to a genetic algorithm in order to predict the optimal timing for larvicide and adulticide application to maximally reduce the mosquito population while minimizing costs. Figure 6.6 shows an example output for *Aedes aegypti* assuming mean seasonal temperatures in New Orleans under current conditions. Figure 6.7 shows the same output, but under the assumption of a season-wide increase in average temperature of 3°C due to global warming.

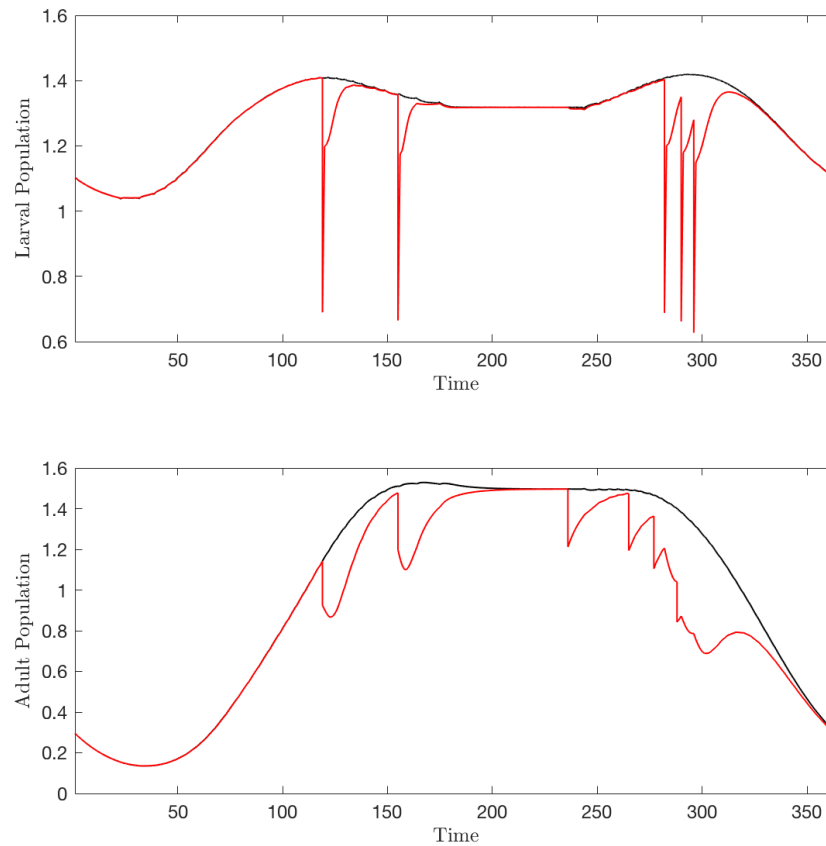


Figure 6.6 Mosquito larval and adult population abundances as a function over a season, but in an unmanaged system (black) and under management (red) applying both larvicide and adulticide. Total larvicide and adulticide costs for management were \$4967 and \$5078 respectively, with effort focused throughout the spring, summer and fall, particularly for larvicide.

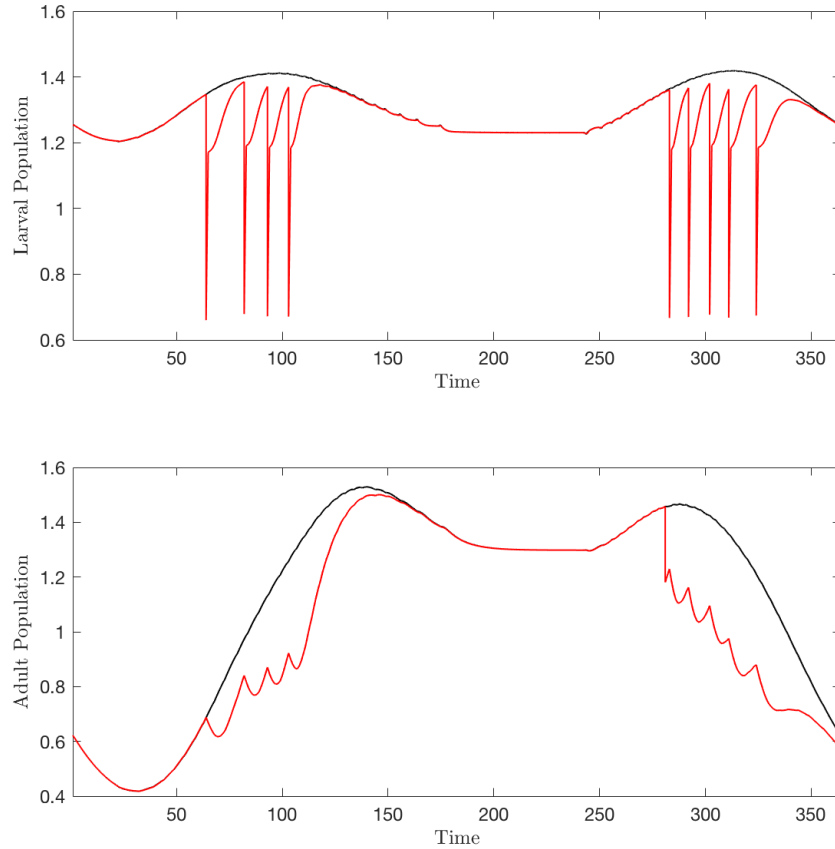


Figure 6.6 Mosquito larval and adult population abundances as a function over a season, but in an unmanaged system (black) and under management (red) applying both larvicide and adulticide. Total larvicide and adulticide costs for management were \$9934 and \$1693 respectively, with effort focused more in the spring and fall.

Similar figures can be made for different locations, based on NOAA data on mean seasonal temperatures, altered according to various climate change scenarios. Likewise, we can examine each of the different mosquito species for which we have fully parameterized models.

PART 7: GUI

As a final step towards bringing our work to its target audience, we developed a GUI that allows vector management practitioners to input information on population abundances throughout the year, and then use this information to predict the optimal timing of larvicide and adulticide treatments based on the phenology of the vectors. Briefly, the GUI works by fitting a curve to the inputted seasonal data, and then using this to parameterize an underlying vector dynamics model. Figure 7.1 shows the basic user interface linking management personnel to the admittedly complex mathematical models that we developed as part of the current grant.

The screenshot displays the 'Mosquito Control Resource Optimization' web application. The interface is divided into a left sidebar and a main content area. The sidebar contains a file upload section with a 'Choose CSV or excel File' header, a 'Browse...' button, and a text input field containing 'Culex.csv'. Below this are four dropdown menus for 'Count Column' (set to 'count'), 'Date Column' (set to 'dateCollected'), 'Latitude Column', and 'Longitude Column'. The main content area has a top navigation bar with 'Instructions and Github Repo' on the left and 'Provide Feedback' with a bug icon on the right. Below the navigation bar are four tabs: 'Getting Started' (active), 'Data Summary', 'Mosquito Population Model', and 'Resource Optimization Model'. The 'Getting Started' tab contains an 'Overview' section with a paragraph about the project's aim, an 'Instructions' section with a paragraph about input requirements, and a bulleted list of requirements and user inputs. The requirements include consistent date formats, an example data sheet, and feedback. The user inputs include mosquito life span, percent of population knocked down, number of treatments, and days between treatments.

