

# The effect of the infection within the individual host on its propagation in the population



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## ABSTRACT

We consider nested or multiscale models to study the effect of the temporal evolution of the disease within the host in the population dynamics of the disease, for one and two infectious agents. We assumed a coupling between the within-host infection rate and the between-host transmission rate. The age of infection within each individual in a population affects the probability of transmission of the disease to a susceptible host and this will affect the temporal evolution of the disease in the host population. To analyze the infection within the host, we consider bacterial-like and viral-like infections. In the model for two infectious agents, we found that, when strain 2 has a basic reproduction number  $R_{02}$  greater than the basic reproduction number  $R_{01}$  of strain 1, strain 2 replaces strain 1 in the population. However, if  $R_{02} > R_{01}$  but the values are closer, the replacement does not occur immediately and both strains can coexist for a long time. We applied the model to a scenario in which patients infected with the hepatitis C virus (HCV) are cleared of HCV when super-infected with the hepatitis A virus (HAV). We compared the time for the replacement of HCV by HAV in the population considering instantaneous and non-instantaneous replacement within the individuals. The model developed can be generalized for more than two infectious agents.

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## 1. Introduction

The connection between the dynamics of epidemics spread in the human (host) population with that of the within-host infection has been the focus of a substantial theoretical literature (Coombs, Gilchrist, & Ball, 2007; Gilchrist & Coombs, 2006; Handel & Rohani, 2015; Mideo, Alizon, & Day, 2008; Murillo, Murillo, & Perelson, 2013; Park, Loverdo, Schreiber, & Lloyd-

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Smith, 2013; Scholle, Ypma, Lloyd, & Koelle, 2013; Shen, Xiao, & Rong, 2015; Sofonea, Alizon, & Michalakis, 2015). However, as mentioned by Sofonea et al. (2015), there is a lack of general models for multiple infections, with few exceptions (Lion, 2013; May & Nowak, 1995; Sofonea et al., 2015).

In a previous paper, Burattini, Coutinho, and Massad (2008) developed a very simple nested model for competition between two (or more) virus strains. The basic assumption of that paper was that if an individual is infected with a strain 1 (with basic reproduction number within the individual  $R_{01}$ ) and is super-infected with the strain 2 (with basic reproduction number within the individual  $R_{02}$ ) then if  $R_{02} > R_{01}$  strain 2 *immediately* replaces strain 1 in the individual organism. Using this simple model, we calculated the influence of the competition of virus strains in the spread of diseases in the human (host) population. This model was applied to understand viral response to treatment (Amaku, Burattini, Coutinho, & Massad, 2010a) and to viral evolution in plants (Amaku, Burattini, Coutinho, & Massad, 2010b). This is a good approximation if  $R_{02}$  is much greater than  $R_{01}$ . However, if  $R_{02}$  is not much greater than  $R_{01}$ , the two strains can survive for a time within the individual organism. The ideas were elaborated in another paper (Amaku et al., 2010a), where mutation between strains of viruses was considered.

As mentioned above, the models given in Burattini et al. (2008) and Amaku et al. (2010a) considered instantaneous replacement, in which the strain that wins the competition within hosts replaces the other strain instantaneously. The main purpose of this paper is to consider the spread of the infections in the human (host) population when the basic reproduction numbers of the strains are not very different and therefore we cannot use the assumption of instantaneous replacement.

The content of this paper is as follows. In Section 2, we consider only one strain of a parasite and the effect of the temporal evolution of the disease within a host in the population dynamics of hosts. This type of model is called a nested or multiscale model (Coombs et al., 2007; Gilchrist & Coombs, 2006; Handel & Rohani, 2015; Mideo et al., 2008; Murillo et al., 2013; Park et al., 2013; Scholle et al., 2013). We propose a model for the connection between the infectiousness in the population and the within-host transmission, with variants for bacterial and viral infections. The individuals in the population are distinguished by the instant in which they are infected by the pathogen. Thus, we develop a model different from previous models for multiple infections, based on the time of infection instead of the age of infection, an alternative approach used in the literature (Ianneli, 1994; Magal, McCluskey, & Webb, 2010).

