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Mathematical models for vector-borne diseases: effects of periodic environmental variations

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"what is tiny
can be killed using a hand,
can harm millions of lives?"

Donal Bisanzio

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Introduction

My thesis deals with mathematical models for the dynamics of vector-borne infection, especially West Nile virus.
West Nile virus is a mosquito-borne disease of the *Flaviviridae* family. It is neuro-pathogenic for birds, humans, horses and other mammals. The most serious manifestation of this virus is a fatal encephalitis in humans and more frequently in horses. It may very often cause death in some bird species. West Nile virus is mainly transmitted through the bite of infected vectors, that acquire the virus by feeding on infected birds. It is maintained by bird-mosquito cycle while humans, horses and other mammals are considered as dead-end host for the virus (Bisanzio et al. [2011], Hayes et al. [2005]). Since the mammals are secondary hosts and they do not play any role in the maintenance and in the amplification of the virus, we focused our attention on the mosquito-bird cycle transmission only.
Although the vector responsible of the transmission, *Culex Pipiens* mosquito, is active only during the summer, there are evidences of re-occurrence of the virus from a year to another year(Monaco et al. [2011]) and so the infection overwinters in some way.
This is a peculiarity of many vector-borne diseases. We assume that overwintering of the infection occurs in the vector population.
To survive winter, mosquitoes enter diapause: during this stage of spontaneous stop of development, the organism of the mosquitoes is inactive, i.e. the metabolic activity decreases. The transmission may occur during certain periods of the year only, depending on the seasonality of the species, and so, in the case of West Nile virus, not in winter.

The aim of the thesis was to investigate the effect of this particular kind

of periodicity, due to the inactivity of many vectors, and so to the absence of transmission during winter, on the dynamics of a general vector-borne disease.
To model the transmission between vectors and hosts, we used a semi-discrete system (Mailleret and Lemesle [2009]), i.e. a particular class of hybrid dynamical systems that undergoes continuous dynamics, but repeatedly are subjected to discrete changes. The summer seasons, in which infection transmission occurs, are modeled with ordinary differential equations, whereas the winter seasons are modeled in an extremely simple way only with the survival probabilities, i.e. a discrete change.

In Chapter 1, a very short introduction to the mechanisms of transmission and the distribution of the vector-borne disease is given. Moreover, some mathematical models helpful in studying epidemiological features of a disease, especially in the case of vector-borne disease, are reviewed.

In Chapter 2, a really simplify model is examined. It is supposed the presence of a single host population, which is certainly not realistic for West Nile virus, but it may be useful as first step. Moreover all parameters, including host and vector population size, are assumed to be constant during the summer seasons. For this model, a threshold parameter is identifIED for both SIS and SIR epidemiological framework presented. A complete description of the global behavior in the case of infections of SIS type is obtained and some illustrative simulations are showed.
The resulting threshold is compared with the definition of R_0 proposed by Nicolas Bacaër and coworkers for models of vector-borne disease in a periodic environment.

A more realistic model for West Nile virus is presented in Chapter 3. This model was developed during a period visiting the Emory University, Georgia (USA), at the Department of Environmental Science, Laboratory of Epidemiology of Vector-borne Disease. More details in mosquito life cycle are introduced and time-dependence in the demographic parameters is assumed; the model results in a dynamics of bird and mosquito populations qualitatively similar to what observed in the United States or in Southern Europe.

Since exact parameter value for West Nile virus are difficult to obtain, simulations were computed using parameters generated using *Latin Square Hypercube sampling* and keeping only the samples yielding simulations of the populations and of West Nile virus infection compatible with some constraints imposed for realism. The analysis of the resulting simulations highlights some qualitatively features of the phenomenon and show how, according to the values of the parameters of the populations, it is possible to observe dynamics of endemic type, similar to the USA, or limited and short epidemic, as usually occurred in Europe. The analysis also highlights the uncertainty of the estimate of the parameters based on few available data.

Finally in Chapter 4, the spatial spread of a general vector-borne disease is considered. The simpler semi-discrete SIR model, presented and analyzed in Chapter 2, is expanded introducing the space in a very easy way, considering, as a first step, a one-dimensional region.

Chapter 1

Mathematical models for vector-borne diseases

1.1 A short introduction to vector-borne diseases

According to WHO, vector-borne disease constitute 17% of the estimated global amount of all infectious disease. Malaria, the most life-threatening vector-borne disease is caused by a parasite *Plasmodium*, transmitted via infected mosquitoes. It is estimated that in 2012 malaria caused 627.000 deaths.
Vector-borne disease are carried by vectors, such as mosquitoes, tick and sand-flies, that are organisms that transmit pathogens and parasites from one infected host to another one.

These diseases are commonly found in tropical and sub-tropical regions and places where access to safe drinking-water and sanitation systems is problematic. The increment in traveling to and from tropical regions has helped the circulation of diseases that are constantly being discovered.

Several vector-borne infections have emerged in recent years as diseases of considerable and widespread importance, among which Lyme disease and West Nile virus.
For instance, the rapid spread of West Nile virus is facilitated by the fact

that the mosquitoes involved in the transmission are a very competent vector of the infective agent. In fact, West Nile virus was introduced in 1999 to New York and from this point has spread very rapidly into most of the United States: West Nile virus has reached in 2004 California and Canada causing large arboviral meningoencephalitis outbreaks. This example shows the risk of the introduction of exotic vector-borne infections to Europe and North America. Many factors that may facilitate the introduction and establishment of disease vectors, reservoirs or pathogens in new geographic areas could lead to the emergence of a disease in the European Union (EU). These factors include international travel and trade, e.g. legal and illegal trade in animals and animal products, new agricultural practices and land-use patterns, socio-demographic evolution and climatic changes. (ECDC [2013])

1.1.1 Climate variability and change: potential impacts on vector-borne diseases.

Periodic fluctuations are frequent in the dynamics of disease transmission. For example, children diseases are influenced by opening and closing of the school. In these instances, contact rates vary seasonally, so that periodic behavior of the incidence can be observed. Periodic changes in birth rates of population, that may be lead to a periodic behaviour of a disease, are evidenced in many biological works also. (Cushing [2006], Schwartz [1992], Wang and Zhao [2008])

Periodic fluctuations are common especially in the dynamics of vector-borne disease.

Vector-borne diseases are transmitted by blood-feeding arthropods. The pathogens involved in this type of disease spend part of their life cycle in the vector blood. Since life cycle of vectors in general is ruled by environmental factors and many vector-borne diseases show a clear distinct seasonal pattern, it is expected that this kind of infections are weather sensitive. Temperature, photo-period, precipitations and other weather variables may affect in many ways both vectors and pathogens they transmit. High temperatures, for example, may increase or reduce the survival rate of the vectors and also

their behavior and ecology. Thus, the probability of transmission may be decreased or increased by high temperatures.

The life-cycle of the mosquitoes is influenced by the temperature and photo-period. In temperate climates, they are active only during the summer season, when the temperature is close a certain temperature. When photo-period and temperature decrease, they start entering diapause to survive winter.
During winters the transmission of the virus does not occur and so it is clear, facing the study of infection that involve these type of population, that is very important considering the environmental factors that may lead to a periodic fluctuation in the incidence of the disease.

1.2 Mathematical deterministic models

Mathematical models have been, and they still are, a very important tool that helps us to understand epidemiology (Anderson and May [1991]).

The goal of mathematical modeling of infectious diseases is to identify those mechanisms that cause outbreaks and spread of the disease, to describe in a rational way these events and to establish how to control a disease.
Formulation of a model usually depends on the aspects that the modeler prefers to deal with. This aspects could come from the branches different from mathematics, such as biology, epidemiology, demography etc... It may be very hard to learn all the knowledge of a specific field and build a model that exactly takes in account all of them.
Moreover, limited available data and not sufficient epidemiological informations can hinder the efforts of the modeler in modeling the spread of the etiological agent, if his aims go beyond the theoretical exploration and the intrinsic interest.

A first distinction within the wide variety of mathematical approaches mostly undertaken in infectious disease epidemiology can be made between deterministic and stochastic models. For instance, mathematical epidemiology uses models based on difference, differential, integral or functional differential equations. These kind of models are named *deterministic models*.

Deterministic models first appeared in the literature in 20^{th} century (Bailey et al. [1975], Hamer [1906], Ross [1916]) and culminated with the work by Kermack and McKendrick [1927]. Deterministic models have had a very important role in the description of the spread of an infection.
Using for instance a system of differential equations, once the initial conditions and parameter values have been fixed, it is possible to obtain solutions as functions of time that are unique.

On the other hand, in stochastic models, there are transition probabilities at each step of moving from one population state to another. The same set of parameter values and initial conditions will lead to an ensemble of different output.

In simple deterministic models for epidemics, it is possible to obtain a precise threshold which allows to determines whether an epidemic will occur or will not occur. Instead, a stochastic model may lead, for instance, to probabilities that a disease would occur or can give informations as mean time of extinction. Thus the approach, concepts and appropriate questions are quite different for stochastic models.

Both deterministic and stochastic epidemiological models have other limitations besides being only approximations of reality. Obviously, the natural world is buffed by stochasticity. But, stochastic model are considerably more complicated.
Especially when the aim is to model a disease, deterministic models do not take into account the role of chance that the disease is subjected to. A set of initial conditions lead to exactly one solution in a deterministic model; thus no information is available on the reliability or the confidence in the results.

Through a sensitivity analysis, it is possible to understand the dependence of parameter values, by examining the effect of chance in a single parameter value on the final result. A parameter in a model is said to be sensitive if small changes in the parameter lead to big changes in the results.

On the other hand, these changes are embedded in stochastic models, but it is harder to get analytical results for these models. Moreover, computational results are also harder since simulations could require many computer runs in order to detect patterns and get quantitative results. Deterministic

model are rapid to simulate, relative easy to parametrize and capture the average of epidemic behaviour, i.e. they can be considered a valid tool for predictions in large populations. On the other hand, stochastic approches can be appropriate to model the spread of a disease in small populations, as well as in the early and final stage of an epidemic.

The mathematical models we will consider in this thesis are *deterministic compartmental models* at population level. When we want to analyse the spread of a disease in a population, we focus, not on the pathogen population, but on the number of infected individuals of the species involved in the transmission, neglecting the mechanism that make the single individual sick. This is because the time scale, at which the infection transmission between individuals occurs, is slower than the time scale of the dynamics of the pathogen invasion and growth within the individuals.

These type of model allow us to divide the entire population, involved in the transmission, into compartments that usually describe the infectious state (i.e. susceptible, infected, recovered individuals) and can also include other forms of classes involved in the disease control, for instance.
In the specific case of vector-borne disease both host and vector population are split into compartments of the infectious state.
One of the first and famous model of vector-borne disease is Ross-Macdonald model. In 1957 Macdonald (Macdonald et al. [1957]) combined a Ross model (Ross [1911]) with epidemiological and entomological field data to understand the malaria transmission. Several models have been published as a Ross-Macdonald model. Their model is based on the following assumptions:

- Total mosquito and human population sizes, V and H , are constant
- Mosquitoes can be susceptible or infectious, I
- Humans are either susceptible or infectious, Y
- no incubation periods
- The biting rate is proportional to the number of mosquitoes but independent of the number of humans

The previous assumptions translate in the following formulation (Anderson and May [1991]):

$$\dot{Y} = abI\left(\frac{H-Y}{H}\right) - \xi Y$$
$$\dot{I} = ac(V-I)\frac{Y}{H} - \delta I$$

where a represents the mosquito biting rate, b the mosquito to human transmission probability per bite, c the human to mosquito transmission probability per bite , ξ the human recovery rate and δ mosquito death rate.

A very important novelty introduced with this model has been the definition of the basic reproductive number R_0 for this type of models. The basic reproductive number is the average number of secondary infections that result if a single infectious individual is introduced into an entirely susceptible population and Ross [1911] defined it as

$$R_0 = R_0^{HV} R_0^{VH}$$

i.e. , the product of the number of humans infected by a mosquitoes and the number of mosquitoes infected by a person.

A systematic historical review suggests that several mathematicians and scientists contributed to development of the Ross-Macdonald model over a period of 70 years (Smith et al. [2012]). Several models have been proposed for malaria, including deterministic compartmental models (Anderson and May [1991], Aron and May [1982], Chitnis et al. [2006]) and stochastic (Dietz et al. [1974]) individual-based models (Eckhoff [2011], McKenzie et al. [2001]), while West Nile virus, that is the main object of this thesis, has been modelled by Thomas and Urena [2001], who formulated a difference equation model for West Nile virus, and Wonham et al. [2004] who, on the basis of the classical Ross-McDonald malaria model (Anderson and May [1991], Macdonald et al. [1957]), considered a system of ordinary differential equation modeling West Nile virus transmission in the mosquito and bird populations. Their study has been extended in several directions, such as the study of temporal mosquito bird cycle transmission of West Nile virus

(Cruz-Pacheco et al. [2005]) or heterogeneity in the competence of reservoir species (Simpson et al. [2012]) or also involving human and equine population in the model (Laperriere et al. [2011]).

Moreover, epidemiological mechanisms of vector-borne disease may lead to periodic solutions. Periodicity can arise in different ways, for example through extrinsic forcing by a model parameter, such as contact rate.
Aron and May [1982] examine the dynamical consequences of seasonal and other variations in the total mosquito population. Most mathematical models of vector-borne disease that include the effects of seasonality assume sinusoidal fluctuations in transmission coefficients or other parameters (Bacaër [2007], Bacaër and Guernaoui [2006], Chitnis et al. [2012]) Bacaër and Guernaoui [2006] developed a mathematical model of a vector-borne disease, in particular cutaneous leishmaniasis, to estimate some of the parameters of the transmission cycle and to estimate the classical epidemic threshold R_0. This specific study has led to a new general definition of the basic reproduction number R_0 in a periodic environment.

1.2.1 Semi-discrete models

Continuous-time and discrete-time models are the two most classical approaches to study biological phenomena. The first one is used overall when the populations involved are characterized by overlapping generations. When the interactions between compartments of a population happen randomly in time, the processes can be considered, from a macroscopic point of view, as continuous, and in general ordinary differential equation models are used to describe those connections. Examples of such system are the Lotka-Volterra predator–prey model, the Kermack-McKendrick susceptible-infected-removed (SIR) epidemic model.
These models are embedded in a continuous representation of the processes in which time and abundances of the populations are real valued and can take any value. Continuous-time models are useful because we can use the tools provided by calculus.

However some biological phenomena occur at certain time only or con-

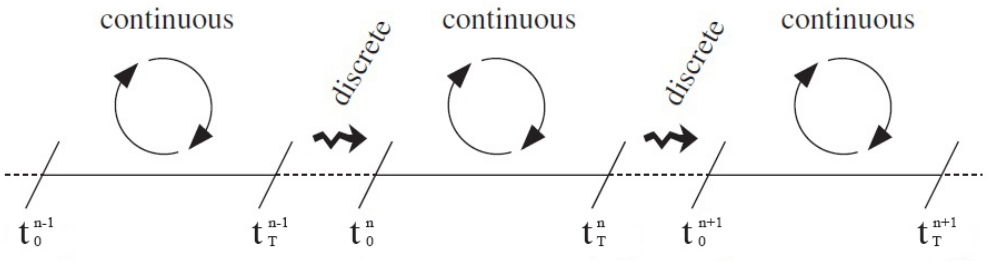


Figure 1.1: *Graphical representation of semi-discrete models*

centrated in a short time intervals, such as seasonal reproductions, egg deposition, vulnerability of some animals to attacks during a certain period of their life cycle only. Since 1970's discrete-time modeling has attracted more and more attention in population biology. These models were particularly developed by consumer-resource modeling community with respect to the host-parasitoid interaction (Murdoch et al. [2003]). Both modeling have a long history in biological sciences, however there are a lot of processes that cannot be thoroughly described with either formalism. In fact those processes can involved some phenomena that are of a continuous nature and some other that are of a discrete one. They undergo continuous dynamics most of the time, but at some given instants they are subjected to discrete changes, termed pulse too. For example, epidemiological systems with seasonal reproduction, emigration processes that start when the population reaches a density threshold, the survival of some insect that are strongly influenced by the season, are related to this particular class of phenomena. To build a suitable model, it is necessary to take into account both discrete and continuous parts. A system of ordinary differential equations describes the dynamics of this kind of processes during the continuous part. The discrete part, that occur at some given moments, is referred to as an 'impulsive' or 'pulsed' system.

These type of models are termed *semi-discrete models*. They are, as I stated before, a particular class of hybrid dynamical systems. In Figure 1.1, there is a schematic representation of the dynamics of the semi-discrete models.

Let x be the vector of state variables at time t and t_T be the instants when the discrete changes occur. The following system represents a semi-discrete model

$$\begin{cases} \dot{x}(t) = f(x,t) & x \neq t_0 \\ x(t_0^{n+1}) = F(x(t_T^n), t_T^n) \end{cases}$$

with t_0^{n+1} denoting the instant just after $t = t_T^n$. $f(\cdot)$ is the continuous ordinary differential equation followed by the system and $F(\cdot)$ is the discrete component (also termed the pulse or impulse) that may also depend on time. In general, $(t_T^{n+1} - t_T^n)$ is a constant for all n, but there are examples where it is not (Liu et al. [2005]).

An important part of the semi-discrete models are related to the seasonal processes. In these cases $(t_T^{n+1} - t_T^n)$ is in general equal to the length of the year or following season, at each instant t_T^n , time t is reset to zero and the state vector corresponding to the n^{th} year may be denoted with a subscript n on x.

The discrete part of the model may sum up what happens within a continuous period of time. There are many insects that are active and interact with other species during the summer, but are mainly resting in the winter. It is possible use a semi-discrete model to represent what happens during the summer with its continuous part and what happens during the winter with its discrete part (Ghosh and Pugliese [2004]). Hence, strictly speaking, in these cases actually, t_0^n is not always the instant just after t_T^{n-1}, but represent a jump from the number of insect at the end of the n^{th} summer to the number of those at the begin of the following summer. When epidemiological phenomena are seasonal influenced, especially in vector-borne disease, as in the cases we will deal with in this thesis, the initial condition of the ordinary differential equations that describe the dynamics during a season are given by a function of the size of the state variable at the end of the previous season.

1.2.2 Impulsive reaction-diffusion models

West Nile virus is a vector-borne disease transmitted by bite of infected mosquitoes that acquire the virus by feeding on infected birds. West Nile

virus is endemic in Africa, the Middle East and western Asia. In late August 1999 the first outbreak of West Nile in North America was reported in New York City. Over the next five years, the epidemic has spread spatially across the continental United States, north into Canada, and southwards into the Caribbean islands and Latin America. It seems that the spread of West Nile virus comes from the interaction of disease dynamics and bird and mosquito movement.

On the other hand, in Europe a different spatial diffusion can be observed. For example, 10 years after the first outbreak, West Nile virus reoccurred in Italy causing death and clinical signs in horses and humans (Calistri et al. [2010], Savini et al. [2008]). West Nile infection outbreaks were also reported in 2009. As in the previous year, the virus West Nile virus has been able to cause disease in horses and humans and, similarly, no birds fatalities were recorded. The infection re-occurred in the same places of the 2008 and moved westerly and southerly involving new areas and regions. Monaco et al. [2011]

From the previous example, it emerges that understanding the spread of vector borne diseases is of great importance to establish which measures might be effective before they are actually carried out.
Lewis et al. [2006] analyzed the spread of West Nile virus by spatially extending the non-spatial dynamical model of Wonham et al. [2004] to include diffusive movement of birds and mosquitoes. Instead in Liu et al. [2006], a mathematical model to understand the spatial spread patterns in the establishment phase of West Nile virus in a region consisting of multiple patches has been used. In the literature a large part of mathematical models on spread are proposed in terms of reaction-diffusion equations(Lewis et al. [2006]). Most reaction-diffusion epidemic models are space-dependent extensions of the classical Kermack-McKendrik model(Kermack and McKendrick [1927]). These types of model assume that the spreading is ruled by random diffusion and that dispersal and growth take place continuously in time and space. A reaction-diffusion equation consists of a reaction term and a diffusion term, i.e. the typical form is as follows:

$$u_t = D\Delta u + f(u)$$

where $u = u(x,t)$ is a state variable and describes density of the population at position $x \in \Omega \in R^n$ at time t (Ω is a open set). Δ denotes the Laplace operator. So the first term on the right hand side describes the "diffusion", including D as diffusion coefficient. The second term, $f(u)$ is a smooth function $f : R \to R$ and describes processes which really "change" the present u, i.e. something happens to it (birth, death ...), not just diffuse in the space.

Facing the study of the spatial spread of vector-borne disease, since the vector population are not active during a season and so the interaction between host and vector population occurs within another season, we can not consider a classical reaction-diffusion model, but we need to take into account both discrete and continuous components. Lewis and Li [2012] proposed a simple impulsive reaction-diffusion equation model to study the persistence and the spread of species with a reproductive stage and a dispersal stage in bounded and unbounded domains.

In the case of vector-borne diseases, it is possible to use this type of approach considering the extension of a non-spatial semi-discrete model to include diffusive movement of hosts and vectors.

The formulation will consist of a system of nonlinear reaction-diffusion equations for the disease transmission period and a discrete map describing the overwintering of the disease due to the survived infected vector.

Chapter 2

A simple semi-discrete model of a vector-borne disease

2.1 Introduction

Several vector-borne infections have emerged in recent years as diseases of considerable and widespread importance, principally among them Lyme disease and West Nile virus. According to the WHO, vector-borne disease constitute 17% of the estimated global amount of all infectious disease. Malaria, the most life-threatening vector-borne disease is caused by a parasite *plasmodium*, transmitted via infected mosquitoes. It is estimated that in 2012 Malaria caused 627.000 deaths.(WHO [2014])

The basic reproductive number R_0 is the average number of secondary infections that result if a single infectious individual is introduced into an entirely susceptible population. It seems immediately clear that $R_0 < 1$ means that every infected individual can spawn less than one new infected individual, and it is possible to predict that the infection will disappear from the population. When $R_0 > 1$, the infection is able to invade the susceptible population and the disease can persist and increase .
The analysis of this threshold is an extremely important and useful aspect in studying a disease. It allows us to determine which control measures (how and when to apply them) would be most effective in reducing R_0 below one.

