Ross-Macdonald Models: Which one should we use?

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Abstract

Ross-Macdonald models are the building blocks of most vector-borne disease models. Even for the same disease, different authors use different model formulations, but a study of the dynamical consequences of assuming different hypotheses is missing. In this work we present different formulations of the basic Ross-Macdonald model together with a careful discussion of the assumptions behind each model. The most general model presented is an agent based model for which arbitrary distributions for latency and infectious periods for both, host and vectors, is considered. At population level we also developed a deterministic Volterra integral equations model for which also arbitrary distributions in the waiting times are included. We compare the model solutions using different distributions for the infectious and latency periods using statistics, like the epidemic peak, or epidemic final size, to characterize the epidemic curves. The basic reproduction number ($R_0$) for each formulation is computed and compared with empirical estimations obtained with the agent based models. The importance of considering realistic distributions for the latent and infectious periods is highlighted and discussed. We also show that seasonality is a key driver of vector-borne disease dynamics shaping the epidemic curve and its duration.

Keywords:
Ross-Macdonald Model, Epidemiology, Delayed Model, Agent Based Model

1. Introduction

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Vector-borne diseases are caused by different types of parasites, including viruses and bacteria, which are transmitted by vectors as mosquitoes, sandflies, ticks, and kissing-bugs, among others. According to the World Health Organization, every year there are more than 700 thousand deaths as a consequence of vector-borne diseases [47].

Mosquito-borne diseases of humans include malaria, dengue, zika, chikungunya, yellow fever (see for example [41, 11, 20]). Different triatomine species transmit *Trypanosoma cruzi* the causal agent of Chagas disease (see for example [37] and references there in) while Leishmaniasis is transmitted by several species of sandflies [9].

Vector-borne diseases are also common zoonotic diseases. Some forms of Leishmaniasis cannot be transmitted from humans to sandflies and the parasite population survives in a wild cycle including small rodents, dogs, cows and several species of birds as hosts [3, 9]. West Nile Virus may be transmitted to humans but it is maintained in a cycle which includes several species of birds [46]. *Trypanosoma cruzi*, the causal agent of Chagas disease is also transmitted to different animals including dogs, marsupials, rodents, and others hosts [23].

Ross model was published in 1911 [35] and remains as the basis of countless models for vector-borne diseases. Ross considered a simple model for malaria, with births and deaths but with constant populations and infectious periods exponentially distributed. Humans and mosquitoes may be in only two classes: Affected and Unaffected (what here we will denoted by $H_i, H_s, V_i, V_s$). Then, Ross model in continuous time reads

\[
\frac{dH_i}{dt} = \beta_i m \frac{V_i}{V} (H - H_i) - r_i H_i \\
\frac{dV_i}{dt} = \beta_i \frac{H_i}{H} (V - V_i) - \mu_i V_i
\]

where $H$ and $V$ are the numbers of humans and mosquitoes, $m$ is the number of mosquitoes per human ($V/H$), $r_h$ is the recovery rate for humans, $\mu_v$ is the mortality rate for mosquitoes, and $\beta_j$ are the transmission parameters which may be decomposed as $\beta_j = b f p_j$ with $b$ the mosquitoes biting rate, $f$ the proportion of bites in humans, and $p_j$ the probability of transmission per bite. Ross formulation is still used but it is not advisable. The parameter $m$ is in fact a dynamical variable. For the original Ross model this was not a problem as he considered constant populations. However, both vector and host populations may vary in time, therefore,
an equivalent formulation, more frequently used, and preferable is

\[
\frac{dH_i}{dt} = \beta_i V_i \frac{H_i}{H} - r_i H_i \quad (1)
\]

\[
\frac{dV_i}{dt} = \beta_v V_i \frac{H_i}{H} - \mu_v V_i \quad (2)
\]

Models with these rates of infection are broadly known as Ross-Macdonald models, albeit Macdonald’s contribution to the Ross model is not reflected in this model formulation. Macdonald modified the original Ross model, integrating biological information about the mosquito latency period, and introduced the exposed class for vectors [26]. Later he considered also the case of super-infection in Malaria disease dynamics (see for an extensive discussion [40]).

For the Ross model, the basic reproduction number ($R_0$), defined as the number of secondary host cases produced by a typical infectious host in a completely susceptible population is

\[
R_0 = \frac{\beta_h \beta_v}{r_i \mu_v} \frac{V}{H}
\]

This celebrated result from Ross [35] shows that the basic reproduction number is proportional to the number of vectors per host ($V/H$), and therefore, disease transmission may be interrupted if the number of vectors per host is reduced below some threshold.

Since the pioneering work of Ross, several extensions of his basic model (Eqs. 1-2) were developed including the addition of exposed classes, superinfection, spatiality, time-varying populations, age structure and more (see for example [16, 8, 6, 26, 40, 29, 36]), and applied to the study of different infectious diseases such as malaria, dengue, yellow fever, cutaneous Leishmaniasis, Chagas disease, West Nile virus, among others (see for example [44, 39, 26, 2, 43, 46] and references therein).

In this work we present a detailed analysis of some general Ross-Macdonald models. We show that the inclusion of exposed classes as well as the distribution of the latent and infectious periods, have significant dynamical consequences. We also show that seasonality is a major factor shaping the epidemics curves.

This paper is arranged as follow. In the next section we discuss the general assumptions common of all models presented. In Section 3 several deterministic Ross-Macdonald models are developed considering exposed classes and different distributions for the waiting periods. The basic reproduction number is computed in each case. A stochastic agent based model (ABM) is developed in Section
4. Numerical results, such as epidemic curves, epidemic final sizes, the basic reproduction number are computed for each model and compared between them in Section 5. The key role of seasonality is also discussed. Finally present the discussion of the results and conclusions.

2. General assumptions and parameters

In a Ross-Macdonald model it is assumed that populations are homogeneously mixed. Vector’s bites are evenly divided among hosts, that is, every time a vector bites, chooses a host at random. This hypothesis leads to a frequency dependent transmissions terms proportional to \( V_iH_s/H \) and \( V_sH_i/H \). This central hypothesis is perhaps what define what a Ross-Macdonald model is. However we want to stress that this assumption is only realistic for small populations like a household. The use of Ross-Macdonald type of models for larger populations will be analyzed elsewhere.

**Demography.** Immigration and emigration are not considered as we are interested in the simplest cases. Births are assumed to take place at a (density-independent) rate \( \Lambda \). Deaths may be described by the mortality or by the survival function. Mortality (\( \mu \)) is the number of deaths per individual and per unit of time. In general it is an age-dependent rate. The survival function, \( \tilde{F}(a) \), is the proportion of individuals still alive at age \( a \), and it is related with the mortality by \( \tilde{F}(a) = 1 - e^{-\int_0^a \mu(s)ds} \).

**Epidemiology.** Populations are divided in some of the following epidemiological classes: Susceptible, Latent, Infectious, and Recovered. Latent (or Exposed) individuals are infected but not infectious (and therefore are unable to transmit the disease). Recovered individuals are immune, and therefore do not participate of the transmission process. Duration of the latent period may be described for a survival function of the age of infection, \( \tilde{F}_e(s) \) which gives the proportion of latent individuals who remain latent at age of infection \( s \) (age of infection is the time elapsed since first infection). Analogously, \( \tilde{F}_i(s) \) is the proportion of infectious individuals who remain infectious after a time \( s \) after the end of latency. Alternatively we can use the, (in general) age-of-infection dependent, progression rates (from latency to infectiousness) or recovery rates (from infectiousness to recovery).