Mosquito Control Resource Optimization

Instructions and Github Repo Provide Feedback 🐛

Choose CSV or excel File

Browse... Culex.csv

Upload complete

Count Column

count

Date Column

dateCollected

Latitude Column

Longitude Column

Getting Started Data Summary Mosquito Population Model Resource Optimization Model

Overview

This project aims to make an accessible model for mosquito control resource optimization. The model uses data provided by users to estimate the mosquito populations in the sampling area for the sampling timeperiod, and the optimal time to apply a treatment or multiple treatments.

Instructions

This application accepts CSV and excel files (.xls, .xlsx) as inputs. None of your data are stored long term on the Rshiny servers. At the moment, only a single spreadsheet can be uploaded. If you have multiple years of data, please consolidate to one spread sheet.

- Consistent date formats are required
- [Example Data Sheet](#)
- [Provide Feedback 🐛](#)
- Minimum data requirements for model:
 - Count data
 - Date Collected
- User Inputs:
 - Mosquito Life span in days
 - Percent of poplotion knocked down by treatment
 - Number of treatments applied
 - Number of days between treat

Figure 7.1 GUI interface aimed at aiding vector management practitioners in selecting the optimal timing of larvicide and adulticide treatments to best balance vector reduction and management costs.

Figure 7.2 shows a sample output of the fitted input data, that is then used to predict optimal timing of management strategies based on historical phenology data. Figure 7.3 shows the controlled versus uncontrolled population of mosquitoes predicted based on a particular set of management criteria (estimated mosquito lifespan, allowable costs, etc.)

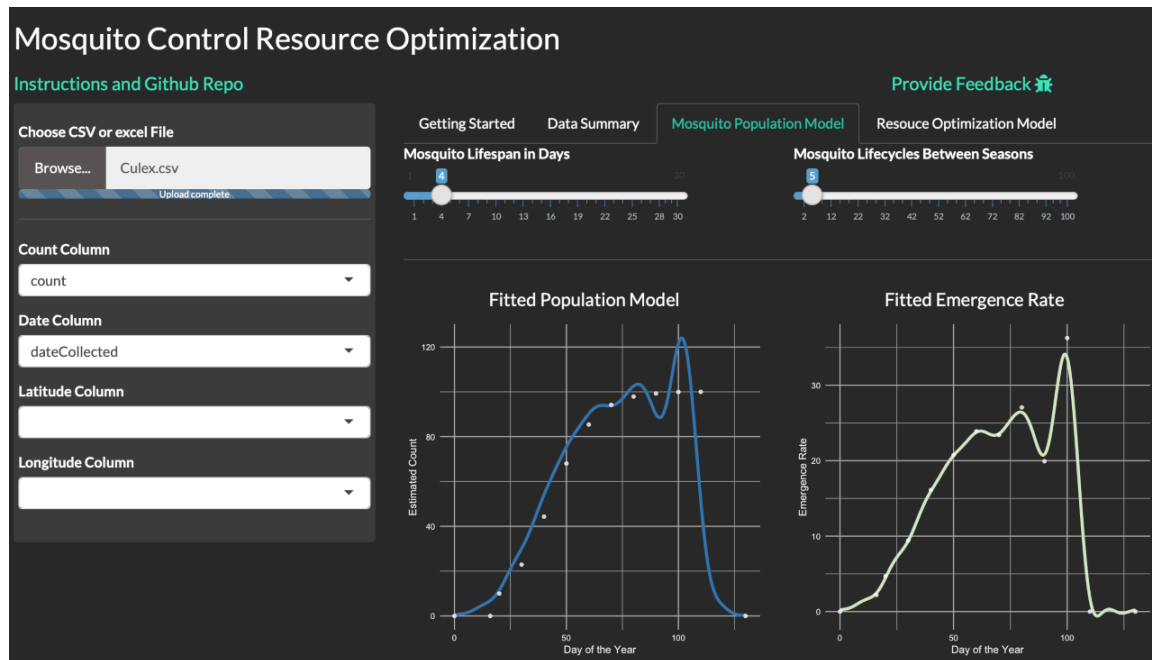


Figure 7.2 Sample fitted curves from the GUI

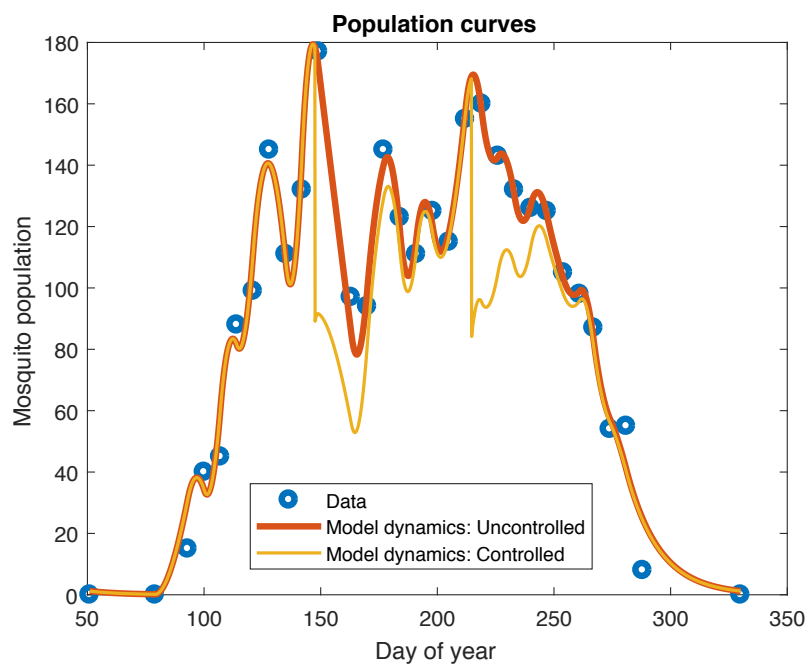


Figure 7.3 Sample output illustrating the degree of vector reduction achievable by optimally distributing management actions based on historical phenology data.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

Through a series of models, we have successfully improved the mechanistic detail incorporated into control models, and clarified when simplifying assumptions are valid and when they are not. We have additionally explored several interesting features of the management landscape, including variation in accessibility to habitat patches for the purposes of control. Using some of the insight gained from these models, we have developed new models for specific diseases, as well as specific vectors (*Culex*, *Aedes* and *Culiseta*) responsible for the majority of native North American vector-borne diseases. These models allow us to understand how changing conditions due to global change might impact everything from vector biology through to disease spread and disease dynamics. Finally, we have incorporated many of our findings into a GUI that is aimed at direct application by mosquito management practitioners based on relevant data collected on a regular basis (e.g. adult counts in CDC light traps). This transitions our findings to the relevant audience, where they can be broadly applied to improve management of vector-borne diseases.

In the future, we would like to extend our models to some of the more specific diseases that we had initially anticipated modeling. We believe that this is still a highly valid and important endeavor, and that our recent findings will improve our ability to tackle this goal, ultimately increasing the accuracy and resolution with which we will be able to predict vector-borne disease dynamics and vector-borne disease control, both now and in the future.