In 1957 Macdonald (Macdonald et al. [1957]) combined a Ross model (Ross [1911]) with epidemiological and entomological field data to understand the malaria transmission. The Ross-MacDonald model is the earliest and also simplest mathematical model describing a mosquito-borne infection transmission between host and vector populations.
Ross introduced the definition of R_0 for malaria as the product of the number of humans infected by a mosquitoes and the number of mosquitoes infected by a person.

Following the earlier attempt in Heesterbeek and Roberts [1995], a general definition of the basic reproduction number for a vector-borne disease in a periodic environment is presented in Bacaër and Guernaoui [2006] and in Bacaër [2007]. Then also Wang and Zhao [2008] established the basic reproduction ratio for a large class of periodic compartmental epidemic models.

In this chapter, we consider an extreme form of seasonality consisting in two discrete distinct seasons, summer and winter; furthermore, for the sake of simplicity, we assume that all the parameters, including population sizes of host and vector population, are constant during the summer season. The infection dynamics is assumed to be of SI type for the vectors and SIS or SIR for the hosts. In both cases, we obtain a threshold parameter S_0, easily computable, that determines, similarly to the parameter R_0 of Bacaër and Guernaoui [2006], whether the infection will persist or not over the years. A complete description of the global behavior of the infection has been obtained for the SI-SIS case; for the SI-SIR case, no analytical results exist on the infection behavior above the threshold, and we present simulations of some illustrative instances.

The threshold S_0 has been explicitly compared to the definition of R_0 in Bacaër and Guernaoui [2006], showing that they share, as expected, the threshold property, but identifying also their differences. The assumption of distinct seasons allows for a simpler analysis, by making it possible to reduce, at least in principle, the problem to a discrete one. While we have analyzed very simple (perhaps simplistic) cases, it is possible to apply the same ideas to more realistic models involving, for instance, multiple hosts and the relative feeding preference of the vector, the different stages in the

life cycle of the mosquitoes, and also allowing for parameters to vary within a season.

2.2 An SIS model

We construct a semi-discrete model (Mailleret and Lemesle [2009]) using a SIS epidemiological framework to model the enzootic transmission in a host population with a single vector population. The model incorporates the infection transmission between a vector and a generic host population.

A semi-discrete model represents what happens during the summer with its continuous part, when the vector population is active and interacts with other species; what happens during the winter, in this case the survival of a proportion of the individuals, is represented with its discrete part (Mailleret and Lemesle [2009]).

Transmission occurs as a continuous process during summer while in winter there is no transmission and the infection persists only because of surviving infected vectors. To simplify the analysis, we make strong assumptions about the two populations during the summer season: we suppose that the total vector and host populations are constant during the summer and they have the same size every year. So H represents the population of host and V the vector population, they satisfy:

$$\begin{cases} \dot{H}(t) = \Lambda_H - \mu_H H(t) \\ \dot{V}(t) = \Lambda_V - \mu_V V(t) \end{cases}$$

where Λ_i is the recruitment rate and μ_i the death rate related to host $(i = H)$ or vector $(i = V)$ population.

These assumptions translate into the following model. We divide the years in two periods: one (named $(0, T)$) during which infection transmission occurs due to mosquitoes being active. A second period $(T, 1)$ (having chosen 1 year as the time unit) where no infections occur. In n^{th} summer, the variables S_h^n, I_h^n, S_v^n and I_v^n represent the densities of susceptible and infected hosts and vectors at time $t \in [0, T]$.

They satisfy the following system of differential equations:

$$\begin{cases} \dot{S}_h^n(t) = \Lambda_H + \gamma_H I_h^n(t) - \mu_H S_h^n(t) - \frac{\alpha\beta_H}{N_H} I_v^n(t) S_h^n(t) \\ \dot{I}_h^n(t) = \frac{\alpha\beta_H}{N_H} I_v^n(t) S_h^n(t) - \gamma_H I_h^n(t) - \mu_H I_h^n(t) \\ \dot{S}_v^n(t) = \Lambda_V - \mu_V S_v^n(t) - \frac{\alpha\beta_V}{N_H} I_h^n(t) S_v^n(t) \\ \dot{I}_v^n(t) = \frac{\alpha\beta_V}{N_H} I_h^n(t) S_v^n(t) - \mu_V I_v^n(t) \end{cases} \tag{2.2.1}$$

where γ_H is the rate at which the infected hosts recover and become susceptible again. Instead, due to its short life, a vector never recovers from the infection.

We assume that the biting rate α is constant and equal for each type of host. The transmission probability is the probability that an infected individual produces a new case in a susceptible member of the other species. The transmission probabilities from vectors to hosts and from hosts to vectors are denoted by β_H and β_V, respectively. This system of equation will hold for each summer season $n = 1, 2, \ldots$. To these equations, we associate initial conditions, depending on the previous year variables; to be precise:

$$\begin{cases} S_h^n(0) = N_H \\ I_h^n(0) = 0 \\ S_v^n(0) = N_V - \delta I_v^{n-1}(T) \\ I_v^n(0) = \delta I_v^{n-1}(T) \end{cases} \tag{2.2.2}$$

where $S_h + I_h = N_H = \frac{\Lambda_H}{\mu_H}$ is the constant number of hosts during the summer. They are assumed to be all susceptibles, in fact those infected, that have survived at the end of the previous year, will have recovered from infection because of the short infection period (Simpson et al. [2012]).
$S_v + I_v = N_V = \frac{\Lambda_V}{\mu_V}$ is the total population size of the vectors, which is constant in the considered period. Here δ is the probability of infected vectors to survive the winter.

The first orthant in the S_h, I_h, S_v, I_v space is positively invariant for system (2.2.1) since the vector field on the boundary does not point to the

exterior. Furthermore, since $S_h + I_h = N_H$, and $S_v + I_v = N_V$ are constant, all trajectories in the first orthant enter or stay inside the region

$$T_+ = \{S_h + I_h = N_H, Sv + Iv = N_V\}$$

In order to simplify the system, we normalize host and vector population through the following substitutions

$$s_H = \frac{S_h}{N_H},\ i_H = \frac{I_h}{N_H},\ s_V = \frac{S_v}{N_V} \text{ and } i_V = \frac{I_v}{N_V}$$

In the next system, s_H and i_H represent the fraction of susceptible and infected hosts and s_V and i_V will be the fraction of susceptible and infected vectors.

$$\begin{cases} \dot{s}_H^n = \mu_H + \gamma_H i_H^n - \mu_H s_H^n - \alpha\beta_H \frac{N_V}{N_H} s_H^n i_V^n, & s_H(0) = 1 \\ \dot{i}_H^n = \alpha\beta_H \frac{N_V}{N_H} s_H^n i_V^n - \gamma_H i_H^n - \mu_H i_H^n, & i_H(0) = 0 \\ \dot{s}_V^n = \mu_V - \mu_V s_V^n - \alpha\beta_V i_H^n s_V^n, & s_V^n(0) = 1 - \delta i_V^{n-1}(T) \\ \dot{i}_V^n = \alpha\beta_V i_H^n s_V^n - \mu_V i_V^n, & i_V^n(0) = \delta i_V^{n-1}(T) \end{cases} \tag{2.2.3}$$

From the previous assumptions about the vector and host populations, it follows that the total vector and host populations are constant and in the normalized system, we obtain $s_H + i_H = 1$ and $s_V + i_V = 1$.

Last remark allows us to reduce the model, obtaining

$$\begin{cases} \dot{i}_H^n = \alpha\beta_H \frac{N_V}{N_H}(1 - i_H^n) i_V^n - (\gamma_H + \mu_H) i_H^n, & i_H(0) = 0 \\ \dot{i}_V^n = \alpha\beta_V i_H^n (1 - i_V^n) - \mu_V i_V^n, & i_V^n(0) = \delta i_V^{n-1}(T) \end{cases} \tag{2.2.4}$$

Furthermore we can also write the isoclines of the model in the following way

$$\begin{aligned} i_H(i_V) &= \frac{\mu_V}{\alpha\beta_V} \frac{i_V}{1 - i_V}; \\ i_V(i_H) &= \frac{(\gamma + \mu_H)}{\alpha\beta_H} \frac{N_H}{N_V} \frac{i_H}{1 - i_H}; \end{aligned}$$

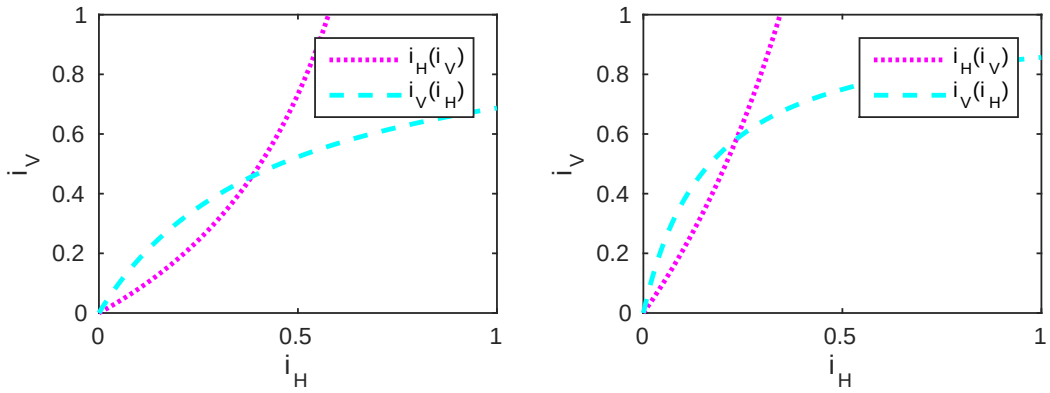


Figure 2.1: *Examples of isoclines of model 2.2.3 with different values of parameters*

2.2.1 A short-term threshold R

We wish to evaluate a threshold R for the spread of the disease taking into account only the active season. R represents the number of new cases that one infected individual produces in a completely susceptible population in a host-vector system. According to Van den Driessche and Watmough [2002], by linearizing system (2.2.3) in the disease free equilibrium $x^* = (1, 0, 1, 0)$ at the beginning of the active season, we obtain

$$\Delta = \begin{pmatrix} 0 & \alpha\beta_H \frac{N_V}{N_H} \\ \alpha\beta_V & 0 \end{pmatrix} \qquad \Gamma = \begin{pmatrix} \gamma_H + \mu_H & 0 \\ 0 & \mu_V \end{pmatrix} \tag{2.2.5}$$

with Δ nonsingular. Thus, the basic reproduction number for a vector-host system with constant coefficients is

$$R = \alpha \sqrt{\frac{N_V}{N_H} \frac{\beta_H \beta_V}{\mu_V(\gamma_H + \mu_H)}}$$

Near the disease free equilibrium, each infected host produces $\alpha\beta_V/\mu_V$ new infected vectors over its expected infectious period, and each infected vector produces $\alpha\beta_H N_V/(\gamma_H + \mu_H)N_H$ new infected hosts over its expected infectious period. The square root arises from the two 'generations' required for an infected vector or host to 'reproduce' itself.

2.2.2 S_0: A long-term threshold quantity

The short-term R, presented in the previous section, is the number of new infected introduced by one infected individual. This does not take winters into account however.
We will define S_0 as the average number of infected vectors produced at the start of the following year by a vector that is infected at the start of the year. Let us consider system (2.2.4), from the initial condition we have that

$$i_V^n(0) = \delta i_V^{n-1}(T)$$

Since $s_H(t) + i_H(t) = 1$ and $s_V(t) + i_V(t) = 1$, $i_V^{n-1}(T)$ can be seen as a function of initial data $i_H^{n-1}(0)$ and $i_V^{n-1}(0)$, but $i^{n-1}(0)$ is fixed, so it depends only on $i_V^{n-1}(0)$. Hence, we can define $F : \mathbb{R} \to \mathbb{R}$

$$F(i_V^n(0)) = i_V^n(T, i_V^n(0)) \tag{2.2.6}$$

and write the initial condition of the following season by

$$i_V^n(0) = \delta F(i_V^{n-1}(0)) \tag{2.2.7}$$

This can be seen as a discrete dynamical system in the variables

$$\{i_V^n(0), n \in \mathbb{N}\}$$

.
The following theorem is well known

Theorem 1. *Let $G : \mathbb{R}^k \to \mathbb{R}^k$ and $\bar{x}$ be an equilibrium of $N_{n+1} = G(N_n)$. Then*

- *If $\rho(DG(\bar{x})) < 1$ then $\bar{x}$ is asymptotically stable*
- *If $\rho(DG(\bar{x})) > 1$ then $\bar{x}$ is unstable*

with ρ the dominant eigenvalue.

We can consider the case $k = 1$ when $\rho(DG(\bar{x}))$ corresponds to $|G'(\bar{x})|$.
Now we define $S_0 := \delta F'(0)$ and apply Theorem 1 to (2.2.7) with $G(x) = \delta F(x)$.
If $S_0 < 1$, $i_V^n(0) \equiv 0$, i.e. the disease free equilibrium of (2.2.3) is asymptotically stable. If $S_0 > 1$ it is unstable.
It is possible to provide a biological interpretation of S_0: if $\tilde{i_V}$ infected vectors are introduced at the beginning of a season, they will produce $\delta F(\tilde{i_V})$ infected vector at beginning of the next season.
If $\tilde{i_V} \approx 0$, $F(\tilde{i_V}) = F'(0)\tilde{i_V}$ and we can say that each infected vectors produces on average $\delta F'(0)$ infected vectors at the beginning of the next year.
Below we compute explicitly S_0 in simple cases. In the following section we will analyze the global behaviour of (2.2.7).
In order to compute $F'(0)$, we use the equation of variation (Hartman [1964]) to compute the derivative of the solution of the system (2.2.4) with respect to the initial value $i_V(0)$. Let indeed $i_V(0) = Q$ and $w = \frac{\partial i_H}{\partial Q}$ and $z = \frac{\partial i_V}{\partial Q}$; they satisfy

$$\begin{cases} \dot{w} = \alpha\beta_H \frac{N_V}{N_H}(1-w)i_V - \alpha\beta_H \frac{N_V}{N_H}(1-i_H)z - (\gamma_H + \mu_H)w & w(0) = 0 \\ \dot{z} = \alpha\beta_V(1-z)i_H + \alpha\beta_V(1-i_V)w - \mu_V z & z(0) = 1 \end{cases} \tag{2.2.8}$$

i.e,

$$\begin{pmatrix} \dot{w} \\ \dot{z} \end{pmatrix} = M(t) \begin{pmatrix} w \\ z \end{pmatrix} \tag{2.2.9}$$

with

$$M(t) = \begin{pmatrix} -\alpha\beta_H \frac{N_V}{N_H} i_V(t) - (\gamma_H + \mu_H) & \alpha\beta_H \frac{N_V}{N_H}(1 - i_H(t)) \\ \alpha\beta_V(1 - i_V(t)) & -(\alpha\beta_V i_V(t) + \mu_H) \end{pmatrix}$$

where $i_H(t)$ and $i_V(t)$ are the solutions of the system (2.2.4) with $i_H(0) = 0$ and $i_V(0) = Q$.
With the aim to compute S_0, we set $Q = 0$ obtaining $i_H(t) = i_V(t) = 0$.

Then, evaluating the system (2.2.9), we obtain the following linearized system

$$\begin{pmatrix} \dot{w} \\ \dot{z} \end{pmatrix} = \begin{pmatrix} -(\gamma_H + \mu_H) & \alpha\beta_H \frac{N_V}{N_H} \\ \alpha\beta_V & -\mu_V \end{pmatrix} \begin{pmatrix} w \\ z \end{pmatrix}$$

i.e.

$$\begin{cases} w' = -(\gamma_H + \mu_H)w + \alpha\beta_H \frac{N_V}{N_H} z & w(0) = 0 \\ z' = \alpha\beta_V w - \mu_V z & z(0) = 1 \end{cases} \tag{2.2.10}$$

We have thus obtained $S_0 = \delta F'(0) = \delta z(T)$, z solution of (2.2.10)

2.2.3 Global behaviour

In the previous section, we computed S_0 defining $F(i_V(0))$ as (2.2.6). Now we can use the following theorem:

Theorem 2. *Let $G : [0,1] \to [0,1]$ an increasing and concave function, such that $G(0) = 0$. Consider the system $N_{n+1} = G(N_n)$*
If $G'(0) \leq 1$, the disease free equilibrium is globally attractive.
If $G'(0) \geq 1$, there exists a unique equilibrium point $\hat{x}$ that is globally attractive.

We wish to apply this result to system (2.2.7). First of all, we have that

$$F'(Q) = z(T)$$

shown in system (2.2.9). Looking at this system, we can observe that the matrix M has nonnegative off-diagonal terms, hence for Corollary 1 of (Hirsch and Smith [2003]) the fundamental matrix $U_M(t,s) \geq 0$ and so we have

$$\begin{pmatrix} w \\ z \end{pmatrix}(t) = U_M(t,s) \begin{pmatrix} 0 \\ 1 \end{pmatrix} \geq 0$$

And so, $w(t) \geq 0$ and also $z(t) \geq 0$. F is defined in (2.2.6) and maps $[0,1]$ into $[0,1]$ as $i_V(t)$, defined through (2.2.3) and knowing that $s_V + i_V = 1$, satisfies $0 \leq i_V(t) \leq 1$. Hence, as $\delta \leq 1$, $G(1) = \delta F(1) \leq \delta \leq 1$.

To prove the concavity, we need to compute the derivatives of $w = \dfrac{\partial i_H}{\partial Q}$ and $z = \dfrac{\partial i_V}{\partial Q}$. Let $u = \dfrac{\partial^2 i_H}{\partial Q^2}$ and $v = \dfrac{\partial^2 i_V}{\partial Q^2}$, where i_H, i_V are the solution functions of system (2.2.3): $F''(Q) = v(T)$. By differentiating system (2.2.3) once, we obtained (2.2.8). If we differentiate with respect to Q once again, we obtain

$$\begin{pmatrix} \dot{u} \\ \dot{v} \end{pmatrix} = M \begin{pmatrix} u \\ v \end{pmatrix} - 2wz \begin{pmatrix} \alpha\beta_H \frac{N_V}{N_H} \\ \alpha\beta_V \end{pmatrix} \tag{2.2.11}$$

with $u(0) = v(0) = 0$.
Its solution is

$$\begin{pmatrix} u \\ v \end{pmatrix}(t) = -2 \int_0^t U_M(t,s) \begin{pmatrix} \alpha\beta_H \frac{N_V}{N_H} \\ \alpha\beta_V \end{pmatrix} w(s)z(s)ds$$

This expression is non positive, because $w(s), z(s) \geq 0$ and also the fundamental matrix of system (2.2.3) is nonnegative, i.e. $U_M(t,s) \geq 0$. Hence F is concave. The hypothesis of Theorem 2 hold.

Summarizing, if $S_0 < 1$ the disease free equilibrium is locally stable and also globally attractive. If $S_0 > 1$ the disease free equilibrium is locally unstable and there is an endemic equilibrium that is globally attractive.

2.3 SIR model

In this chapter we assume, more realistically for infections like West Nile virus, that the recovered hosts become permanently immune instead of becoming susceptible again; hence the model for the host infection becomes SIR. The immune hosts at the beginning of the summer season are the hosts that were immune or infected at the end of the previous season and that survived winter (again we assume that the hosts recover over the winter season).

These assumptions translate into the following model. In summer n, the variables $S_h^n, I_h^n, R_h^n, S_v^n$ and I_v^n(densities of susceptible, infected and recovered hosts and vectors time t of summer n) satisfy the system of differential

equations:

$$\begin{cases} \dot{S}_h^n(t) &= \Lambda_H - \mu_H S_h^n(t) - \alpha\beta_H S_h^n(t) I_v^n(t) \\ \dot{I}_h^n(t) &= \alpha\beta_V S_h^n(t) I_v^n(t) - \gamma_H I_h^n(t) - \mu_H I_h^n(t) \\ \dot{R}_h^n(t) &= \gamma_H I_h^n(t) - \mu_H R_h(t) \\ \dot{S}_v^n(t) &= \Lambda_V - \mu_v S_v^n(t) - \alpha\beta_V I_h^n(t) S_v^n(t) \\ \dot{I}_v^n(t) &= \alpha\beta_V I_h^n(t) S_v^n(t) - \mu_V I_v^n(t) \end{cases} \tag{2.3.1}$$

with initial conditions

$$\begin{cases} S_h^n(0) &= N_H - R_h^n(0) \\ I_h^n(0) &= 0 \\ R_h^n(0) &= \rho(R_h^{n-1}(T) + I_h^{n-1}(T)) \\ S_v^n(0) &= N_V - \delta I_v^{n-1}(T) \\ I_v^n(0) &= \delta I_v^{n-1}(T) \end{cases} \tag{2.3.2}$$

where $S_h + I_h + R_h = N_H = \frac{\Lambda_H}{\mu_H}$ is the constant number of host during the summer. They are assumed to be all susceptibles or immune, in fact those infected, that have survived at the end of the previous year, will have recovered from infection because of the short infection period (Simpson et al. [2012]).
$S_v + I_v = N_V = \frac{\Lambda_V}{\mu_V}$ is the total population size of the vectors, which is constant in the considered period. Here δ is the probability of infected vectors to survive the winter and ρ is the survival probability of host. All other parameters have the same meaning as in the SIS model. We normalize the model and reduce the model, obtaining

$$\begin{cases} \dot{i}_H^n = \alpha\beta_H \frac{N_V}{N_H}(1 - i_H^n - r_H^n) i_V^n - (\gamma_H + \mu_H) i_H^n, \\ \dot{r}_H^n = \gamma_H i_H^n - \mu_H i_H^n, \\ \dot{i}_V^n = \alpha\beta_V i_H^n (1 - i_V^n) - \mu_V i_V^n, \end{cases} \tag{2.3.3}$$

with the following initial conditions

$$\begin{aligned} i_H(0) &= 0 \\ r_H(0) &= \rho(i_H^{n-1}(T) + r_H^{n-1}(T)) \\ i_V^n(0) &= \delta i_V^{n-1}(T) \end{aligned}$$

where i_H and r_H represent the fraction of infected and immune hosts and i_V the fraction of infected vectors.

