Unstable Dynamics of Vector-Borne Diseases: Modeling Through Delay-Differential Equations

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July 16, 2011

Abstract

Vector-borne diseases provide unique challenges to public health because the epidemiology is so closely tied to external environmental factors such as climate, landscape, and population migration, as well as the complicated biology of vector-transmitted pathogens. In particular, this close link between the epidemiology, the environment, and pathogen biology means that the traditional view that many vector-borne diseases are relatively stable in numerous regions does not provide a complete picture of their complexity. In fact, several regions exist with low levels of endemicity most of the time, punctuated by severe, often explosive, epidemics. These regions are considered unstable transmission settings. Ordinary differential equation (ODE) models have thus far dominated the study of vector-borne disease and have provided considerable insight into our understanding of transmission and effective control in stable transmission settings. To address the short-comings of autonomous ODE models, we present a class of models, differential-delay equation (DDE) models, that have the potential to better describe unstable endemic settings for vector-borne disease. These models develop naturally out of the biology

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of diseases transmitted by vectors because of the extrinsic and intrinsic incubation periods and vector maturation process necessary for successful transmission of vector-transmitted pathogens. In this chapter, we introduce five examples of vector-borne diseases that span the globe, and discuss the clinical implications of unstable transmission of these diseases. Next, we present the original ODE version of the Ross-Macdonald model for vector-borne diseases, modify this model by introducing different types of naturally occurring delays, then illustrate how these models can exhibit more complex behavior such as oscillations via Hopf bifurcation and chaos via period-doubling, that the ODE model cannot produce. Finally, we explore the possibility for delay-models to contribute to our understanding of unstable transmission settings, which in turn will inform the development of effective control strategies for these epidemic-prone regions.

KEYWORDS: vector-borne diseases, malaria, mathematical models, delay-differential equations, reproduction number, unstable dynamics, oscillations, chaos.

AMS SUBJECT CLASSIFICATION: 92D30, 92D40

1 Introduction

During the late 19th century, it was discovered that mosquitoes are capable of transmitting diseases. Since then, arthropods have been identified as responsible for the spread of many other diseases. Although discovering this transmission mechanism led to new insights into how to better control these vector-borne diseases, more than one hundred years later, vector-borne diseases continue to pose a significant burden worldwide [16]. The development of vector resistance to insecticides, changes in public health programs, climate change, changes in agricultural practices, the increased mobility of humans, and urban growth are all factors that contribute to the difficulty in controlling and eliminating vector-borne diseases. To further complicate matters, vector-borne diseases typically occur in developing countries with limited resources and access to health care. Because controlled epidemiological experiments are usually not possible, mathematical models have played an important role in developing a better understanding for how to mitigate the burden of these diseases. This chapter presents several examples of important vector-borne diseases, illustrating the diversity in this class of infectious diseases and consequently the need for mathematical models to address this diversity. We then discuss the difference between stable and unstable transmission settings and the implications these different settings have for public health. In Section 2, we introduce the Ross-Macdonald model for vector-borne diseases and consider several modifications of this model by introducing different types of delays relevant to the biology of vector-borne diseases. Finally, we discuss the contribution that these delay-differential equation models can make to better understanding unstable vector-borne disease transmission settings.

1.1 The Diversity of Vector-Borne Diseases

The formulation of mathematical models should take into consideration the epidemiology of each vector-borne disease. Some important vector-borne diseases that remain prevalent today include malaria, dengue, Chagas disease, leishmaniasis, and St. Louis encephalitis. Dengue, Chagas disease, and leishmaniasis are included in the World Health Organizations list of neglected tropical diseases [51]. These five diseases are caused by different types of pathogens, are transmitted by different vectors, have different clinical manifestations, result in different levels of immunity, and have different geographical distributions. To add to this complexity, while a disease may be endemic in one region, the same disease can exhibit an epidemic pattern of transmission in another region. Understanding how to model unstable transmission as well as stable transmission of vector-borne diseases is important because of the different implications that these unique transmission settings have for public health.

1.1.1 Malaria

Malaria, a disease transmitted between Anopheles mosquitoes and mammals, is considered the most important vector-borne disease [16], causing an estimated 190 - 311 million clinical episodes, and 708,000 - 1,003,000 deaths in 2008 worldwide [3]. Malaria is responsible for the fifth greatest number of deaths due to infectious diseases and is the second leading cause of death in Africa behind HIV/AIDS [3]. Four Plasmodium parasite species are responsible for malaria infection in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Of these, *P. falciparum* causes the most severe clinical symptoms and is responsible for the greatest number of deaths due to malaria infection. However, recent severe clinical cases of *P. vivax* malaria have started to change the perception that *vivax* malaria is relatively benign [23]. In fact, cases of *P. vivax* monoinfection have been reported with clinical manifestations similar to those of severe infection with *P. falciparum* malaria. These severe manifestations include cerebral malaria, anemia, respiratory distress syndrome, and acute renal failure [23]. The widespread distribution of *P. vivax*, causing roughly 100-300 million clinical cases each year, is cause for concern [23]. In regions with endemic malaria, the number of clinical cases can place a significant burden on the social and economic welfare of that population [29], even if mortality rates are fairly low. People living in regions with moderate *P. vivax* endemicity experience 10 to 30 or more episodes of malaria throughout their childhood and working life, each episode resulting in about 5 to 15 days absent from work or school. Consequently, malaria, which typically afflicts poor, developing countries, continues the cycle of poverty by hampering the education and productivity of those at risk [29].

1.1.2 Leishmaniasis

In contrast to malaria infection in humans, which is caused by four Plasmodium species and transmitted by mosquitoes, leishmaniasis, another dangerous vector-borne disease, is caused by over 20 leishmanial parasite species and is transmitted by roughly 30 different species of sandflies. The clinical manifestations of leishmaniases can be divided into four categories: cutaneous leishmaniasis, muco-cutaneous leishmaniasis, visceral leishmaniasis (VL) or kala-azar, and post-kala-azar dermal leishmaniasis (PKDL). Cutaneous leishmaniasis is characterized by ulcers or nodules in the skin that eventually heal spontaneously, but slowly, causing disfiguring scars. According to the World Health Organization, there are roughly 1.5 million new cases of cutaneous leishmaniasis each year [53]. Several months or years after an initial episode of cutaneous leishmaniasis, some patients suffer from more severe ulcers that do not spontaneously heal [4] and can partially or completely destroy the mucous membranes of the nose, mouth, throat cavities, and surrounding tissues [55]. This more severe clinical manifestation is called muco-cutaneous leishmaniasis [4, 55]. The most dangerous manifestation of leishmaniasis is visceral leishmaniasis, which is fatal if untreated [4]. As with malaria, visceral leishmaniasis primarily affects those in less developed countries and the burden on these countries is great, with approximately 500,000 new cases arising each year, 90% of which occur in only 5 countries: India, Bangladesh, Nepal, Sudan, and north-eastern Brazil [19]. 50% of visceral leishmaniasis cases occur in India, Bangladesh, and Nepal alone [33]. Treatments for VL exist but are expensive and impractical because treatment either requires a long hospitalization for proper administration of intravenous treatment, or because patients must self-treat with an oral drug and adhere to that treatment for four weeks [33]. Another concern is that monotherapies increase selective pressure, leading to parasite resistance [33]. Olliaro et al. [33] estimated that the 2006 average household cost of an episode of VL in India is US$209 - an enormous expense considering the median household income was US$49 per month. Even when treatment is administered, treated visceral leishmaniasis cases are sometimes followed (0-6 months post-treatment in Sudan and 6 months-3 years post-treatment in India) by PKDL [4]. PKDL is characterized by highly infectious nodular lesions on the skin. These parasite-containing lesions act as a reservoir for anthroponotic (vector-to-human) VL between epidemics [4]. While the global distribution of visceral leishmaniasis is not as expansive as the distribution of malaria, it places second (behind malaria) for the highest mortality caused by parasitic disease, resulting in more than 50,000 deaths each year, and subsequently placing an unfortunate strain on the health and well-being of the people in a few developing countries.

1.1.3 Chagas disease

Chagas disease is another parasitic infection caused by the protozoan *Trypanosoma cruzi* [39]. This vector-borne disease is transmitted by the reduviid bugs of the subfamily Tri-

atominae to humans and over 150 species of domestic animals and wild animals [39]. *T. cruzi* is an enzootic disease, which only leads to infection in humans if the vector has adapted to human dwellings. The *T. cruzi* parasites reside in the feces of infected reduviid bugs. When one of these bugs takes a blood-meal from a human, it defecates on the host, allowing infected fecal matter to enter the host through the mucosa of the eye, nose, or mouth [38]. Transmission of Chagas disease can also occur through blood transfusion and vertically from mother to child [39, 38]. Unlike malaria and leishmaniasis, roughly 10% of all Chagas cases are a result of transfusions and is the primary transmission mechanism in urban areas [38, 39]. 5000 to 18,000 cases per year are congenitally transmitted, and occasionally cases are a result of the consumption of contaminated food [38, 39]. Most cases of Chagas disease occur in Latin America, where *T. cruzi* is endemic. However, more recently, the immigration of people from Latin America to the US, Canada, parts of Europe and the western Pacific, has led to an increase in the number of cases in these non-endemic regions [39]. Chagas disease manifests in different stages. The initial phase lasts 4 to 8 weeks and is often asymptomatic. If symptoms do occur, the onset is roughly 1 to 2 weeks after acquiring the infection vectorially. Other transmission mechanisms have different incubation periods. During this acute phase, the *T. cruzi* parasite along with the host's immunoinflammatory response can cause tissue and organ damage. 5-10% of vectorially infected patients with acute symptoms do not survive the acute phase. However, in 90% of infected individuals, the acute phase will end spontaneously, even without treatment, and approximately 30-40% of those individuals will develop a chronic form of the disease usually 10-30 years later presenting as cardiac, digestive, or cardiodigestive disease. This chronic phase, called the determinate form of chronic disease, lasts for the remainder of the patient's life and can be fatal if the patient develops Chagas heart disease. The remaining 60-70% who recover from the acute phase but never develop clinical symptoms thereafter, have the intermediate form of chronic Chagas disease. These individuals have developed the antibodies against *T. cruzi*, but show none of the ailments characteristic of the determinate form. Although progress has been made to control Chagas disease in Latin America, the various mechanisms of transmission compounded with human movement continues to place several countries, including non-endemic areas, at risk [39].