Literature Cited

PART 1:

- [1] G. Macdonald. *The epidemiology and control of malaria*. Oxford University Press, 1957.
- [2] R. Ross. *Report on the prevention of malaria in Mauritius*. Waterlow and Sons Limited, 1908.
- [3] R. Ross. *The prevention of malaria*. John Murray, 2 edition, 1911.
- [4] R. Ross. Some quantitative studies in epidemiology. *Nature*, 87:466–467, 1911.
- [5] D. L. Smith, K. E. Battle, S. I. Hay, C. M. Barker, T. W. Scott, and F E McKenzie. Ross, Macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens. *PLoS Pathogens*, 8:e1002588, 2012.
- [6] R. C. Reiner Jr et al. A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970 - 2010. *J. Royal Soc. Interface*, 10:20120921, 2013.
- [7] S. Mandall, R. R. Sarkar, and S. Sinha. Mathematical models of malaria - a review. *Malar. J.*, 10:202, 2011.
- [8] C. Favier, D. Schmit, C. D. M. Muller-Graf, B. Cazelles, N. Degallier, B. Mondet, and M. A. Dubois. Influence of spatial heterogeneity on an emerging infectious disease: the case of dengue epidemics. *Proc. R. Soc. Lond. B. Biol. Sci.*, 272:1171–1177, 2005.
- [9] J. E. Simpson, P. J. Hurtado, J. Medlock, G. Molaei, T. G. Andreadis, A. P. Galvani, and M. A. Duik-Wasser. Vector host-feeding preferences drive transmission of multi-host pathogens: West Nile virus as a model system. *Proc. R Soc. Lond. B Biol. Sci.*, 279:925–933, 2012.
- [10] J. G. Dushoff. *Modeling the effects of host heterogeneity on the spread of human diseases*. PhD thesis, Princeton University, January 1997.
- [11] S. Alitzer, A. Dobson, P. Hosseini, P. Hudson, M. Pascual, and P. Rohani. Seasonality and the dynamics of infectious diseases. *Ecol. Lett.*, 9:467–484, 2006.
- [12] M. Otero and H. G. Solari. Stochastic eco-epidemiological model of dengue disease transmission by *Aedes aegypti* mosquito. *Math. Biosci.*, 223:32–46, 2010.
- [13] F. B. Augusto, N. Marcus, and K. O. Okosun. Application of optimal control to the epidemiology of malaria. *Electron. J. Differential Equations*, 2012:1–22, 2012.
- [14] F. Augusto and S. Lenhart. Optimal control of the spread of malaria superinfectivity. *J. Biol. Syst.*, 21:1340002, 2014.
- [15] H. McCallum, N. Barlow, and J. Hone. How should pathogen transmission be modelled? *Trends Ecol. Evol.*, 16:295–300, 2001.
- [16] M. J. Wonham, M. A. Lewis, J. Renclawowicz, and P. van den Driesche. Transmission assumptions generate conflicting predictions in host-vector disease models: a case study in West Nile virus. *Ecol. Lett.*, 9:706–725, 2006.

- [17] H. W. Hethcote. The mathematics of infectious diseases. *SIAM Rev.*, 42:599–653, 2000.
- [18] E. Miller, J. Dushoff, and A. Huppert. The risk of incomplete personal protection coverage in vector-borne disease. *J. Royal Soc. Interface*, 13:20150666, 2016.
- [19] C. Bowman, A. B. Gumel, P. van den Driessche, J. Wu, and H. Zhu. A mathematical model for assessing control strategies against west nile virus. *Bull. Math Bio.*, 67:1107–1133, 2005.
- [20] C. Chiyaka, J. M. Tchuente, W. Garira, and S. Dube. A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria. *Appl. Math Comput.*, 195:641–662, 2008.
- [21] F. B. Augusto and J. M. Tchuente. Control strategies for the spread of malaria in humans with variable attractiveness. *Math Pupil. Stud.*, 20:82–100, 2013.
- [22] F. B. Augusto, S. Y. Del Valle, K. B. Blauneh, C. N. Ngonghala, M. J. Goncalves, N. Li, R. Zhao, and H. Gong. The impact of bed-net use on malaria prevalence. *J. Theor. Biol.*, 320:58–65, 2013.
- [23] C. N. Ngonghala, S. Y. Del Valle, R. Zhao, and J. Mohammed-Awel. Quantifying the impact of decay in bed-net efficacy on malaria transmission. *J. Theor. Biol.*, 363:247–261, 2014.
- [24] A. Dobson. Population dynamics of pathogens with multiple host species. *Am. Nat.*, 164:S64–S78, 2004.
- [25] F. Keesing, R. D. Holt, and R. S. Ostfeld. Effects of species diversity on disease risk. *Ecol. Lett.*, 9:485–498, 2006.
- [26] F. Keesing et al. Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature*, 468:647–652, 2010.
- [27] R. S. Ostfeld and F. Keesing. Effects of host diversity on infectious disease. *Annu. Rev. Ecol. Evol. Syst.*, 43:157–182, 2012.
- [28] E. Miller and A. Huppert. The effects of host diversity on vector-borne disease: The conditions under which diversity will amplify or dilute disease risk. *PLoS ONE*, 11:e80279, 2013.
- [29] S. J. Moore, C. R. Davies, N. Hill, and M. M. Cameron. Are mosquitoes diverted from repellent-using individuals to non-users? Results of a field study in Bolivia. *Trop. Med. Int. Health*, 12:532–539, 2007.
- [30] G. F. Killeen and T. A. Smith. Exploring the contribution of bed nets, cattle, insecticides, and excito-repellency to malaria control: a deterministic model of host seeking behavior and mortality. *Trans. Royal Soc. Trop. Med. Hyg.*, 101:867–880, 2007.
- [31] W. Gu and R. J. Novak. Predicting the impact of insecticide-treated bed nets on malaria transmission: the devil is in the detail. *Malar. J.*, 8:256, 2009.
- [32] H. Liu, JW Xu., XR Guo, J. Havumaki, YX Lin, GC Yu, and DL Zhou. Coverage, use and maintenance of bed nets and related influence factors in Kachin Special Region II, northeastern Myanmar. *Malar. J.*, 14:212, 2015.

- [33] P. S. Larson, N. Minakawa, G. O. Dida, S. M. Njenga, E. L. Ionides, and M. L. Wilson. Insecticide-treated net use before and after mass distribution in a fishing community along Lake Victoria, Kenya: successes and unavoidable pitfalls. *Malar. J.*, 13:466, 2014.
- [34] C. S. McBride. Genes and odors underlying the recent evolution of mosquito preference for humans. *Curr. Biol.*, 26:R41–R46, 2016.
- [35] J. I. Raji and M. DeGennaro. Genetic analysis of mosquito detection in humans. *Curr. Opin. Insect Sci.*, 20:34–38, 2017.
- [36] T. Dekker, M. Grier, and R. T. Carde. Carbon dioxide instantly sensitizes female yellow fever mosquitoes to human skin odors. *J. Exp. Biol.*, 208:2963–2972, 2005.
- [37] T. Dekker and R. T. Carde. Moment-to-moment flight manoeuvres of the female yellow fever mosquito (*Aedes aegypti* L.) in response to plumes of carbon dioxide and human skin odour. *J. Exp. Biol.*, 214:3480–3494, 2011.
- [38] P. N. Dawkins, F. E. Kellogg, and R. H. Wright. Host-finding and repulsion of *Aedes aegypti*. *Can. Entomol.*, 97:239–263, 1965.
- [39] F. van Breugel, J. Riffell, A. Fairhill, and M. H. Dickinson. Mosquitoes use vision to associate odor plumes with thermal targets. *Curr. Biol.*, 25:2123–2129, 2015.
- [40] C. J. McMeniman, R. A. Corfas, B. J. Matthews, S. A. Ritchie, and L. B. Vosshall. Multimodal integration of carbon dioxide and other sensory cues drives mosquito attraction to humans. *Cell*, 156:1060–1071, 2014.
- [41] E. S. Lacey, A. Ray, and R. T. Carde. Close encounters: contributions of carbon dioxide and human skin odour to finding and landing on a host in *Aedes aegypti*. *Physio. Entomol.*, 39:60–68, 2014.
- [42] W. A. Foster and F. A. Eischen. Frequency of blood-feeding in relation to sugar availability in *Aedes aegypti* and *Anopheles quadrimaculatus*. *Ann. Entomol. Soc. Am.*, 80:103–108, 1987.
- [43] H. Briegel and E. Horler. Multiple blood meals as a reproductive strategy in *Anopheles* (diptera: Culicidae). *J. Med. Entomol.*, 30:975–985, 1993.
- [44] M. J. Klowden and H. Briegel. Mosquito gonotrophic cycle and multiple feeding potential: Contrasts between *Anopheles* and *Aedes*. *J. Med. Entomol.*, 31:618–622, 1994.
- [45] A. Lynd and P. J. McCall. Clustering of host-seeking activity of *Anopheles gambiae* mosquitoes at the top surface of a human-baited bed net. *Malar. J.*, 12:267, 2013.
- [46] J. F. Sutcliffe and S. Yin. Behavioural responses of females of two anopheline mosquito species to human-occupied, insecticide-treated and untreated bed nets. *Malar. J.*, 13:294, 2014.
- [47] J. Spitzen, T. Koelewijn, W. R. Mukabana, and W. Takken. Effect of insecticide-treated bed nets on house-entry by malaria mosquitoes: The flight response recorded in a semi-field study in Kenya. *Acta Trop.*, 172:180–185, 2017.