In Section 3, we consider the model for more than one infectious agent. In particular, we develop a nested model that consists of a host population and two invading parasites, restricting ourselves to the case where the invading parasites are virus-like that grow by invading susceptible cells. We analyze the occurrence of coinfections. We show in this more general context that the competitive exclusion principle (Bremermann & Thieme, 1989) holds. This principle was applied in a schematic way to the cell population of individual hosts in two previous papers (Amaku et al., 2010a; Burattini et al., 2008). In those papers, the principle ruled out the existence of hosts infected with both viruses. The fact that hosts can harbour the two infections simultaneously for short periods of time complicates the population dynamics in comparison with the two previous papers (Amaku et al., 2010a; Burattini et al., 2008) mentioned before. We apply the model in a scenario in which patients infected with the hepatitis C virus (HCV) are cleared of HCV when super-infected with the hepatitis A virus (HAV). Finally, in the Conclusions, we discuss our findings.

The case in which the two invading parasites grow within the individual hosts according to some law that is independent of the number of cells of the host (bacterial-like infections) will be considered in another paper.

## 2. Model for one infectious agent

### 2.1. The equations at the population level

Let  $i(t, \tau)d\tau$  be a density given by the number of persons at time  $t$  that were infected between  $\tau$  and  $\tau + d\tau$ . We consider that those persons die at a rate  $\mu_h$  assumed constant. Thus we have

$$\frac{\partial i(t, \tau)}{\partial t} = -\mu_h i(t, \tau), \quad t \geq \tau, \quad (1)$$

$$i(t, \tau) = 0, \quad t < \tau \quad (2)$$

or, for  $t \geq \tau$ ,

$$i(t, \tau) = i(\tau, \tau)e^{-\mu_h(t-\tau)}. \quad (3)$$

To calculate  $i(\tau, \tau)$ , we consider that susceptible individuals at time  $\tau$ ,  $S(\tau)$ , become infected when interacting with any individual infected at time  $\tau'$  prior to  $\tau$  (Nowak & May, 2004). The transmission rate depends on a parameter function  $\beta(\tau - \tau')$  which as we are going to see depends on the internal (individual) evolution of the disease and will be calculated in Subsection 2.2 for two models of infections (bacteria and virus).

Note that we assumed that the infection rate depends on the age of infection,  $t - \tau$ . As mentioned, we assumed this because we are going to study the variation of the infection rate with the progression of the disease within each individual. Other factors may influence  $\beta(\tau - \tau')$ . In this paper, for simplicity, we are not going to consider any of these aspects.

Thus we have

$$i(\tau, \tau) = S(\tau) \int_{-\infty}^{\tau} \beta(\tau - \tau') i(\tau, \tau') d\tau' \tag{4}$$

or

$$i(t, \tau) = S(t) \left[ \int_{-\infty}^{\tau} \beta(\tau - \tau') i(\tau, \tau') d\tau' \right] e^{-\mu_h(t-\tau)} \theta(t - \tau), \tag{5}$$

where  $\theta(t - \tau)$  is the Heaviside function.

Knowing  $i(t, \tau)$  we can write an equation for  $S(t)$ . We have

$$\frac{dS(t)}{dt} = -S(t) \left[ \int_{-\infty}^t \beta(t - \tau') i(t, \tau') d\tau' \right] - \mu_h S(t) + \Lambda(t), \tag{6}$$

where  $\Lambda(t)$  is the rate of new susceptible that enter into the population.

A general model at the population level is composed by equations (1), (2), (4) and (6). We present below some specific developments regarding the model.

The number of infected people  $I(t)$  in the population satisfies the equation:

$$\frac{dI(t)}{dt} = S(t) \left[ \int_{-\infty}^t \beta(t - \tau') i(t, \tau') d\tau' \right] - \mu_h I(t). \tag{7}$$

The variables and parameters of the model for one infectious agent are described in [Table 1](#).

For simplicity, we assume a SI (Susceptible – Infected) model for which the population is constant.

Then we set

$$\Lambda(t) = \mu_h S(t) + \mu_h I(t). \tag{8}$$

With this choice, the system of equations (6) and (7) becomes

**Table 1**

Summary of the variables and parameters of the model for one infectious agent. The values of the parameters were arbitrarily chosen. Rates have units of inverse of time ( $T^{-1}$ ).