2.3.1 S_0: The long-term threshold quantity

In this case, to define S_0 we consider system (2.3.3). The initial conditions can be written as

$$\begin{aligned} i_V^n(0) &= \delta i_V^{n-1}(\tau, i_V^{n-1}(0), r_H^{n-1}(0)) \\ r_H^n(0) &= \rho(r_H^{n-1}(\tau, i_V^{n-1}(0), r_H^{n-1}(0)) + r_H^{n-1}(\tau, i_V^{n-1}(0), r_H^{n-1}(0)) \end{aligned}$$

emphasizing the dependence on initial data $i_V^{n-1}(0)$ and $r_H^{n-1}(0)$.
We can define

$$\mathbf{G}(i_V^{n-1}(0), r_H^{n-1}) = (G_1(i_V^{n-1}(0), r_H^{n-1}), G_2(i_V^{n-1}(0), r_H^{n-1}))$$

where

$$G_1(i_V^n(0), r_H^n(0)) = \delta i_V^n(\tau, i_V^n(0), r_H^n(0)) \tag{2.3.4}$$

$$G_2(i_V^n(0), r_H^n(0)) = \rho(x_I^n(\tau, i_V^n(0), r_H^n(0)) + x_r^n(\tau, i_V^n(0), r_H^n(0)) \tag{2.3.5}$$

And so we have that

$$\begin{pmatrix} i_V^n \\ r_H^n \end{pmatrix}(0) = \mathbf{G}(i_V^{n-1}(0), r_H^{n-1}(0)) \tag{2.3.6}$$

Let us fix $i_V^n(0) = Q$ and $r_H^n(0) = R$.
Let us define S_0 as the dominant eigenvalue of the matrix

$$J_{long} = \begin{pmatrix} \frac{\partial G_1}{\partial Q} & \frac{\partial G_1}{\partial R} \\ \frac{\partial G_2}{\partial Q} & \frac{\partial G_2}{\partial R} \end{pmatrix}$$

where the derivatives are computed at $(0, 0)$.
Using Theorem 1, we have that if $S_0 < 1$, $(0, 0)$ is asymptotically stable for system (2.3.6); if $S_0 > 1$ it is unstable. Furthermore it is not difficult to prove that, when $S_0 > 1$, (2.3.6) has a unique positive equilibrium
In Appendix A, it is proved that $\frac{\partial G_1}{\partial R} = 0$, so that the dominant eigenvalue is the largest value on the principal diagonal. Moreover $\frac{\partial G_2}{\partial R} < 1$, hence $S_0 \geq 1 \Leftrightarrow \frac{\partial G_1}{\partial Q} \geq 1$: in this case $S_0 = \frac{\partial G_1}{\partial Q}$. It is also shown that $\dfrac{\partial G_1}{\partial Q} = \delta z(T)$ with z solution of (2.2.10).
Hence, S_0 is identical to the vaalue obtained in the SIS model.

2.4 Comparing the R_0 definition of Bacaër

Let suppose that we have the system

$$p'(t) = (A(t) + B(t))p(t) \quad \texttt{in} \ \mathbb{R}^n \tag{2.4.1}$$

with $A(t)$ and $B(t)$ T-periodic matrices, where $A(t)$ represents new infections and $B(t)$ other transitions, including death. Assume that $A(t)$ is nonnegative for all t and that the off-diagonal elements of $B(t)$ are non negative. U_B is the fundamental matrix relative to the system $q'(t) = B(t)q(t)$. Assume furthermore $|U_B(t, t-s)| \leq e^{-\mu s}$. For more details, see *Example 1* of (Bacaër et al. [2012, Sec.3]).

R_0 can be defined (Bacaër [2007], Bacaër and Guernaoui [2006]) as the spectral radius of the operator

$$L : p(t) \to \int_0^\infty A(t)U_B(t, t-s)p(t-s)ds$$

on the space of continuous T-periodic functions. From Bacaër et al. [2012, Sec.3], this integral converges.
An alternative characterization of R_0 that may be simpler in some cases is

that R_0 is the number such that

$$\rho(U_{\frac{A}{R_0}+B}(T)) = 1.$$

In fact Wang and Zhao [2008] in Theorem 2.2 show that

$$R_0 = 1 \Leftrightarrow \rho(U_{A+B}(T)) = 1, \tag{2.4.2}$$

Let us define now the operator $\hat{L}$ as

$$\hat{L} : p(t) \to \int_0^\infty \frac{A}{R_0}(t) U_B(t, t-s) p(t-s) ds;$$

clearly $\rho(\hat{L}) = 1$ and from (2.4.2), we obtain $\rho(U_{\frac{A}{R_0}+B}(T)) = 1$ i.e., the required condition.

Now, comparing the definition by Bacaër [2007] with our results, we observe that

$$x^n(t) := x(nT + t) \text{ and } y^n(t) := y(nT + t)$$

where x and y represent the host ad vector populations in the following system, obtained by reducing system (2.2.3)

$$\begin{cases} \dot{x}^n = \alpha\beta_H \frac{N_V}{N_H}(1 - x^n)y^n - \gamma_H x^n - \mu_H x^n, & x^n(0) = 0 \\ \dot{y}^n = \alpha\beta_V x^n(1 - y^n) - \mu_V y^n, & y^n(0) = \delta y^{n-1}(T). \end{cases} \tag{2.4.3}$$

We see that the system can be written as the limiting case of

$$\begin{pmatrix} x \\ y \end{pmatrix}' = (\Delta - \Gamma_s) \begin{pmatrix} x \\ y \end{pmatrix} \qquad in \ \ [0, T]$$

$$\begin{pmatrix} x \\ y \end{pmatrix}' = -\Gamma_w \begin{pmatrix} x \\ y \end{pmatrix} \qquad in \ \ [T, 1]$$

where $\Gamma_s = \Gamma$ is defined in (2.2.5) as well as Δ, Γ_w represents instead the

transition matrix during the winter as

$$\Gamma_w = \begin{pmatrix} \delta_x & 0 \\ 0 & -\frac{log(\delta)}{1-T} \end{pmatrix}$$

and we consider the limit as $\delta_x \to \infty$
Hence (2.4.3) is reduced to (2.4.1) with

$$A(t) = \begin{cases} \Delta & 0 \leq t - [t] < T \\ 0 & T \leq t - [t] < 1 \end{cases}$$

and

$$B(t) = \begin{cases} -\Gamma_s & 0 \leq t - [t] < T \\ -\Gamma_w & T \leq t - [t] < 1 \end{cases}$$

Using the theorem above, we can obtain R_0 by computing $\rho(\hat{L}) = 1$ with these matrices. Observing that for $\delta_x \to \infty$, $e^{\Gamma_w(1-T)} = \begin{pmatrix} 0 & 0 \\ 0 & \delta \end{pmatrix}$, the fundamental matrix of the system in the total period 1 is

$$U_{\frac{A}{R_0}+B}(1) = \begin{pmatrix} 0 & 0 \\ 0 & \delta \end{pmatrix} U_{\frac{A}{R_0}+B}(T)$$

so that

$$1 = \rho(U_{\frac{A}{R_0}+B}(1)) = \delta(U_{\frac{A}{R_0}+B}(T))_{22}.$$

On the other hand, if we compute S_0 as above, we obtain

$$S_0 = \delta(U_{A+B}(T)_{22}).$$

We then see that S_0 is generally a different quantity than R_0 except when both are equal to 1. Indeed we observe that

$$S_0 \geq 1 \Leftrightarrow R_0 \geq 1$$

$$S_0 \leq 1 \Leftrightarrow R_0 \leq 1.$$

S_0 can be considered as a threshold quantity as well as R_0, but is more easily computable.

2.5 Some simulations

In this section, we present some numerical solutions of the model (2.2.3) and (2.3.3). The simulations were performed mostly using values similar to those used by Simpson et al. [2012] for West Nile Virus that have units per day. Figures 2.2 and 2.3 represent the dynamics of infected hosts and infected vectors in two simulations of the SIS model.

Parameter	Definition	Value
γ_H	recovery rate of the host	[0.195-0.091]
μ_H	death rate of the host	0.0014
μ_V	death rate of the vector	0.1
β_H	transmission probability from vectors to hostse	0.44
β_V	transmission probability from hosts to vectors	0.974
α	biting rate	0.14
$\frac{N_V}{N_H}$	proportion of vector/host populations	
δ	survival probability of vector summer-winter	
ρ	survival probability of the host summer-winter	

Table 2.1: *Many symbols and numerical values used in simulations (rates have units per day)*

We maintained the short-term threshold greater than 1, hence the infection initially increases; then, varying the vector survival probability during the winter, we considered cases with $S_0 < 1$ or > 1.
In Figure 2.3 the disease from the second year seems to decrease but then to reach a stable level for many years with $S_0 = 1.35$. In Figure 2.2, S_0 is less than 1, namely $S_0 = 0.13$. In this case the infection is present for a few years before disappearing completely.
Then, since that we are dealing with vector-borne disease in general, we try to change some parameters. As an example, we set $\beta_H = 0.14$; $\beta_V = 0.374$; $\frac{N_V}{N_H} = 60$, differently from what we did to obtain the simulations in Figure 2.2 and 2.3 where we use $\frac{N_V}{N_H} = 7$. We obtained the pattern showed in Figure 2.4.

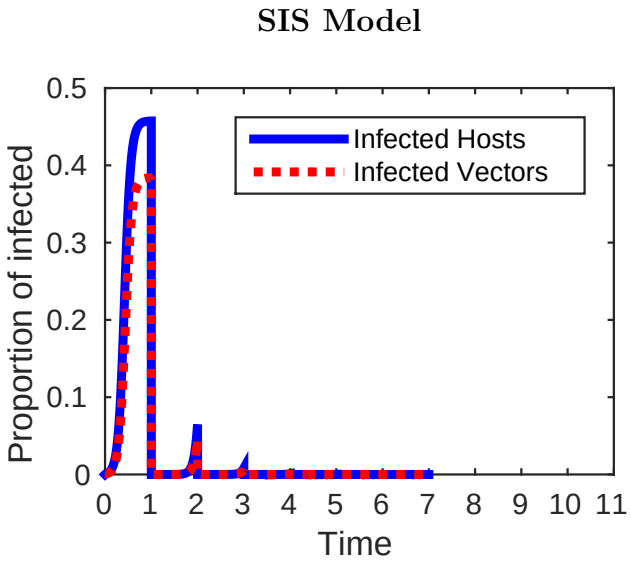


Figure 2.2: *A numerical solution of model SIS with parameters* $\delta = 8 * 10^{-8}$*;* $R = 1.73$,$S_0 = 0.135$. *In blue are the infected hosts, in red are the infected vectors*

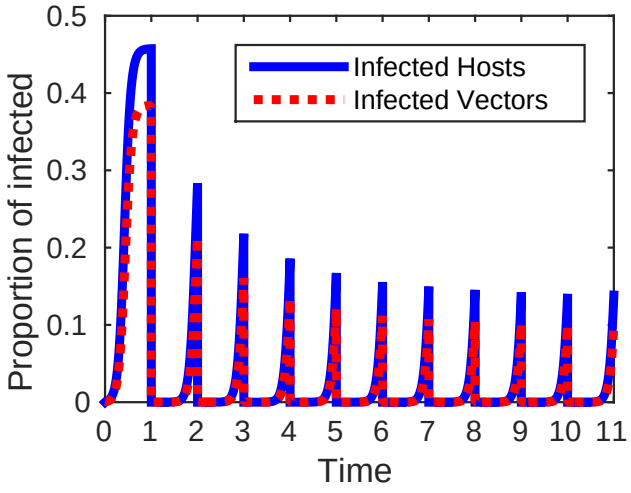


Figure 2.3: *A numerical solution of model SIS with parameters* $\delta = 8 * 10^{-7}$*;* $R = 1.73$*;* $S_0 = 1.35$. *In blue are the infected hosts, in red are the infected vectors*

Simulations of the SIR model are presented in Figures 2.5 and 2.6. In the first one, with a small S_0 ($S_0 = 0.135$) the infected essentially disappear from the second year. Also in Figure 2.6, with $S_0 = 2.35$, we observe that the infection considerably decreases, but not disappear. On the other hand,

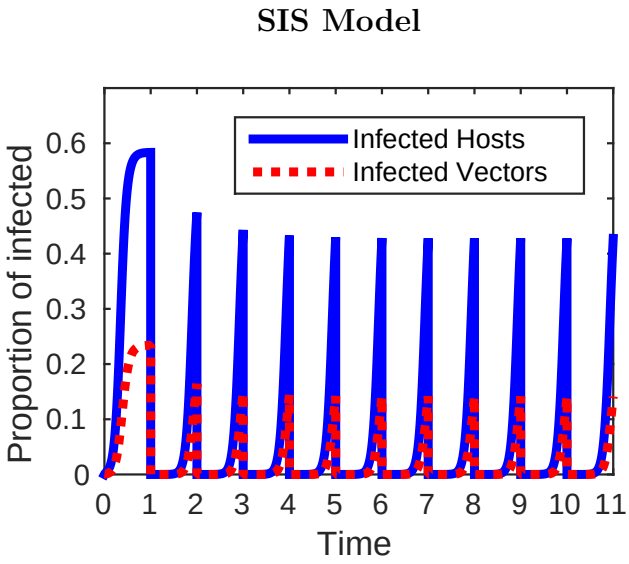


Figure 2.4: *A numerical solution of model SIS with parameters* $\delta = 8 * 10^{-7}$*;* $\beta_H = 0.14$*;* $\beta_V = 0.374$*;* $\frac{N_V}{N_H} = 60$*;* $R_0 = 1.77$*;* $S_0 = 3.09$*. In blue are the infected hosts, in red are the infected vectors*

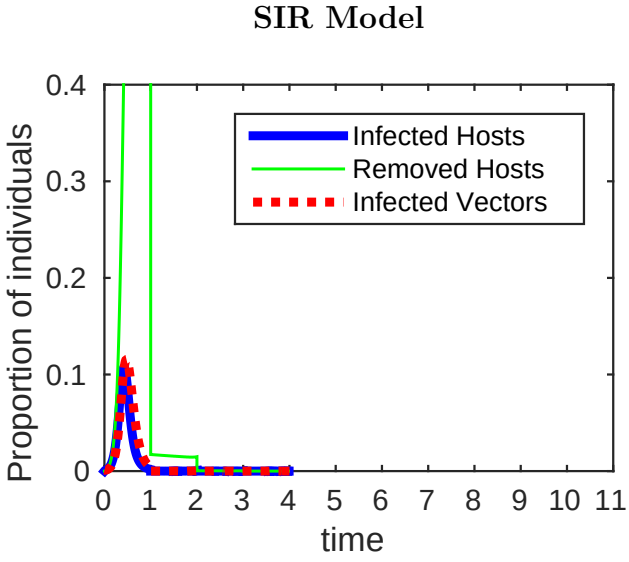


Figure 2.5: *A numerical solution of model SIR with parameters* $\delta = 8 * 10^{-8}$*;* $\rho = 0.02$*;* $R_0 = 1.73$*;* $S_0 = 0.135$*. In blue are the infected hosts, in green are the removed hosts, in red line are the infected vectors*

when we ran the model with the same parameters that we used to plot the simulation showed in Figure 2.7, we obtained a third pattern. The disease seems to vanish in the second year. But after several years the infection

spreads again, apparently reaching a stationary state

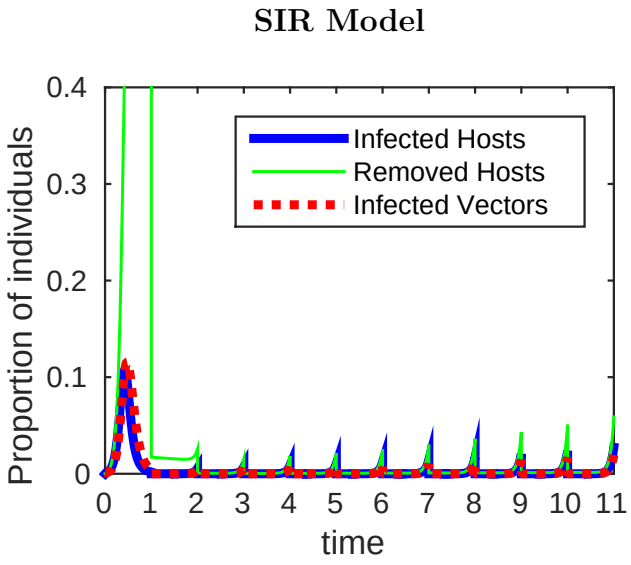


Figure 2.6: *A numerical solution of model SIR with parameters* $\delta = 8 * 10^{-7}$*;* $\rho = 0.02$*;* $R_0 = 1.73$*;* $S_0 = 1.35$ *In blue are the infected host, in green are the removed host, in red line are the infected vectors*

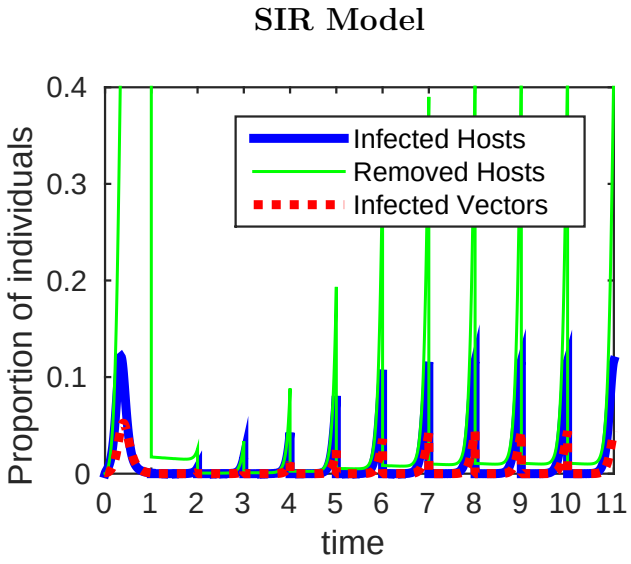


Figure 2.7: *A numerical solution of model SIR with parameters* $\delta = 8 * 10^{-7}$*;* $\rho = 0.02$*;* $\beta_H = 0.14$*;* $\beta_V = 0.374$*;* $\frac{N_V}{N_H} = 60$*;* $R_0 = 1.77$*;* $S_0 = 3.09$*. In blue are the infected host, in green are the removed host, in red line are the infected vectors*

2.6 Discussion

The aim of this chapter was to formulate a model for a vector-borne disease considering the seasonality of the vector population. We consider an extreme form of seasonality consisting in two distinct season: summer and winter. We started from an SIS model that is not realistic for almost every vector-borne disease, but is simpler to analyze.

We supposed that both populations involved in the transmission are constant, although it is known for example, (see for example Cruz-Pacheco et al. [2009]), that often mosquito populations, responsible of the transmission of many vector borne disease, considerably increase at the end of the summer. Persistence of infection through winter is ensured in the model by overwintering vectors. The main result obtained has been the computation of a threshold quantity (S_0) for this class of model. If $S_0 < 1$, the infection goes extinct; if $S_0 > 1$ the infection tends to a stable stationary state every season. When $S_0 < 1$, while the short-term $R > 1$, the simulations show an infection outbreak in the first season, possibly followed by smaller outbreaks in the next few years. This behaviour may be reminiscent of the outbreaks of West Nile virus in Southern Europe, for instance.
The same threshold S_0 is valid for a more realistic SIR model. A typical behaviour when $S_0 > 1$ is a large outbreak in the first year of introduction, followed by a decrease and another outbreak after several years.

Several papers, that model vector-borne disease without taking seasonality into account, consider migration of the birds involved in the transmission (López et al. [2008]), the intermediates stages of mosquito life cycle and their distribution in relation with the transmission of the virus (Wonham et al. [2004]), the feeding preferences (Simpson et al. [2012]) and also the heterogeneity of the hosts (Kilpatrick et al. [2006]).

We believe that it could be worthwhile combining some of these features with the discrete-continuous nature of this model to obtain a more realistic description of the behaviour of vector-borne disease.

In the next Chapter, we will take into consideration a specific vector-borne disease, such as West Nile virus. We try to combine some of the features listed

before with a semi-discrete model using an SIR epidemiological framework.

Chapter 3

A seasonal model for West Nile Virus

3.1 West Nile virus

West Nile Virus (WNV) is a mosquito-borne virus of the *Flaviviridae* family, which is a neuropathogen for humans, horses and birds. West Nile virus is mainly transmitted through the bite of infected vectors, that acquire the virus by feeding on infected birds. It is maintained by a bird-mosquito cycle while humans, horses and other mammals are considered as dead-end host for the virus (Bisanzio et al. [2011], Hayes et al. [2005]).
Because of their local abundance, vector competence in the laboratory (Turell et al. [2005]) and frequent reports of infection with West Nile virus in nature (Andreadis et al. [2004], Apperson et al. [2004]), several mosquito species have tested positive for West Nile virus (see Center for Disease Control [CDC]) and have been involved as bridge vectors or epidemic vectors, i.e. those responsible for transmission to humans.

Nevertheless, there are evidences including data documenting *Culex (Cx.) pipiens* feeding both birds and mammals (Hamer et al. [2008]). *Culex (Cx.) pipiens* species is considered as the main epizootic and endemic vector of West Nile virus in Europe (Hubálek and Halouzka [1999]) and Northeastern and North Central United States (Apperson et al. [2004], Molaei et al. [2006]). This is one of the most widespread mosquitoes, with a distribution covering

all temperate regions and so we will consider that species as the vector of transmission.

In bird species, playing the role of reservoir/amplifying hosts, viraemia lasts 1-7 days post infection (depending on infected species). During this period, birds are able to transmit West Nile virus to susceptible mosquitoes and, subsequently, develop life-long immunity (Mannelli et al. [2012]). Birds can be classified as highly competent hosts (HCH) or mildly competent hosts (MCH) (Komar [2003]; Castillo-Olivares and Wood [2004]), according to the duration of viraemia.
For the sake of simplicity, in what follows we will consider one general type of reservoir hosts without distinguishing between hosts differing in competence.