- [48] M. DeGennaro, C. S. McBride, L. Seeholzer, T. Nakagawa, E. J. Dennis, C. Goldman, N. Jasinskiene, A. A. James, and L. B. Vosshall. *orco* mutant mosquitoes lose strong preference for humans and are not repelled by volatile DEET. *Nature*, 498:487–491, 2013.
- [49] M. Pellegrino, N. Steinbach, M. C. Stensmyr, B. S. Hanson, and L. B. Vosshall. A natural polymorphism alters odour and DEET sensitivity in an insect odorant receptor. *Nature*, 478:511–514, 2011.
- [50] Y. Lee, S. H. Kim, and C. Montell. Avoiding DEET through insect gustatory receptors. *Neuron*, 67:555–561, 2010.
- [51] Z. Syed and W. S. Leal. Mosquitoes smell and avoid the insect repellent DEET. *Proc. Natl. Acad. Sci.*, 105:13598–13603, 2008.
- [52] W. S. Leal. The enigmatic reception of DEET - the gold standard of insect repellents. *Curr. Opin. Insect Sci.*, 6:93–98, 2014.
- [53] M. DeGennaro. The mysterious multi-modal repellency of DEET. *Fly*, 9:45–51, 2015.
- [54] L. Yakob. How do biting disease vectors behaviourally respond to host availability? *Parasit. Vectors*, 9:468, 2016.
- [55] J. Antonovics, Y. Iwasa, and M. P. Hassell. A generalized model of parasitoid, venereal, and vector-based transmission processes. *Amer. Nat.*, 145:661–675, 1995.
- [56] C. S. Holling. Some characteristics of simple types of predation and parasitism. *Can. Entomol.*, 91:385–398, 1959.
- [57] C. S. Holling. The components of predation as revealed by a study of small-mammal predation of the european pine sawfly. *Can. Entomol.*, 91:293–320, 1959.
- [58] C. S. Holling. The functional response of invertebrate predators to prey density. *Mem. Entomol. Soc. Can.*, 98:5–86, 1966.
- [59] N. Chitnis, A. Schapira, T. Smith, and R. Steketee. Comparing the effectiveness of malaria vector-control interventions through a mathematical model. *Am. J. Trop. Med. Hyg.*, 10:230–240, 2010.
- [60] K. Blayne, Y. Cao, and H. Kwon. Optimal control of vector-borne diseases: treatment and prevention. *Discrete Continuous Dyn. Syst. Ser. B*, 11:587–611, 2009.
- [61] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.*, 28:365–382, 1990.
- [62] P. van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.*, 180:29–48, 2002.
- [63] O. JT Briet, D. Hardy, and T. A. Smith. Important of factors determining the effective lifetime of a mass, long-lasting, insecticidal net distribution: a sensitivity analysis. *Malar. J.*, 11, 2012.

PART 2:

- H. D. Pratt and C. G. Moore. *Mosquitoes of public health importance and thier control*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, revised edition, 1993.
- F. B. Augusto, N. Marcus, and K. O. Oksun. Application of optimal control to the epidemiology of malaria. *Electr. J. Differ. Equ.*, 2012:1 – 22, 2012.
- L. Esteva and C. Vargas. Analysis of a dengue disease transmission model. *Discrete Continuous Dyn. Syst. Ser. B*, 150:131 – 151, 1998. doi: 10.1016/S0025-5564(98)10003-2.
- H. S. Rodrigues, M. T. T. Monteiro, and D. F. M. Torres. Bioeconomic perspectives to an optimal control dengue model. *Int. J. Comput. Math.*, 90:1 – 22, 2013.
- L. S. Sepulveda and O. Vasileva. Optimal control approach to dengue reduction and prevention in Cali, Columbia. *Math. Meth. Appl. Sci.*, 39:5475 – 5496, 2016. doi: 10.1002/mma.3932.
- H. Gwalani, F. Hawamdeh, A. R. Mikler, and K. Xiong. Modeling the 2013 zika outbreak in French Polynesia: Intervention strategies. *Appl. Syst. Innov.*, 1:31, 2018. doi: 10.3390/asi1030031.
- D. H. Barmark, C. O. Dorso, M. Otero, and H. G. Solari. Modeling interventions during an dengue outbreak. *Epidemio. Infect.*, 142:545–561, 2014. doi: 10.1017/S0950268813001301.
- M. Oki, T. Sunahara, M. Hashizume, and T. Yamamoto. Optimal timing of insecticide fogging to minimize dengue cases: Modeling dengue transmission among various seasonalities and transmission intensities. *PLoS One*, 5:e1367, 2011. doi: 10.1371/journal.pntd.0001367.

- M. N. Burattini, M. Chen, A. Chow, F. A. B. Coutinho, K. T. Goh, L. F. Lopez, S. Ma, and E. Massad. Modelling the control strategies against dengue in Singapore. *Epidemiol. Infect.*, 136:309 – 319, 2008. doi: 10.1017/S0950268807008667.
- J. P. Chavex, T. Gotz, S. Siegmund, and K. P. Wijaya. An SIR-Dengue transmission model with seasonal effects and impulsive control. *Math. Biosci.*, 289:29 – 39, 2017. doi: 10.1016/j.mbs.2017.04.005.
- G. Knerer, C. S. M. Currie, and S. C. Brailsford. Impact of combined vector-control and vaccination strategies on transmission dynamics of dengue fever: a model-based analysis. *Health Care Manag. Sci.*, 18:205 – 217, 2015. doi: 10.1007/s10729-013-9263-x.
- F. B. Augusto. Optimal control and cost-effectiveness analysis of a three age-structured transmission dynamics of chikungunya virus. *Discrete Continuous Dyn. Syst. Ser. B*, 22: 293–320, 2017. doi: 10.3934/dcdsb.2017034.
- S. A. Gourley, R. Liu, and J. Wu. Some vector borne diseases with structured host populations: Extinction and spatial spread. *SIAM J. Appl. Math.*, 2:408–433, 2007. doi: 10.1137/050648717.
- E. Schaefer, K. Caillouet, and S. Robertson. Methods for prophylactic management of west nile virus using a stage-structured avian host-vector model with vaccination, larvicide, and adulticide. *Nat. Resour. Model.*, 31:e12165, 2018. doi: 10.1111/nrm.12165.
- C. Bowman, A. B. Gumel, P. van den Driessche, J. Wu, and H. Zhu. A mathematical model for assessing control strategies against West Nile virus. *Bull. Math. Biol.*, 67: 1107–1133, 2005. doi: 10.1016/j.bulm.2005.01.002.