1.1.4 Dengue

Not all vector-borne diseases are caused by protozoan parasites. Dengue and dengue hemorrhagic fever (DHF), a complication of Dengue, are examples of tropical vector-borne diseases caused by four serotypes (DEN-1, DEN-2, DEN-3, DEN-4) of the dengue virus [15]. The principal vector of dengue virus is the *Aedes aegypti* mosquito [15]. This mosquito prefers taking blood-meals from humans and typically bites during the day. Because of the *A. aegypti* mosquito's preference for biting humans [15] and its ability to breed in containers holding rainwater (such as tires and cisterns) [50], it is considered

a predominantly urban vector. In 1981, the America's experienced its first major DHF outbreak resulting from importation of a new strain of DEN-2 from Southeast Asia, and by 1995, DHF spread to 14 countries in the Americas, several of which experienced endemic DHF [15]. The geographic distribution of dengue continues to grow, resulting in roughly 50 million dengue cases worldwide each year [50], spanning more than 100 countries [18]. One of the difficulties posed by dengue is the circulation of the 4 different serotypes, which do not confer immunity to one another. Consequently, an individual may become infected up to 4 times during his/her lifetime [15]. Furthermore, a secondary dengue infection can increase the likelihood of developing DHF, a potentially lethal complication of dengue [17].

1.1.5 St. Louis encephalitis

St. Louis encephalitis (SLE) is another example of a vector-borne disease caused by a virus. Unlike malaria, leishmaniasis, Chagas disease, and dengue, the St. Louis encephalitis virus (SLEV) is endemic to North America [11]. The first known SLE epidemic occurred in 1933 and there have been at least 41 SLE outbreaks in North America since spanning from as far south as Tampa, Florida, to as north as Toronto, Canada. Different species of *Culex* mosquito are responsible for transmission in different regions of the US and southern Canada. SLEV is an enzootic disease, requiring transmission between vertebrate hosts (usually wild birds) and mosquitoes, before it becomes prevalent enough in the mosquito population to spill-over to humans. This pre-epidemic period where the number of SLEV-infected mosquitoes increases dramatically is referred to as amplification. This amplification period might coincide with seasons when there are a lot of nestling birds that are more susceptible to infection and more vulnerable to being bitten. Some nestling birds also have higher-titer viremias and remain infectious longer because of their less-developed immune systems. Symptoms of SLE infection in humans, which are most common in people over age 59, include sustained fever above 100°F, altered consciousness, or neurologic disfunction. Most infections, however, are asymptomatic. SLE epidemics do not occur yearly, but may last for months at a time, interfering with the economy of the affected region as well as the daily lives of the people. Unfortunately, outbreaks of SLE are difficult to predict. The right combination of SLEV in the environment, climatic conditions for adequate mosquito breeding and shortening of the extrinsic incubation period, and sufficient amplification hosts such as nestling birds is necessary for spillover to the human population to occur. Some studies indicate that freezes prime south Florida for SLE epidemics [11]. Another study using a hydrodynamic model to predict mosquito abundance and SLEV transmission dynamics in Florida suggests that drought can facilitate the amplification of SLEV, and consequently the spillover to humans [44].

While the burden of epidemics in North America caused by SLEV is small relative to the burden tropical vector-borne diseases place on developing countries, the complex

interactions leading to these outbreaks makes the disease very unpredictable, and consequently a system to better predict the occurrence of outbreaks is of interest [11]. This disease also highlights that North America, while better equipped to handle epidemics, is not immune to the problems caused by vector-borne diseases that developing countries are all too familiar with. To a lesser degree, vector-borne diseases can burden the health-care system and hinder a state's economy as they do in the developing world, meaning that constant surveillance is still necessary even in developed countries.

1.2 Stable versus Unstable Transmission and their relative impact on Public Health

Malaria provides an ideal backdrop for understanding the differences between stable and unstable transmission settings and the implications each has for public health. In many countries, malaria transmission is stable, with perhaps some peaks and valleys in prevalence throughout the year as a result of seasonality. However, within these countries, some regions may provide less than ideal conditions for the transmission of malaria, and hence experience relatively low prevalences of the disease. These low-endemicity regions are called "unstable" if long periods of low prevalence are disrupted by epidemics [22].

In regions with stable malaria, the likelihood of acquiring multiple infections is higher than in regions with unstable malaria. As a result, many individuals become clinically immune to malaria in stable transmission regions [22, 14]. In these regions, children are the age-group at greatest risk for symptomatic malaria since they lack sufficient exposures to malaria to acquire clinical immunity. In contrast, individuals of all ages in unstable transmission settings do not have the immune response that adults acquire in stable transmission regions [22, 14]. Unfortunately, this lack of acquired clinical immunity can result in violent outbreaks of malaria when conditions in the region change to favor disease transmission [22]. In fact, case fatality rates are up to 10 times greater during an epidemic in an unstable transmission region than in a stable region for the most part because the clinical manifestations of the disease are much more severe in individuals who have not developed immunity. Transmission intensity is negatively correlated with the severity of disease in children. Children are still at greatest risk in unstable regions as they are in stable regions, however when severe malaria does occur in slightly older individuals (8-15 year-olds), these patients are more likely to develop cerebral malaria. The lack of acquired immunity in epidemic-prone areas results in a more even distribution of clinical cases across age groups [22].

Public health facilities in regions with unstable malaria are not prepared for the surge in cases during epidemics. Instead, these facilities tend to adapt to a patient load typical of an inter-epidemic period when transmission is fairly low. Once an outbreak erupts, the patient load strains the capacity of health facilities and depletes health facilities of the resources necessary to properly care for the clinically ill. The combination of low-

immunity to malaria in patients and inadequate care creates a recipe for high mortality rates during epidemics in regions with unstable malaria. Overwhelmed health care facilities also result in underreporting of cases, and subsequently the true burden of these outbreaks in unstable transmission regions is unknown [22].

Epidemics of leishmaniasis, Chagas, dengue, and St. Louis encephalitis also occur. The mechanisms that are thought to stimulate these outbreaks are similar for these different diseases. Migrations of people from non-endemic regions to endemic regions often result in outbreaks of malaria because lack of exposure to malaria in these individuals makes them highly susceptible to clinical manifestations of the disease [22]. Similarly, movement of non-immune individuals in southern Sudan as a consequence of civil war contributed to a series of devastating epidemics of visceral leishmaniasis from 1984 to 1994 [43]. Changes in the environment that enhance transmission potential, such as changes in climate and landscape, as well as the pullback of control programs and increased vector and pathogen resistance, can also prime a region for malaria epidemics [22]. The same mechanisms produce epidemics in several other vector-borne diseases, including those discussed here with the possible exception of Chagas disease [16]. Microepidemics of Chagas disease are thought to be due to orally transmitted Chagas resulting from contaminated food [38]. Population growth and unplanned urbanization have also contributed to epidemic disease as humans continue to encroach on environments where vector-borne diseases are more readily transmitted [16, 18, 21]. While each vector-borne disease confers different immunities in their hosts, it is likely that outbreaks of these diseases pose a similar burden on public health systems to that of epidemic malaria in unstable transmission regions. Consequently, finding means to better understand various vector-borne diseases in unstable settings is an important issue.

Autonomous ordinary differential equations are frequently used for endemic vector-borne diseases, however, other types of differential equation models may be more appropriate for modeling disease in unstable transmission settings. In particular, incorporating delays which occur naturally in vector-borne diseases by expressing the problem as a system of delay-differential equations (DDEs) can result in solutions to the system that exhibit sustained or transient oscillations, as well as more complicated chaotic behavior. Mathematicians have included seasonality in ordinary differential equation models for disease to reflect intra-annual fluctuations that are common in diseases spread by vectors. However, case data for malaria indicates that transmission can show inter-annual fluctuations with a relatively stable period, suggesting that there may be an intrinsic mechanism driving these oscillations. In the following section, we present a simple model for vector-borne disease transmission and extend this model to include different delays that arise naturally in vector-borne disease transmission and give rise to complex dynamics.

2 Models of Vector-Borne Diseases with Delays

Ordinary differential equation (ODE) models of vector-borne diseases have a long history. Following his discovery in the late 19th century that female *Anopheles* mosquitoes are the vector responsible for malaria transmission [28], Ronald Ross developed the first model of malaria in 1911 [40]. This model was later improved on by G. Macdonald in the 1950s. Ever since, the Ross-Macdonald type models have been successfully used to guide health officials in choosing and implementing control strategies to restrict the impact of many vector-borne diseases. Analysis of the Ross-Macdonald model for malaria transmission suggested that imagicides would be a more effective means of vector control than larvicides [24], the vector population does not need to be exterminated but simply reduced below a key threshold, and a multi-faceted approach to malaria control would be more effective than any single type of intervention [28]. People began to build upon the original Ross-Macdonald model, introducing additional complexities such as human immunity. Such a model was developed and confronted with data in the Garki project in Nigeria [28], a project devoted to understanding the epidemiology of malaria and determining effective control interventions in West Africa [31]. Just as introducing human immunity into the Ross-Macdonald model was a natural extension in the Garki project, incorporating delays is another intuitive way to extend the original model. In the following section, we first introduce a simple Ross-Macdonald type ODE model of a vector-borne disease without immunity. We reduce the model to a classical two equation model. Then, we consider several modifications of the vector-borne ODE models by introducing delay into them. Although the epidemiology of each vector-borne disease is unique, the models presented in the following section provide a framework that captures the features common across many vector-borne diseases as well as a framework from which we can build models tailored to a particular disease.