All the periods considered (lifespan, latency period, infectious period) are random variables which may be characterized by a probability distribution. The simple, and commonly used case of exponentially distributed periods correspond to
constant, age independent, rates. For example using a constant mortality rate $\mu$
imply the assumption of an exponentially distributed lifespan.

Parameters defining the different periods distributions are:

- $T_h$: Host life expectancy (mean lifespan)
- $T_v= T_{vi}$: Vector life expectancy, mean infectious period for vectors
- $T_{he}$: Mean latency period for exposed hosts
- $T_{hi}$: Mean infectious period for hosts
- $T_{ve}$: Mean latency period for vectors

For the limiting cases of exponentially distributed or fixed periods these parameters values completely define the probability distributions. In the general case other parameters like the variance of the distribution should be provided. In all cases we considered that vectors are infectious for life.

**Entomological parameters.** Biting rate on hosts (number of bites per vector, per unit of time, on hosts) is denoted by $b$. Probabilities of transmission per bite are $p_h$ and $p_v$ (from vectors to hosts and from hosts to vectors respectively). Finally we define $\beta_h = p_h b$, and $\beta_v = p_v b$.

**Basic reproduction numbers.** For a general Ross-Macdonald model the basic reproduction number may be obtained by simple bookkeeping [15]. One infectious host will produce an average of $\beta_v V \frac{1}{H}$ infected vectors per unit of time. If the mean infectious period for hosts is $T_{hi}$, then the total number of infected vectors is $\beta_v V \frac{1}{H} T_{hi}$. Only a fraction $f_v$ will survive the latency period, and therefore, the total number of infectious vectors produced by the initial infectious host is $\beta_v V \frac{1}{H} T_{hi} f_v$. Each infectious vector would produce $\beta_h T_{vi}$ host infections ($T_{vi}$ is the mean infectious period for vectors) and only a fraction $f_h$ will survive the host latency period. Finally the basic reproduction number is given by

$$R_0 = \beta_h \beta_v T_{hi} T_{vi} f_h f_v \frac{V}{H} \quad (3)$$

3. **Deterministic Ross-Macdonald models**

In a Ross-Macdonald model there are host and vector populations (of size $H$ and $V$ respectively) homogeneously mixed. Each population is subdivided in epidemiological classes. For example, susceptible and infectious host and vector populations ($H_s, H_i, V_s, V_i$). Vectors bite at the rate $b$ (daily number of bites per
vector, for example). If \( p_h \) is the probability of infection transmission to hosts per bite, \( p_v \) the probability of vector infection per bite on infectious hosts, then, the rate of infection of susceptible hosts is given by \( p_h b V_i \frac{H}{H} \) while the rate of infection of susceptible vectors by \( p_v b V_s \frac{H}{H} \). These functional forms for the infection rates are characteristic of all the Ross-MacDonald type models. In the following we will present, discuss and compare the more common deterministic models (without age structure).

3.1. Basic Model

One of the most simple, general, and used model is the SIR model for hosts and a SI model for vectors. Mortalities are denoted by \( \mu \) while recovery rates by \( r \). \( \Lambda \)'s are the recruitment rates. We will assume that all the periods are exponentially distributed and therefore we obtain the following Basic model:

\[
\frac{dH_s}{dt} = \Lambda_h - \beta_h V_i \frac{H_s}{H} - \mu_h H_s \quad (4)
\]

\[
\frac{dH_i}{dt} = \beta_h V_i \frac{H_s}{H} - (r_h + \mu_h)H_i \quad (5)
\]

\[
\frac{dH_r}{dt} = r_h H_i - \mu_h H_r \quad (6)
\]

\[
\frac{dV_s}{dt} = \Lambda_v - \beta_v V_s \frac{H_i}{H} - \mu_v V_s \quad (7)
\]

\[
\frac{dV_i}{dt} = \beta_v V_s \frac{H_i}{H} - \mu_v V_i \quad (8)
\]

where \( \mu_h = 1/T_h \) and \( \mu_v = 1/T_v \). Mean infectious period for host includes recovery and mortality, and therefore in this case is given by \( T_{hi} = 1/(r_h + \mu_h) \), from where recovery rate \( r_h \) can be estimated. In this work we will consider only the case \( \mu_h = 0 \), but for many species of hosts, \( \mu_h \ll r \) and therefore we may approximate the recovery rate by \( 1/T_h \). Vectors are assumed to be infectious for life and then \( \mu_v = 1/T_{vi} = 1/T_v \).

Because in this model there are not latency periods, \( f_h = f_v = 1 \) and the basic reproduction number (Eq. 3) becomes

\[
R_0^{(1)} = \frac{\beta_h \beta_v}{(r_h + \mu_h) \mu_v} V \quad (9)
\]
The assumption of constant mortality for vectors is plausible as for insects we expect an approximately constant daily probability of death. For hosts like birds, constant mortality is also usually observed. However hosts like humans present a survival of type I: low mortality for ages below the mean followed by a steep decrease in survival. In this case an age structured model for the host population should be used (see for example [36]). However in those cases we have that $\mu_h \ll \mu_v$ and therefore we may disregard birth and deaths in the host population when studying the short-term dynamics like in a single outbreak, the case we are considering in this work.

Infectious period is also assumed exponentially distributed, a not realistic assumption. Hosts may lose immunity becoming susceptible again, a case we do not consider in this work.

3.2. Basic Model with exposed classes

For both, hosts and vectors, there are latent periods and therefore a more realistic model is a $S\,EIR$ model for hosts and a $S\,EI$ model for vectors (as in most cases vectors are infectious for life). The basic model with latent classes (SEIR-SEI model) is:

\[
\frac{dH_s}{dt} = \Lambda_h - \beta_h V_i \frac{H_s}{H} - \mu_h H_s
\]

\[
\frac{dH_e}{dt} = \beta_h V_i \frac{H_s}{H} - (k_h + \mu_h) H_e
\]

\[
\frac{dH_i}{dt} = k_h H_e - (r_h + \mu_h) H_i
\]

\[
\frac{dH_r}{dt} = r_h H_i - \mu_h H_r
\]

\[
\frac{dV_s}{dt} = \Lambda_v - \beta_v V_s \frac{H_i}{H} - \mu_v V_s
\]

\[
\frac{dV_e}{dt} = \beta_v V_s \frac{H_i}{H} - (k_v + \mu_v) V_e
\]

\[
\frac{dV_i}{dt} = k_v V_e - \mu_v V_i
\]

Here, $k_h$ and $k_v$ are the progression rates from latency to infectiousness, and in this context are given by $k_j = 1/T_{je}$ with $T_{je}$ the mean latency periods ($j = h$ for hosts, and $j = v$ for vectors).
In this case the basic reproduction number is

\[
R_0^{(2)} = \frac{\beta_h \beta_v}{(r_h + \mu_h) \mu_v} \left( \frac{k_v}{k_v + \mu_v} \right) \left( \frac{k_h}{k_h + \mu_h} \right) \frac{V}{H}
\]

where \( f_j = k_j/(k_j + \mu_j) \) are the fractions of exposed individuals who survive the latency period.