- F. B. Augusto and I. M. Elmojtaba. Optimal control and cost-effective analysis of malaria/visceral leishmaniasis co-infection. *PLoS ONE*, 12:e0171102, 2017. doi: 10.1371/journal.pone.0171102.
- A. Bustamam, D. Aldila, and A. Yuwanda. Understanding dengue control for short- and long-term intervention with a mathematical model approach. *J. Appl. Math.*, 2018, 2018. doi: 10.1155/2018/9674138.
- L. Yakob and A. C. A. Clements. A mathematical model of chikungunya dynamics and control: The major epidemic on reunion island. *PLoS ONE*, 8:e57448, 2013. doi: 10.1371/journal.pone.0057448.
- P. van den Driessche. Reproduction numbers of infectious disease models. *Infectious Disease Modelling*, 2:288 – 303, 2017. doi: 10.1016/j.idm.2017.06.002.
- O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. On the definition and the computation of the basic reproduction ratio R_0 in heterogeneous populations. *J. Math. Biol.*, 28:365 – 382, 1990. doi: 10.1007/BF00178324.
- P. van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.*, 180:29 – 48, 2002. doi: 10.1016/S0025-5564(02)00108-6.
- J. T. Griffin. The interaction between seasonality and pulsed interventions against malaria in their effects on the reproduction number. *PLoS Comput. Biol.*, 11:e1004057, 2015. doi: 10.1371/journal.pcbi.1004057.
- N. Bacaer and S. Guernaoui. The epidemic threshold of vector-borne diseases with seasonality: The case of cutaneous leishmaniasis in chichaoua, morocco. *J. Math. Biol.*, 56:421 – 436, 2006. doi: 10.1007/s00285-006-0015-0.

- W. Wang and XQ. Zhao. Threshold dynamics for compartmental epidemic models in periodic environments. *J. Dyn. Diff. Equat.*, 20:699 – 717, 2008. doi: 10.1007/s10884-008-9111-8.
- Fatmawati and H. Tasman. An optimal control strategy to reduce the spread of malaria resistance. *Math. Biosci.*, 262:73 – 79, 2015. doi: 10.1016/j.mbs.2014.12.005.
- F. Agosto and S. Lenhart. Optimal control of the spread of malaria superinfectivity. *J. Biol. Syst.*, 21:1340002, 2013. doi: 10.1142/S0218339013400020.
- K. O. Okosun, R. Ouifki, and N. Marcus. Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity. *BioSystems*, pages 136 – 145, 2011. doi: 10.1016/j.biosystems.2011.07.006.
- Y. Lou and XQ. Zhao. A reaction diffusion malaria model with incubation period in the vector population. *J. Math. Biol.*, 62:543 – 568, 2011. doi: 10.1007/s00285-010-0346-8.
- D. Zhu, J. Ren, and H. Zhu. Spatial-temporal basic reproduction number and dynamics for a dengue disease diffusion model. *Math Method Appl. Sci.*, 41:5388 – 5403, 2018. doi: 10.1002/mma.5085.
- A. Faraji and I. Unlu. The eye of the tiger, the thrill of the fight: Effective larval and adult control measures against the asian thiger mosquito, *Aedes albopictus* (diptera: Culicidae), in north america. *J. Med. Entoml*, 53, 2016. doi: 10.1093/jme/tjw096.

- J. A. S. Bonds. Ultra-low-volume space sprays in mosquito control: a critical review. *Med. Vet. Entomol.*, 26:121 – 130, 2012. doi: 10.1111/j.1365-2915.2011.00992.x.
- J. E. Cilek. Application of insecticides to vegetation as barriers against host-seeking mosquitoes. *J. Am. Mosq. Control Assoc.*, 24:172 – 176, 2008. doi: 10.2987/8756-971X(2008)24[172:AOITVA]2.0.CO;2.
- M. A. Doyle, D. L. Kline, and S. A. Allan and P. E. Kaufman. Efficacy of residual bifenthrin applied to landscape vegetation against *aedes albopictus*. *J. Am. Mosq. Control Assoc.*, 25:179 – 183, 2009. doi: 10.2987/08-5804.1.
- R. Boyce, A. Lenhart, A. Kroeger, R. Velayudhan, B. Roberts, and O. Horstick. *Bacillus thuringiensis israelensis (Bti)* for the control of dengue vectors: Systematic literature review. *Trop. Med. Int. Health*, 18:564 – 577, 2013. doi: 10.1111/tmi.12087.
- D. Bainov and P. Simeonov. *Impulsive differential equations: Periodic solutions and applications*, volume 66 of *Pitman monographs and surveys in pure and applied mathematics*. Longman Scientific and Technical, Harlow Essex, England, 1993.
- A. D’Onofrio. Pulse vaccination strategy in the sir epidemic model: Global asymptotic stable eradication in presence of vaccine failures. *Math. Comput. Model.*, pages 473 – 489, 2002. doi: 10.1016/S0895-7177(02)00177-2.
- R. J. Smith?, A. B. Hogan, and G. N. Mercer. Unexpected infection spikes in a model of respiratory syncytical virus vaccination. *Vaccines*, 5, 2017. doi: 10.3390/vaccines5020012.
- B. M. Miller and E. Ja. Rubinovich. Optimal impulse control problem with constrained number of impulses. *Math. Comput. Simul.*, 34:23 – 49, 1992. doi: 10.1016/0378-4754(92)90095-X.

- M. Chahim, R. F. Hartl, and P. M. Kort. A tutorial on the deterministic impulse control maximum principle: Necessary and sufficient optimality conditions. *Eur. J. Oper. Res.*, 219:18 – 26, 2012. doi: 10.1016/j.ejor.2011.12.035.
- R. Leander, S. Lenhart, and V. Protopopescu. Optimal control of continuous systems with impulse controls. *Optim. Control Appl. Meth.*, 26:535 – 549, 2014. doi: 10.1002/oca.2128.
- N. Bacaer. Approximation of the basic reproduction number R_0 for vector-borne diseases with a periodic vector population. *Bull. Math. Biol.*, 69:1067 – 1091, 2007. doi: 10.1007/s11538-006-9166-9.
- S. Lenhart and J. T. Workman. *Optimal control applied to biological methods*. Mathematical and computational biology series. Chapman and Hall/CRC, Boca Raton, Fl.
- F. Verhulst. Singular perturbation methods for slow-fast dynamics. *Nonlinear Dyn.*, 50: 747–753, 2007. doi: 1007/s11071-007-9236-z.
- J. A. Anderson and J. M. Bell. *Number theory with applications*. Prentice Hall, Upper Saddle River, NJ, 1997.