2.1 ODE Models of Vector-Borne Diseases

Transmission in vector-borne diseases involves at least two species, the vector and the host, as we saw in our five examples. Since most vectors once infected do not recover, the simplest model for the vector is an SI model. Let us denote the susceptible vectors by S_v and the infected vectors by I_v. A susceptible vector becomes infected upon biting an infected human I_H with a biting rate a and probability of transmission of the disease given by p. The dynamical system that describes the vector is given by the following differential equations:

$$\begin{aligned} S_v' &= \Lambda_v - paS_vI_H - \nu S_v \\ I_v' &= paS_vI_H - \nu I_v \end{aligned} \tag{2.1}$$

Here, Λ_v is the birth rate of the vectors, and μ is the death rate of the vectors. Since the vectors, such as the mosquito, usually have a very short life-cycle, demography should be included. The total vector population size $N_v = S_v + I_v$ is then given by the constrained

logistic equation $N_v' = \Lambda_v - \mu N_v$ whose solution can be obtained in explicit form. Since $N_v(t)$ is essentially a given function of t, we may express the number of susceptible vectors in terms of infected vectors $S_v = N_v - I_v$ and replace it in the second equation of system (2.1), thus reducing the two-dimensional vector system to one equation

$$I_v' = pa(N_v(t) - I_v)I_H - \mu I_v \tag{2.2}$$

Now, we turn to the system for the humans. Although humans usually recover from an infection, for most vector-borne diseases recovery is not permanent and the recovered individual can become re-infected. As a starting point, we model the transmission of a vector-borne disease in humans with an SIS model. Some of the vector-borne diseases, such as chikungunya, occur as outbreaks, and in this case, omitting births and deaths for humans is acceptable. Other vector-borne diseases, such as malaria, are endemic and inclusion of demography in the human portion of the model is necessary. We begin with the simplest host model – an SIS model without demography. However, involving host's demography will result in the same limiting system that we will study, so we lose no generality by assuming that there is no demography in the host population. Susceptible hosts in class S_H become infected when bitten by an infectious vector. If we assume that infected vectors bite at the same rate as susceptible vectors, namely a, with q denoting the probability of transmission, then the model takes the form.

$$\begin{aligned} S_H' &= -qaS_H I_v + \alpha I_H \\ I_H' &= qaS_H I_v - \alpha I_H \end{aligned} \tag{2.3}$$

where α is the recovery rate. The total host population size N_H is constant. We can reduce the host system by replacing the susceptible hosts S_H with $S_H = N_H - I_H$ in the second equation. The system above (2.3) reduces to the following equation

$$I_H' = qa(N_H - I_H)I_v - \alpha I_H \tag{2.4}$$

The system for the infected vectors and infected humans becomes

$$\begin{aligned} I_v' &= pa(N_v(t) - I_v)I_H - \mu I_v \\ I_H' &= qa(N_H - I_H)I_v - \alpha I_H \end{aligned} \tag{2.5}$$

The right-hand side of this system depends on the unknown dependent variables I_v and I_H, and the known function of time $N_v(t)$. This makes the right-hand side explicitly dependent on time, and the model **non-autonomous**. However, system (2.5) depends on time only through the function $N_v(t)$ which has a limit as time goes to infinity, namely,

$$N_v(t) \to \frac{\Lambda_v}{\mu_v} = N_v.$$

Since all solutions of the original system are bounded, results on asymptotically autonomous systems [48] allow us to replace system (2.5) with the following limiting system

$$\begin{aligned} I_v' &= pa(N_v - I_v)I_H - \mu I_v \\ I_H' &= qa(N_H - I_H)I_v - \alpha I_H \end{aligned} \tag{2.6}$$

The limiting system (2.6) is an autonomous system, which is easier to work with. It only contains as dynamic variables the number of infected humans and the number of infected mosquitos. Sometimes a rescaled version of the system is considered where the proportions of infected humans and the proportion of infected mosquitoes are incorporated. In malaria, for instance, it is known from studies that only a small proportion of the mosquitoes are actually infected. The fraction of infected mosquitoes varies around 1% [2].

System (2.6) has been thoroughly analyzed. To state the results on the global behavior we define the reproduction number of the vector-borne disease. Transmission of vector-borne diseases involves two transmission cycles, namely host to vector and vector to host, and each of these transmission processes may be characterized by its own disease reproduction number. These two numbers may be combined to form a single dimensionless number that indicates whether or not, and to some extent how seriously, the vector-host system is open to invasion by the parasite. The Kermack-McKendrick-Macdonald approach places one infected human in a population of susceptible vectors; this will result in $\mathcal{R}_H$ secondary infected vectors. Similarly, placing one infected vector in a population of susceptible humans, will produce $\mathcal{R}_M$ infected humans, where

$$\mathcal{R}_H = \frac{paN_H}{\alpha}, \qquad \mathcal{R}_M = \frac{qaN_v}{\mu}.$$

To connect these definitions to the mathematical expressions for R_H and R_M, consider the incidence term in the equation for the vectors $pa(N_v - I_v)I_H$ which gives the number of secondary infections of vectors I_H infected hosts will produce per unit of time. Then, one infected host will produce paN_v infected vectors in an entirely susceptible vector population per unit of time. One infected host is infectious for $1/\alpha$ time units, hence we obtain $\mathcal{R}_H$. Similar reasoning leads to the expression for $\mathcal{R}_M$. To account for the secondary **host** infections that one infected host will produce, we notice that one infected host will produce $\mathcal{R}_H$ infected vectors, each of which will produce $\mathcal{R}_M$ infected hosts, giving

$$\mathcal{R}_0 = \mathcal{R}_H \mathcal{R}_M$$

secondary host infections. This expression gives the classical reproduction number of vector-borne diseases. The reproduction numbers of some of the vector-borne diseases with human host are given in Table 1. These reproduction numbers are defined as the number of secondary infections that one infected individual will produce in an entirely susceptible population.

The model (2.6) has two equilibria: a disease free equilibrium $\mathcal{E}_0 = (0, 0)$, and an endemic equilibrium, $\mathcal{E}^* = (I_v^*, I_H^*)$ where

$$I_H^* = N_H \frac{\mathcal{R}_0 - 1}{\frac{paN_H}{\mu} + \mathcal{R}_0}, \qquad I_v^* = N_v \frac{\mathcal{R}_0 - 1}{\frac{qaN_v}{\alpha} + \mathcal{R}_0}. \tag{2.7}$$

Table 1: Vector-borne diseases and their reproduction numbers

Disease	$\mathcal{R}_0$	Region	Years	References
Malaria	1-3000	Africa	-	[46]
Dengue	2.0-3.09	Colima, Mexico	2002	[7]
Dengue	8.0	Bandung, Indonesia	2003-2007	[47]
Chagas disease	1.25	Brazil	2006	[26]
Yellow Fever	2.38-3.59	New Orleans	1878	[10]
Chikungunya	0.35-2.3	Reunion Island	2005-2006	[12]
CCHF[a]	2.18	-	-	[27]
TBE[b]	1.58	-	-	[27]

[a] Crimean-Congo hemorrhagic fever (CCHF)
[b] Tick-borne encephalitis (TBE)

From these expressions it is clear that the endemic equilibrium exists and is positive if and only if $\mathcal{R}_0 > 1$. Furthermore, it can be established that the disease-free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. In addition, the endemic equilibrium is locally and globally stable, whenever it exists. This means that *all* solutions that start from positive initial conditions converge to the endemic equilibrium.

2.2 Models of Vector-Borne Diseases with Delays

Delay differential equations differ from ordinary differential equations in that the derivative at any time depends on the solution at prior times. The simplest constant delay equations have the form

$$x'(t) = F(t, x(t), x(t-\tau_1), x(t-\tau_2), \ldots, x(t-\tau_k))$$

where the time delays τ_j are positive constants. Additional information is required to specify a system of delay differential equations. Because the derivative in the equation above depends on the solution at the previous time $t - \tau_j$, it is necessary to provide an initial history function, or a vector of functions, to specify the value of the solution before time $t = 0$.

Interest in such systems arises when traditional pointwise modeling assumptions are replaced by dependence of the rate of change on the prior population numbers.

As mentioned in the introduction, delays occur naturally in vector-borne diseases because steps in the development of the vector and the pathogen take a significant amount of time, particularly compared to the lifespan of the vector. This makes delay differential equations a natural choice for modeling vector-borne diseases. Three typical time delays have so far been incorporated in mathematical models of vector-borne diseases. These are:

2.2.1 Delays related to the extrinsic incubation period

When the pathogen enters the body of the vector, some time elapses before the vector becomes infectious. This time period is called the **extrinsic incubation period**. Inclusion of the extrinsic incubation period in the dynamics of the vector is particularly important as the length of that period is often of duration comparable to the mean lifespan of the vector. For instance, the extrinsic incubation period of *Plasmodium* species that cause malaria is about two weeks, while on average, a female mosquito is known to live anywhere between 15 to 100 days. These incubation periods tend to be shorter at higher temperatures and longer at lower temperatures for several pathogens, including Plasmodium parasites, dengue viruses, and the St. Louis encephalitis virus [41, 35]. The fact that vectors may or may not survive the extrinsic incubation period affects significantly the dynamics of the infectious disease. This makes imperative the inclusion of the extrinsic incubation period as a delay in the vector-host epidemic models. Furthermore, delay models of this type include the probability that the vector survives the extrinsic incubation period.