The assumptions in this model are the same discussed above but here it is also assumed that latent periods are exponentially distributed a not realistic assumption neither. Once again \( k_h \gg \mu_h \) and then \( \frac{k_h}{k_h + \mu_h} \approx 1. \)

3.3. Models with arbitrary distributions for the waiting periods

The assumption of exponentially distributed periods is appealing because the corresponding ODE models have constant parameters. However latency or infectious periods are, in general, random variables with non-exponential distributions.

In our case, where we are considering that vectors remain infectious for life, the infectious period is the vector lifespan. In this case a constant mortality is a realistic choice and therefore the infectious period is exponentially distributed. However this is not the case of vector’s latent period or the latent and infectious host’s periods.

As an example we will first consider the simple case of a \( SIR - SI \) model. For vectors we have the equations\(^7\)[8]. For the host population we will consider that the infectious period (\( T_h \)) is a random variable with probability distribution function \( f(s) \). As usual, the cumulative distribution is denoted by \( F(s) \). The complementary cumulative distribution, \( \bar{F}(s) = 1 - F(s) \), is known as the survival function and gives the probability that an individual infected in \( s = 0 \) remains infected at time \( s \). Because only the fraction \( \bar{F}(t - s) \) of the infections produced at time \( s \) survives until time \( t \) we obtain the integral Volterra equations

\[
\begin{align*}
H_s(t) &= H_s(0) - \int_0^t \frac{\beta_h}{H} V_i(s) H_s(s) ds \\
H_i(t) &= H_i(0) \bar{F}(t) + \int_0^t \frac{\beta_h}{H} V_i(s) H_s(s) \bar{F}(t - s) ds \\
H_r(t) &= H - H_s(t) - H_i(t)
\end{align*}
\]

Differentiation of Volterra equation gives the following system of integro-differential equations,
for hosts and vectors we have the following Volterra integral equations model,

\[
\frac{dH_s}{dt} = -\beta_h V_i \frac{H_s}{H} \\
\frac{dH_i}{dt} = H_i(0) \frac{d\hat{F}}{dt} + \beta_h V_i \frac{H_s}{H} \hat{F}(0) + \int_0^t \frac{\beta_h}{H} V_i(s) H_s(s) \frac{d\hat{F}}{dt} (t-s) ds
\]

\[
= -H_i(0)f(t) + \beta_h V_i \frac{H_s}{H} - \int_0^t \frac{\beta_h}{H} V_i(s) H_s(s)f(t-s) ds
\]

Realistic distributions for infectious or latent periods are bell shaped and therefore survival function is of type I. Then, a simple but realistic distribution is obtained for the limiting case of fixed infectious period \( T_{hi} \). In this case the survival function is a step function, the probability density distribution is \( \delta(t - T_{hi}) \), and therefore we obtain the delayed equation

\[
\frac{dH_i}{dt} = -H_i(0)\delta(t - T_{hi}) + \beta_h V_i \frac{H_s}{H} - \beta_h V_i(t - T_{hi}) \frac{H_s(t - T_{hi})}{H} \tag{18}
\]

In the general case of arbitrary distributions in latency and infectious periods for hosts and vectors we have the following Volterra integral equations model,

\[
H_s(t) = H_s(0) - \int_0^t \beta_h V_i(s) \frac{H_s(s)}{H} ds \tag{19}
\]

\[
H_e(t) = H_e(0) \hat{F}_{he}(t) + \int_0^t \beta_h V_i(s) \frac{H_s(s)}{H} \hat{F}_{he}(t-s) ds \tag{20}
\]

\[
H_i(t) = H_i(0) \hat{F}_{hi}(t) + \int_0^t \int_0^\tau \beta_h V_i(s) \frac{H_s(s)}{H} \left\{ -\frac{d\hat{F}_{he}(\tau-s)}{dt} \right\} \hat{F}_{hi}(t-\tau) d\tau ds \tag{21}
\]

\[
H_v(t) = H - H_s(t) - H_e(t) - H_i(t) \tag{22}
\]

\[
V_s(t) = V_s(0)e^{-\mu t} + \int_0^t \Lambda_v e^{-\mu(t-s)} ds - \int_0^t \beta_v V_s(s) \frac{H_i(s)}{H} ds \tag{23}
\]

\[
V_e(t) = V_e(0)e^{-\mu t} + \int_0^t \beta_v V_s(s) \frac{H_i(s)}{H} \hat{F}_{ve}(t-s) e^{-\mu(t-s)} ds \tag{24}
\]

\[
V_i(t) = V_i(0)e^{-\mu t} + \int_0^t \beta_v V_s(s) \frac{H_i(s)}{H} \left\{ -\frac{d\hat{F}_{ve}(\tau-s)}{dt} \right\} e^{-\mu(t-s)} d\tau ds \tag{25}
\]

where \( \hat{F}_{je}, \hat{F}_{ji} \) are the survival functions for the exposed and infectious populations (\( j = h \) for host and \( j = v \) for vectors).
3.3.1. Gamma distributed periods

Realistic probability distribution functions for infectious or latent periods are bell shaped and therefore the survival functions are of type I. While accurate numerical solutions of a system of ordinary differential equations like model \(10-16\) are easily obtained using a Runge-Kutta scheme, for example, integral systems like \(19-25\) are not that amenable.

Gamma distributions are flexible functions with two parameters, the shape parameter \(k\) and the scale parameter \(\theta\). Some features of this distribution are particularly appealing. The exponential distribution is a special case of the Gamma distribution when \(k = 1\), while for \(k \to \infty\) the Gamma distribution converges to the Dirac delta function. Most importantly, for integer values of \(k\) the system \(19-25\) is equivalent to a system of ordinary differential equations with constant rates (see for example [38] and Appendix B). This result allows to obtain numerical solutions of the system of integral equations using a simple numerical scheme like Runge-Kutta.

3.3.2. Delayed Model

A simple but realistic distribution for the latent or infectious periods is obtained in the limiting case of fixed periods when the survival functions are step functions, and therefore the probability density distributions are Dirac delta distributions, \(\delta(s-T_{he}), \delta(s-T_{hi}), \delta(s-T_{ve})\). In this limiting case, the integro-differential system obtained by differentiation of the integral equations system (see model \(A.8-A.14\) in the Appendix A) reduces to a system of differential delayed equations,
\[
d\frac{dH_s}{dt} = -\beta_h V_i \frac{H_s}{H} \\
d\frac{dH_e}{dt} = \beta_h V_i \frac{H_s}{H} - \beta_h V_i (t - T_{he}) \frac{H_e(t - T_{he})}{H} \\
d\frac{dH_i}{dt} = H_i(0) \delta(t - T) + \beta_h V_i (t - T_{he}) \frac{H_i(t - T_{he})}{H} - \beta_h V_i (t - T_{he} - T_{hi}) \frac{H_i(t - T_{he} - T_{hi})}{H} \\
d\frac{dH_r}{dt} = \beta_h V_i (t - T_{he} - T_{hi}) \frac{H_i(t - T_{he} - T_{hi})}{H} \\
d\frac{dV_s}{dt} = \Lambda_v - \beta_v V_s \frac{H_i}{H} - \mu_v V_s \\
d\frac{dV_e}{dt} = \beta_v V_s \frac{H_i}{H} - e^{-\mu_v T_{ve}} \beta_v V_s (t - T_{ve}) \frac{H_i(t - T_{ve})}{H} - \mu_v V_e \\
d\frac{dV_i}{dt} = e^{-\mu_v T_{ve}} \beta_v V_s (t - T_{ve}) \frac{H_i(t - T_{ve})}{H} - \mu_v V_i \\
\]

where \(T_{ve}, T_{he}, \text{ and } T_{hi}\) are the (fixed) latency and infectious periods of vectors and hosts. As discussed above, vector’s infectious period is assumed exponentially distributed as we considered a constant vector mortality rate. Host mortality is disregarded and then all latent host become infectious (and then \(f_h = 1\)). However only a fraction \(f_v = e^{-\mu_v T_{ve}}\) of infected vectors survive the latency period becoming infectious.