West Nile virus is widely distributed in Africa, the Middle East, Asia, and southern Europe and was recently introduced to North America. The 1999 outbreak of human encephalitis in New York City due to infection with West Nile virus represented the first documented introduction of this virus into the Western Hemisphere. Then the virus branched out into many US states and has persisted since then sometimes decreasing and sometimes increasing in terms of number of cases. In 2012 there was another peak in incidence (CDC [september 2013]). In Southern Europe the dynamics of the infection seems to be different. There were a few introductions in several areas of this continent, followed by spatial expansions in the following year and decreases or even disappearances in the initial areas. The infection prevalence seems to move like a wave during the years (ECDC [2013])
The model we will develop is not tailored to a specific area, but assumes a generic temperate climate; its aim is to investigate whether different parameter values can lead to different qualitative behaviors, reminiscent of the different dynamics of West Nile virus infection observed in different areas.

Several models have already been developed for West Nile virus.
As far as we know, the first models were presented by Thomas and Urena [2001], who formulate a difference equation model for West Nile virus, and Wonham et al. [2004] who, on the basis of the classical Ross-McDonald malaria model (Anderson and May [1991], Macdonald et al. [1957]), con-

sider a system of ordinary differential equation modelling West Nile virus transmission in the mosquito and bird populations. Their study has been extended in several directions, such as the study of temporal mosquito bird cycle transmission of West Nile virus (Cruz-Pacheco et al. [2005]) or heterogeneity in the competence of reservoir species (Simpson et al. [2012]) or also involving human and equine population in the model (Laperriere et al. [2011]).

Many of these papers do not take into account the seasonality of the species involved in the transmission, while it is well known that periodic fluctuations are common in the dynamics of disease transmission, especially for vector borne diseases. Indeed the weather influences the biology of vectors in different forms like changes in reproduction, population size, and blood feeding (Reiter [2001]).

In some models (Bacaër [2007], Bacaër and Guernaoui [2006]) seasonality is introduced by assuming sinusoidal fluctuations in transmission coefficients or other parameters. Instead, here we aim at a reasonably realistic, but still rather simple system. In this respect one fundamental feature of mosquito-borne infections in temperate climates is that in winter there are no active mosquitoes, thus no infection transmission. Correspondingly, the model will be based on a system of differential equations describing demography and infection transmission during the summers coupled by rules for population survival and stage transition during winters.

Indeed the mechanisms that allow for the efficient overwintering and subsequent amplification of West Nile virus have not been elucidated. In the literature, different explanations have been proposed for the overwintering of West Nile virus: it may occur through infection amplification during bird migrations, but this is not completely understood (Dawson et al. [2007], Owen et al. [2010], Wheeler et al. [2012]). Otherwise, overwintering could be due to mosquitoes: as they generally survive winter as diapausing adults, it is possible that mosquito larvae, infected vertically, would then enter diapause as they develop into adults, without taking a blood meal, and survive winter; they could then transmit the infection in the following season (Baqar et al. [1993], Goddard et al. [2003]). Alternatively, adult mosquitoes infected by

feeding on a infected avian host could then enter diapause and survive the winter (Nasci et al. [2001]). Indeed, Bailey et al. [1982], analyzed data provide evidences to support the theory that a significant number of diapausing *Culex pipiens*, which have taken a prehibernation blood meal, do not develop eggs and can survive the winter at rate comparable to diapausing non blood fed mosquitoes and vertical transmission of West Nile virus is neglectible.
In this paper, we will assume that West Nile virus overwintering occurs through the mosquito population, according to either one of the above mechanisms.

3.2 Model formulation

We start by modeling the populations involved in the transmission, birds and mosquitoes, in a disease free state. We divide the years in two periods: one (named $(0, T)$) during which infection transmission occurs due to mosquitoes being active. A second period $(T, 1)$ (having chosen 1 year as the time unit) where no infections occur.

3.2.1 Bird population

The bird population is modeled taking into account, in an extremely simple way, the breeding season and the outgoing migration. Let b_1 the fertility, m_1 the outgoing migration and d_1 the mortality of the bird population. We assume that the death rate is constant over the summers, while births and migration are concentrated in part of the season. Precisely, we assume that at time $t = 0$ the migrating birds have already arrived at the region being modelled and the breeding season is starting. Egg hatching occurs, at constant rate, up to time t_1^*; after t_1^*, as there are no births or immigrations, the bird population decreases because of deaths, and, beyond time t_2^*, also because of outgoing migration.

The bird population dynamics is then described by the following equation:

$$\dot{N}_B(t) = N_B(t)(P(t)b_1 - d_1 - Q(t)m_1) \qquad N_B(0) = k_B \tag{3.2.1}$$

where

$$P(t) = \begin{cases} 1 & \text{if } t < t_1^* \\ 0 & \text{if } t > t_1^*. \end{cases} \qquad \text{and} \qquad Q(t) = \begin{cases} 1 & \text{if } t < t_2^* \\ 0 & \text{if } t > t_2^*. \end{cases}$$

with $0 < t_1^* < t_2^* < T$.

We will assume that its initial condition $N_B(0)$ is a fixed constant k_B. In Figure 3.1 a general population of birds is shown as example.

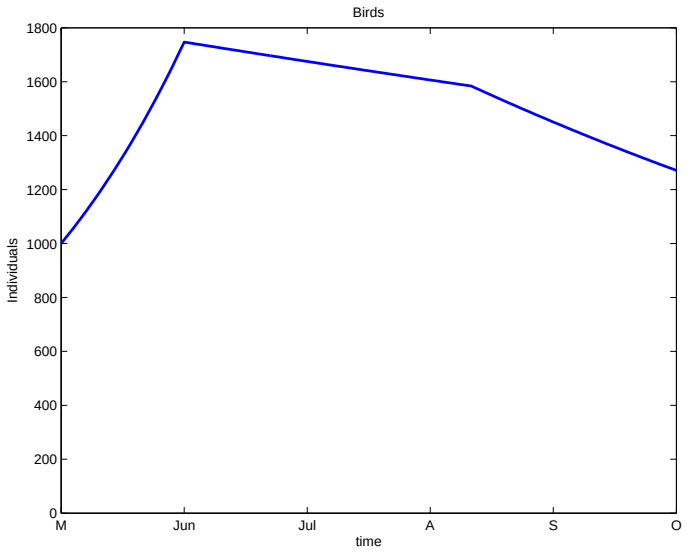


Figure 3.1: *Bird population in a disease free state in the period* $(0, T)$

3.2.2 Mosquito population

Mosquitoes go through four separated and distinct stages of its life cycle and they are as follow: Egg, Larva, Pupa and Adult. Only female mosquitoes bite animals and drink blood. They require a blood meal to obtain the necessary nutrients for the development and maturation of eggs. Blood is digested during the gonotrophic cycle and the nutrients transferred to the ovaries or developing eggs.

In what follows, we consider only females and neglect explicit consideration of immature stages; instead, because of its importance for infection transmis-

sion, we take into account the gonotrophic cycle by dividing adult females into two stages: the compartment of resting mosquitoes, $G(t)$, composed by the mosquitoes that, after a blood meal, need a period to digest and metabolize it; $F(t)$, the feeding adults that look for hosts on which to feed on. Their dynamics can be described by the following simple model

$$\begin{cases} \dot{F}(t) = f(t)G(t) - d(t)F(t) - \alpha F(t) + \epsilon G(t) \\ \dot{G}(t) = \alpha F(t) - \epsilon G(t) - d(t)G(t) \end{cases} \tag{3.2.2}$$

In the model, α is the rate at which mosquitoes leave the feeding stage, meaning that $1/\alpha$ is the mean length of the questing period: it is assumed that its length does not depend on host density, as their number is never a limiting resource. Similarly the mean length of the resting period is $\frac{1}{\epsilon}$, so that they leave the compartment $G(t)$ at rate ϵ.
Finally, by neglecting immature stages, we assume that newborn mosquitoes move directly to the stage F.
To obtain a more realistic and coherent model, it would be better considering the maturation period of the four immature stage. The simplest way to do that is to assume a constant delay. Mosquitoes that become adult at time t arise from eggs layed at time $t - \tau$, where τ is the delay induced by the maturation period. The model (3.2.2) modified by incorporating delay, becomes:

$$\begin{cases} \dot{F}(t) = f(t)G(t-\tau) - d(t)F(t) - \alpha F(t) + \epsilon G(t) \\ \dot{G}(t) = \alpha F(t) - \epsilon G(t) - d(t)G(t) \end{cases} \tag{3.2.3}$$

To model the seasonal dynamics of the mosquito population, we use the functions $b(t)$, representing the fertility over time, $p(t)$, the probability that new adults enter diapause at time t, and $d(t)$, the mortality. Consequently, the rate at which mosquitoes enter the adult stage is $f(t) = b(t)(1 - p(t))$.

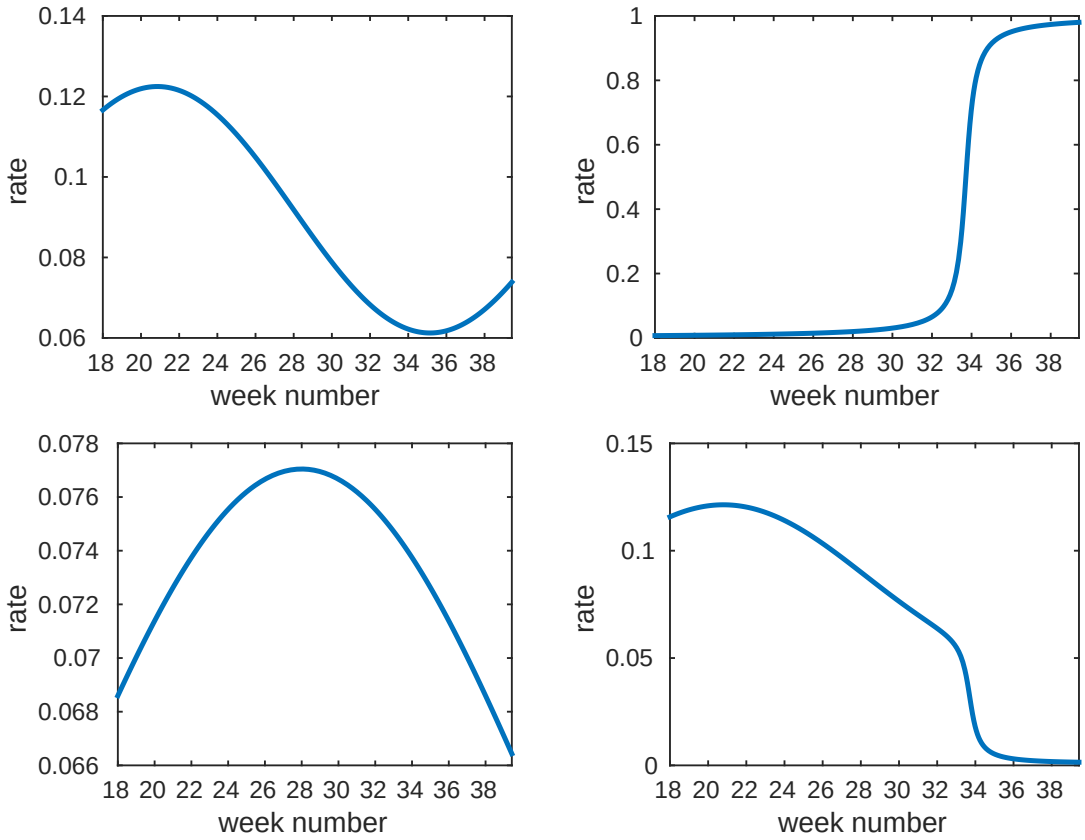


Figure 3.2: *fertility rate function $b(t)$, diapause rate function $p(t)$, mortality rate function $d(t)$ and recruitment rate function $f(t)$ using* (3.2.4) *with parameter values $A = 0.4$,$B = 0.2$, $s_1 = 30$, $s_2 = 110$, $s_3 = 20$, $L_1 = 100$ and $L_3 = 180$*

We use the following empirically derived functions:

$$\begin{aligned} b(t) &= b_2(0.75 + 0.25\sin((t+s_1)\tfrac{\pi}{L_1})) \\ p(t) &= 0.5 + \tfrac{1}{\pi}\arctan(A(t-s_2)) \\ d(t) &= d_2(1 + B\sin((t+s_3)\tfrac{\pi}{L_3})) \end{aligned} \tag{3.2.4}$$

These functions, used in the model, are extrapolated coupling response of mosquitoes to temperature and photo-period (Rosà et al. [2014]) to an average temperature cycle in a warm-temperate climate. In Figure 3.2 an example is shown for specific values of the parameters A, B .... that will be used in the rest of the paper.

In Figure 3.3 the total population of the mosquitoes is represented: a

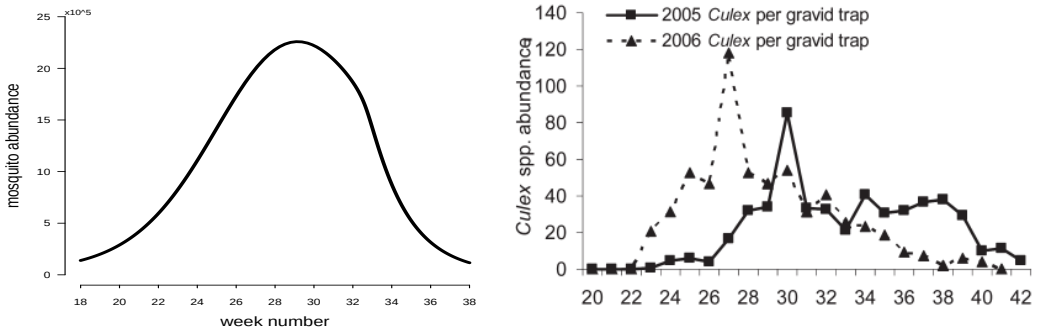


Figure 3.3: *Total mosquitoes using model* (3.2.2)–(3.2.4) *(to the left) and mosquito abundance by Hamer et al, 2008 (to the right). In our model the time, expressed in days, is from the beginning of May to the end of September*

simulation of our model is plotted on the left and the abundance of *Culex Pipiens* mosquitoes on the right. From these figures it comes to light that the simulations follow a similar pattern of the collected and analyzed data in Hamer et al, 2008.

3.3 The complete model

We build a model using a standard SIR epidemiological framework to model enzootic transmission between an avian population and the *Culex Pipiens* mosquito population. The avian hosts are divided into classes of susceptible (S_B), infected (I_B) and recovered (R_B) individuals, so the total population size is $N_B(t) = S_B(t) + I_B(t) + R_B(t)$. Newborn birds are all susceptibles (Hamer et al, 2008); after becoming infected, birds recover at rate γ and develop life-long immunity to further West Nile infection. They can also die because of West Nile infection at rate μ_{WN}.
It is assumed that mosquitoes do not recover from infection with West Nile virus. The population is divided into four compartments, i.e. S_M, E_M, G_M and I_M. S_M and I_M represent the feeding mosquitoes that are, respectively, susceptible and infected from West Nile virus. E_M and G_M represent those in the gonotrophic cycle that have or have not been infected.
When a susceptible mosquito bites (at rate $\alpha\frac{I_B}{N_B}$) an infected bird, it becomes

infected with probability β_M and enters the gonotrophic cycle. We assume that the latent period is completed during the resting period, so it will be infectious by the time of the following feeding period.

Both E_M and G_M produce eggs. E_M mosquitoes give birth to already infected mosquitoes with probability ν of vertical transmission.
When a bird is bitten by an infected mosquito (compartment I_M), it will become infected with a probability β_B. The relative flow chart is shown in Figure 3.4. The following system of differential equation, with $t \in [0, \tau]$,

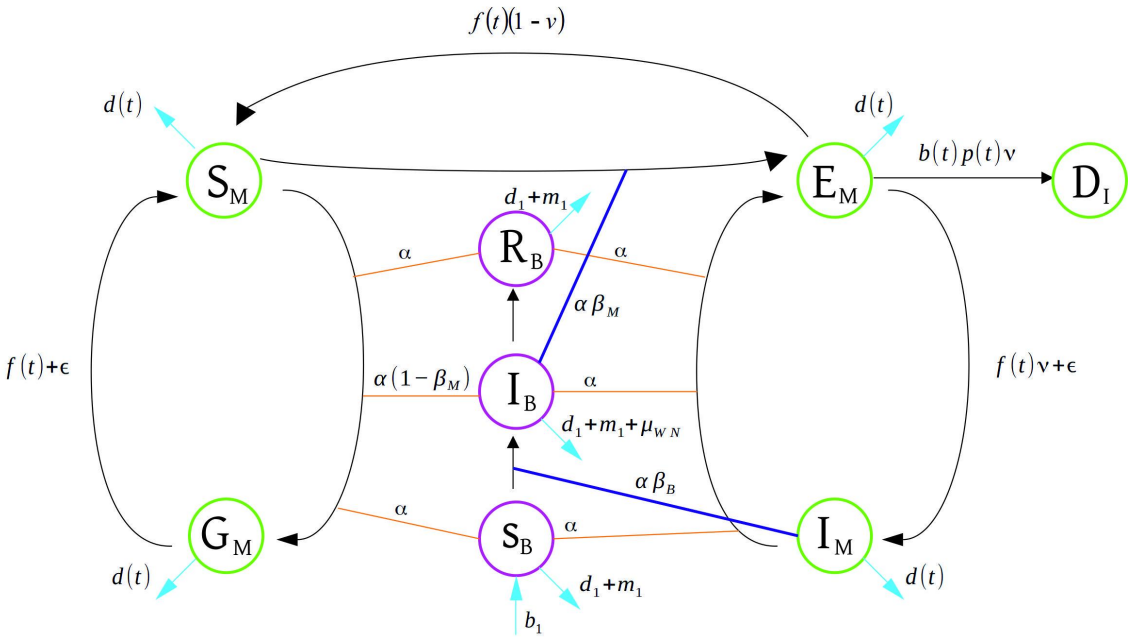


Figure 3.4: *Flow chart*

describes West Nile virus transmission between vectors and hosts, and incorporate the vector biting rate (α), the transmission rates β_B from vector to

host and β_M from host to vector during the summer season of length T.

$$\begin{cases} \dot{S}_B(t) = Pb_1N_B(t) - d_1S_B(t) - \alpha\frac{\beta_B I_M(t)}{N_B(t)}S_B(t) - Qm_1S_B(t) \\ \dot{I}_B(t) = \alpha\frac{\beta_B I_M(t)}{N_B(t)}S_B(t) - \gamma I_B(t) - \mu_{WN}I_B(t) - d_1I_B(t) - Qm_1I_B(t) \\ \dot{R}_B(t) = \gamma I_B(t) - d_1R_B(t) - Qm_1R_B(t) \\ \dot{S}_M(t) = f(t)((1-\nu)E_M(t-\tau) + G_M(t-\tau)) - d(t)S_M(t) - \alpha S_M(t) + \epsilon G_M(t) \\ \dot{E}_M(t) = \alpha\frac{\beta_M I_B(t)}{N_B(t)}S_M(t) - \epsilon E_M(t) - d(t)E_M(t) + \alpha I_M(t) \\ \dot{G}_M(t) = \alpha\frac{S_B(t)+R_B(t)+(1-\beta_M)I_B(t)}{N_B(t)}S_M(t) - \epsilon G_M(t) - d(t)G_M(t) \\ \dot{I}_M(t) = f(t)\nu E_M(t-\tau) + \epsilon E_M(t) - d(t)I_M(t) - \alpha I_M(t) \\ \dot{D}_I(t) = b(t)p(t)\nu E_M(t). \end{cases} \tag{3.3.1}$$

The compartment D_I represents the number of vertically infected mosquitoes that goes in diapausa.
To simplify the analysis, in the rest of the chapter we do not take into account the maturation period and so we assume that the newborn mosquitoes move directly to the adult stage: in this case $\tau = 0$ and we obtain the following model:

$$\begin{cases} \dot{S}_B(t) = Pb_1N_B(t) - d_1S_B(t) - \alpha\frac{\beta_B I_M(t)}{N_B(t)}S_B(t) - Qm_1S_B(t) \\ \dot{I}_B(t) = \alpha\frac{\beta_B I_M(t)}{N_B(t)}S_B(t) - \gamma I_B(t) - \mu_{WN}I_B(t) - d_1I_B(t) - Qm_1I_B(t) \\ \dot{R}_B(t) = \gamma I_B(t) - d_1R_B(t) - Qm_1R_B(t) \\ \dot{S}_M(t) = f(t)((1-\nu)E_M(t) + G_M(t)) - d(t)S_M(t) - \alpha S_M(t) + \epsilon G_M(t) \\ \dot{E}_M(t) = \alpha\frac{\beta_M I_B(t)}{N_B(t)}S_M(t) - \epsilon E_M(t) - d(t)E_M(t) + \alpha I_M \\ \dot{G}_M(t) = \alpha\frac{S_B(t)+R_B(t)+(1-\beta_M)I_B(t)}{N_B(t)}S_M(t) - \epsilon G_M - d(t)G_M(t) \\ \dot{I}_M(t) = f(t)\nu E_M(t) + \epsilon E_M(t) - d(t)I_M(t) - \alpha I_M(t) \\ \dot{D}_I(t) = b(t)p(t)\nu E_M(t); \end{cases} \tag{3.3.2}$$

This system of equation will hold for each summer season $n = 1, 2, \ldots$. Its initial conditions depend on the final conditions of the system of the previous summer, as explained in the next Section.

3.4 Overwintering and disease persistence in the multi-year model

We denote by $S_B^n(t)$, $I_B^n(t)\ldots$, $t \in [0,T]$, $n = 1, 2, \ldots$ the densities of birds or mosquitoes in the different compartments depicted in Fig. 3.4 at time t of summer n. These variables will satisfy equations (3.3.2) for each n and $t \in [0,T]$. The initial conditions will depend on the overwintering mechanism of West Nile virus.