To incorporate the delay caused by the extrinsic incubation period, we modify equations (2.6). We include the delay in the incidence term, as well as the probability that the vector survives that delay. The vectors that become infectious at time t were infected at time $t-\tau$ where τ is the delay induced by the extrinsic incubation period. In practical terms τ is, in fact, given by the length of the extrinsic period. For instance, in malaria, since the length of the extrinsic incubation period is about two weeks, then $\tau \approx 0.5$ months. The number of vectors becoming infectious is given by the number of vectors infected $t-\tau$ units ago: $pa(N_v - I_v(t-\tau))I_H(t-\tau)$ discounted by the probability of survival of the vector, given by $e^{-\mu\tau}$. Including the probability of survival of the vector is important. In malaria, for instance, only 40% of the vectors survive the intrinsic incubation period [9], even in optimal environmental conditions.

With the inclusion of the delay corresponding to the extrinsic incubation period, model (2.6) becomes:

$$\begin{aligned} I_v' &= pae^{-\mu\tau}(N_v - I_v(t-\tau))I_H(t-\tau) - \mu I_v \\ I_H' &= qa(N_H - I_H)I_v - \alpha I_H \end{aligned} \tag{2.8}$$

The first equation in the system above is a differential-delay equation where the unknown functions depend on the delay. In order to solve the system above, we need to know $I_v(\theta)$ and $I_H(\theta)$ for $\theta \in [-\tau, 0]$.

2.2.2 Delays related to the intrinsic incubation period

Besides the incubation period in the vector, vector-borne pathogens also have an incubation period within the host. This incubation period is called the **intrinsic incubation period**. Although the intrinsic incubation period is much shorter relative to the host lifespan, it is often customary to include it as a delay in the vector-host model. For

instance, the intrinsic incubation period of malaria is 6 to 25 days, while the average lifespan of humans is roughly 70 years. Although the probability that the host survives the intrinsic incubation period is very large, this probability is still included in vector-borne disease models.

To incorporate the delay caused by the intrinsic incubation period, we modify again equations (2.6). We include the delay in the incidence term, as well as the probability the host survives that delay. Hosts that become infectious at time t were infected at time $t-\tau$, where τ is the delay induced by the intrinsic incubation period. The number of those becoming infectious is given by the number of those infected $t-\tau$ units ago: $qa(N_H - I_H(t-\tau))I_v(t-\tau)$, discounted by the probability of survival of the host as infectious, given by $e^{-\alpha\tau}$.

The model (2.6), modified by incorporating delay within the host, becomes:

$$\begin{aligned} I_v' &= pa(N_v - I_v)I_H - \mu I_v \\ I_H' &= qae^{-\alpha\tau}(N_H - I_H(t-\tau))I_v(t-\tau) - \alpha I_H \end{aligned} \tag{2.9}$$

The second equation in the system above is a differential-delay equation where the unknown functions depend on the delay. We need to know $I_v(\theta)$ and $I_H(\theta)$ where $\theta \in [-\tau, 0]$ in order to solve the system above.

Inclusion of delay in response to the intrinsic incubation period is of less importance as the host has a relatively high probability of surviving the incubation period once infected, and subsequently becoming infectious. For this reason, models as the one above are typically not considered. However, models that involve two delays, one to include the extrinsic incubation period, and another to include the intrinsic incubation period, are of particular interest. We include here the Ross-Macdonald model with two delays, introduced by [41]. If $\tau_1 > 0$ is the delay caused by the extrinsic incubation period and τ_2 is the delay caused by the intrinsic incubation period, then the combination of model (2.8) and model (2.9) results in the following differential-delay model with two delays:

$$\begin{aligned} I_v' &= pae^{-\mu\tau_1}(N_v - I_v(t-\tau_1))I_H(t-\tau_1) - \mu I_v \\ I_H' &= qae^{-\alpha\tau_2}(N_H - I_H(t-\tau_2))I_v(t-\tau_2) - \alpha I_H \end{aligned} \tag{2.10}$$

The above model was considered by Ruan *et al.* [41] who established the following results. The reproduction number of the model (2.10) is given by

$$\mathcal{R}_0 = \frac{pqa^2 N_v N_H e^{-\mu\tau_1} e^{-\alpha\tau_2}}{\mu\alpha},$$

which can also be interpreted as the product of the human and vector reproduction numbers. When $\mathcal{R}_0 < 1$, then the system has a unique disease-free equilibrium $\mathcal{E}_0 = (0,0)$ which is locally stable. If $\mathcal{R}_0 > 1$, then the system also has an endemic equilibrium $\mathcal{R}^* = (I_v^*, I_H^*)$ and the disease-free equilibrium is unstable. Furthermore, when $\tau_1 = 0$, there exists τ_2^* such that the endemic equilibrium is locally asymptotically stable for $\tau_2 \in [0, \tau_2^*)$. Finally, for $\tau_2 \in [0, \tau_2^*)$ there exists $\tau_1^*(\tau_2^*)$ such that the endemic equilibrium

is locally asymptotically stable for $\tau_1 \in [0, \tau_1^*)$ and $\tau_2 \in [0, \tau_2^*)$. Ruan *et al.* do not consider the special but important case when the extrinsic incubation period is taken into account ($\tau_1 \neq 0$) while the intrinsic incubation period is not ($\tau_2 = 0$).

It is important to note that delay equations can be simulated just as the ordinary differential equations using computer algebra systems such as MATLAB, Mathematica and others. In particular, using such computer systems delay differential equations can be fitted to data – both prevalence and incidence data. When fitted to human incidence data, the human incidence term $qae^{-\alpha\tau_2}(N_H - I_H(t-\tau_2))I_v(t-\tau_2)$ has to be fitted to the given data at time t.

2.2.3 Delays related to the maturation period of the vector

The last source of delays in vector-borne models comes from the adaptive maturation delays of the vector. Many vectors, which are arthropods, undergo several life stages before they reach adulthood and are able to transmit the disease. For instance, a mosquito's life-cycle consists of three successive juvenile phases (egg, larva, pupa) before reaching the adult phase. It usually takes about 1-2 weeks before mosquitoes mature to adulthood, a time frame which is large relative to the average lifespan of the mosquito. To account for this delay, delay-differential equation models with delay in recruitment are composed. Such models have been previously considered by Fan *et al.* [13] in the discussion of the impact on dynamics of the mosquito-borne pathogen West Nile Virus, and by Ngwa *et al.* [32] in the discussion of a model, focused on the vector, with maturation delays. Prolonged developmental times are also experienced by other vectors, such as triatomines (Triatominae, Reduviidae), the vectors of Chagas disease [30].

To develop a vector-borne disease model with maturation delays, we need to use a baseline ODE model that incorporates recruitment of the vector. Hence, model (2.6) is not appropriate. We need to go back to model (2.1). Development of juvenile stages of vectors is density dependent and it is best modeled through a Ricker's type function as a recruitment rate into the population of adult vectors. If we denote the maturation delay by τ, then the total number of vectors that produce offsprings at time $t-\tau$ is $N_V(t-\tau)$. Suppose d_v is the death rate of juvenile vectors. Then, the probability of a juvenile vector surviving the juvenile stages and becoming an adult is $e^{-d_v\tau}$. The Ricker density dependent model assumes that the per capita birth rate declines exponentially with population size, so a term of the form $e^{-\rho N_v(t-\tau)}$ is included, where $1/\rho$ is the size of the vector population at which progeny production is maximized for a given total adult population size. Finally, r is the maximum per capita per unit of time vector progeny production rate. We replace the constant recruitment rate of the vector in model (2.1) with the recruitment rate $rN_V(t-\tau)e^{-\rho N_v(t-\tau)}e^{-d_v\tau}$. The model with maturation delay

of the vector becomes

$$\begin{aligned} S_v' &= rN_V(t-\tau)e^{-\rho N_v(t-\tau)}e^{-d_v\tau} - paS_vI_H - \nu S_v \\ I_v' &= paS_vI_H - \nu I_v \\ S_H' &= -qaS_HI_v + \alpha I_H \\ I_H' &= qaS_HI_v - \alpha I_H \end{aligned} \tag{2.11}$$

The total population size of the vector in this model is given by the following delay-differential equation:

$$N_v' = rN_V(t-\tau)e^{-\rho N_v(t-\tau)}e^{-d_v\tau} - \nu N_v. \tag{2.12}$$

The equation for the total vector population size (2.12) has been completely analyzed [8], and oscillations in that model have been found. Because the total population size of the vector is not necessarily asymptotically constant, the equation for the susceptible vectors cannot be eliminated from the above model. However, since the total population size for the human host remains constant, the susceptible human host population can still be removed.

3 Unstable Dynamics of Vector-Borne Diseases and Delay Differential Equation Models

Vector-borne diseases exhibit different patterns of occurrence. Parasitic and bacterial diseases, such as malaria and Lyme disease, tend to produce a high disease incidence that is not typically confounded with major epidemics. An exception to this rule is plague, a bacterial disease that does cause outbreaks. In contrast, many vector viral diseases, such as Yellow fever, dengue, Japanese encephalitis, and chikungunya commonly cause major epidemics.