Therefore the basic reproduction number is given by

\[
R_0^{(3)} = \beta_h \beta_v \frac{1}{T_{hi}} e^{-\mu_v T_{ve}} \frac{V}{H} \\
\]

3.4. Relationship between the Basic reproduction numbers, and the basic modified model

Suppose that we are studying a host-vector system for which there are estimations of the parameters as the mean latency and infectious periods. If latency periods are disregarded and we assume that all the periods are exponentially distributed, we may use the basic model (4-8) for which the basic reproduction number is
\[ R_0^{(1)} = \frac{\beta_h \beta_v}{(r_h + \mu_h) \mu_v} V. \]

However, a more realistic model should include the latency periods. Under the most common, but unrealistic, assumption of exponentially distributed periods the corresponding model is \[10\,16\] and the basic reproduction number is

\[ R_0^{(2)} = R_0^{(1)} \left( \frac{k_v}{k_v + \mu_v} \right) < R_0^{(1)}. \]

The delayed model \[27\,32\] is a more realistic choice for which the basic reproduction number is

\[ R_0^{(3)} = \beta_h \beta_v T_h \frac{1}{\mu_v} e^{-\mu_v T_v} \frac{V}{H}. \]

Because \( \frac{k_v}{k_v + \mu_v} \geq e^{-\mu_v T_v} \), the basic reproduction numbers for the different models satisfy

\[ R_0^{(1)} > R_0^{(2)} > R_0^{(3)}. \]

Therefore we expect larger and faster epidemics for the simple SIR–SI model (Eqs. \[4\,8\]) than the obtained with the more realistic models.

However, it is possible to implicitly include the effect of latency in the vector population in the basic model \[4\,8\] modifying the equation \[8\] as

\[ \frac{dV_i}{dt} = e^{-\mu_v T_v} \beta_v V_s H_i \frac{V}{H} - \mu_v V_i \] (35)

The basic reproduction number for the Basic modified model (Eq. 35) is \( R_0^{(3)} \), the same as the most realistic Delayed model.

4. A stochastic agent based Ross-Macdonald model

A stochastic version of an ordinary differential equations model like \[10\,16\] is straightforward. Consider, for example, the simple Ross model

\[ \frac{dH_i}{dt} = \beta_h V_i \frac{H_s}{H} - r_h H_i \]
\[ \frac{dV_i}{dt} = \beta_v V_s \frac{H_i}{H} - \mu_v V_i \]

12
In this case there are only four events: host infection, vector infection, human recovery, and vector death. The rates of the deterministic model define the probabilities of occurrence of the events per unit of time or transition rates. Thus, for example, probability of human infection in an interval $\delta t$ is given by

$$P(H_s \rightarrow H_i, \delta t) = \beta_h V_i \frac{H_s}{H} \delta t + o(\delta t)$$

where $o(\delta t)$ are higher order terms for which $\lim_{\delta t \to 0} \frac{o(\delta t)}{\delta t} = 0$.

The interval between consecutive events is exponentially distributed with parameter equal to the sum of the all transition rates. This kind of stochastic models are markovian, the probability of occurrence of any event depend only of the present values of the variables.

A stochastic version of the integral Volterra equations model like (19-25) is not that easy (see for example [27]) as the corresponding stochastic model is non-markovian, the dynamics depends of the history of the system. One alternative is to consider Gamma distributed periods with integer shape parameter values, for which the equivalent systems becomes markovian and therefore it is possible to use the stochastic simulation scheme outlined above.

We preferred to develop an agent based model (ABM) for which the simulation of periods with arbitrary distributions is straightforward. Agent based models are a computational tool which allows to simulate populations dynamics considering the features of each individual in the population and the interaction between them [22]. Agent based models are considered the most realistic models where some features, like the mobility of each individual, can be easily incorporated [12, 31].

Our model considers a SEIR model for the host population and a SEI model for the vector population.

4.1. Modeling disease transmission, progression and recovery.

For each host and vector, the followings attributes were considered:

- The epidemiological status (State) which may take the values SUSCEPTIBLE, EXPOSED, INFECTIOUS, RECOVERED.
- The age of infection (the time elapsed from first infection).
- The age of infectiousness (the time elapsed since progression to the infectious status).
We considered a fixed time step $\Delta t$.

For each vector we generated a (pseudo)random number $u$ with uniform distribution in the interval $(0,1)$. If $u < 1 - \exp(-b\Delta t)$ the vector bites a host selected at random which may be infected (if the vector is infectious and the host susceptible) or transmit the infection (if the vector is susceptible and the host infectious) with probabilities $p_h$ and $p_v$ respectively.

Latent or infectious periods are random variables with some probability distribution. We considered the general and flexible case where periods are Gamma distributed. Special cases of the Gamma distribution include exponential distribution (for the shape parameter $k = 1$) and the limiting case of fixed period ($k \to \infty$).

Waiting periods in the different epidemiological classes were simulated in the following way. For each newly infected individual we drew a pseudo random number from the corresponding Gamma distribution. This simulated value of the latency period ($\tau_e$), plus the current time $t$, was stored in the variable $T_{\text{change}}$. In all cases $T_{\text{change}}$ is a future time at which the individual will change the epidemiological status.

When the age of infection becomes greater or equal to $\tau_e$ we changed the agent’s state from EXPOSED to INFECTIOUS (in our implementation this is equivalent to the condition $t \geq T_{\text{change}}$). In a similar way, for each newly infectious individual we drew a value for the infectious period ($\tau_i$) and stored it in $T_{\text{change}}$ (as before $T_{\text{change}}$ is the simulated infectious period plus the actual time $t$). When the age of infectiousness reach (or surpass) this value the state of the individual was changed from INFECTIOUS to RECOVERED. For the cases of fixed waiting times the transitions are deterministic and are determined by the values selected for the different (fixed) periods.

Other distributions for the latent and infectious periods may be easily incorporated as long a generator of random numbers for the corresponding distribution is available.

4.2. Modeling births and deaths.

We disregarded host births and deaths. For the vector population we considered a constant mortality ($\mu_v = 1/T_v$) and a constant birth rate $\Lambda_v$. Thus, the probability of a vector dying in a time interval $\Delta t$ is equal to $1 - e^{-\mu_v \Delta t}$. On the other hand, the number of newborns vectors in a time step $\Delta t$ was modelled by a Poisson random variable with parameter $\Lambda_v \Delta t$.