As discussed in the Introduction, we consider two different mechanisms for overwintering, assuming either survival of unfed diapausing adults, infected through vertical transmission; or survival of adult mosquitoes that have been infected by feeding on an infected bird. In both cases, we assume that all infected bird recover during the winter and, if alive, they will be immune at the beginning of the following year; ρ is the birds' probability of surviving winter. As already mentioned, the total density of birds at the beginning of each summer is a constant k_B.

We assume, also for mosquitoes, a constant density k_M at the beginning of each summer; no mosquito will be in the gonotrophic cycle or in diapause: hence $S_M^n(0) + I_M^n(0) = k_M$. In summary, the initial conditions are

$$\begin{cases} S_B^n(0) = k_B - R_B^n(0) \\ I_B^n(0) = 0 \\ R_B^n(0) = \rho(I_B^{n-1}(T) + R_B^{n-1}(T)) \\ S_M^n(0) = k_M - I_M^n(0) \\ E_M^n(0) = 0 \\ G_M^n(0) = 0 \\ D_I^n(0) = 0 \end{cases} \tag{3.4.1}$$

We still have to assign $I_M^n(0)$ that will depend on the overwintering mechanism. In the first case (transmission through unfed diapausing adult females) we obtain

$$I_M^n(0) = \delta_v D_I^{n-1}(T) \tag{3.4.2}$$

where δ_v is the probability of surviving winter for a diapausing female. Note that $D_I^{n-1}(T) > 0$ only if the probability of vertical transmission ν is positive. This will be then assumed; otherwise, infection persistence would be impossible.

The second overwintering is that normal adults can survive winter, yielding

$$I_M^n(0) = \delta I_M^{n-1}(\tau) \tag{3.4.3}$$

where now δ is the probability of surviving winter for adult females.

In this case we assume, for the sake of simplicity, that $\nu = 0$, as vertical transmission is not needed for infection persistence.

3.4.1 S_0: a long-term threshold quantity

The solution of (3.3.2) with initial conditions (3.4.1) can be seen as a function $y(t; I_M(0), R_B(0))$ where $y(t)$ is the vector

$$(S_B(t), I_B(t), R_B(t), S_M(t), E_M(t), G_M(t), I_M(t), D_I(t))$$

as the initial conditions (3.4.1) are fixed but for the values $I_M(0)$ and $R_B(0)$.

One can then summarize the whole system as a discrete map

$$(I_M^n(0), R_B^n(0)) = F(I_M^{n-1}(0), R_B^{n-1}(0)). \tag{3.4.4}$$

If (3.4.2) hold, the map

$$F(Q, R) = (\delta_v y_8(T; Q, R), \rho(y_2(T; Q, R) + y_3(T; Q, R))). \tag{3.4.5}$$

Using instead (3.4.3), we have

$$F(Q, R) = (\delta y_7(T; Q, R), \rho(y_2(T; Q, R) + y_3(T; Q, R))). \tag{3.4.6}$$

It is then easy to see that the persistence of the disease can be determined through a quantity, that we name S_0, defined as $\rho(F'(0, 0))$, the spectral radius of the Jacobian matrix of F. S_0 can be seen as the derivative of

the Poincaré map of the periodic (because of the sequence of summers and winters) system, as introduced by (Bacaër and Guernaoui [2006], Wang and Zhao [2008]). The infection will persist over the years when $S_0 > 1$, while it will go extinct for $S_0 < 1$.

As shown in the Appendix, $\rho(F'(0,0)) > 1$ if and only if the same is true for its first entry, $F'_{11}(0,0)$; thus it is convenient using this element as the definition

$$S_0 = F'_{11}(0,0) = \frac{\partial I_M^n(0)}{\partial I_M^{n-1}(0)}.$$

This derivative can be computed by differentiating (3.3.2) with respect to the initial condition $Q = I_M(0)$ and obtaining the variational system

$$\begin{cases} \dot{w} &= \alpha\beta_B z - (\gamma + \mu_{WN} + d_1 + Qm_1)w & w(0) &= 0 \\ \dot{z} &= b(t)(1-p(t))\nu u + \epsilon u - d(t)z - \alpha z & z(0) &= 1 \\ \dot{u} &= \alpha\beta_M w\frac{S_M(t)}{N_B(t)} - \epsilon u - d(t)u + \alpha z & u(0) &= 0 \\ \dot{\phi} &= b(t)p(t)\nu u & \phi(0) &= 0 \\ \dot{S}_M &= b(t)(1-p(t))E_M - d(t)S_M - \alpha S_M + \epsilon E_M & S_M(0) &= k_M \\ \dot{E}_M &= \alpha S_M - \epsilon E_M - d(t)E_M & E_M(0) &= 0 \\ \dot{N}_B &= Pb_1 N_B - d_1 N_B - Qm_1 N_B & N_B(0) &= k_B \end{cases} \tag{3.4.7}$$

where $\frac{\partial I_B}{\partial Q} = w, \frac{\partial I_M}{\partial Q} = z$, $\frac{\partial E_{iM}}{\partial Q} = u$, $\frac{\partial D_I}{\partial Q} = \phi$. The other derivatives are not introduced, beacuse they are not needed to compute S_0.

S_0 can be obtained from (3.4.7) in the two cases, either as

$$S_0^v = \delta_v \phi(T) \tag{3.4.8}$$

or as

$$S_0^h = \delta_h z(T). \tag{3.4.9}$$

3.5 Model parameters

3.5.1 Parameters

The resulting model is rather rich of parameters. There exist several information for the demography of several bird species is rather well known. We have then decided to set the parameters to average values of passerine species. (Noon and Sauer [1992])

Precisely, we chose as average life of an adult bird 2 years, implying that the death rate is $d_1 = 1/(365 * 2days)$.
The summer is considered to last 150 days from May 1 to September 30; thus, survival over the summer is approximately 0.81; consistently, ρ (survival over winter) has to be set to 0.74.

We assume that the breeding season starts on May 1 and ends after 30 days, during which period every couple of adult birds produces two offsprings; this means that the birth rate is $b_1 = 0.023\ (days)^{-1}$. We assume that migration starts at the end of August with a rate differing from species to species and from region to region. As a value that seems to produce realistic population values we choose $m_1 = 0.03\ (days)^{-1}$.

As for the other parameters, although some estimates exist also about mortality and fertility of adult mosquitoes Bowman et al. [2005], Simpson et al. [2012], we believe that actual values may be very different under field condition. Thus, we use literature data to obtain ranges for each parameter; (see Table 3.1); then we use the Latin Hypercube sampling (Marino et al. [2008]) to obtain samples of acceptable parameter values. A sample was deemed to be acceptable, if it gave rise to solutions satisfying some constraints, specified below.

The sample was realized in two stages. First of all, we generated 10000 samples of the parameters involving mosquito population, b_2,d_2 and k_M, obtaining a (10000x3) matrix. For each sample, we solved (3.2.1) and (3.2.2) and selected only those such that the solution satisfied some constraints related to population dynamics without infection (Rosà et al. [2014]).

Precisely, we asked first that the peak density of the mosquito population is approximately 1000 times the peak density of birds. The second condi-

Parameter	range/value	description
b_1	0.02	*birth rate of birds*
d_1	0.0014	*death rate of birds*
m_1	0.003	*out-coming migration rate birds*
k_B	10^3	*bird density at the start of summer*
b_2	$(0, 0.5]$	*fertility function coefficient*
d_2	$(0, 0.2]$	*mortality function coefficient*
k_M	$[10^4, 2 \cdot 10^5]$	*mosquito density at the start of the summer*
α	$[0.2, 0.7]$	*biting rate*
β_B	$[0, 1]$	*vector to host transmission rate*
β_M	$[0, 1]$	*host to vector transmission rate*
γ	$[0.1, 0.3]$	*recovery rate of birds*
μ_{WN}	$[0, 0.5]$	*death rate of birds due to WNV infection*
ϵ	$[0, 0.2]$	*resting rate of mosquitoes*
ν	$[0, 0.1]$	*vertical transmission probability*

Table 3.1: *Parameters value and meaning. The rates have units per days*

tion is that mosquito density at the start (early May) and the end (late September) of the season is about 5% of the peak density.

These constraints were implemented by considering a simulation acceptable only if

$$\left|\log(\max_{t\in(0,T)}(N_M(t))) - \log(10^3 \max_{t\in(0,T)}(N_B(t)))\right| \leq \log(1.5) \tag{3.5.1}$$

and

$$\left|\log(N_M(0)) - \log(\max_{t\in(0,T)}(N_M(t)))\right| \leq \log(1.4) \tag{3.5.2}$$

$$\left|\log(N_M(T)) - \log(\max_{t\in(0,T)}(N_M(t)))\right| \leq \log(1.4) \tag{3.5.3}$$

Then each selected parameter was combined with another matrix of samples of dimensions (3000x6) including the parameters involved in the transmission α, β_B, β_M, γ, μ_{WN}, ϵ and ν.

For each resulting combination of parameters, we solved (3.3.2) with the following initial conditions that can reproduce what could be the situation after some year. Thus, a certain proportion of the birds will be immune

(because of infections having occurred in the previous years) and a small fraction of the emerging mosquitoes will be infected, after over-wintering:

$$\begin{cases} S_B^1(0) = 0.6k_B \\ I_B^1(0) = 0 \\ R_B^1(0) = 0.4k_B \\ S_M^1(0) = 0.9999k_M \\ G_M^1(0) = 0 \\ E_M^1(0) = 0 \\ I_M^1(0) = 0.001k_M \end{cases}$$

In words, the constraints required to the solution were:

1. that the peak of infected mosquito were a couple of weeks after the peak of the total population of the mosquitoes (the middle of July);

2. enough susceptible birds were left at the end of season.

Precisely, let $t^* \in [0, T]$ such that

$$I_M(t^*) = \max_{t \in (0,T)} (I_M(t))$$

these constraints were implemented as

1.
$$t^* > \frac{3}{5}T \tag{3.5.4}$$

2.
$$S_B^n(T) > 0.02\ k_B \quad \forall\ n = 1, 2, ... \tag{3.5.5}$$

The following constraint must hold when assuming no vertical transmission :
more infected mosquitoes were present at the end of the season than at the start (otherwise the infection could not persist, as the simulations were

started with a very low number of infected mosquitoes), namely,

$$I_M(T) > I_M(0) \tag{3.5.6}$$

From this evaluation, depending on the assumptions made on the vertical transmission (see Section (3.4)), we obtained 198 sets of parameters that satisfy the constraint for the model without vertical transmission and 3271 for the model with vertical transmission.

3.5.2 A posteriori parameter distributions

We show in Figure 3.5 the histograms of the distributions of the parameters γ, μ_{WN}, ν and ϵ, obtained through Latin Hypercube Sampling and satisfying constraints (3.5.1), (3.5.2), (3.5.3), (3.5.4), (3.5.5) and (3.5.6) in the case with vertical transmission. These distributions appear close to the uniform used as prior. In Figure (3.6) the same is shown for the parameters β_B, β_M and α. In these cases, one sees an apparent mode with more likely values for the biting rate α in the interval $[0.45, 0.7]$, and for the transmission probabilities β_B in $(0, 0.2]$ and β_M in $[0.1, 0.2]$. The fourth panel in the same Figure shows a 2-dimensional plot of the joint distribution of β_B and β_M. An expected, strong negative correlation emerges between the estimates of the two parameters with a higher frequency of samples with $\beta_M > \beta_B$, in agreement with values used in most models.

In the case of the model without vertical transmission, the values produced by Latin hypercube sampling and satisfying the constraints (3.5.1), (3.5.2), (3.5.3), (3.5.4) and (3.5.5) are plotted in Figure (3.7) and (3.8). From Figure (3.7) we can see that the posterior distribution of most parameters appears close to uniform, similarly to the case with vertical transmission.

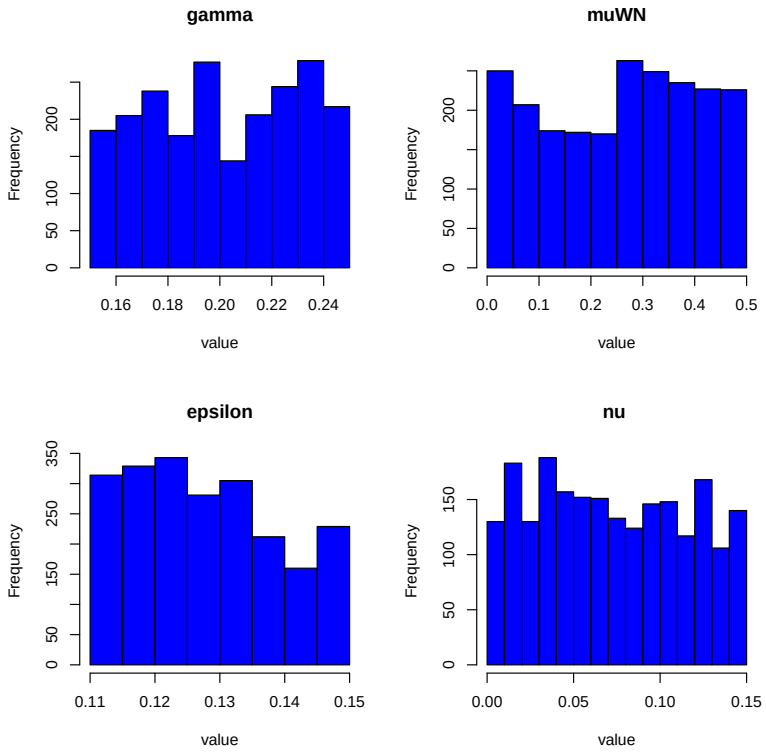


Figure 3.5: *Distributions of the feasible choice of parameters for the model with vertical transmission*

Exceptions, as can be seen from Figure 3.8, are the biting rate α where values are concentrated in upper half $[0.5, 0.7]$ of the prior distribution, and β_B where most values of the posterior distribution are below 0.2. Concerning the latter, panel d) of Figure 3.8 shows that the estimates of probabilities of transmission, β_M and β_B, are, as expected, negatively correlated and in general $\beta_M > \beta_B$.

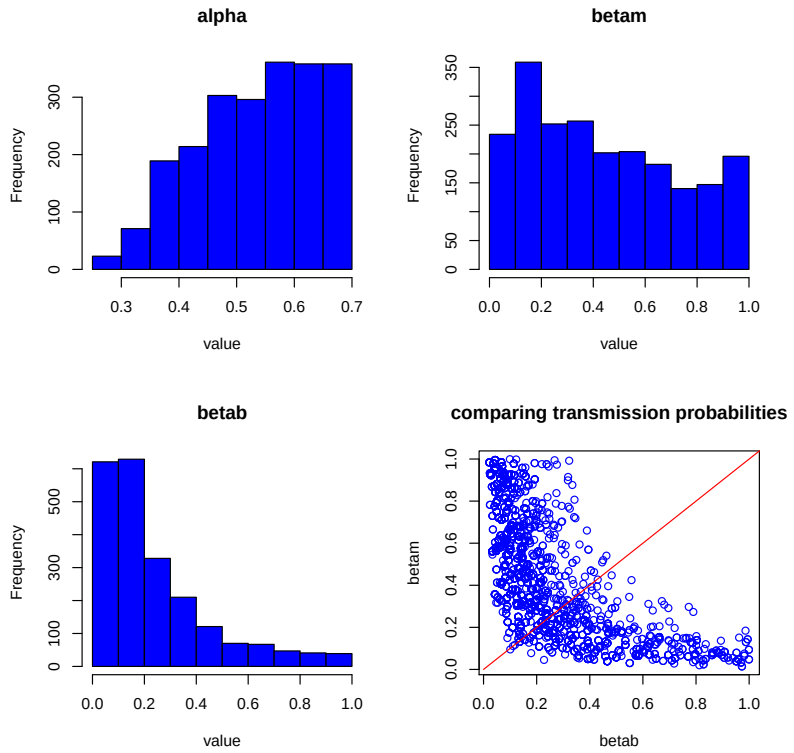


Figure 3.6: *Distribution of parameters involved in the transmission and comparing plot of the transmission rates for the case with vertical transmission*

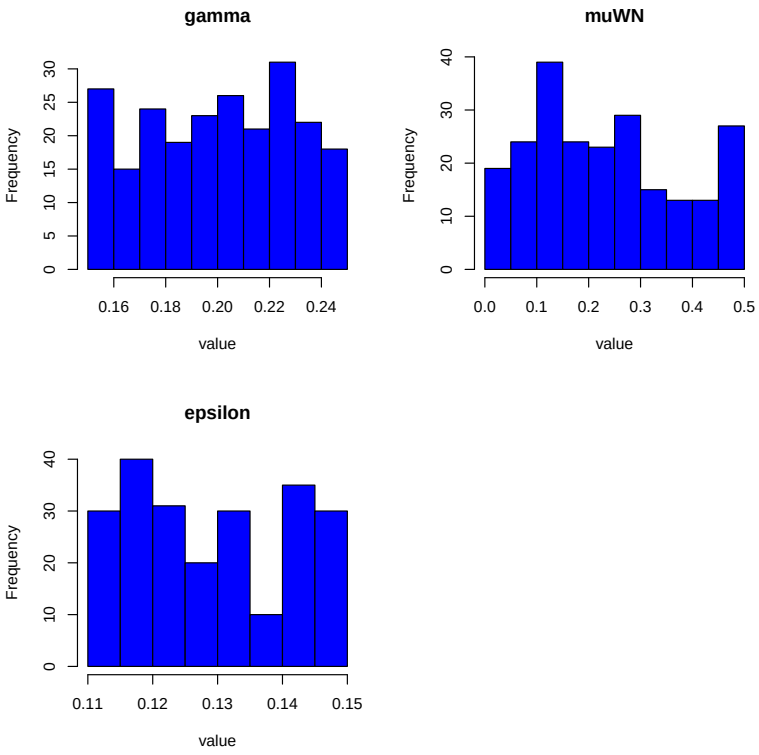


Figure 3.7: *Distributions of the feasible choice of parameters for the model without vertical transmission*

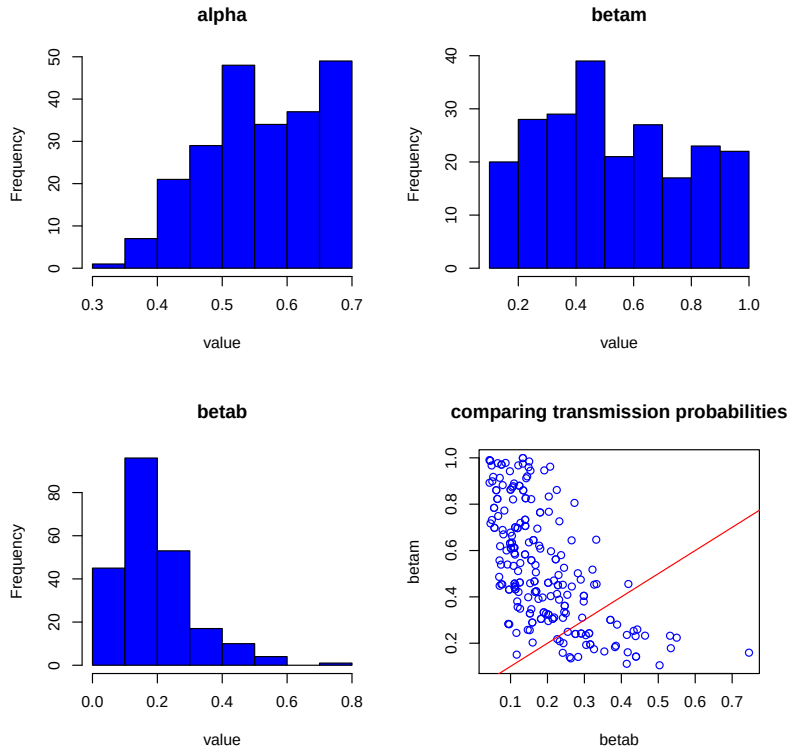


Figure 3.8: *Distribution of parameters involved in the transmission and comparing plot of the transmission rates for the case with no vertical transmission*

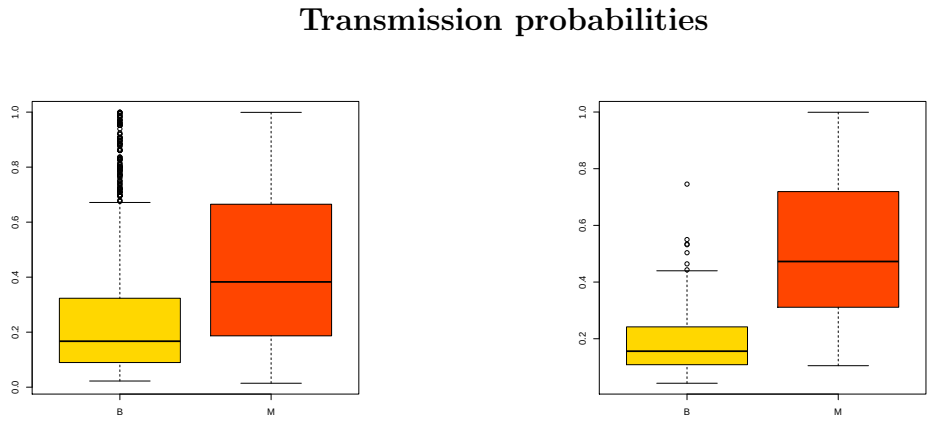


Figure 3.9: *in yellow the values of β_B are shown and in orange the values of β_M of the model with/without vertical transmission (left/right respectively)*

3.6 Some simulations

We ran simulations of the model, starting from two initial conditions in the first year.

The first one considers the case of an initial introduction of the infection starting from one migrating bird that had been infected in its winter grounds. Thus the initial conditions are the following

$$\begin{cases} S_B^1(0) = k_B - 1 \\ I_B^1(0) = 1 \\ R_B^1(0) = 0 \\ S_M^1(0) = k_M \\ G_M^1(0) = 0 \\ E_M^1(0) = 0 \\ I_M^1(0) = 0 \end{cases} \tag{3.6.1}$$

For these initial conditions, we ran some simulations of the model, each time choosing the parameter values from the posterior distribution shown in the previous Section; the parameter (δ_v according to the over-wintering scheme considered) have been chosen so as to yield a required value of S_0.