3.1 Unstable Dynamics of Vector-Borne Diseases: Malaria as a Case Study

Even though the dynamics of malaria, one of the most prominent and deadly vector-borne diseases, is typically stable and persistent, exceptions to this observation exist as we illustrated in section 1.2. These exceptions have serious implications for modeling, response, and control of malaria. Unstable dynamics of malaria can occur in two distinct regimes:

1. relatively low baseline prevalence with occasional major outbreaks;
2. nearly oscillatory behavior where high prevalence follows low prevalence in consecutive years.

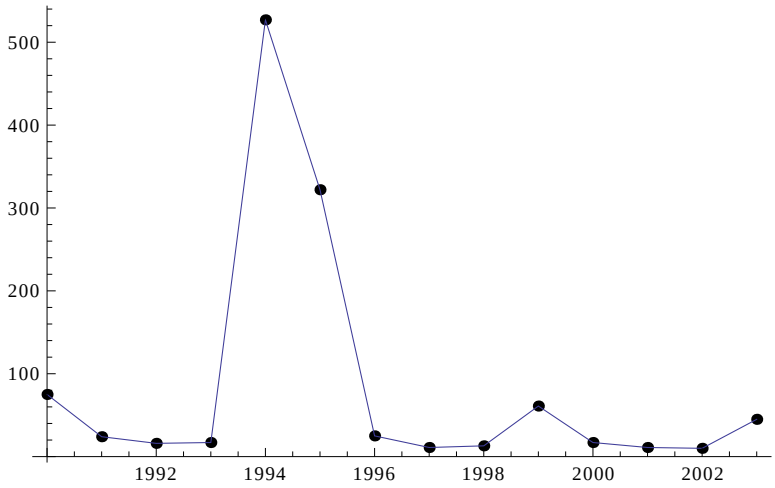

Figure 1: Number of malaria cases in Egypt for the years 1990-2003. The data exhibit background oscillatory dynamics with an outbreak in 1994. Data taken from [52].

The disease dynamics of several countries, including Botswana, Egypt, Iraq, Kyrgyzstan and Turkmenistan, have exhibited the first type of instability since 1990. The case of Egypt is illustrated in Figure 1 where a major outbreak occurred in 1994 and resulted in nearly 10 times the usual number of cases. Brazil, and particularly Haiti in the period 1990-2000, are examples of the second type of dynamics where the malaria prevalence oscillates between high and low with a relatively stable median. The number of cases in Haiti is given in Figure 2.

Major outbreaks or epidemics of malaria occur primarily in regions where the overall transmissibility of the disease is low. The unstable nature of malaria in such regions, and of other vector-borne diseases, present serious clinical threat to the populations of the affected areas. Inter-epidemic periods of very low transmissibility, particularly when long, allow for the immunity in the population to wane. Thus, during an outbreak or epidemic, young children are at higher risk of contracting malaria, while older children and adults are much more vulnerable to serious complications of the disease compared with stable transmission settings. The randomness of the outbreaks has a serious detrimental impact on the ability to predict, prepare for, and control the outbreak. Consequently, the outbreaks present a burden to the health care system of epidemic-prone countries.

Nearly oscillatory behavior, although more predictable, requires significant flexibility and adaptability of the response network. Similar difficulties arise in the control of malaria in such areas. The reasons for the inter-annual cycles of malaria, exhibited in such areas, are not completely understood, which complicates the efficient control of the disease in years of higher prevalence.

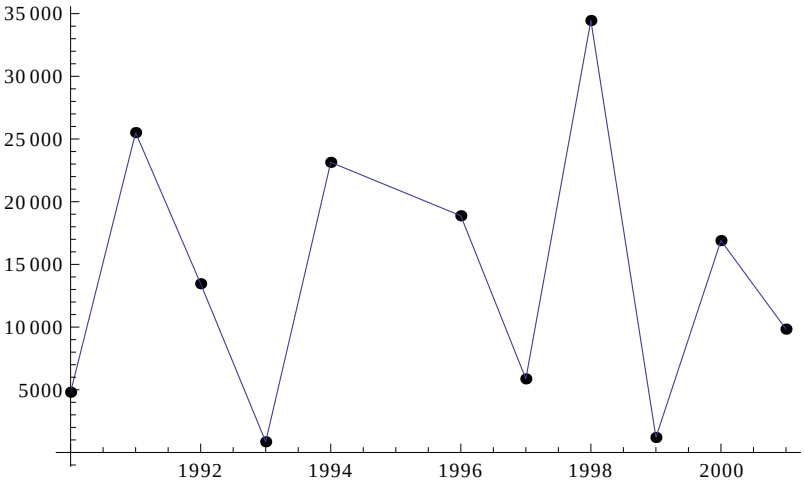

Figure 2: Number of *P. falciparum* cases in Haiti for the years 1990-2001. The data exhibit clear oscillatory dynamics. Data taken from [54].

3.2 Capturing Oscillatory Dynamics and Chaos with Delay Models

Traditionally, vector borne diseases have been modeled by ordinary differential equations. The delays introduced by the incubation and maturation periods can be included in ODE models by incorporating additional stages in the model. For instance, the incubation periods can be modeled via exposed compartments in the vector and/or the host systems. Such models have been considered in [6]. However, these compartmental ODE systems are only an adequate modeling tool when the disease exhibits stable dynamics as they typically predict convergence to an equilibrium. Ordinary differential equations in general display a low potential for complex dynamics. Oscillatory dynamics in ODEs occurs in two or higher dimensional systems. Chaos can only be obtained from three or higher dimensional systems. Yet, even high dimensional ODE models tend to have globally stable equilibria. In contrast, delay-differential equations can exhibit complex dynamics – oscillations and chaos – even in one dimensional models. Moreover, delay-differential models of vector-borne diseases, unlike their ODE counterparts, are capable of showing such complex dynamics. This makes them a better modeling tool for unstably transmitted vector-borne diseases. The idea that vector-borne disease models with delay can model oscillatory dynamics is not new. Several articles suggest that delay models of vector-borne diseases can exhibit oscillatory behavior. Wei *et al.* consider a model of a vector-borne disease with permanent immunity and delay. They show that the endemic equilibrium can be destabilized via Hopf bifurcation. More recently Saker [42] established the presence of Hopf bifurcation in the vector-host model with two delays (2.10). Other authors have also found oscillations in delay-differential equation models of vector-borne diseases [20, 36, 49].

In what follows we show that delay equations, even a simple single delay equation, are capable of displaying oscillations and chaos. To obtain this single equation, we begin from the delay model with two delays (2.10). The single delay equation that we derive is suitable to model malaria, and other vector borne diseases, where the extrinsic and intrinsic incubation periods are nearly equal in duration.

3.2.1 Reducing the Delay Model to a Single Equation

Biologists often use various methods to reduce the dimension of a system describing vector-borne disease. The newly obtained system does not necessarily have the same dynamical behavior as the original one but it is still useful in obtaining initial insights into the disease dynamics.

Justification for the reduction in dimension is typically based on the assumption that the lifespan of the vector is much shorter than the duration of infectiousness of the humans, that is, we assume that $\mu >> \alpha$ and this leads to much faster equilibration of the dynamics of the vector population compared with the host population. This assumption is common for vector- borne diseases transmitted by mosquitoes, such as malaria [5]. Furthermore, we assume that the intrinsic incubation period is approximately equal to the extrinsic incubation period, that is $\tau_1 = \tau_2 = \tau$. This is certainly the case in malaria where the incubation period in the humans typically lasts between 10 days and four weeks. The extrinsic period is often temperature-dependent but lasts 10-18 days. If we assume that the two incubation periods are the same, the model with two delays (2.10) becomes:

$$\begin{aligned} I_v' &= pae^{-\mu\tau}(N_v - I_v(t-\tau))I_H(t-\tau) - \mu I_v \\ I_H' &= qae^{-\alpha\tau}(N_H - I_H(t-\tau))I_v(t-\tau) - \alpha I_H \end{aligned} \tag{3.1}$$

Furthermore, since the vector dynamics has reached equilibrium, we have $I_v' = 0$. At equilibrium, the population numbers at time t and $t-\tau$ are approximately the same. Hence, from the first equation we have

$$I_v(t-\tau) = \frac{pae^{-\mu\tau}N_v I_H(t-\tau)}{pae^{-\mu\tau}I_H(t-\tau) + \mu}.$$

Substituting I_v in the second equation, we obtain the following single delay equation for the dynamics of the humans:

$$I_H' = \frac{pa^2qe^{-\alpha\tau}e^{-\mu\tau}N_v I_H(t-\tau)}{pae^{-\mu\tau}I_H(t-\tau) + \mu}(N_H - I_H(t-\tau)) - \alpha I_H \tag{3.2}$$

It is helpful to normalize this equation by setting $x = I_H/N_H$. The equation for the proportion of humans infected becomes:

$$x' = \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}x(t-\tau)}{pae^{-\mu\tau}x(t-\tau) + \mu}(1 - x(t-\tau)) - \alpha x(t) \tag{3.3}$$

where $m = N_v/N_H$ is the ratio of the number of vectors to the number of humans and aN_H has been replaced again by a.