4.3. Simulation procedure

The simulation procedure used is described in the following pseudo-code:
1. Initialization of variables and parameters
   (a) Set the host \((H(0))\) and vector \((V(0))\) population sizes, and the initial conditions \(H_s(0), H_e(0), H_i(0), V_s(0), V_e(0), V_i(0)\).
   (b) Set the time step \(\Delta t\), the simulation duration \(t_{sim}\) and the current time \(t\) equal to 0.
   (c) Set the values of parameters \(\mu_v, p_v, p_h, k_v, k_h, \gamma_h, b\).
2. While \(t \leq t_{sim}\) and \(0 \leq H_e(t) + H_i(t) + V_e(t) + V_i(t)\) (this last sentence interrupts the program when infections cannot take place anymore)
   (a) A random number of susceptible vector are added to the population according to a Poisson distribution with parameter \(\mu_v \Delta t\)
   (b) For each vector in the population
      i. A uniform random number in the interval \((0, 1)\) is generated.
      ii. If the number is less than or equal to \(b \Delta t\), the vector bites.
         The host bitten is chosen at random.
         If the vector is susceptible and the host bitten is infected
         A uniform random number in the interval \((0, 1)\) is generated.
         If the number is less than or equal to \(p_v\), the mosquito becomes exposed
         \(vector.State = EXPOSED, V_s(t) = V_s(t) - 1, V_e(t) = V_e(t) + 1\)
         Generate a latency period \(\tau_e\) according to the corresponding Gamma distribution.
         Set an exposed time \(vector.T_change = t + \tau_e\).
      iii. A uniform random number in the interval \((0, 1)\) is generated.
      iv. If the number is less than or equal to \(1 - e^{-\mu_v \Delta t}\)
         The vector dies and it is removed from vector population.
      v. Else

If the vector is exposed and $\text{vector}.T_{\text{change}}$ is less than or equal to the current time $t$
\[
\text{vector}.S_{\text{tate}} = \text{INFECTED}, \ V_v(t) = V_v(t)-1, \ V_i(t) = V_i(t) + 1
\]

(c) For each host
i. If the host is exposed and $\text{host}.T_{\text{change}}$ is less than or equal to the current time $t$
\[
\text{host}.S_{\text{tate}} = \text{INFECTED}, \ H_e(t) = H_e(t) - 1, \ H_i(t) = H_i(t) + 1
\]
Generate a infectious period $\tau_i$ according to the corresponding Gamma distribution.
Set an infectious time $\text{vector}.T_{\text{change}} = t + \tau_i$.

ii. If the host is infected and $\text{host}.T_{\text{change}}$ is less than or equal to the current time $t$
\[
\text{host}.S_{\text{tate}} = \text{RECOVERED}, \ H_i(t) = H_i(t)-1, \ H_r(t) = H_r(t) + 1
\]

5. Some numerical results

The simulations start with one host infectious, and all the other individuals susceptible. We used the day as the unit of time.

5.1. Vector to host ratio

Host population was constant along the simulations. For the vector population we considered two cases, constant populations and seasonal varying populations. In the first case, the population may fluctuate stochastically about the deterministic equilibrium which was the initial population in our simulations. In the second the population presents seasonal oscillations around this value. The ratio vector per host was set in 1. This value vary from system to system and along the year in seasonal environments. For *Aedes aegypti* for example values of 0.5 and 1.1 per human were estimated [34] [19]. Studies in malaria estimated the number of anophelines per person in the range 3 to 4 depending on the location [25]. A typical household in high risk areas of *T. cruzi* transmission has an average of 5 human host while triatomine population may vary from some few individuals to several hundreds [24] [42].

5.2. Parameter values

Vectors life expectancy was set in 10 days, which is of the order of values obtained for most species of mosquito [14] and sandflies [10]. Kissing bugs has a longer life expectancy of about 5 months [42].
Probabilities of transmission \((p_h, p_v)\) are in general asymmetrical and there is a wide range of variation. For malaria those probabilities were estimated in the order of 0.48 and 0.022 [14], while for dengue are close to 1. In this work we used \(p_{hv} = p_{vh} = 0.75\).

Human mean latency period is of the order of one week for dengue and about 10 days for malaria [28], while in the case of Chagas this period is between 4 and 15 days [18]. In our simulations we considered a host mean latency period of 6 days.

Host mean infectious period is about 3 days for dengue [30], 2 or 4 months for malaria [28]. In the case of Chagas, the acute phase is between 0 and 90 days, period in which the risk to transmit the infection is higher [13]. We used a value of 5 days in our simulations.

Latent period for vectors was set in 7 days, a value about the observed in dengue infected mosquitoes.

The biting rate \(b\) is a parameter harder to estimate. We considered two values, \(b = 0.3/\text{day}\) and \(b = 0.5/\text{day}\), in order to have two cases, low and high basic reproduction numbers. This values are of the order observed for mosquitoes and were used for Ross and Macdonald in their seminal works [25].

### 5.3. Epidemic curves

In figure 1 we compare numerical solutions of the models for low and high values of the basic reproduction number \((b = 0.3\) and \(b = 0.5\), respectively) considering the parameter values in the table 1.

| Parameter | Value     |
|-----------|-----------|
| \(p_v\)   | 0.75      |
| \(p_h\)   | 0.75      |
| \(T_{he}\) | 6 [days]  |
| \(T_{hi}\) | 5 [days]  |
| \(T_{ve}\) | 7 [days]  |
| \(T_v\)   | 10 [days] |

Table 1: Parameter values used in the simulations. In all cases we set host mortality equal to zero \((\mu_h=0)\) while \(\mu_v = 1/T_v = 0.1 \text{ days}^{-1}\).

In table 2 we show the corresponding \(R_0\) and some statistics of the epidemic curves (number of infected host at the epidemic peak, time at which the peak is reached and the final epidemic size as proportion of the total host population size)
for each of the simulations presented in figure 1 corresponding to the different deterministic models.

Similar results obtained with the agent based model are presented in table 3, where we considered only the case of exponentially distributed periods (corresponding to the SEIR-SEI model (Eqs. 10-16), and fixed periods (corresponding to the Delayed model (Eqs. 26-32).

Because for the same parameter values the basic reproduction number of the basic model is greater than the basic reproduction numbers of the other models (see inequality 34), the basic model produces faster epidemics with a higher epidemic final size.

For $b = 0.3$ (low $R_0$’s), the epidemic final size for the basic model is about two times the epidemic final size obtained with the other models, while the epidemic peak is almost 20 times higher than the obtained with the delayed model (see table 2).

The modified basic model (35) has the same basic reproduction number than the delayed model and both models predict almost the same final epidemic sizes. However, the first one produces higher peaks in shorter times, resulting in a epidemic that spreads through the population faster and runs out earlier. It is important to note that considering latency periods in hosts and vectors always produces lower epidemics, in comparison with the basic model.

To compare the solution of the deterministic SEIR-SEI (Eqs. 10-16) and delayed models (Eqs. 26-32) with the ABM results, we realized simulations...
| Model                | $R_0$ | Epidemic Peak | Time | Epidemic Final Size |
|----------------------|-------|---------------|------|---------------------|
| Basic model          | 2.53  | 759           | 113  | 0.86                |
| Basic model modified | 1.26  | 69.7          | 415  | 0.365               |
| SEIR-SEI model       | 1.49  | 114.3         | 461.25 | 0.559              |
| Delayed model        | 1.26  | 42.5          | 733.4| 0.37                |

Table 2: Basic reproduction number, peak of the epidemic, duration from source case introduction to peak and epidemic final size for the solutions of the different Ross-Macdonald models considered in figure 1 left panel (top) and right panel (bottom).