PART 3

- [1] Weaver SC, Charlier C, Vasilakis N, Lecuit M. Zika, chikungunya, and other emerging vector-borne viral diseases. *Annu Rev Med.* 2018;69:395–408.
- [2] World Health Organization. Handbook for integrated vector management. Geneva: World Health Organization; 2012.
- [3] Roiz D, Wilson AL, Scott TW, Fonseca DM, Jourdain F, Müller P, et al. Integrated *Aedes* management for the control of *Aedes*-borne diseases. *PLoS Negl Trop Dis.* 2018;12:e0006845.
- [4] Uncini A, Shahrizaila N, Kuwabara S. Zika virus infection and Gullain-Barré syndrome: A review focused on clinical and electrophysiological subtypes. *J Neurol Neurosurg Psychiatry.* 2016;88:266–271.
- [5] Wen Z, Sing H, Ming G. How does Zika cause microcephaly? *Genes Dev.* 2017;31:849–861.
- [6] Weaver SC, Costa F, Garcia-Blanco MA, Ko AI, Ribeiro GS, Sadde G, et al. Zika virus: history, emergence, biology, and prospects for control. *Antiviral Res.* 2016;130:69–80.
- [7] Centers for Disease Control and Prevention. Florida investigation links four recent Zika cases to local mosquito-borne virus transmission; July 29th, 2016. [cited 2019 September 5]. Available from <https://www.cdc.gov/media/releases/2016/p0729-florida-zika-cases.html>.
- [8] Centers for Disease Control and Prevention. CDC updates guidance for Wynwood (FL) neighborhood with active Zika transmission; September 19th, 2016. [cited 2019 September 5]. Available from <https://www.cdc.gov/media/releases/2016/p0919-updated-zika-guidance.html>.
- [9] Centers for Disease Control and Prevention. CDC updates guidance related to local Zika transmission in Miami-Dade County, Florida; October 19th, 2016. [cited 2019 September 5]. Available from <https://www.cdc.gov/media/releases/2016/p1019-zika-florida-update.html>.
- [10] Centers for Disease Control and Prevention. Interim CDC recommendations for Zika vector control in the continental United States; January 18, 2019. [cited 2019 September 5]. Available from <https://www.cdc.gov/zika/public-health-partners/vector-control-us.html>.
- [11] Centers for Disease Control and Prevention. CDC updates guidance for Little River (FL) area with active Zika transmission; December 2nd, 2016. [cited 2019 September 5]. Available from <https://www.cdc.gov/media/releases/2016/s1202-zika-updated-guidance.html>.

- [12] Centers for Disease Control and Prevention. CDC updates Zika guidance for South Miami Beach (FL) area; December 9th, 2016. [cited 2019 September 5]. Available from <https://www.cdc.gov/media/releases/2016/s1209-zika-guidance.html>.
- [13] Stoddard PK. Managing *Aedes aegypti* populations in the first Zika transmission zones in the continental United States. *Acta Tropica*. 2018;187:108–118.
- [14] Celeste P, Novick CG, Novik LF. Local transmission of Zika virus in Miami-Dade County: The Florida Department of Health rises to the challenge. *J Public Health Man*. 2019;25:277–287.
- [15] Faraji A, Unlu I. The eye of the tiger, the thrill of the fight: Effective larval and adult control measures against the asian tiger mosquito, *Aedes albopictus* (Diptera: Culicidae), in North America. *J Med Entomol*. 2016;53:1029–1047.
- [16] Tedesco C, Ruiz M, McLafferty S. Mosquito politics: Local vector control policies and the spread of West Nile virus in the Chicago region. *Health Place*. 2010;16:1188 –1195.
- [17] Lutambi AM, Chitnis N, Briët OJT, Smith TA, Penny MA. Clustering of vector control interventions has important consequences for their effectiveness: A modelling study. *PLoS One*. 2014;9:e97065.
- [18] Yamashita WMS, Das SS, Chapiro G. Numerical modeling of mosquito population dynamics of *Aedes aegypti*. *Parasites Vectors*. 2018;11:245.
- [19] Lenhart S, Workman JT. *Optimal Control Applied to Biological Models*. Boca Raton London New York: Chapman Hall/CRC; 2007.
- [20] Harington LC, Scott TW, Lerdthusnee K, Coleman RC, Costero A, Clark CG, et al. Dispersal of the dengue vector *Aedes aegypti* within and between rural communities. *Am J Trop Med Hyg*. 2005;72:209 – 220.
- [21] Demers J, Robertson SL, Bewick S, Fagan WF. Implicit versus explicit control strategies in models for vector-borne disease epidemiology;. *BiorXiv*:10.1101/753475v1 [Preprint]. 2019 [cited 2019 September 5]. Available from: <https://www.biorxiv.org/content/10.1101/753475v1>.
- [22] Diekmann O, Heesterbeek JAP, Metz JAJ. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *J Math Biol*. 1990;28:365–382.
- [23] van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math Biosci*. 2002;180:29–48.

- [24] van den Driessche P, Watmough J. Further notes on the basic reproduction number. In: Brauer F, Wu J, van den Driessche P, editors. *Mathematical Epidemiology*. Berlin Heidelberg: Springer-Verlag; 2008. p. 159–178.
- [25] Tien JH, Shuai Z, Eisenberg MC, van den Driessche P. Disease invasion on community networks with environmental pathogen movement. *J Math Biol*. 2015;70:1065–1092.
- [26] Zhang F. *Matrix Theory: Basic Results and Techniques*. 2nd ed. New York Dordrecht Heidelberg London: Springer; 2011.
- [27] Sakurai JJ, Napolitano J. *Modern Quantum Mechanics*. 2nd ed. San Francisco: Addison-Wesley; 2011.
- [28] Kato T. *Perturbation Theory for Linear Operators*. 2nd ed. Berlin Heidelberg New York: Springer-Verlag; 1995.
- [29] Saura S, Martínez-Millán J. Landscape patterns simulation with a modified random clusters method. *Landsc Ecol*. 2000;15:661 – 678.
- [30] Dufourd C, Dumont Y. Impact of environmental factors on mosquito dispersal in the prospect of sterile insect technique control. *Comput Math Appl*. 2013;66:1695 – 1715.
- [31] Takahashi LT, Maidana NA, Jr WCF, Pulino P, Yang HM. Mathematical models for the *Aedes aegypti* dispersal dynamics: travelling waves by wing and wind. *Bull Math Biol*. 2005;67:509528.
- [32] Mohar B. Graph Laplacians. In: Beineke LW, Wilson RJ, editors. *Topics in Algebraic Graph Theory*. Cambridge: Cambridge University Press; 2005. p. 113–130.
- [33] Berman A, Plemmons RJ. *Non-Negative Matrices in the Mathematical Sciences*. 2nd ed. Philadelphia, PA: Society for Industrial and Applied Mathematics; 1994.
- [34] Augusto FB, Bewick S, Fagan WF. Mathematical model of Zika virus with vertical transmission. *Infect Dis Model*. 2017;2:244–267.