Delay equations, just like ODEs, have equilibria. The value x^* is an equilibrium of model (3.3) if it satisfies the equation

$$\frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}x^*}{pae^{-\mu\tau}x^* + \mu}(1 - x^*) - \alpha x^* = 0. \tag{3.4}$$

This equation clearly has the solution $x^* = 0$ which gives the disease-free equilibrium. To investigate the stability of the disease-free equilibrium, we linearize the equation. We look for a solution $x(t) = x^* + y(t)$ where $y(t)$ is the perturbation around the equilibrium, and $x^* = 0$. This means that we have to replace x with y and linearize the nonlinear term. Notice that

$$\frac{1}{pae^{-\mu\tau}x(t-\tau) + \mu} = \frac{1}{\mu(pa/\mu e^{-\mu\tau}y(t-\tau) + 1)} \approx \frac{1}{\mu}\left[1 - pa/\mu e^{-\mu\tau}y(t-\tau)\right].$$

Hence, the linearization around the disease-free equilibrium is given by:

$$y' = \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}y(t-\tau)}{\mu} - \alpha y(t).$$

Because we now have a linear system, we look for a solution of the form $y(t) = \bar{y}e^{\lambda t}$, and subsequently obtain the following characteristic equation

$$\lambda + \alpha = \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}e^{-\lambda\tau}}{\mu}.$$

The above equation is a **transcendental equation**, that is an equation containing a transcendental function of λ, namely $e^{\lambda\tau}$. λ can be a real or complex variable. If we think of λ as a real variable, the left-hand side of the above equation is an increasing linear function of λ while the right-hand side is a decreasing function of λ. This equation always has a unique real solution which is positive if and only if $\mathcal{R}_0 > 1$ where we define the reproduction number $\mathcal{R}_0$ to be

$$\mathcal{R}_0 = \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}}{\mu\alpha}. \tag{3.5}$$

So if $\mathcal{R}_0 > 1$, the disease-free equilibrium is unstable. If $\mathcal{R}_0 < 1$, the unique real eigenvalue is negative. We show that all other eigenvalues, which are complex, have negative real parts. Assume we have an eigenvalue $\lambda = b + ci$, where i is the imaginary unit, that has a nonnegative real part, that is $b \geq 0$. Then $|\lambda + \alpha| = \sqrt{(b+\alpha)^2 + c^2} \geq$

$b+\alpha \geq \alpha$. At the same time

$$\begin{aligned} &\left|\frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}e^{-\lambda\tau}}{\mu}\right| \\ &\quad = \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}|e^{-\lambda\tau}|}{\mu} \\ &\quad = \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}e^{-b\tau}}{\mu} \\ &\quad \leq \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}}{\mu} \end{aligned} \tag{3.6}$$

which contradicts the fact that $\mathcal{R}_0 < 1$, that is $\alpha > \frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}}{\mu}$. Hence, because all the eigenvalues have negative real parts, the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$. We note that if $\mathcal{R}_0 = 1$, then $\lambda = 0$ is an eigenvalue and we cannot use this argument to make conclusions. We consider again the equation for the equilibria. Canceling x^*, the non-trivial endemic equilibria satisfy the equation

$$\frac{pa^2qme^{-\alpha\tau}e^{-\mu\tau}}{pae^{-\mu\tau}x^* + \mu}(1 - x^*) - \alpha = 0. \tag{3.7}$$

Multiplying by the denominator, we obtain a linear equation in x^* which can be solved to give the unique endemic equilibrium.

$$x^* = \frac{\mathcal{R}_0 - 1}{pa/\mu e^{-\mu\tau} + \mathcal{R}_0}. \tag{3.8}$$

It is clear from this expression that the endemic equilibrium exists and is positive if and only if $\mathcal{R}_0 > 1$. To investigate the stability of the endemic equilibrium, we linearize around it. Set $x(t) = x^* + y(t)$, where $y(t)$ is the perturbation of the endemic equilibrium. The perturbation y can take positive and negative values. Furthermore, to simplify the notation, we will denote $Q = pa^2qme^{-\alpha\tau}e^{-\mu\tau}$ and $P = pae^{-\mu\tau}$. Substituting in the delay equation (3.3) we obtain the following equation for the perturbation

$$y'(t) = \frac{Q(x^* + y(t-\tau))}{P(x^* + y(t-\tau)) + \mu}[1 - x^* - y(t-\tau)] - \alpha(x^* + y(t)). \tag{3.9}$$

Taking into account the equation for the equilibrium

$$\frac{Qx^*(1-x^*)}{Px^* + \mu} = \alpha x^* \tag{3.10}$$

and linearizing as in the case of the disease-free equilibrium, we obtain the following equation for the perturbation y:

$$y'(t) = \frac{Q(1-x^*)y(t-\tau)}{Px^* + \mu} - \frac{Qx^*}{Px^* + \mu}\left[\frac{P(1-x^*)y(t-\tau)}{Px^* + \mu} + y(t-\tau)\right] - \alpha y(t). \tag{3.11}$$

This equation can be simplified as follows:

$$y'(t) = \frac{Q(1-x^*)y(t-\tau)}{Px^*+\mu}\left[1 - \frac{Px^*}{Px^*+\mu}\right] - \frac{Qx^*y(t-\tau)}{Px^*+\mu} - \alpha y(t). \tag{3.12}$$

Using the equation for the equilibrium (3.10) and the fact that $\mathcal{R}_0 = Q/(\alpha\mu)$, we obtain the following simplified linearized equation

$$y'(t) = \frac{\alpha\mu}{Px^*+\mu}(1-\mathcal{R}_0x^*)y(t-\tau) - \alpha y(t). \tag{3.13}$$

Looking for the exponential solution $y(t) = \bar{y}e^{\lambda t}$, we obtain the following characteristic equation

$$\lambda + \alpha = \frac{\alpha\mu}{Px^*+\mu}(1-\mathcal{R}_0x^*)e^{-\lambda\tau}. \tag{3.14}$$

If $\mathcal{R}_0x^* < 1$, the coefficient in front of the term $e^{-\lambda\tau}$ is positive and smaller than α, which corresponds to the case when $\mathcal{R}_0 < 1$ in the characteristic equation for the disease-free equilibrium. A similar argument can show that all roots of the equation (3.14) have negative real parts, and the endemic equilibrium is locally asymptotically stable. We summarize these results in the following Theorem:

Theorem 1 *If $\mathcal{R}_0 < 1$ the differential delay equation (3.3) has only the disease-free equilibrium $x^* = 0$ which is locally asymptotically stable. If $\mathcal{R}_0 > 1$ the differential delay equation (3.3) has the disease-free equilibrium and a unique endemic equilibrium x^*. If $\mathcal{R}_0 > 1$ the disease-free equilibrium is unstable. The endemic equilibrium is locally asymptotically stable, if in addition $\mathcal{R}_0x^* < 1$.*

This Theorem suggests a rather curious conclusion – the endemic equilibrium is stable if $x^* < 1/\mathcal{R}_0$. Since the reproduction number of malaria $\mathcal{R}_0$ is often large, then the equilibrium is stable if the fraction of infected individuals is rather small. This suggests that in countries, like Egypt, where the year to year prevalence is typically very low, outbreaks such as the one that occurred in 1994 may not be possible to capture with this simple single-equation model of malaria and may be a result of stochastic events.

3.2.2 Oscillations and Chaos in the Delay Differential Equation

If $\mathcal{R}_0x^* > 1$, then the coefficient on the right-hand side of the characteristic equation (3.14) is negative, and the equation can have as principal eigenvalues (eigenvalues with the largest real part) a pair of complex conjugate eigenvalues. However, as a parameter changes, this pair of principal eigenvalues may cross the imaginary axis giving rise to a stable oscillatory solution. At the same time, the principal eigenvalues start having positive real part and the endemic equilibrium becomes unstable. This process that gives rise to a stable oscillatory solution is called **Hopf bifurcation**. The result is valid for ODEs and delay-differential equations. For differential delay equations, it is given in the Hopf bifurcation Theorem below:

Theorem 2 *Consider the differential delay equation*

$$x'(t) = F(x(t), x(t-\tau_1), \ldots, x(t-\tau_{n-1}), \mu) \tag{3.15}$$

where μ is a parameter. If:

a. *F is analytic in x and μ in a neighborhood of $(\mathbf{0}, 0)$ in $\Re^n \times \Re$.*

b. *$F(\mathbf{0}, \mu) = 0$ for μ in an open interval containing 0, and $x(t) = 0$ is an isolated stationary solution of (3.15).*

c. *The characteristic equation of (3.15) has a pair of complex conjugate eigenvalues λ and $\bar{\lambda}$ such that $\lambda(\mu) = b(\mu) + i\omega(\mu)$ where $\omega(0) = \omega_0 > 0$, $b(0) = 0$ and $b'(0) \neq 0$.*

d. *The remaining eigenvalues of the characteristic equation have strictly negative real parts.*

Then, the differential delay equation (3.15) has a family of Hopf periodic solutions.

One can apply Theorem 2 to show rigorously that Hopf bifurcation occurs in equation (3.3). Instead, we will build a specific numerical example of such an oscillatory solution. To find sustained oscillations in equation (3.3), we need to find values of the parameters for which such oscillations occur. We begin from the characteristic equation (3.14), which we simplify further, and write as

$$\lambda + \alpha = \rho e^{-\lambda\tau} \tag{3.16}$$

where $\rho = \frac{\alpha\mu}{Px^*+\mu}(1-\mathcal{R}_0 x^*)$. We recall that we have assumed that $\rho < 0$. Let $\lambda = b + i\omega$. We separate the real and the imaginary part:

$$\begin{aligned} b + \alpha &= \rho e^{-b\tau}\cos[\omega\tau] \\ \omega &= \rho e^{-b\tau}\sin[\omega\tau]. \end{aligned} \tag{3.17}$$

Now we ask the question: Can we find parameters $\alpha > 0$ and $\rho < 0$ such that the system above has positive solution $b > 0$ and $\omega > 0$? We solve in terms of α and ρ

$$\begin{aligned} \alpha &= -b + \omega\cot[\omega\tau] \\ \rho &= \omega e^{b\tau}\csc[\omega\tau]. \end{aligned} \tag{3.18}$$

As we have seen earlier, some of the parameters that have physical meaning can be pre-estimated, or at least reasonable biological ranges can be determined for them. In the equations above, we assume values for b and τ and interpret α and ρ as functions of ω. Using a computer algebra system we can make a parametric plot of α and ρ in the (α, ρ)-plane. This plot is shown in Figure 3.