Following the procedure explained above considering the same parameter values (table 1), population sizes and initial conditions used with the deterministic models.

For $b = 0.3$ (Fig. 2 - left panel and Fig. 3 - left panel) stochasticity dominates the dynamics and realizations of the ABM are qualitatively and quantitatively different of the deterministic solutions (see table 3). Epidemic peak is lower in the deterministic case than in the mean value obtained with the ABM simulations. Also, the deterministic values of the epidemic peak and the time at which it is reached are not within the corresponding 95% confidence intervals. Not only individual realizations are qualitatively different from the deterministic solutions but the mean of those realizations do not converge to the deterministic results.

This behaviour of the stochastic realizations is due to the fact that for low values of the basic reproduction number the stochastic effects dominate the disease dynamics. In this case stochastic dynamics is not a deterministic drift with noise [4], and therefore we cannot expect that stochastic fluctuations average out.

For higher values of $R_0$ ($b = 0.5$) stochastic dynamics is quasi deterministic and the realizations of the ABM are similar in shape and size to the deterministic solutions (Fig. 2 - right panel and 3 - right panel). The stochasticity may produce a shift of the epidemic curve (to the left or to the right of the deterministic result), but it does not greatly affect the height of the peak neither the amplitude of the epidemic curve.
| Type of model    | \( b \) | Epidemic Peak Mean (95% CI) | Time Mean (95% CI) | Epidemic Final Size Mean (95% CI) |
|-----------------|--------|-----------------------------|-------------------|----------------------------------|
| Exponential     | 0.3    | 144.64 (141.36, 147.92)     | 362.99 (352.1, 373.89) | 0.5622 (0.5577, 0.5666)          |
|                 | 0.5    | 842.88 (838.60, 847.16)     | 131.94 (129.80, 134.08) | 0.9664 (0.9660, 0.9668)          |
| Fixed           | 0.3    | 69.48 (67.07, 71.89)        | 517.91 (497.24, 538.58) | 0.3580 (0.3496, 0.3664)          |
|                 | 0.5    | 714.5 (710.89, 718.22)      | 166.30 (163.59, 169.02) | 0.9418 (0.9412, 0.9423)          |

Table 3: Peak of the epidemic, duration from source case introduction to peak and epidemic final size for the solutions of the different ABM Ross-Macdonald models considering 200 simulations.
5.3.1. Fixed periods vs bell shaped distributed periods

By far the most used distribution for the waiting times is the exponential distribution, which in the deterministic case leads to model 10-16. However, as already discussed, this is an unrealistic assumption for most cases. Latency and infectious periods are expected to have a bell shaped distribution. In the general case the model 19-25 should be used but numerical solutions are harder to obtain in this case. Bell shaped distributions may be modelled by the Gamma distribution, which with two independent parameters (the shape parameter $k$ and the scale parameter $\theta$) may control mean and variance (see 3.3.1). When a Gamma distribution is used for the probability density distribution of the waiting times, a very useful property of system 19-25 is that for integer values of the shape parameter, the
system of integral equations is equivalent to a larger system of ordinary differential equations (see Appendix B). Thus, for \( k = 1 \), system [B.1] [B.13] reduces to the SEIR-SEI model [10] [16] while for \( k \to \infty \) it converges to the delayed model [26] [32].

In figure 4 we show different Gamma distributions for different values of the shape parameter \( k \). For \( k = 10 \) there is a high variability in the waiting periods but solutions are close to the solutions obtained with fixed periods \( (k = \infty, \text{see fig. 5}) \). For \( k = 50 \) both cases are almost identical.

![Gamma distributions](image)

Figure 4: Probability density function of Gamma distribution considering \( \tau = 7 \) and different values of \( k \): 1, 2, 5, 10 and 50.

5.4. Effects of seasonality

Seasonality is a key driver of disease dynamics in most vector-borne diseases. Seasonality affects vector population dynamics because, for example, vector’s activity is temperature dependent. In the present case we only consider that vector recruitment is affected by seasonality (mostly by variations in rainfall). As an simple example we considered harmonic variations of the form

\[
\Lambda_v = \Lambda_0[1 + \epsilon \sin(\omega t)].
\]

For \( \epsilon = 0 \) we recover the case of constant recruitment used in fig. [1]. For \( 0 < \epsilon \leq 1 \) the vector population oscillates with frequency \( \omega \).

As we show in fig. [1] duration of epidemics may last almost two years. Seasonal variation of vector populations significantly reduces epidemic duration. In
Figure 5: Solutions of deterministic models (Host infectious population) considering the parameters in Table 1. Left panel: low $R_0 (b = 0.3)$, right panel, high $R_0 (b = 0.5)$. From left to right: SEIR-SEI, model with gamma distribution for waiting periods (Eqs. B.1 - B.13) considering $k = 1, 2, 5, 10$ and 50, and delayed model (Eqs. 26 - 32). For $k = 1$ model (Eqs. B.1 - B.13) reduces to model (Eqs. 10 - 16).

In Figure 6, we compare numerical solutions of the delayed model (Eqs. 26 - 32) for different values of $\epsilon$. Duration of epidemics range between approximately 10 months to a couple of months for $\epsilon = 0.5$ and $\epsilon = 1$.

Figure 6: Numerical solutions of the delayed model (Eqs. 26 - 32) for $\epsilon = 0$ (no seasonality, black line), $\epsilon = 0.5$ (red) and $\epsilon = 1$ (blue), for $b = 0.3$ (left panel) and $b = 0.5$ (right panel).

Fig. 7 shows numerical solutions of the ABM considering fixed periods and seasonality. We can see that in the case in which $R_0$ is higher ($b = 0.5$) the ABM results are similar to the deterministic model. Conversely, considering $b = 0.3$, the curves obtained from the AMB are qualitatively similar to the deterministic case,
since the same amount of peaks can be clearly observed in both cases. However, the values reached in these peaks in the case of ABM are higher, in general, in the first and second one and lower in the third one.

Figure 7: Numerical solutions of the delayed model (Eqs. 26 - 32) with $\epsilon = 0.5$ (red) and the corresponding ABM considering fixed periods (other colours curves), for $b = 0.3$ (left panel) and $b = 0.5$ (right panel). In black line the solution of the delayed model (Eqs. 26 - 32) without seasonality ($e = 0$).

5.5. Computing $R_0$ from the agent based model

To compute $R_0$ in the case of the agent based model, we have to follow the infectious generation of hosts and vectors. So, the procedure realized is as follow. The first infected host is the only host of first infected generation. The vectors infected by a host of first generation, are vectors of first infected generation. When a vector of first infected generation, infects a susceptible hosts, these host are second infected generation. In general, when a host of infected generation $m$ infects a vector, the infected generation of the vector is $m$. Then, when a vector of infected generation $m$ infects a host, then infected generation of the host is $m + 1$.