3.6.1 Model with vertical transmission

Starting from the case with vertical transmission and initial conditions (3.6.1), we let the simulations run for 20 years, and looked at the infection dynamics in the last year of simulations (in all cases, the simulations had reached a stationary situation over the years).

In Figure 3.10, we show the 2-dimensional plot displaying on the two axes the peak times of infected birds and of infected mosquitoes in the first year obtained by solving the system for each set of parameters. It can be seen that the infection peak in the mosquito population occurs before, or at most simultaneously, than the peak of the bird population. This is in agreement with what it is generally observed in reality (Hamer et al. [2008]).

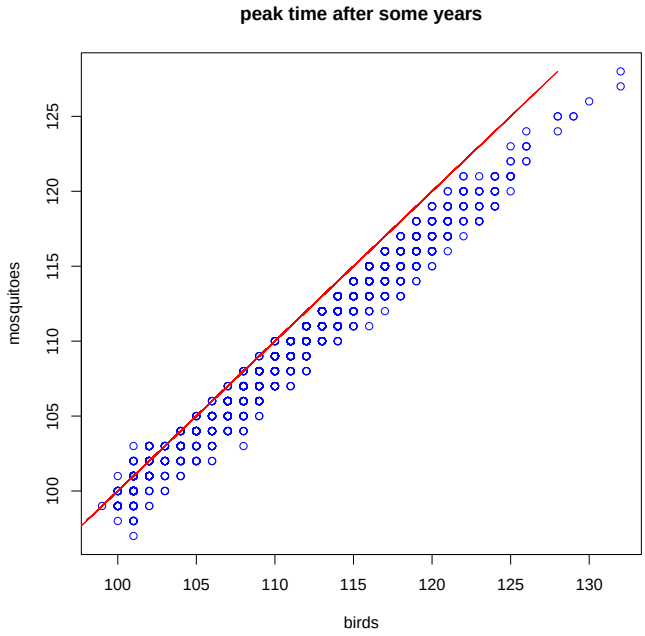
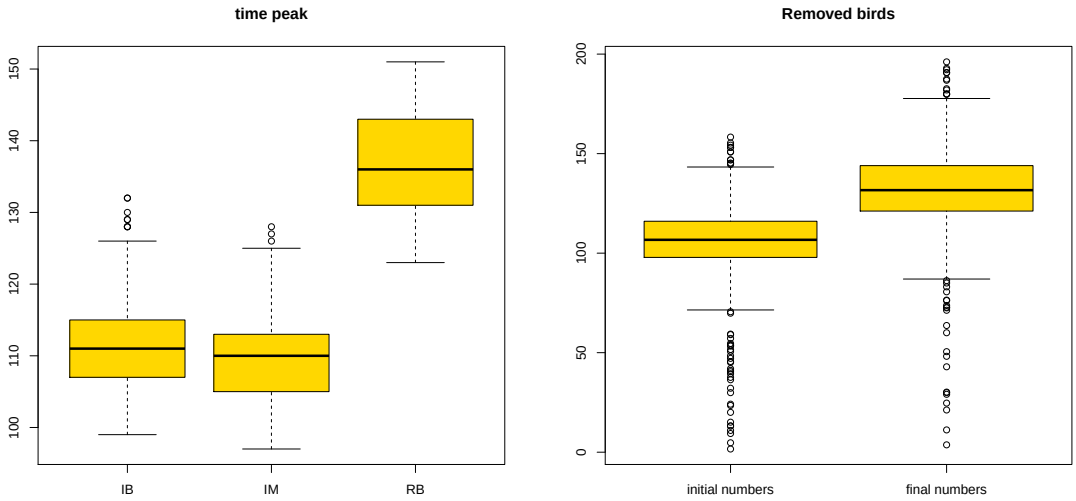


Figure 3.10: *Peak time of infected bird versus peak time of infected mosquitoes*



(a) *Peak time* ***(b)*** *Removed Birds*

Figure 3.11: *On the left peak time of infected bird, peak time of infected mosquitoes and peak time of removed birds and on the right initial and final R_B after some years*

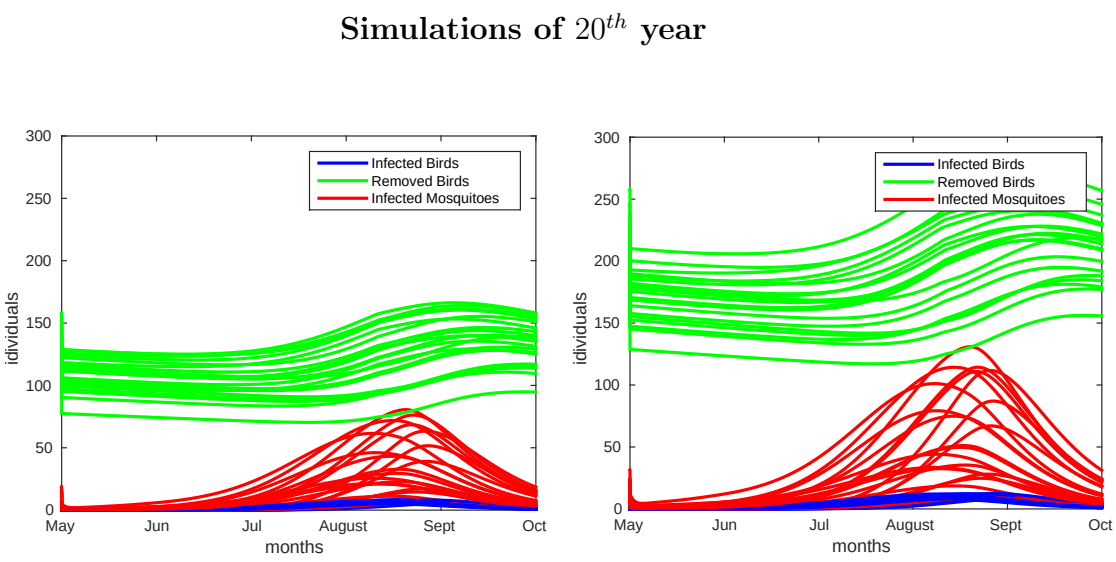


Figure 3.12: *Plot of the 20^{th} year of some simulations starting with only one infected bird for $S_0 = 2$, Figure 3.12a, and for $S_0 = 3$, Figure 3.12b . In red are plotted the infected mosquitoes, in blue the infected birds and in green the removed birds*

In Figure 3.11b the frequencies of the number of birds belonging to the compartment of removed (R_B) are displayed for the beginning and the end of the 20^{th} season.

Using the initial conditions (3.6.1) for the first year, we displayed some simulations focusing on the 20^{th} year plotting the functions of the compartments I_B, R_B and I_B in Figure 3.12.

The pattern over the 20 years is shown in the simulations starting with the initial conditions (3.6.1). We show only the simulations obtained with the first six extracted parameter values that, for the sake of clarity, are listed in Table 3.2, and having set $S_0 = 2$.

Figure 3.14 displays simulations of the model with vertical transmission obtained using the same set of parameters, but having set δ_v so as to obtain $S_0 = 0.8,\ 1.5,\ 2,\ 4$. Even when $S_0 < 1$, persistence of the disease can be detected for at least the first two years. For values of $S_0 > 1$, after the initial outbreak, the infection decreases sharply both in mosquitoes and birds; then

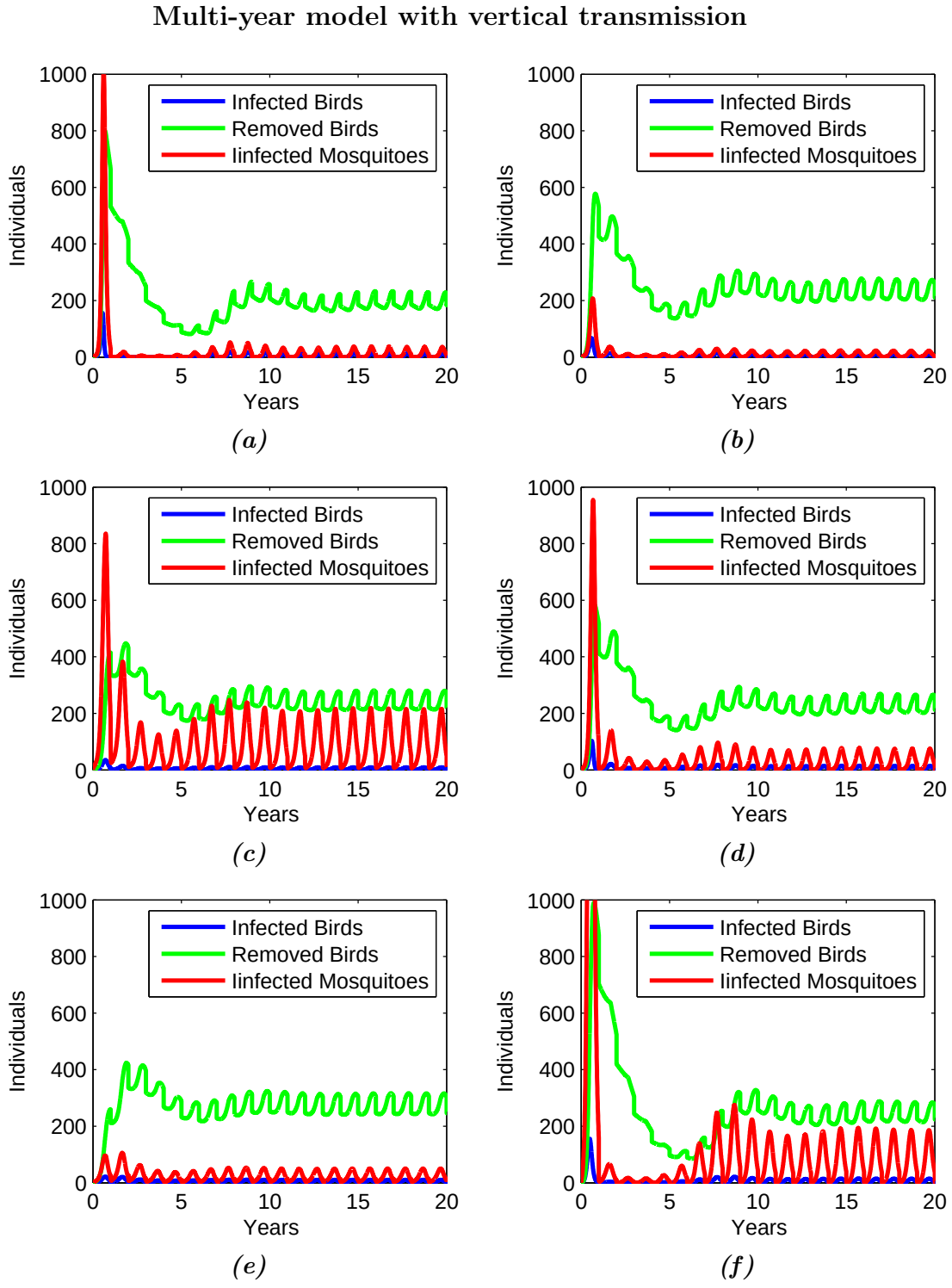


Figure 3.13: *Simulations of the model with vertical transmission with different sets of parameters in Table 3.2 for* $S_0 = 2$

Fig	(3.13a)	(3.13b)	(3.13c)	(3.13d)	(3.13e)	(3.13f)
b_2	0.1266	0.1266	0.1062	0.1062	0.1062	0.1062
d_2	0.0624	0.06244	0.0549	0.0549	0.0549	0.0549
k_M	91446,7	91446,7	193717,5	193717,5	193717,5	193717,5
α	0.6236	0.3852	0.5936	0.5032	0.5761	0.2618
β_B	0.2428	0.7274	0.0328	0.1851	0.1006	0.0780
β_M	0.1563	0.1520	0.5591	0.1655	0.0952	0.8120
γ	0.1838	0.2157	0.2393	0.1606	0.2160	0.1522
μ_{WN}	0.1664	0.2778	0.1224	0.2309	0.0056	0.0554
ϵ	0.1463	0.1164	0.1226	0.1205	0.1495	0.1196
ν	0.0345	0.3632	0.0287	0.0359	0.0517	0.0581 à

Table 3.2: *Value of the parameters related to the plots in Figure 3.13*

the disease starts increasing, converging to a stationary solution that depends on the value of S_0.

The results regarding the model without vertical transmission are displayed in the Appendix B, since they are qualitatively quite similar to the case with vertical transmission.

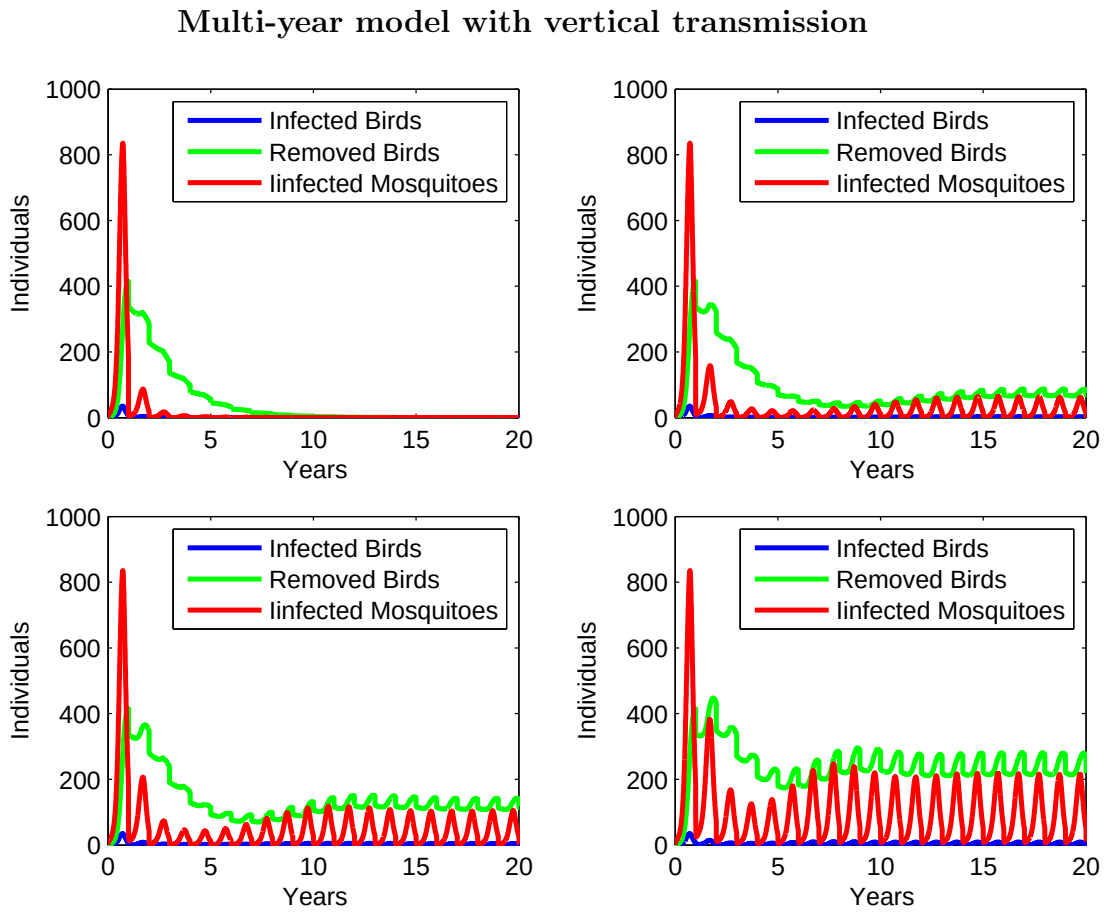


Figure 3.14: *Simulations of the model with vertical transmission with the same sets of parameters for different vale of* $S_0 = 0.8, 1.5, 2, 4$

3.7 Conclusions

The model examined in this chapter is built on a standard SIR-SIS host-vector epidemic model, and focuses on the effects of a realistic seasonal dynamics, and on the mechanisms of infection overwintering. Concerning the last aspect, we considered two different possibilities, both involving the mosquitoes.
The first mechanism assumes that infection is transmitted to the following year by mosquitoes that have entered diapause as unfed adults in the previous year, and must have become infected by vertical transmission. The second mechanism assumes instead that a fraction of (non-diapausing) adult mosquitoes survive the winter and, if they had been infected during feeding, can transmit the infection in the following year.

The resulting model is rather rich in parameters. Independent estimates on most of them is scarce; hence we used the Latin Hypercube sampling scheme and rejected those samples that yielded solutions that did not satisfy some realistic constraints.

The posterior distribution (the one obtained after rejection of samples) of most parameters is similar to the prior distribution, so that inference on parameter values is limited. However, parameter rejection resulted in a multivariate distribution that yields rather consistent model simulations. Among the most obvious results, a highly negative correlation between the probabilities of transmission (from mosquito to bird β_B and from bird to mosquito β_M) has emerged: in essence the product of these probabilities can be estimated with some accuracy from field data, but not the single value of β_M or β_B, although it is more likely (see Fig. 3.9) obtaining estimates with $\beta_M > \beta_B$ (as has been used in most models), especially in the case of overwintering without vertical transmission.

The choices used on how mosquito fertility, mortality and diapausing depend on time within a season yield a mosquito seasonal dynamics that follows a pattern similar to the one seen in the data from (Hamer et al. [2008]), as shown in Figure 3.3. Indeed, the functions used are simply descriptive and not based on physiological mechanisms. It would be worthwhile examining

the possibilities of using laboratory data (as in Ciota et al. [2014]) on the dependence on temperature of demographic parameters of *Culex* mosquitoes, coupled with an average temperature profile in the area of interest. Possibly, other climatic factors beyond temperature are relevant for life history traits in the field (certainly, it is well known that diapause is induced through photoperiod), as is demonstrated in the recent analysis by Rosà et al. [2014].

Comparing seasonal infection dynamics as predicted by model simulations to actual data is more difficult, as there are very limited longitudinal data. A relevant feature emerging from the simulations is that the time of the season when infected mosquitoes reach the maximum (peak-time) occurs consistently before peak-time of infected birds; this seems in agreement with field observations (Hamer et al. [2008]).

The general multi-year pattern shows that after a large outbreak following the first introduction, a drop in cases occurs for several years, followed from an increase towards a stationary level, often with oscillations, especially if S_0 is relatively large. Such a pattern is somewhat reminiscent of the trend in human cases in United States from 1999 to 2013 (CDC [2014]).

From the simulation with $S_0 < 1$, we can note an infection persistence for 2-3 years, then a decrease and finally the disappearance of the disease. For $S_0 > 1$ in both models, with or without vertical transmission (see Appendix B), after decreasing, the disease reaches a stable point.

Chapter 4

Spatial spread

4.1 Introduction

West Nile virus is a vector-borne disease transmitted through the bite of infected mosquitoes that acquire the virus by feeding on infected birds. West Nile virus is endemic in Africa, the Middle East and western Asia. In late august 1999 the first outbreak of West Nile in North America was reporter in New York City. Over the next five years, the epidemic has spread spatially across the continental United States, north into Canada, and southward into the Caribbean islands and Latin America. It seems that the spread of West Nile virus comes from the interaction of disease dynamics and bird and mosquito movement. From the previous example, it emerges that understanding the spread of vector borne diseases is of great importance to establish which measures might be effective before they are actually carried out.

On the other hand, in Europe a different spatial diffusion can be observed. For example, 10 years after the first outbreak, West Nile virus reoccurred in Italy causing death and clinical signs in horses and humans (Calistri et al. [2010], Savini et al. [2008]). West Nile infection outbreaks were also reported in 2009. As in the previous year, the virus West Nile virus has been able to cause disease in horses and humans and, similarly, no birds fatalities were recorded. The infection re-occurred in the same places of the 2008 and moved westerly and southerly involving new areas and regions (Monaco et al. [2011]).

Lewis et al. [2006] analyzed the spread of West Nile virus by spatially extending the non-spatial dynamical model of Wonham et al. [2004] to include diffusive movement of birds and mosquitoes. Instead in Liu et al. [2006], a mathematical model to understand the spatial spread patterns in the establishment phase of West Nile virus in a region consisting of multiple patches has been used. In literature a large part of mathematical models on spread are proposed in terms of reaction-diffusion equations(Lewis et al. [2006]). Most reaction-diffusion epidemic models are space-dependent extensions of the classical Kermack-McKendrik model(Kermack and McKendrick [1927]). These types of models assume that the spreading is ruled by random diffusion and that dispersal and growth take place continuously in time and space. A reaction-diffusion equation comprises a reaction term and a diffusion term, i.e. the typical form is as follows:

$$u_t = D\Delta u + f(u)$$

where $u = u(x,t)$ is a state variable and describes density of the population at position $x \in \Omega \in R^n$ at time t (Ω is a open set). Δ denotes the Laplace operator. So the first term on the right hand side describes the "diffusion", including D as diffusion coefficient. The second term, $f(u)$ is a smooth function $f : R \to R$ and describes processes which really "change" the present u, i.e. something happens to it (birth, death, transmission ...), not just diffuse in the space.

Facing the study of the spatial spread of vector-borne diseases, since the vector population are not active during a season and so the interaction between host and vector populations occurs within the summer season, we cannot consider just a classical reaction-diffusion model, but we need to take into account both discrete and continuous components. Lewis and Li [2012] proposed simple impulsive reaction-diffusion equation model to study the persistence and the spread of species with a reproductive stage and a dispersal stage in bounded and unbounded domains.
In the case of vector-borne diseases, it is possible to use this type of approach considering the dormant stage and the disease dispersal stage.

The formulation will consist of a system of nonlinear reaction-diffusion equations that holds in the disease transmission period and a discrete map describing the survival of the vector responsible of the transmission during the dormant season. We chose to consider the SIR system analyzed in Chapter 2 that represents, in a very simple way, the transmission of a vector-borne disease during the active season of a vector with the related initial condition that allow the persistence of the disease for several year.

To solve the system of nonlinear reaction-diffusion equation, we used the Crank-Nicolson method. (Giles [2010])

Finally, we will present also some simulations for the spatial spread of the disease considering, as a first step, a one-dimensional domain.