PART 4

1. Christofferson RC. Arbovirus Phenotype Alters Transmission Potential: Louisiana State University; 2011.
2. Egger JR, Ooi EE, Kelly DW, Woolhouse ME, Davies CR, Coleman PG. Reconstructing historical changes in the force of infection of dengue fever in Singapore: implications for surveillance and control. *Bulletin of the World Health Organization*. 2008;86(3):187-96.
3. Reisen WK. Landscape epidemiology of vector-borne diseases. *Annual review of entomology*. 2010;55:461-83.
4. Parham PE, Waldock J, Christophides GK, Hemming D, Agosto F, Evans KJ, et al. Climate, environmental and socio-economic change: weighing up the balance in vector-borne disease transmission. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 2015;370(1665):20130551.
5. Benedict MQ, Levine RS, Hawley WA, Lounibos LP. Spread of the tiger: global risk of invasion by the mosquito *Aedes albopictus*. *Vector-Borne and Zoonotic Diseases*. 2007;7(1):76-85.
6. Rust RS, Thompson WH, Matthews CG, Beaty BJ, Chun RW. Topical Review: La Crosse and Other Forms of California Encephalitis. *Journal of child neurology*. 1999;14(1):1-14.
7. Calisher CH. Medically important arboviruses of the United States and Canada. *Clinical Microbiology Reviews*. 1994;7(1):89.
8. Jones TF, Craig AS, Nasci RS, Patterson LE, Erwin PC, Gerhardt RR, et al. Newly recognized focus of La Crosse encephalitis in Tennessee. *Clinical infectious diseases*. 1999;28(1):93-7.
9. Haddow AD, Agricola Odoi. The incidence risk, clustering, and clinical presentation of La Crosse virus infections in the eastern United States, 2003–2007. *PLoS One*. 2009;4(7):e6145.

10. Grimstad P. California group virus disease. The arboviruses: epidemiology and ecology. 1988;2:99-136.
11. Leisnham PT, Juliano SA. Impacts of climate, land use, and biological invasion on the ecology of immature *Aedes* mosquitoes: implications for La Crosse emergence. Ecohealth. 2012;9(2):217-28.
12. McJunkin JE, de los Reyes EC, Irazuzta JE, Caceres MJ, Khan RR, Minnich LL, et al. La Crosse encephalitis in children. New England Journal of Medicine. 2001;344(11):801-7.
13. Nasci R, Moore C, Biggerstaff B, Panella N, Liu H, Karabatsos N, et al. La Crosse encephalitis virus habitat associations in Nicholas County, West Virginia. Journal of medical entomology. 2000;37(4):559-70.
14. Sprenger D, Wuithiranyagool T. The discovery and distribution of *Aedes albopictus* in Harris County, Texas. Journal of the American Mosquito Control Association. 1986;2(2):217-9.
15. Moulton DW, Thompson WH. California group virus infections in small, forest-dwelling mammals of Wisconsin Some ecological considerations. The American journal of tropical medicine and hygiene. 1971;20(3):474-82.
16. Cully JJ, Streit T, Heard P. Transmission of La Crosse virus by four strains of *Aedes albopictus* to and from the eastern chipmunk (*Tamias striatus*). Journal of the American Mosquito Control Association. 1992;8(3):237-40.
17. Grimstad P, Kobayashi J, Zhang M, Craig Jr G. Recently introduced *Aedes albopictus* in the United States: potential vector of La Crosse virus (Bunyaviridae: California serogroup). Journal of the American Mosquito Control Association. 1989;5(3):422-7.

18. Gerhardt RR, Gottfried KL, Apperson CS, Davis BS, Erwin PC, Smith AB, et al. First isolation of La Crosse virus from naturally infected *Aedes albopictus*. Emerging infectious diseases. 2001;7(5):807.
19. Westby K, Fritzen C, Huang J, Jaske E, Paulsen D, Jones C, et al. La Crosse encephalitis in Eastern Tennessee: evidence of invasive mosquito (*Aedes albopictus* and *Ochlerotatus japonicus*) involvement in the transmission of an indigenous disease. American Journal of Tropical Medicine and Hygiene. 2011;85(supplement):374.
20. Matser A, Hartemink N, Heesterbeek H, Galvani A, Davis S. Elasticity analysis in epidemiology: an application to tick-borne infections. Ecology letters. 2009;12(12):1298-305.
21. Blower SM, Dowlatabadi H. Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. International Statistical Review/Revue Internationale de Statistique. 1994:229-43.
22. Gauld L, Hanson R, Thompson W, Sinha S. Observations on a natural cycle of La Crosse virus (California group) in Southwestern Wisconsin. The American journal of tropical medicine and hygiene. 1974;23(5):983-92.
23. Barker C, Paulson S, Cantrell S, Davis B. Habitat preferences and phenology of *Ochlerotatus triseriatus* and *Aedes albopictus* (Diptera: Culicidae) in southwestern Virginia. Journal of Medical Entomology. 2003;40(4):403-10.
24. Szumlas DE, Apperson CS, Powell EE, Hartig P, Francy DB, Karabotsos N. Relative abundance and species composition of mosquito populations (*Diptera: Culicidae*) in a La Crosse virus-endemic area in western North Carolina. Journal of medical entomology. 1996;33(4):598-607.

25. Kappus KD, Calisher CH, Baron RC, Davenport J, Francy DB, Williams RM. La Crosse virus infection and disease in western North Carolina. *The American journal of tropical medicine and hygiene*. 1982;31(3 Pt 1):556-60.
26. Beaty BJ, Thompson WH. Emergence of La Crosse virus from endemic foci. Fluorescent antibody studies of overwintered *Aedes triseriatus*. *The American journal of tropical medicine and hygiene*. 1975;24(4):685-91.
27. Lisitza M, DeFoliart G, Yuill T, Karandinos M. Prevalence rates of LaCrosse virus (California encephalitis group) in larvae from overwintered eggs of *Aedes triseriatus*. *Mosquito News*. 1977.
28. Wonham MJ, Lewis MA, Rencławowicz J, Van den Driessche P. Transmission assumptions generate conflicting predictions in host–vector disease models: a case study in West Nile virus. *Ecology Letters*. 2006;9(6):706-25.
29. DeFoliart GR. *Aedes triseriatus*: vector biology in relationship to the persistence of La Crosse virus in endemic foci. *Progress in clinical and biological research*. 1983;123:89.
30. Erwin PC, Jones TF, Gerhardt RR, Halford SK, Smith AB, Patterson LE, et al. La Crosse encephalitis in Eastern Tennessee: clinical, environmental, and entomological characteristics from a blinded cohort study. *American journal of epidemiology*. 2002;155(11):1060-5.
31. Scheffel SL. Comparison of mosquito abundance, distribution, and parity between a high and a low prevalence site for La Crosse encephalitis in eastern Tennessee. 2006.
32. Bevins SN. Invasive mosquitoes, larval competition, and indirect effects on the vector competence of native mosquito species (*Diptera: Culicidae*). *Biological Invasions*. 2008;10(7):1109-17.

33. Lounibos L, O'meara G, Escher R, Nishimura N, Cutwa M, Nelson T, et al. Testing predictions of displacement of native *Aedes* by the invasive Asian tiger mosquito *Aedes albopictus* in Florida, USA. *Biological Invasions*. 2001;3(2):151-66.
34. Kampen H, Werner D. Out of the bush: the Asian bush mosquito *Aedes japonicus japonicus* (Theobald, 1901)(*Diptera, Culicidae*) becomes invasive. *Parasit Vectors*. 2014;7(1):59.
35. Sardelis MR, Turell MJ, Andre RG. Laboratory transmission of La Crosse virus by *Ochlerotatus japonicus* (*Diptera: Culicidae*). *Journal of Medical Entomology*. 2002;39(4):635-9.
36. Harris MC, Dotseth EJ, Jackson BT, Zink SD, Marek PE, Kramer LD, et al. La Crosse Virus in *Aedes japonicus japonicus* Mosquitoes in the Appalachian Region, United States. *Emerging infectious diseases*. 2015;21(4):646.
37. Ingersoll TE, Sewall BJ, Amelon SK. Improved analysis of long-term monitoring data demonstrates marked regional declines of bat populations in the eastern United States. *PloS one*. 2013;8(6):e65907.
38. Blehert DS, Hicks AC, Behr M, Meteyer CU, Berlowski-Zier BM, Buckles EL, et al. Bat white-nose syndrome: an emerging fungal pathogen? *Science*. 2009;323(5911):227-.
39. Reiskind MH, Wund MA. Experimental assessment of the impacts of northern long-eared bats on ovipositing *Culex* (*Diptera: Culicidae*) mosquitoes. *Journal of medical entomology*. 2009;46(5):1037-44.