Let $H_m$ be the number of infected-host generation $m$. Then, $R_0$ can be estimated as $R_0 \approx H_3 / H_2$ [5]. Due to the stochasticity of the ABM simulations, it is important to realize a considerable number of simulations and then calculate the mean of the $R_0$ value estimated for each simulation. An $R_0$ estimation considering 200 realizations of the simulations analyzed in the previous section is presented in the table 4. In all the cases the deterministic value of $R_0$ is within the 95% confidence interval.

As we can see in Eqs. [17] and [34] given the parameters of the host and vector populations, $R_0$ is a linear function of the relation $V/H$. So, varying the relation $V/H$, we can obtain different values of $R_0$. 

24
Considering the parameters in the table and a biting rate equal to 0.3 \((b = 0.3)\), we estimated the value of \(R_0\) from the agent based model for different values of \(V/H\). The results considering exponentially distributed periods and fixed period are shown in the Fig. 8, respectively. In all the cases, an initial population of 10000 hosts was considered, with only one infected host. Each estimation of the basic reproduction number was realized with 200 simulations.

Table 4: Estimation of \(R_0\) from the ABM model considering 200 simulations.

| Type of model | \(b\) | Deterministic \(R_0\) | Estimation \(R_0 \approx H_3/H_2\) Mean (95% CI) |
|---------------|-------|-------------------|----------------------------------|
| Exponential periods | 0.3 | 1.25 | 1.28 (1.01, 1.54) |
|                 | 0.5 | 3.49 | 3.60 (3.16, 4.05) |
| Fixed periods   | 0.3 | 1.49 | 1.45 (1.21, 1.69) |
|                 | 0.5 | 4.14 | 4.03 (3.60, 4.46) |

Figure 8: Empirical estimates of the Basic reproduction numbers (squares, bars are 95% confidence interval) obtained with the ABM for the cases of exponentially distributed periods (left) and fixed period (right). Continuous line are the corresponding theoretical values given by expressions (17) and (3.4).

As can be seen in the figure, numerical estimations of the basic reproductive number are in the 95% confidence interval estimated from the 200 ABM simulations.

6. Discussion and Conclusions

The use of mathematical models in epidemiology has a long and fruitful tradition. However different hypotheses about the systems under study may lead to,
in some cases, significant different results (see for example [1, 45, 46]).

In this work we present different formulations of the Ross-Macdonald model using ordinary differential equations, Volterra integral equations and agent based modelling. In the most general case we included latency periods in both vectors and hosts. We also considered general distributions for latency and infectious periods including two simple cases: exponentially distributed periods and fixed periods.

As we show in this work, disregarding latency periods has a dramatic effect in the dynamics. This is quite apparent for low basic reproduction numbers (see Fig. 1). As in most vector-borne diseases vector’s latency periods and life expectancy are of the same order of magnitude, disregarding latency overestimate the basic reproduction number, and therefore we observed faster epidemics with significantly higher peaks. A substantial improvement is achieved with the simple modification (35) which produces the same values of $R_0$ as the delayed model but still the epidemic curves are significantly different.

Not only the inclusion of latency periods is important but also its distributions. Using exponentially distributed periods leads to slightly smaller basic reproduction numbers and still a noticeable differences in the epidemic curves.

For the most realistic case of bell-shaped distributed waiting periods we show that numerical solutions of the Volterra integral system [19][25] are close to the solutions of the simpler delayed model [26][32] for which numerical simulations may be easily obtained using a Runge-Kutta scheme, for example. For us, the delayed model is therefore the model of choice as it combines realism and simplicity.

A central assumption of the Ross-Macdonald models is homogeneous random mixing: probability of biting in a susceptible host is proportional to the fraction of susceptible host in the entire population. This hypothesis may hold for some local, relatively small, populations. Larger populations may be modelled using a meta-population approach, for example. If local populations have some degree of synchronization, the total population disease dynamics could be quasi-deterministic (see for example [21]), and perhaps a Ross-Macdonald model may describe the global dynamics of the system. In this work we considered populations of $10^4$ individuals, a large enough population for which it is not obvious that the assumption of homogeneous mixing holds.

For both, high and low values of the basic reproduction number, solutions of the deterministic models and the estimation of the $R_0$ of the agent based model are statistical similar (see fig. 8 and table 4), although the epidemic curve may be significantly different from the deterministic solution, especially for low $R_0$ value (see fig. 2 and 3).
Deterministic models, like the SEIR-SEI model\cite{10,16}, are simple ordinary differential equations systems with constant parameters, more amenable for analysis. Numerical integration is straightforward using Runge-Kutta of fourth order, for example. The more realistic choice of fixed periods is modelled by delayed differential equations. Analysis is more complex for these type of models but numerical integration is easily implemented too.

For the agent based model there are not differences, neither in the difficulty of the coding or in the computational cost for both cases, and therefore non-exponentially distributed periods (like fixed periods) is the recommended choice.

In our simulations we considered parameter values compatible with some vector-borne diseases in humans like dengue. In all cases the number of vectors per host was set equal to one at demographic equilibrium. For low values of the basic reproduction number epidemics obtained with the (most realistic) fixed period models have a duration of more than two years (see Fig. 3, left panel), which is never observed in real epidemics. This results highlights the importance of including seasonality when modelling some vector-borne diseases. Vector populations usually have seasonal fluctuations, driven by rainfall, for example, which shape the duration of the epidemics (see fig. 6). However, outbreaks sizes are generally a function not only of the abundance of vectors, but also of other variables such as climate, community immunity, host mobility, among others. Vector activity is strongly affected by temperature and therefore not only seasonal variations are significant but also habitat conditions as the use of air conditioning. The two values of $\epsilon$ used correspond to moderate seasonal variations in vector abundance ($\epsilon = 1/2$) as expected in endemic settings, and to marked variations in vector abundances as observed in non-endemic populations.

As the homogeneous mixing assumption is expected to hold only for relatively small populations, stochasticity should be considered when modelling such cases. Larger populations may be modelled using a metapopulation approach, something we will explore in forthcoming works.

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Appendix A. General SEIR-SEI model with arbitrary distributions for the waiting time

We will consider the general case of a SEIR-SEI model. For the host and vector populations we assume that the latency period ($T_{he}$ for hosts and $T_{ve}$ for vectors) and the infectious period for hosts ($T_{hi}$) are random variables with probability density distributions $f_{he}(s)$, $f_{ve}$ and $f_{hi}(s)$, respectively. The cumulative distributions are denoted by $F_{he}(s)$, $F_{ve}$ and $F_{hi}(s)$, respectively. The complementary cumulative distribution, $\bar{F}_{s}(s) = 1 - F_{s}(s)$, is known as the survival function and gives the probability that an individual infected in $t = 0$ remains infected (or exposed, depending of the case) at time $s$.