4.2 An SIR model

We start this section considering the following simple SIR model described in Chapter 2

$$\begin{cases} \dot{S}_h^n(t) &= \Lambda_H - \mu_H S_h^n(t) - \alpha\beta_H S_h^n(t) I_v^n(t) \\ \dot{I}_h^n(t) &= \alpha\beta_V S_h^n(t) I_v^n(t) - \gamma_H I_h^n(t) - \mu_H I_h^n(t) \\ \dot{R}_h^n(t) &= \gamma_H I_h^n(t) - \mu_H R_h(t) \\ \dot{S}_v^n(t) &= \Lambda_V - \mu_v S_v^n(t) - \alpha\beta_V I_h^n(t) S_v^n(t) \\ \dot{I}_v^n(t) &= \alpha\beta_V I_h^n(t) S_v^n(t) - \mu_V I_v^n(t) \end{cases} \tag{4.2.1}$$

with initial conditions

$$\begin{cases} S_h^n(0) &= N_H - R_h^n(0) \\ I_h^n(0) &= 0 \\ R_h^n(0) &= \rho(R_h^{n-1}(T) + I_h^{n-1}(T)) \\ S_v^n(0) &= N_V - \delta I_v^{n-1}(T) \\ I_v^n(0) &= \delta I_v^{n-1}(T) \end{cases} \tag{4.2.2}$$

where $S_h + I_h + R_h = N_H = \frac{\Lambda_H}{\mu_H}$ is the constant number of host during the summer, where μ_H is the death rate. They are assumed to be all susceptibles or immune (they recover at rate γ_H) at the beginning of the summer,in fact those infected, that have survived at the end of the previous year, will have recovered from infection because of the short infection period (Simpson et al. [2012]).
$S_v + I_v = N_V = \frac{\Lambda_V}{\mu_V}$ is the total population size of the vectors, which is constant in the considered period. Due to its short life, a vector never recovers from the infection. We assume that the biting rate α is constant and equal for each type of host. The transmission probability is the probability that an infected individuals produces a new case in a susceptible member of the other species. The transmission probabilities from vectors to hosts and from hosts to vectors are denoted by β_H and β_V, respectively. This system of equations will hold for each summer season $n = 2, 3, \ldots$.
Here δ is the probability of infected vectors to survive the winter and ρ is the survival probability of host.
We normalize and reduce the model, obtaining

$$\begin{cases} \dot{i}_H^n = \alpha\beta_H \frac{N_V}{N_H}(1 - i_H^n - r_H^n)i_V^n - \gamma_H i_H^n - \mu_H i_H^n, \\ \dot{r}_H^n = \gamma_H i_H^n - \mu_H i_H^n, \\ \dot{i}_V^n = \alpha\beta_V i_H^n(1 - i_V^n) - \mu_V i_V^n, \end{cases} \tag{4.2.3}$$

with initial conditions

$$\begin{aligned} i_H(0) &= 0 \\ r_H(0) &= \rho(i_H^{n-1}(T) + r_H^{n-1}(T)) \\ i_V^n(0) &= \delta i_V^{n-1}(T) \end{aligned}$$

where i_H and r_H represent the fraction of infected and immune hosts and i_V will be the fraction of infected vectors.

4.3 The impulsive reaction-diffusion model

Now we start considering the spatial spread of the disease. Our mathematical model therefore consists of a system of partial differential equations describing the spatio-temporal evolution of the populations.

Let $u^n(t,x)$ the fraction of infected hosts, $v^n(t,x)$ the fraction of immune hosts and $z^n(t,x)$ the fraction of infected vectors at time t of the n^{th} year at the position x.
The model is given on a spatial domain Ω with smooth boundary $\partial\Omega$; for simplicity we start by considering a one–dimensional domain, that is, $\Omega = [-L, L]$.
In particular we are going to develop a reaction-diffusion system, falling into the category of non-linear parabolic systems defined in the time interval $[0, T]$, where T is the length of the summer.

Actually, the whole model will be an impulsive reaction-diffusion model. Dealing with vector-borne disease, as we state in the previous sections, we need to take into account that the vectors responsible of the transmission in general are active only during the summer. We are not interested in the dispersal of the population involved in the disease during the winter, because it is supposed that the vector population is not moving, the transmission does not occur and the hosts recover in a period shorter than the winter. So the disease does not spread in other places. Therefore our model can be written as

$$\begin{cases} u_t^n(t,x) = D_1 u_{xx}^n(t,x) + \alpha\beta_H \frac{N_V}{N_H}[1 - u^n(t,x) - v^n(t,x)]z^n(t,x) - (\gamma_H + \mu_H)u^n(t,x) \\ v_t^n(t,x) = D_2 v_{xx}^n(t,x) + \gamma_H u^n(t,x) - \mu_H v^n(t,x) \\ z_t^n(t,x) = D_3 z_{xx}^n(t,x) + \alpha\beta_V(1 - z^n(t,x))u^n(t,x) - \mu_V z^n(t,x) \end{cases} \tag{4.3.1}$$

where D_1,D_2 and D_3 are the diffusion coefficients and with initial conditions

$$\begin{aligned} u^n(0,x) &= 0 && \forall x \in \Omega \\ v^n(0,x) &= \rho(u^{n-1}(T,x) + v^{n-1}(T,x)) && \forall x \in \Omega \\ z^n(0,x) &= \delta(z^{n-1}(T,x)) && \forall x \in \Omega \end{aligned}$$

and no-flux boundary conditions, $\forall t \geq 0$

$$\frac{\partial u^n}{\partial x}(t,-L) = \frac{\partial v^n}{\partial x}(t,-L) = \frac{\partial z^n}{\partial x}(t,-L) = 0$$
$$\frac{\partial u^n}{\partial x}(t,L) = \frac{\partial v^n}{\partial x}(t,L) = \frac{\partial z^n}{\partial x}(t,L) = 0$$

4.4 Numerical approximation with Crank-Nicolson method

We used the Crank-Nicolson method, that is a finite difference method, to solve system (4.3.1). Let

$$\Delta x = \frac{2L}{N} \quad \texttt{and} \quad \Delta t = \frac{T}{K}$$

and let

$$x_j = -L + j\Delta x \quad \texttt{and} \quad t_i = i\Delta t$$

We start with a discretization of the system at point $(t_{i+\frac{1}{2}}, x_j)$ for $i = 1, ..., K$, $j = 1, ..., N$ and where K and N are the number of step in which we chose to divide our time and space domain, respectively.
To easily explain the method used to approximate the solutions of the system, in the following paragraphs we use simply u, v, z instead of u^n, v^n, z^n.

Infected birds equation

Looking at the first equation of system (4.3.1), let

$$u_t(t_{i+\frac{1}{2}}, x_j) \approx \frac{u(t_{i+1}, x_j) - u(t_i, x_j)}{\Delta t}$$

the centered difference approximation for u_t at $(t_{i+\frac{1}{2}}, x_j)$.
To approximate the term $u_{xx}(t_{i+\frac{1}{2}}, x_j)$, we use the average second centered difference for $u_{xx}(t_{i+1}, x_j)$ and $u_{xx}(t_t, x_j)$, that is

$$u_{xx}(t_{i+\frac{1}{2}}, x_j) \approx \frac{1}{2}\left[\frac{u(t_{i+1}, x_{j-1}) - 2u(t_{i+1}, x_j) + u(t_{i+1}, x_{j-1})}{\Delta x^2} + \frac{u(t_i, x_{j-1}) - 2u(t_i, x_j) + u(t_i, x_{j-1})}{\Delta x^2}\right]$$

We can star writing the discretization of the first equation of system (4.3.1)

referred to the proportion of infected hosts, as follows

$$\frac{u(t_{i+1},x_j)-u(t_i,x_j)}{\Delta t}=\frac{u(t_{i+1},x_{j+1})+u(t_{i+1},x_{j-1})-2u(t_{i+1},x_j)}{2\Delta x^2}$$
$$+\frac{u(t_i,x_{j+1})+u(t_i,x_{j-1})-2u(t_i,x_j)}{2\Delta x^2}$$
$$+\alpha\beta_H\frac{N_V}{N_H}(1-u(t_i,x_j)-v(t_i,x_j))z(t_i,x_j)$$
$$-\frac{1}{2}(\gamma_H+\mu_H)u(t_{i+1},x_j)-\frac{1}{2}(\gamma_H+\mu_H)u(t_i,x_j)$$

or, letting $\lambda_1=D_1\frac{\Delta t}{\Delta x^2}$, for $i=2,...N-1$

$$-\frac{1}{2}\lambda_1u(t_{i+1},x_{j-1})+(1+\lambda_1+\frac{1}{2}(\gamma_H+\mu_H)\Delta t)u(t_{i+1},x_j)-\frac{1}{2}\lambda_1u(t_{i+1},x_{j+1})=$$

$$\frac{1}{2}\lambda_1u(t_i,x_{j-1})+(1-\frac{1}{2}(\gamma_H+\mu_H)\Delta t-\lambda_1)u(t_i,x_j)+\frac{1}{2}\lambda_1u(t_i,x_{j+1})$$
$$+\alpha\beta_H\frac{N_V}{N_H}\Delta t(1-u(t_i,x_j)-v(t_i,x_j))z(t_i,x_j)$$

Since we chose null-flux boundary conditions, $u(t_i,x_0)=u(t_i,x_1)$ and $u(t_i,x_N)=u(t_i,x_N+1)$.
And so, we obtain for $j=1$

$$(1+\frac{1}{2}\lambda_1+\frac{1}{2}(\gamma_H+\mu_H)\Delta t)u(t_{i+1},x_1)-\frac{1}{2}\lambda_1u(t_{i+1},x_2)=$$

$$(1-\frac{1}{2}\lambda_1-\frac{1}{2}(\gamma_H+\mu_H)\Delta t)u(t_i,x_1)+\frac{1}{2}\lambda_1u(t_i,x_2)$$
$$+\alpha\beta_H\frac{N_V}{N_H}\Delta t(1-u(t_i,x_1)-v(t_i,x_1))z(t_i,x_1)$$

and for $j=N$

$$-\frac{1}{2}\lambda_1u(t_{i+1},x_{N-1})+(1+\frac{1}{2}\lambda_1+\frac{1}{2})(\gamma_H+\mu_H)\Delta t)u(t_{i+1},x_N)=$$

$$\frac{1}{2}\lambda_1u(t_i,x_{N-1})+(1-\frac{1}{2}\lambda_1-\frac{1}{2}(\gamma_H+\mu_H)\Delta t)u(t_i,x_N)$$

$$+\alpha\beta_H \frac{N_V}{N_H}\Delta t(1-u(t_i,x_N)-v(t_i,x_N))z(t_i,x_N)$$

Let us solve this problem (in a matrix form)

$$Au^{i+1} = Bu^i + \alpha\beta_H \frac{N_V}{N_H}\Delta t(1-u^i-v^i)z^i \tag{4.4.1}$$

by implying with $(1-u^i-v^i)z^i$ the component-wise product and where

$$A = \begin{pmatrix} a_{11} & a_{12} & a_{13} & 0 & & \\ a_{21} & a_{22} & a_{23} & \ddots & & \\ & \ddots & \ddots & \ddots & \ddots & \\ & & & \ddots & \ddots & \\ & & & a_{N-2,N-1} & a_{N-1,N-1} & a_{N-1,N} \\ 0 & & & & a_{N,N-1} & a_{NN} \end{pmatrix}$$

$$B = \begin{pmatrix} b_{11} & b_{12} & b_{13} & 0 & & \\ b_{21} & b_{22} & b_{23} & \ddots & & \\ & \ddots & \ddots & \ddots & \ddots & \\ & & & \ddots & \ddots & \\ & & & b_{N-2,N-1} & b_{N-1,N-1} & b_{N-1,N} \\ 0 & & & & b_{N,N-1} & b_{NN} \end{pmatrix}$$

with

$$a_{11} = a_{N,N} = (1+\frac{1}{2}\lambda_1 + \Delta t(\gamma_H+\mu_h)) \qquad b_{11} = b_{N,N} = (1-\frac{1}{2}\lambda_1 - \Delta t(\gamma_H+\mu_h))$$

$$a_k = (1+\lambda_1+\Delta t(\gamma_H+\mu_h)) \qquad b_{kk} = (1-\lambda_1-\Delta t(\gamma_H+\mu_h))$$

$$a_{k,k-1} = a_{k-1,k} = -\frac{1}{2}\lambda_1 \qquad b_{k,k-1} = b_{k-1,k} = \frac{1}{2}\lambda_1$$

Removed birds equation

Let $\lambda_2 = D_2\dfrac{\Delta t}{\Delta x^2}$, for $j = 1,...N$ we can write the discretization of the equation related to the diffusion of the removed birds, obtaining

$$-\frac{1}{2}\lambda_2 v(t_{i+1},x_{j+1})+(1+\frac{1}{2}\Delta t\mu_h+\lambda_2)v(t_{i+1},x_j)-\frac{1}{2}\lambda_2 v(t_{i+1},x_{j-1})=$$

$$(1-\frac{1}{2}\Delta t\mu_h-\lambda_2)v(t_i,x_j)+\frac{1}{2}\lambda_2 v(t_i,x_{j+1})+\frac{1}{2}\lambda_2 v(t_i,x_{j-1})+\Delta t\gamma_H u(t_i,x_j)$$

and in matrix form, we can write

$$\hat{A}v^{i+1}=\hat{B}v^i+\Delta t\gamma_H u^i \tag{4.4.2}$$

Infected mosquitoes equation

In analogous way, we can obtain the following discretization of the equation of infected mosquitoes for $j=1,...N$, by letting $\lambda_3=D_3\dfrac{\Delta t}{\Delta x^2}$

$$(1+\lambda_3+\Delta t\frac{1}{2}\mu_V)z(t_{i+1,x_j})-\frac{1}{2}\lambda_3 z(t_{i+1},x_{j-1})-\frac{1}{2}\lambda z(t_{i+1},x_{j+1})=$$

$$(1-\lambda_3-\Delta t\frac{1}{2}\mu_V)z(t_{i,x_j})+\frac{1}{2}\lambda_3 z(t_i,x_{j-1})+\frac{1}{2}\lambda_3 z(t_i,x_{j+1})+\alpha\beta_V u(t_i,x_j)(1-z(t_i,x_j))\Delta t$$

In this case, the matrix formulation is

$$\tilde{A}z^{i+1}=\tilde{B}z^i+\alpha\beta_V u^i(1-z^i) \tag{4.4.3}$$

Now, by solving the system composed by

$$Au^{i+1}=Bu^i+\alpha\beta_H\frac{N_V}{N_H}\Delta t(1-u^i-v^i)z^i \tag{4.4.4}$$

$$\hat{A}v^{i+1}=\hat{B}v^i+\Delta t\gamma_H u^i \tag{4.4.5}$$

$$\tilde{A}z^{i+1}=\tilde{B}z^i+\Delta t\alpha\beta_V u^i(1-z^i) \tag{4.4.6}$$

with initial conditions in year n

$$\begin{aligned} u^n(t_0, x_j) &= 0 && \forall x_j \\ v^n(t_0, x_j) &= \rho(u^{n-1}(t_K, x_j) + v^{n-1}(t_K, x_j)) && \forall x_j \\ z^n(t_0, x_j) &= \delta(z^{n-1}(t_K, x_j)) && \forall x_j \end{aligned}$$

with the help of mathematical software, such as Matlab, we can obtain the numerical approximation of the system (4.3.1) that holds during the summer.

4.5 Some simulations

In this section, we present some approximation of the model (4.3.1). In each simulations that follow, we chose the values of some parameters such as the diffusion coefficients as $D_1 = D_2 = 0.004$ and $D_3 = 0.00002$, referring to the host and the vector population, respectively, in such a way that $D_3 << D_1 = D_2$. Some other parameters, as recovery rate, host and vector death rate and biting rate are taken equal to values proposed in Simpson et al. [2012], i.e. $\gamma = 0.195$, $\mu_H = 0.0014$, $\mu_V = 0.1$ and $\alpha = 0.14$.

We first consider the spatial spread of the disease within a season.

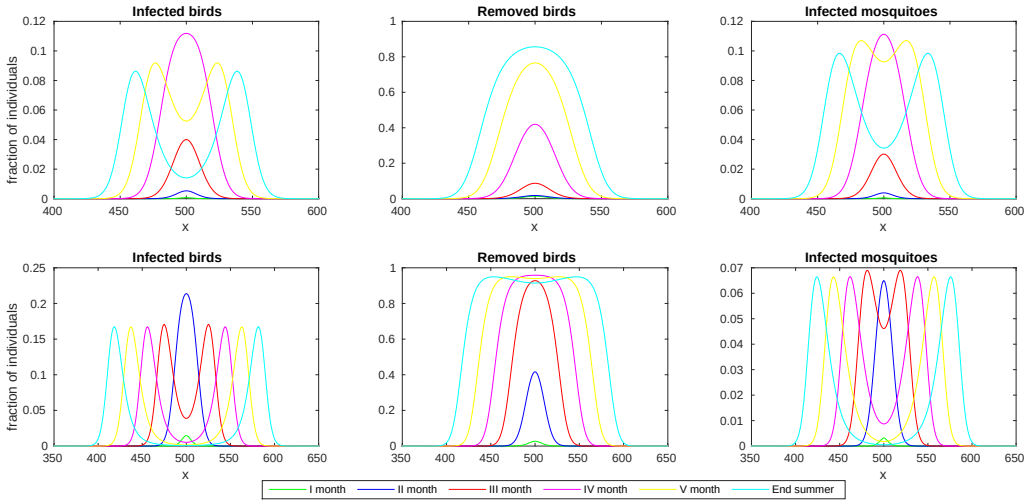


Figure 4.1: *Spatial spread of a vector-borne disease within a season*
At I row: plots obtained with $\frac{N_V}{N_H} = 7$, $\beta_H = 0.44$, $\beta_V = 0.974$ *and* $R = 1.73$
At II row: plots obtained with $\frac{N_V}{N_H} = 100$, $\beta_H = 0.14$, $\beta_V = 0.374$ *and* $R = 2.28$

In Figure 4.1, we show for each compartments, infected hosts, removed hosts and infected vectors two different cases. In both cases, the value of R is grater than one, in the first case $R = 1.73$ and in the second case $R = 2.28$. In the former we also decide to use $\frac{N_V}{N_H} = 7$, $\beta_H = 0.44$, $\beta_V = 0.974$, differently from the value that allow us to perform the simulation in the second row, where we use $\frac{N_V}{N_H} = 100$, $\beta_H = 0.14$, $\beta_V = 0.374$.

Then, we consider a multi-year period to observe some example of spatial

spread of the vector-borne disease.

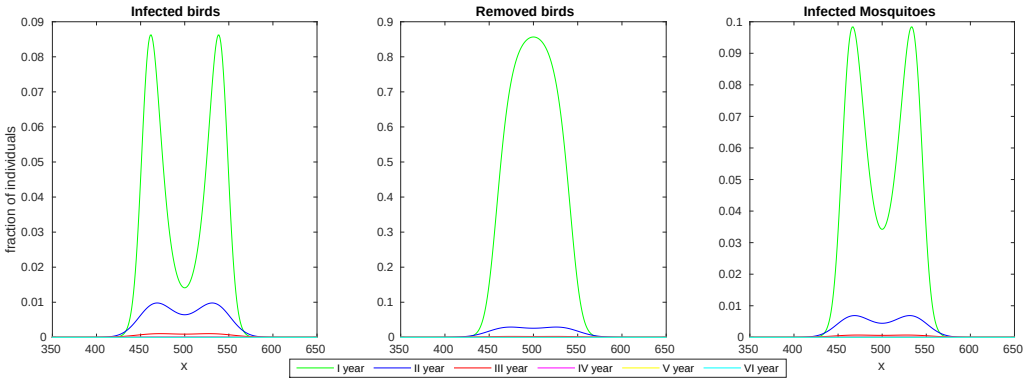


Figure 4.2: *Spatial spread of a vector-borne disease during six years*
Plot obtained with $\frac{N_V}{N_H} = 7$, $\beta_H = 0.44$, $\beta_V = 0.974$, $\delta = 8 \cdot 10^{-8}$ *and* $S_0 = 0.135$

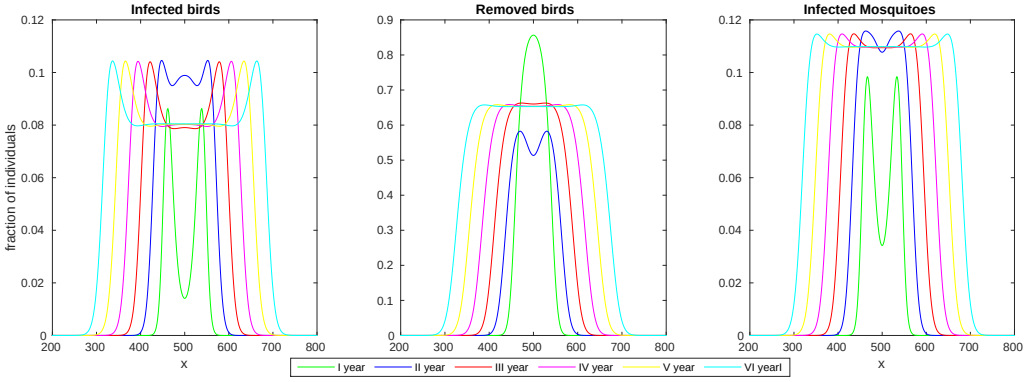


Figure 4.3: *Spatial spread of a vector-borne disease during six years*
Plot obtained with $\frac{N_V}{N_H} = 7$, $\beta_H = 0.44$, $\beta_V = 0.974$, $\delta = 8 \cdot 10^{-6}$ *and* $S_0 = 13.5$

In Figure (4.2) and (4.3), we chose some values of the parameter as $\frac{N_V}{N_H} = 7$, $\beta_H = 0.44$, $\beta_V = 0.974$. By varying the value of survival probability of vectors during the winter, we can obtain two different patterns. With $\delta = 8 \cdot 10^{-8}$, we obtained a value of $S_0 < 1$ and with $\delta = 8 \cdot 10^{-6}$, $S_0 > 1$. Assuming the same values for the survival probabilities used to obtain the plots in Figure (4.2) and (4.3), but varying the other three parameters, we obtained the patterns showed in Figure (4.4) and (4.5). In those figures, we chose $\frac{N_V}{N_H} = 60$, $\beta_H = 0.14$, $\beta_V = 0.374$.