PART 5

- 1 Dick, G., Kitchen, S. & Haddow, A. Zika virus (I). Isolations and serological specificity. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **46**, 509-520 (1952).
- 2 Hayes, E. B. Zika virus outside Africa. *Emerg Infect Dis* **15**, 1347-1350 (2009).
- 3 Lanciotti, R. S. *et al.* Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. *Emerg Infect Dis* **14**, 1232-1239 (2008).
- 4 Duffy, M. R. *et al.* Zika virus outbreak on Yap Island, Federated States of Micronesia. *New England Journal of Medicine* **360**, 2536-2543 (2009).
- 5 Hancock, W., Marfel, M. & Bel, M. Zika virus, French Polynesia, South Pacific, 2013. *Emerging infectious diseases* **20**, 1960-1960 (2014).
- 6 Campos, G. S., Bandeira, A. C. & Sardi, S. I. Zika virus outbreak, Bahia, Brazil. *Emerging infectious diseases* **21**, 1885 (2015).
- 7 Musso, D. Zika Virus Transmission from French Polynesia to Brazil. *Emerg Infect Dis* **21**, 1887 (2015).
- 8 Zanoluca, C. *et al.* First report of autochthonous transmission of Zika virus in Brazil. *Memórias do Instituto Oswaldo Cruz* **110**, 569-572 (2015).
- 9 Nebehay, S. a. H., B. (Reuters, 2016).
- 10 Hennessey, M. Zika virus spreads to new areas—region of the Americas, May 2015–January 2016. *MMWR. Morbidity and Mortality Weekly Report* **65** (2016).
- 11 Agência Saúde; MICROCEFALIA Ministério da Saúde divulga boletim epidemiológico. <http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saude-divulga-boletim-epidemiologico> (2015).
- 12 Tetro, J. A. Zika and microcephaly: causation, correlation, or coincidence? *Microbes and Infection* (2016).
- 13 Vogel, G. A race to explain Brazil's spike in birth defects. *Science* **351**, 110-111 (2016).
- 14 Petersen, E. E. Interim guidelines for pregnant women during a Zika virus outbreak—United States, 2016. *MMWR. Morbidity and mortality weekly report* **65** (2016).
- 15 Salvador, S. *El Salvador urges against pregnancies until 2018 as Zika virus spreads*, <http://www.reuters.com/article/us-health-zika-el-salvador-idUSKCN0UZ2SP> (2016).
- 16 Ioos, S. *et al.* Current Zika virus epidemiology and recent epidemics. *Medecine et maladies infectieuses* **44**, 302-307 (2014).
- 17 Bogoch, I. I. *et al.* Anticipating the international spread of Zika virus from Brazil. *The Lancet* (2016).
- 18 Marcondes, C. B. & Ximenes, M. d. F. F. d. Zika virus in Brazil and the danger of infestation by *Aedes* (*Stegomyia*) mosquitoes. *Revista da Sociedade Brasileira de Medicina Tropical*, 0-0 (2015).
- 19 Porse, C. C. *et al.* Public health response to *Aedes aegypti* and *Ae. albopictus* mosquitoes invading California, USA. *Emerging infectious diseases* **21**, 1827 (2015).
- 20 Faye, O. *et al.* Molecular Evolution of Zika Virus during its emergence in the 20 th century. *PLoS Negl Trop Dis* **8**, e2636 (2014).
- 21 de Melo Freire, C. C., Iamarino, A., de Lima Neto, D. F. & de Andrade Zanotto, P. M. Spread of the pandemic Zika virus lineage is associated with NS1 codon usage adaptation in humans. *bioRxiv*, 032839 (2015).
- 22 Sierra, B. d. I. C., Kouri, G. & Guzmán, M. Race: a risk factor for dengue hemorrhagic fever. *Archives of virology* **152**, 533-542 (2007).
- 23 Andraud, M., Hens, N., Marais, C. & Beutels, P. Dynamic epidemiological models for dengue transmission: a systematic review of structural approaches. *PloS one* **7**, e49085 (2012).
- 24 Wonham, M. J., de-Camino-Beck, T. & Lewis, M. A. An epidemiological model for West Nile virus: invasion analysis and control applications. *Proceedings of the Royal Society of London B: Biological Sciences* **271**, 501-507 (2004).
- 25 Bongaarts, J. & Blanc, A. K. Estimating the current mean age of mothers at the birth of their first child from household surveys. *Population health metrics* **13**, 1 (2015).
- 26 Gubler, D. J. Dengue and dengue hemorrhagic fever. *Clinical microbiology reviews* **11**, 480-496 (1998).
- 27 Fagbami, A. Zika virus infections in Nigeria: virological and seroepidemiological investigations in Oyo State. *Journal of Hygiene* **83**, 213-219 (1979).
- 28 Sawyer, W. The persistence of yellow fever immunity. *Journal of Preventive Medicine* **5**, 413-428. (1931).
- 29 Van den Driessche, P. & Watmough, J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences* **180**, 29-48 (2002).

- 30 Schoenaker, D. A., Jackson, C. A., Rowlands, J. V. & Mishra, G. D. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *International journal of epidemiology* **43**, 1542-1562 (2014).
- 31 (World Health Organization, WHO. 2015, Geneva, Switzerland, 2015).
- 32 Esteva, L. & Vargas, C. Analysis of a dengue disease transmission model. *Mathematical biosciences* **150**, 131-151 (1998).
- 33 Maciel-de-Freitas, R., Marques, W. A., Peres, R. C., Cunha, S. P. & Lourenço-de-Oliveira, R. Variation in *Aedes aegypti* (Diptera: Culicidae) container productivity in a slum and a suburban district of Rio de Janeiro during dry and wet seasons. *Memórias do Instituto Oswaldo Cruz* **102**, 489-496 (2007).

PART 6

1. Rueda, L. M., et al. "Temperature-dependent development and survival rates of *Culex quinquefasciatus* and *Aedes aegypti* (Diptera: Culicidae)." *Journal of medical entomology* 27.5 (1990): 892-898.
2. Gunay, Filiz, Bulent Alten, and Ergi Deniz Ozsoy. "Estimating reaction norms for predictive population parameters, age specific mortality, and mean longevity in temperature?dependent cohorts of *Culex quinquefasciatus* Say (Diptera: Culicidae)." *Journal of Vector Ecology* 35.2 (2010): 354-362.
3. Morin, Cory W., and Andrew C. Comrie. "Modeled response of the West Nile virus vector *Culex quinquefasciatus* to changing climate using the dynamic mosquito simulation model." *International journal of biometeorology* 54.5 (2010): 517-529.