Therefore the evolution of the populations can be described by the integral Volterra equations [17]:

\begin{align*}
H_s(t) &= H_s(0) - \int_0^t \beta_h V_i(s) \frac{H_s(s)}{H} \, ds \\
H_e(t) &= H_e(0) \bar{F}_{he}(t) + \int_0^t \beta_h V_i(s) \frac{H_s(s)}{H} \bar{F}_{he}(t - s) \, ds \\
H_i(t) &= H_i(0) \bar{F}_{hi}(t) + \int_0^t \int_0^{t'} \beta_v V_s(s) \frac{H_i(s)}{H} \left[ -\frac{d\bar{F}_{ve}}{dt}(\tau - s) \right] \bar{F}_{hi}(t - \tau) \, ds \, d\tau \\
H_r(t) &= H - H_s(t) - H_i(t) - H_e(t) \\
V_s(t) &= V_s(0) e^{-\mu t} + \int_0^t \Lambda_v e^{-\mu(t-s)} \, ds - \int_0^t \beta_v V_s(s) \frac{H_s(s)}{H} \, ds \\
V_e(t) &= V_e(0) e^{-\mu t} + \int_0^t \beta_v V_s(s) \frac{H_i(s)}{H} \bar{F}_{ve}(t - s) e^{-\mu(t-s)} \, ds \\
V_i(t) &= V_i(0) e^{-\mu t} + \int_0^t \int_0^{t'} \beta_v V_s(s) \frac{H_i(s)}{H} \left[ -\frac{d\bar{F}_{ve}}{dt}(\tau - s) \right] e^{-\mu(t-s)} \, ds \, d\tau.
\end{align*}

Differentiation of these equations leads to the following system of integro-differential equations,
\[
\begin{align*}
\frac{dH_i}{dt} &= -\beta_h V_i(t) \frac{H_i(t)}{H} \quad \text{(A.8)} \\
\frac{dH_e}{dt} &= -H_e(0) f_{he}(t) + \beta_h V_i(t) \frac{H_i(t)}{H} - \int_0^t \beta_h V_i(s) \frac{H_i(s)}{H} f_{he}(t - s) ds \quad \text{(A.9)} \\
\frac{dH_i}{dt} &= -H_i(0) f_{hi}(t) + \int_0^t \beta_h V_i(s) \frac{H_i(s)}{H} f_{hi}(t - s) ds \\
&\quad - \int_0^t \int_0^\tau \beta_h V_i(s) \frac{H_i(s)}{H} f_{he}(\tau - s) ds \left( f_{hi}(t - \tau) d\tau \right) \quad \text{(A.10)} \\
\frac{dH_e}{dt} &= H_e(0) f_{he}(t) + H_i(0) f_{hi}(t) \\
&\quad + \int_0^t \int_0^\tau \beta_h V_i(s) \frac{H_i(s)}{H} f_{he}(\tau - s) ds \left( f_{hi}(t - \tau) d\tau \right) \quad \text{(A.11)} \\
\frac{dV_s}{dt} &= \Lambda_v - \beta_v V_s(t) \frac{H_i(t)}{H} - \mu V_s(t) \quad \text{(A.12)} \\
\frac{dV_e}{dt} &= -\mu e^{-\mu t} V_e(0) + \beta_v V_s(t) \frac{H_i(t)}{H} \\
&\quad - \int_0^t \beta_v V_s(s) \frac{H_i(s)}{H} f_{ve}(t - s)e^{-\mu(t-s)} ds - \mu V_e(t) \quad \text{(A.13)} \\
\frac{dV_i}{dt} &= -\mu e^{-\mu t} V_i(0) + \int_0^t \beta_v V_s(s) \frac{H_i(s)}{H} f_{ve}(t - s)e^{-\mu(t-s)} ds - \mu V_i(t) \quad \text{(A.14)}
\end{align*}
\]

Appendix B. Model with Gamma distributions for the waiting periods

If the waiting periods are Gamma distributed with mean \( \tau \) and integer shape parameter \( k \), we can apply the *linear trick* \(^{[38]}\) to solve the system of integro-differential differential equations \((A.8-A.14)\).

Suppose that the latency and infectious periods for hosts and the latency period for vectors are all Gamma distributed with means \( \tau_i \) and integer shape parameters \( k_i \) \((i = 1, 2, 3 \) respectively). Then it is possible to divide the exposed human population in \( k_1 \) compartments such that \( H_e = \sum_{j=1}^{k_1} H_{e,j} \). In a similar fashion, the \( H_i \) and \( V_e \) populations may be divided in \( k_2 \) and \( k_3 \) classes respectively.

Then, the system of integro-differential equations is equivalent to the following system of ordinary differential equations,
\[ \frac{dH_s}{dt} = \Lambda_s - \beta_h V_s \frac{H_s}{H} - \mu_s H_s \quad (B.1) \]

\[ \frac{dH_{e,1}}{dt} = \beta_h V_i \frac{H_s}{H} - \frac{k_1}{\tau_1} H_{e,1} - \mu_h H_{e,1} \quad (B.2) \]

\[ \frac{dH_{e,2}}{dt} = \frac{k_1}{\tau_1} (H_{e,1} - H_{e,2}) - \mu_h H_{e,2} \quad (B.3) \]

\[ \vdots \]

\[ \frac{dH_{e,k_1}}{dt} = \frac{k_1}{\tau_1} (H_{e,k_1-1} - H_{e,k_1}) - \mu_h H_{e,k_1} \quad (B.4) \]

\[ \frac{dH_{i,1}}{dt} = \frac{k_3}{\tau_1} H_{e,k_1} - \frac{k_2}{\tau_2} H_{i,1} - \mu_h H_{i,1} \quad (B.5) \]

\[ \frac{dH_{i,2}}{dt} = \frac{k_2}{\tau_2} (H_{i,1} - H_{i,2}) - \mu_h H_{i,2} \quad (B.6) \]

\[ \vdots \]

\[ \frac{dH_{i,k_2}}{dt} = \frac{k_3}{\tau_2} (H_{i,k_2-1} - H_{i,k_2}) - \mu_h H_{i,k_2} \quad (B.7) \]

\[ \frac{dH_r}{dt} = \frac{k_3}{\tau_2} H_{i,k_2} - \mu_h H_r \quad (B.8) \]

\[ \frac{dV_s}{dt} = \Lambda_v - \beta_v V_s \frac{H_i}{H} - \mu_v V_s \quad (B.9) \]

\[ \frac{dV_{e,1}}{dt} = \beta_h V_s \frac{H_i}{H} - \frac{k_3}{\tau_3} V_{e,1} - \mu_v V_{e,1} \quad (B.10) \]

\[ \frac{dV_{e,2}}{dt} = \frac{k_3}{\tau_3} (V_{e,1} - V_{e,2}) - \mu_v V_{e,2} \quad (B.11) \]

\[ \vdots \]

\[ \frac{dV_{e,k_3}}{dt} = \frac{k_3}{\tau_3} (V_{e,k_3-1} - V_{e,k_3}) - \mu_v V_{e,k_3} \quad (B.12) \]

\[ \frac{dV_i}{dt} = \frac{k_3}{\tau_3} V_{e,k_3} \gamma \mu_i V_i \quad (B.13) \]
where $H_e = \sum_{j=1}^{k_1} H_{e,j}$; $H_i = \sum_{j=1}^{k_2} H_{i,j}$, and $V_e = \sum_{j=1}^{k_3} V_{e,j}$.

The Gamma distribution with shape parameter $k = 1$ is an exponential distribution, while for $k \to \infty$, the Gamma distribution tends to a Dirac delta distribution. Thus, as $k$ increases from 1 to $\infty$, the model (Eqs. B.1 - B.13) moves from the SEIR-SEI model (Eqs. 10 - 16) to the delayed model (Eqs. 26 - 32).