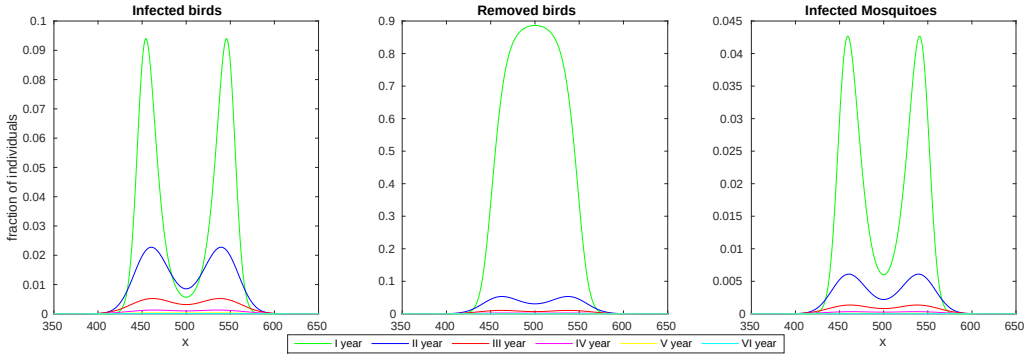


Figure 4.4: *Spatial spread of a vector-borne disease during six years*
Plot obtained with $\frac{N_V}{N_H} = 60$, $\beta_H = 0.14$, $\beta_V = 0.374$, $\delta = 8 \cdot 10^{-8}$ *and* $S_0 = 0.31$

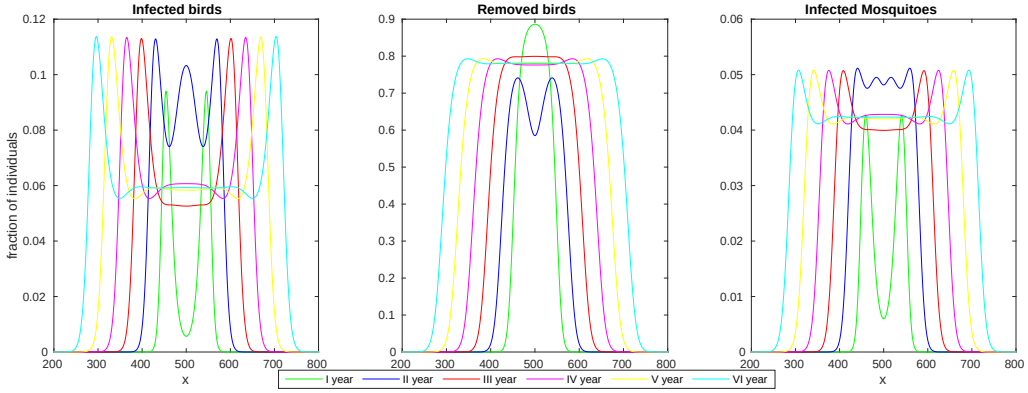


Figure 4.5: *Spatial spread of a vector-borne disease during six years*
Plot obtained with $\frac{N_V}{N_H} = 60$, $\beta_H = 0.14$, $\beta_V = 0.374$, $\delta = 8 \cdot 10^{-6}$ *and* $S_0 = 30,9$

Focusing on Figure (4.2), (4.3), (4.4) and (4.5) and considering $S_0 = 1$ the spreading threshold, we can observe a limited propagation of the disease when we are in the situation with $S_0 < 1$. In fact after the second or third year the infection seems to disappear in the whole domain.
On the other hand, observing the cases in which $S_0 > 1$, it seems that there is a constant spreading speed of traveling wave. Presumably, it would be possible to prove rigorously the existence of traveling waves in the spirit of Lewis and Li [2012].

Appendix A

To prove that $\frac{\partial G_1}{\partial R} = 0$ and $\frac{\partial G_2}{\partial R} < 1$, let us consider the derivatives of (i_H, r_H, i_V), that are the solution functions of system (2.3.3), with respect to $i_V(0) = Q$, i.e.

$$\left.\frac{\partial (i_H, r_H, i_V)^T}{\partial Q}\right|_{Q=0} = U(t) = [u_1, u_2, u_3]$$

where $u_1 = \frac{\partial i_H}{\partial Q}$,$u_2 = \frac{\partial r_H}{\partial Q}$, $u_3 = \frac{\partial i_V}{\partial Q}$.

Let f be defined by the right-hand side of (2.3.3), so that

$$U'(t) = \nabla f(i_H(t, Q, R), i_R(t, Q, R), i_V(t, Q, R))U(t).$$

Evaluating it in $Q = 0$ and $R = 0$ and computing the derivative with respect to Q, we obtain

$$\begin{aligned} \dot{u_1} &= \alpha\beta_H \frac{N_V}{N_H} u_3 - (\gamma_H + \mu_H)u_1 \quad && u_1(0) = 0 \\ \dot{u_2} &= \gamma_H u_1 - \mu_H u_2 && u_2(0) = 0 \\ \dot{u_3} &= \alpha\beta_V u_1 - \mu_V u_3 && u_3(0) = 1 \end{aligned} \tag{A.0.1}$$

One can note that the equations u_1, u_3 are exactly the same as in system (2.2.10) and do not depend on u_2.
From the definition (2.3.4, 2.3.5) of G, we have

$$\frac{\partial G_1}{\partial Q} = \delta u_3(T) \quad \frac{\partial G_2}{\partial Q} = \rho(u_1(T) + u_2(T)).$$

Hence $\dfrac{\partial G_1}{\partial Q} = \delta z(T)$, $z(\cdot\,)$ solution of (2.2.10).
Similarly if we compute the derivatives with respect to R, defining

$$\left.\frac{\partial (i_H, r_H, i_V)^T}{\partial R}\right|_{R=0} = W(t) = [w_1, w_2, w_3]$$

we obtain that

$$\frac{\partial G_1}{\partial R} = \delta w_3(T) \quad \frac{\partial G_2}{\partial R} = \rho(w_1(T) + w_2(T))$$

where

$$\begin{aligned} \dot{w}_1 &= \alpha\beta_H \frac{N_V}{N_H} w_3 - (\gamma_H + \mu_H) w_1 && w_1(0) = 0 \\ \dot{w}_2 &= \gamma_H w_1 - \mu_H w_2 && w_2(0) = 1 \\ \dot{w}_3 &= \alpha\beta_V w_1 - \mu_V w3 && w_3(0) = 0 \end{aligned} \tag{A.0.2}$$

It is easy to see that the solution of (A.0.2) is $w_1(t) \equiv 0$, $w_3(t) \equiv 0$ and $w_2(t) = e^{-\mu_H t}$. Hence

$$\begin{aligned} \frac{\partial G_1}{\partial R} &= \delta w_3(\tau) = 0 \\ \frac{\partial G_2}{\partial R} &= \rho e^{-\mu_H t} < 1 \end{aligned} \tag{A.0.3}$$

Appendix B

The results regarding the model without vertical transmission are displayed in the following Figures.

The results are qualitatively quite similar to the case with vertical transmission.

Fig	(B.1a)	(B.1b)	(B.1c)	(B.1d)	(B.1e)	(B.1f)
b_2	0.1266	0.1266	0.1062	0.1062	0.1062	0.1062
d_2	0.0624	0.06244	0.0549	0.0549	0.0549	0.0549
k_M	91446,7	91446,7	91446,7	193717,5	193717,5	193717,5
α	0.5187	0.5132	0.5562	0.3071	0.5827	0.6891
β_B	0.1013	0.1769	0.0876	0.0992	0.0606	0.1110
β_M	0.6621	0.3181	0.3399	0.9991	0.5784	0.1112
γ	0.1981	0.2334	0.1543	0.1605	0.1982	0.2174
μ_{WN}	0.3476	0.3622	0.0478	0.4646	0.3548	0.1249
ϵ	0.1203	0.1340	0.1346	0.1438	0.1327	0.1175

Table B.1: *Value of the parameters related to the plots in Figure B.1*

Figures B.2 show how the disease reaches a stable point more slowly than in the case of the model with vertical transmission.

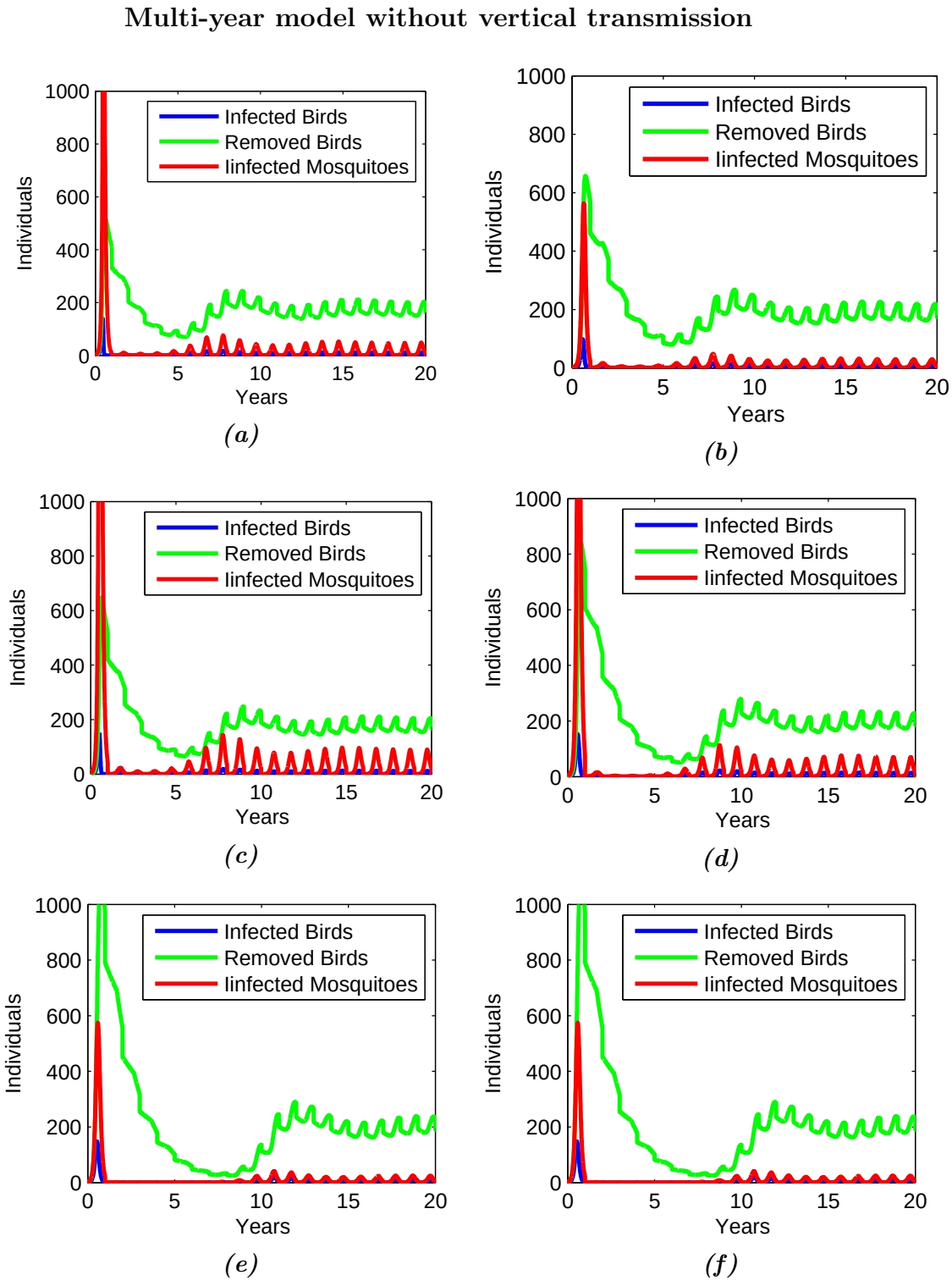


Figure B.1: *Simulations of the model without vertical transmission with different sets of parameters in Table B.1 for* $S_0 = 2$

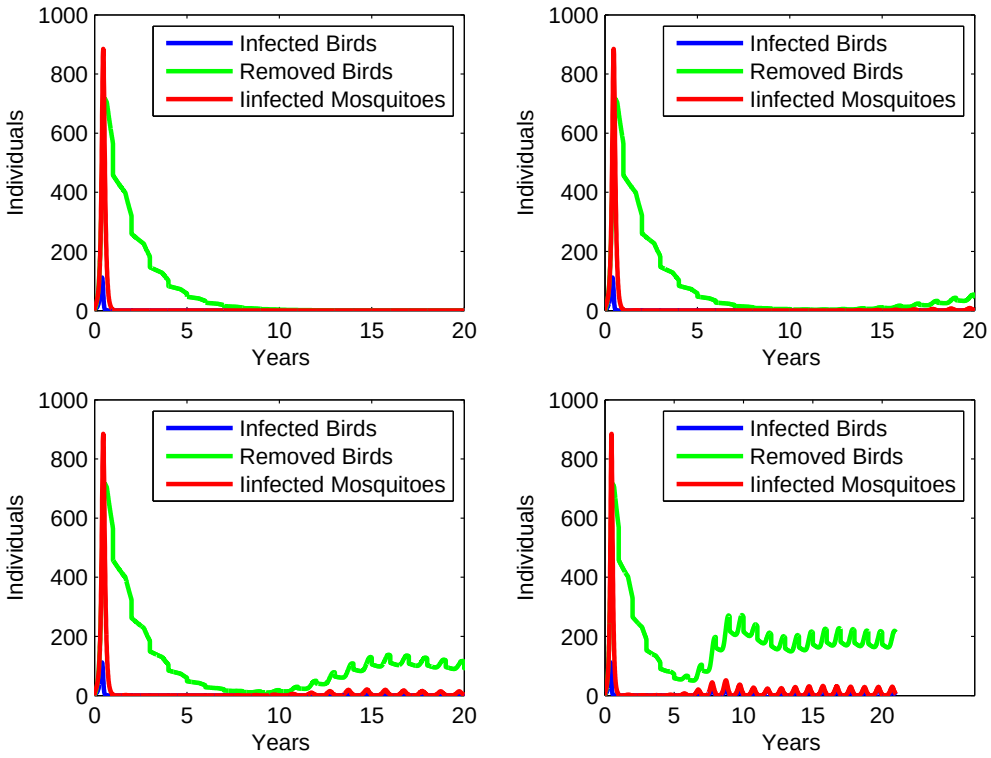


Figure B.2: *Simulations of the model without vertical transmission with the same sets of parameters for different vale of* $S_0 = 0.2, 1.5, 2, 4$

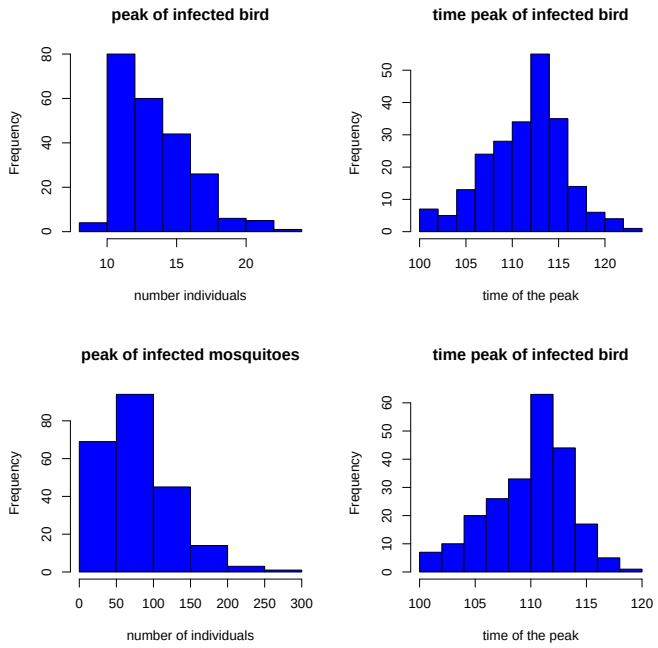


Figure B.3: *Peaks and times of peak of infected birds and mosquitoes (Model without vertical transmission)*

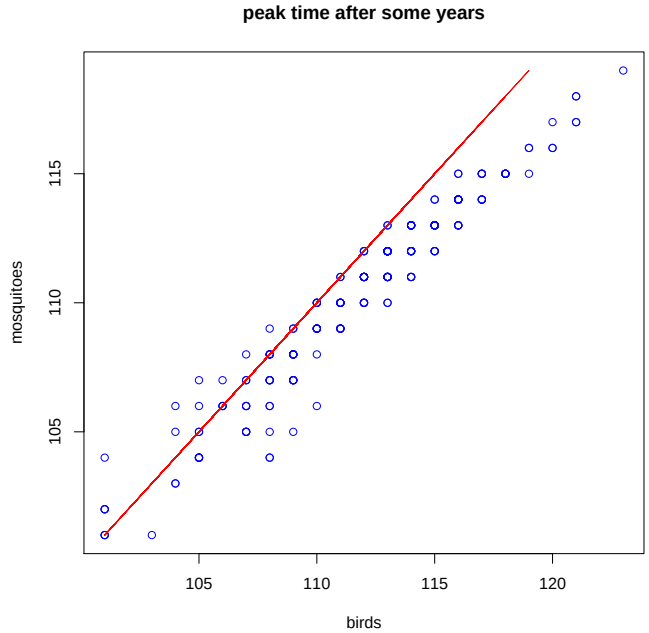


Figure B.4: *Peak time of infected bird versus peak time of infected mosquitoes*

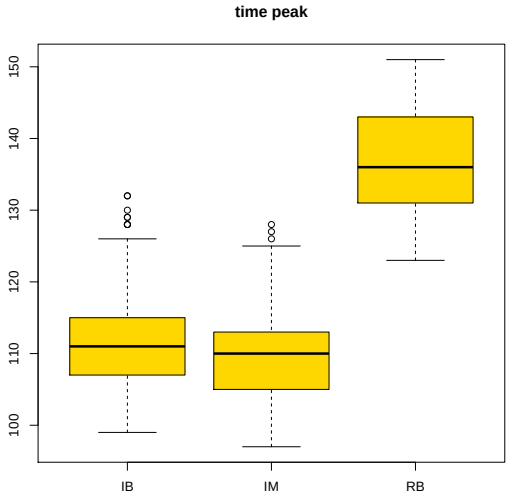


Figure B.5: *Peak time*

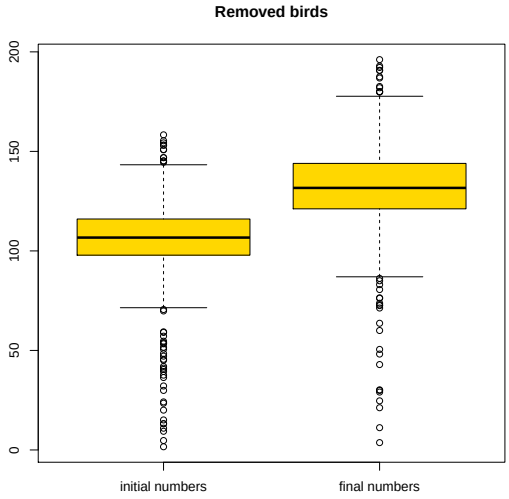


Figure B.6: *Removed Birds*

Figure B.7: *On the left Peak time of infected bird, peak time of infected mosquitoes and peak time of removed birds and on the right Initial and final R_B after some years in the model without vertical transmission*

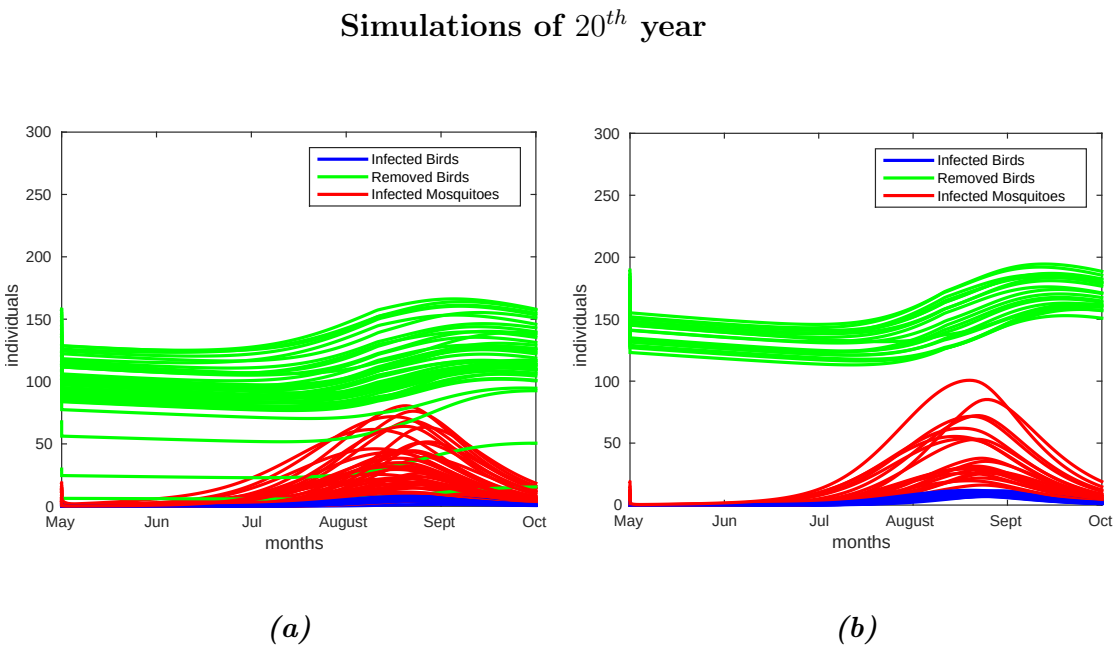


Figure B.8: *Plot of the 20^{th} year of some simulations starting with only one infected bird for $S_0 = 2$, Figure B.8a, and for $S_0 = 3$, Figure B.8b . In red line there are the infected mosquitoes, in blue the infected birds and in green the removed birds*

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