We pick a value for ω, say $\omega = 5.2$. From system (3.18) we obtain the values $\alpha = 2.74768$ and $\rho = -5.94514$. The value of α corresponds to an infectious period

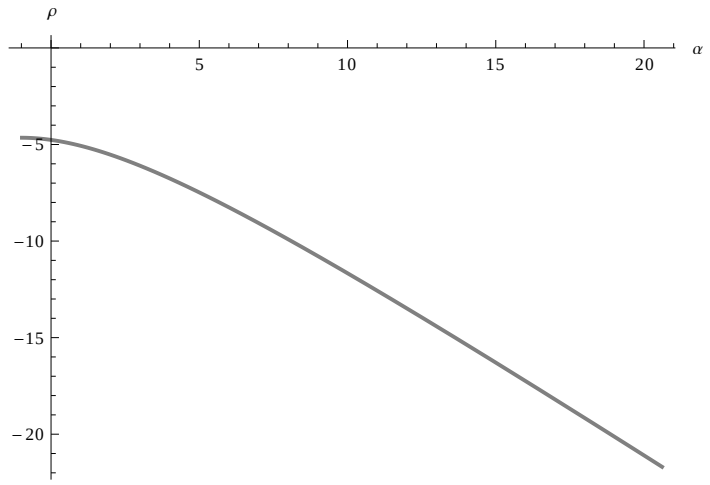

Figure 3: Parametric plot of α and ρ in the (α, ρ)-plane as given by equations (3.18). The values of b and τ are taken as follow: $b = 0.01$, $\tau = 1$. The value of τ which is equal to one year is rather high for *Plasmodium falciparum* malaria. The plot is made for $4.5 \leq \omega \leq 6$.

of $1/2.74768 = 0.3639$ years which is a reasonable duration for *Plasmodium falciparum* malaria. Now we have to assume values for the remaining parameters, so that the combined value of ρ is as given. We assume the value $\mu = 12$, which gives a vector lifespan of one month. This duration is a realistic estimate for a mosquito's lifespan. Furthermore, we have to find Q and P so that the following system holds

$$\begin{aligned} \frac{Q(1-x^*)}{Px^*+\mu} &= \alpha \\ \frac{\mu\alpha(1-\mathcal{R}_0x^*)}{Px^*+\mu} &= \rho. \end{aligned} \tag{3.19}$$

Dividing these two equations we have

$$\frac{\mathcal{R}_0(1-x^*)}{1-\mathcal{R}_0x^*} = \frac{\alpha}{\rho}.$$

From here, assuming a value of $\mathcal{R}_0x^*$, we can compute $\mathcal{R}_0$ as

$$\mathcal{R}_0 = \mathcal{R}_0x^* + \frac{\alpha}{\rho}(1-\mathcal{R}_0x^*).$$

If we take $\mathcal{R}_0x^* = 5$, then $\mathcal{R}_0 = 6.84869$. From here we can compute $x^* = 0.73$. Finally, $Q = \mathcal{R}_0\alpha\mu = 225.816$. From the second equation in system (3.19) we determine $P = 13.9498$. With these parameters we plot the solution of equation (3.3) in Figure 4.

The trajectory in Figure 4 suggests that the endemic equilibrium is indeed unstable. However, the trajectory is not periodic. It is *aperiodic*, suggesting the presence of **chaos** in the model (3.3). What is chaos? There are many definitions of chaos. Perhaps the most useful in biology is the following:

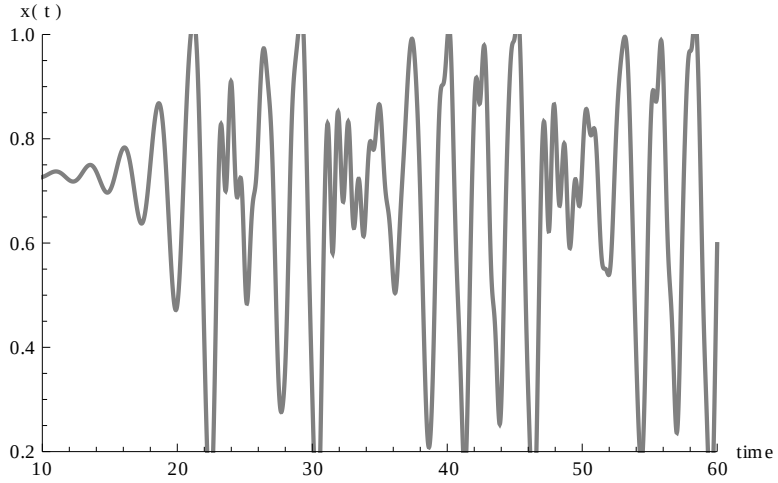

Figure 4: Plot of the solution of equation (3.3) with $P = pae^{-\mu\tau} = 13.9498$, $Q = Pqame^{-\alpha\tau} = 225.816$, $\tau = 1$, $\alpha = 2.74768$, $\mu = 12$ and initial condition $x(0) = 0.73$. The resulting trajectory is aperiodic suggesting presence of chaotic behavior.

Definition 3.1 *Chaos is aperiodic long-term behavior in a deterministic system that exhibits sensitive dependence on initial conditions.*

This definition has several components:

1. *Aperiodic long-term behavior* means that there are trajectories which do not settle down to fixed points, periodic orbits, or quasi-periodic orbits as $t \to \infty$. For practical purposes we require that these aperiodic orbits are not too rare.

2. *Deterministic* means that the system has no random or noisy inputs.

3. *Sensitive dependence on initial conditions* means that nearby trajectories separate exponentially fast.

From Figure 4 we see that the delay malaria model (3.3) has solutions that are aperiodic, that is their trajectory does not repeat even when we run for a long time. Furthermore, the trajectories exhibit sensitive dependence on initial data. If we start very close to the trajectory above, the two trajectories "coincide" for a certain amount of time, called the *time horizon*, after which the two trajectories completely diverge and one doesn't look like the other. The sensitive dependence is illustrated in Figure 5.

The existence of sensitive dependence on initial conditions in simple but chaotic models means that we have lost the ability to make long-term predictions. We can still make short-term predictions based on chaotic models which are valid for the duration of the time horizon. Chaotic behavior emerges from periodic behavior through a process called period doubling. This sequence of period doubling leading to chaos is often demonstrated on a chaos bifurcation diagram which plots the long-term behavior of the

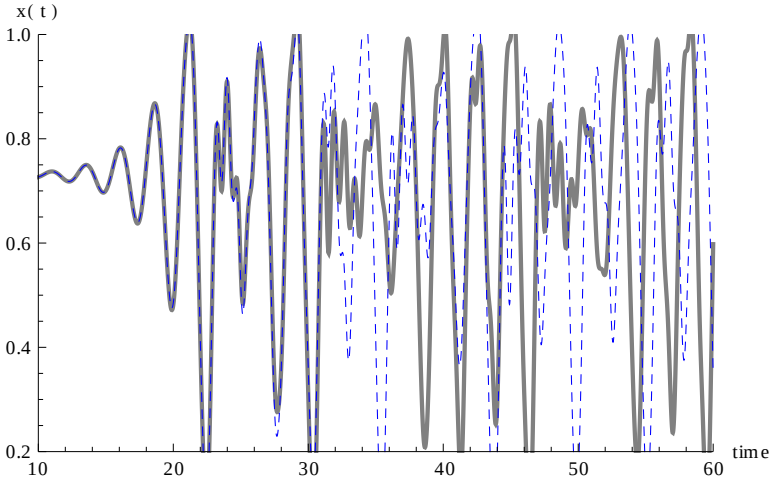

Figure 5: Plot of two solutions of equation (3.3) with $P = pae^{-\mu\tau} = 13.9498$, $Q = Pqame^{-\alpha\tau} = 225.816$, $\tau = 1$, $\alpha = 2.74768$, $\mu = 12$ and initial conditions $x_1(0) = 0.73$ and $x_2(0) = 0.730001$. The two close trajectories coincide for a while and then diverge suggesting sensitive dependence on the initial conditions.

solution with respect to some parameter. Such a chaos bifurcation diagram is plotted in Figure 6. Because chaos emerge from a periodic solution as a result of increase in the delay parameter, this suggests that if we decrease the bifurcation parameter τ, we will obtain a regular periodic solution. This is indeed the case. Figure 7 shows a periodic trajectory produced with the same parameters as above and $\tau = 0.6$.

We see that even first order deterministic delay models can exhibit chaotic behavior and sustained oscillations. This suggests that delay-differential equation models are a suitable tool to produce unstable, oscillatory, nearly oscillatory or chaotic dynamics in vector-borne diseases.

3.3 Delay-Differential Equations as a Modeling Tool for Intrinsic Drivers of Instabilities in Vector-Borne Diseases

The main question that needs to be addressed is: How should we model malaria and other vector-borne diseases so that we can capture the instabilities in the dynamics? There are three possibilities that may be used to model and explain unstable outbreak dynamics or inter-annual oscillations in malaria. These are:

1. The inter-annual cycles are driven by climate, and thus should be modeled by external forcing dependent on rainfall, temperature and other climatic covariates. This hypothesis has been investigated on numerous occasions and a number of articles address the impact of El Nino oscillation, and other climatic variables on the dynamics of malaria [37, 25, 34].

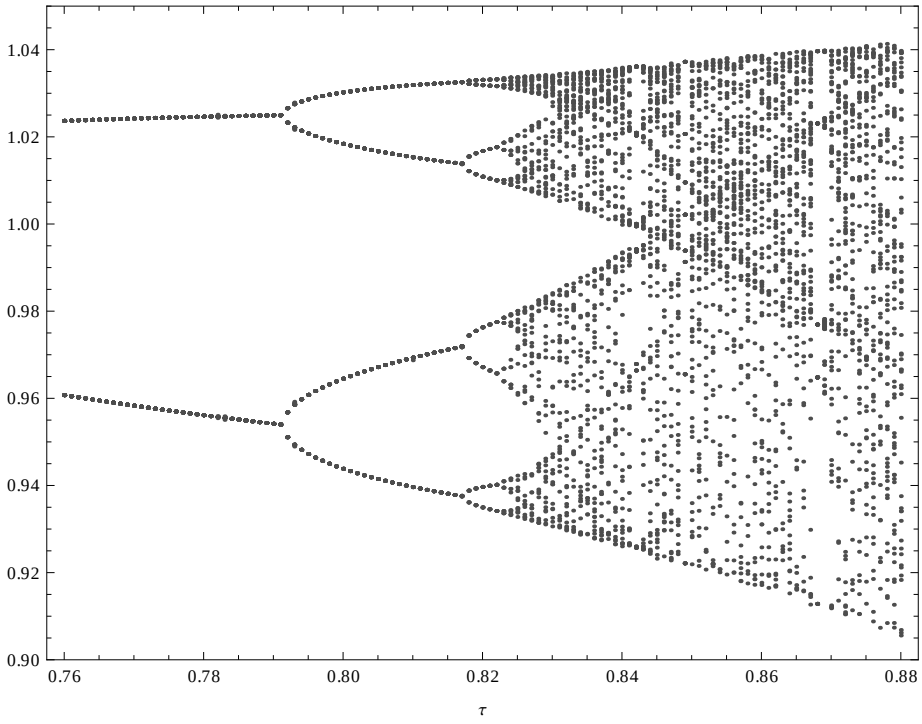

Figure 6: Plot of the chaos bifurcation diagram with $P = pae^{-\mu\tau} = 13.9498$, $Q = Pqame^{-\alpha\tau} = 225.816$, $\alpha = 2.74768$, $\mu = 12$ and initial condition $x(0) = 0.73$. The delay parameter τ is a bifurcation parameter. Long-term behavior of x is plotted on the y axis.

2. The inter-annual cycles are generated by the intrinsic dynamics of the disease. In this case they presumably should be obtained from autonomous differential equation models. Few studies have been carried out that investigate the possibility that intrinsic reasons are responsible for the inter-annual oscillation and unstable outbreak dynamics of vector-borne diseases. The relatively stable dynamics of even multi-dimensional ODE models, and the relatively recent realization that delay models have the potential to produce oscillations have obstructed more serious studies into the possibility the unstable dynamics may be produced by autonomous deterministic differential equation models. Here, we suggest that, if autonomous, non-stochastic differential equation models have the potential to produce the complex dynamics of vector-borne diseases in nature, these should be differential-delay models.

3. The inter-annual cycles are a result of the joint action of climatic and internal mechanisms. In this case, the baseline autonomous differential equation model on

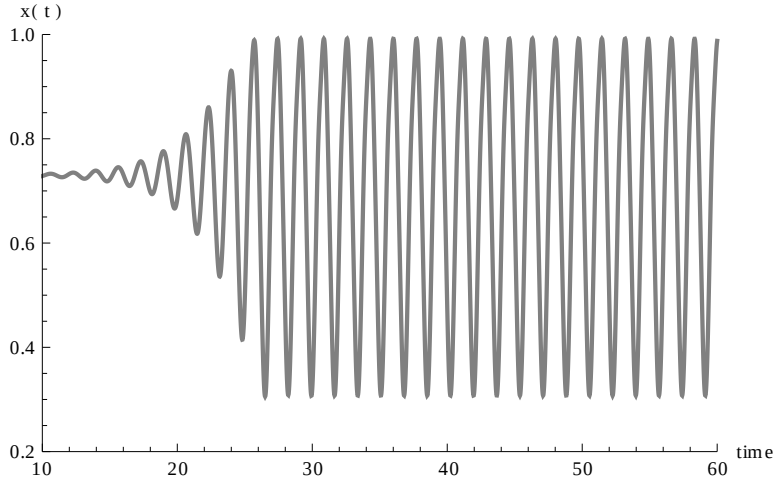

Figure 7: Plot of a periodic solution of equation (3.3) with $P = pae^{-\mu\tau} = 13.9498$, $Q = Pqame^{-\alpha\tau} = 225.816$, $\tau = 0.6$, $\alpha = 2.74768$, $\mu = 12$ and initial condition $x(0) = 0.73$.

which the stochastic and/or externally forced version is built, should also be able to produce oscillations itself. Hence, this baseline model should be a differential-delay model, rather than an ODE model.

In a recent article Laneri *et al.* [25] compare the three options based on an ODE model with external forcing and stochasticity. The results in that article suggested that "the nonlinear dynamics of the disease itself plays a role at the seasonal, but not the inter-annual, time scales." The article seems to settle the question in favor of climatic drivers, but that conclusion is reached in the absence of any understanding in the literature regarding what particular *intrinsic* mechanisms could cause such an unstable, oscillatory or chaotic dynamics. Here, we argue that delay-differential equations are a good modeling tool on which investigation of the intrinsic mechanisms can be built.

4 Discussion

Vector-borne diseases are stable in many regions; however, a closer look reveals that there is diversity in how these diseases manifest in different areas. The mechanisms producing this diversity in disease dynamics are still not well understood. Seasonality in weather is a reasonable mechanism for intra-annual fluctuations in vector-borne disease prevalence because of the dependence of arthropod abundance on rainfall and temperature. However, it is unlikely that climate alone can explain inter-annual oscillations like those observed in Haiti (Figure 2), particularly when the period of these oscillations appears predictable. Because delay-differential equation models are capable of producing inter-annual oscillations, this class of deterministic models appears to be an appropriate choice for exploring the mechanisms behind these less intuitive patterns in disease

prevalence. Such exploration could lead to different insights: either intrinsic aspects of vector-borne diseases can cause inter-annual oscillations, seasonality and intrinsic mechanisms may work together to produce inter-annual oscillations, or perhaps neither of these hypotheses is supported and further research is required to find other possible causes of these unstable disease patterns. Regardless of the outcome, it is likely that studying delay-differential equation models for vector-borne disease will contribute to our understanding of unstable transmission, particularly if these models are confronted with data.

Many of the vector-borne diseases have a more complex biology than the models included in this chapter. For instance, individuals infected with *Plasmodium vivax* malaria who have been treated and have recovered from clinical symptoms may relapse [1]. Furthermore, a malaria infected individual may become bitten by an infectious mosquito and become super-infected with a different strain – a scenario modeled by the concept of multiplicity of infection [45]. One individual can become infected by more than one *Plasmodium* species (co-infection). All these scenarios have been captured by ordinary differential equation models [5]. These ordinary differential equation models with super-infection, co-infection and relapse can be recast to incorporate delays in the same way discussed in this chapter, although if the different strains have different delay times, it may not be possible to eliminate the dynamic equation for the vector. Still, the resulting delay-differential equations will exhibit competition and coexistence of strains in the context of oscillatory behavior and chaos.

Ruan *et al.*'s [41] study of malaria transmission using a delayed Ross-Macdonald model provided the insight that increasing the duration of either the intrinsic or extrinsic incubation periods would result in reducing the basic reproduction number. This finding has important implications for the future of malaria and malaria control. Climate change, for example, could result in prolonging the extrinsic incubation period in some regions, potentially changing the distribution of malaria, or further increasing malaria prevalence in already endemic countries. More optimistically, it also suggests that there is an opportunity for a different approach to malaria control. The current control measures include larvicides, insecticides, bed nets, and treatment. However, a less traditional approach, such as the use of drugs that prolong incubation periods, may also be an effective means of control.

Another concern that arises from our current knowledge about delay-differential equation models for vector-borne diseases, such as the possibility of Hopf bifurcation, is that changes in the incubation periods may alter the dynamics of the disease, causing a stable transmission region to become unstable, or vice versa. Consequently, understanding if and when these transitions are likely to occur may be very important in determining the effects of climate change, or intervention strategies that prolong incubation periods. Ruan *et al.* [41] also suggest that long incubation periods may play an important role in "nonlocal" disease transmission since longer incubation periods means

that humans and mosquitoes are more likely to travel long distances prior to becoming infectious or symptomatic. Thus, delays in vector-borne diseases may play a critical role in understanding the spatial spread of these diseases in addition to understanding unstable transmission. The combination of delays and human migration also could potentially contribute to epidemic patterns of transmission.

The indirect transmission between vector and host, the vector's and pathogen's climate-dependent survival, and the relationship between the pathogen's extrinsic incubation period and temperature contribute to the complexity of vector-borne diseases, challenging our understanding of their dynamic and varied behavior in different regions around the world. Stochastic events such as natural disasters or human migrations further complicate and cloud the picture. Understanding the mechanisms producing unstable transmission patterns in order to improve current control efforts seems like a daunting task. However, history has demonstrated the utility of developing mathematical models to understand complicated phenomena such as disease transmission. Consequently, we should feel encouraged that pursuing the study of delay-differential equations in epidemiology may provide similar insight into the mechanisms driving vector-borne disease dynamics in unstable transmission settings. A better understanding of unstable transmission will then allow public health officials to develop intervention strategies more appropriate for these epidemic-prone regions, alleviating the burden on health facilities during outbreaks and mitigating the risk of high morbidity and mortality within a population.

Acknowledgments

Maia Martcheva acknowledges partial support from NSF grant DMS-0817789. Olivia Prosper acknowledges support from IGERT grant NSF DGE-0801544.

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