	Description	Value
<i>Variable</i>		
$S(t)$	Number of susceptible individuals	
$I(t)$	Number of infected individuals	
$i(t, \tau)$	Density of individuals at time $t$ infected at time $\tau$	
$S_c(t)$	Number of susceptible cells	
$V(t \tau)$	Number of infected cells within an individual infected at $\tau$	
<i>Parameter</i>		
$B$	Parameter that controls the infectiousness of infected hosts	1000
$\beta_0$	Effective contact rate	$1.0 \times 10^{-4} T^{-1}$
$\beta_1$	Rate related to the coupling between within-host and between-host dynamics	$1.0 \times 10^{-4} T^{-1}$
$\alpha_0$	Saturated coefficient of the coupled function (29)	0.1
$\mu_h$	Human (host) death rate	$1.2 \times 10^{-2} T^{-1}$
$r$	Bacteria growth rate	$0.1 T^{-1}$
$K$	Carrying capacity of the host	10000
$\mu_V$	Death rate of infected cells	$0.6 T^{-1}$
$\mu_{V_c}$	Death rate of susceptible cells	smaller than $\mu_V$
$\beta_c$	Contact rate within the host	$1.0 \times 10^{-4} T^{-1}$
$p$	Fraction of susceptible cells infected at the infection event	0.1

$$\frac{dS(t)}{dt} = -S(t) \left[ \int_{-\infty}^t \beta(t - \tau') i(t, \tau') d\tau' \right] + \mu_h I(t) \quad (9)$$

$$\frac{dI(t)}{dt} = S(t) \left[ \int_{-\infty}^t \beta(t - \tau') i(t, \tau') d\tau' \right] - \mu_h I(t), \quad (10)$$

where  $i(t, \tau)$  is given by equation (5).

Equations (5), (9) and (10) describe a system evolving from a distant past ( $t = -\infty$ ) to time  $t$ .

The usual treatment of a SI system found in the literature describes a population of  $N = S + I$  individuals evolving from the time  $t = 0$  and frequently with a constant transmission rate. It is also assumed that a certain number  $I(0) = I_0$  of individuals contract the disease at time  $t = 0$  and that susceptible individuals contract the disease from infected individuals with the rate  $\beta$ . Such a system is described by the following system of differential equations

$$\frac{dS(t)}{dt} = -\beta S(t) I(t) + \mu_h I(t) \quad (11)$$

$$\frac{dI(t)}{dt} = \beta S(t) I(t) - \mu_h I(t), \quad (12)$$

together with the initial conditions  $I(0) = I_0$  and  $S(0) = N - I_0$ . In order to modify our system so it describes a population evolving from time  $t = 0$ , we divide the term  $\int_{-\infty}^t \beta(t - \tau') i(t, \tau') d\tau'$  in two parts.

$$\int_{-\infty}^t \beta(t - \tau') i(t, \tau') d\tau' = \int_{-\infty}^0 \beta(t - \tau') i(t, \tau') d\tau' + \int_0^t \beta(t - \tau') i(t, \tau') d\tau'. \quad (13)$$

The term  $\int_{-\infty}^0 \beta(t - \tau') i(t, \tau') d\tau'$  represents the contribution to the infection from individuals that acquired the disease before  $t = 0$ . With this division, the system of equations (5), (9) and (10) becomes:

$$\frac{dS(t)}{dt} = -S(t) \left[ \int_{-\infty}^0 \beta(t - \tau') i(t, \tau') d\tau' + \int_0^t \beta(t - \tau') i(t, \tau') d\tau' \right] + \mu_h I(t) \quad (14)$$

$$\frac{dI(t)}{dt} = S(t) \left[ \int_{-\infty}^0 \beta(t - \tau') i(t, \tau') d\tau' + \int_0^t \beta(t - \tau') i(t, \tau') d\tau' \right] - \mu_h I(t) \quad (15)$$

and

$$i(t, \tau) = S(\tau) \left[ \int_{-\infty}^0 \beta(\tau - \tau') i(\tau, \tau') d\tau' + \int_0^{\tau} \beta(\tau - \tau') i(\tau, \tau') d\tau' \right] e^{-\mu_h(t-\tau)}. \quad (16)$$

In the context of the usual SI model, the term  $\int_{-\infty}^0 \beta(t - \tau') i(t, \tau') d\tau'$  does not appear because the disease in the usual SI model is introduced at  $t = 0$ . So, in order to compare our model with the usual SI model, we use the mean-value theorem for integrals (Apostol, 1967) and replace it by an effective initial force of infection  $\beta_0 I_0 e^{-\mu_h t}$ . In this initial force of infection,  $I_0$  is the number of individuals at  $t = 0$  that were infected at various times before  $t = 0$  and the constant  $\beta_0$  is an effective contact rate that mimics the fact the individuals infected before  $t = 0$  were infected at various times. Note that no infected individual is allowed to enter the system after  $t = 0$ .

With this substitution, equations (14)–(16) become:

$$\frac{dS(t)}{dt} = -S(t) \left[ \beta_0 I_0 e^{-\mu_h t} + \int_0^t \beta(t - \tau') i(t, \tau') d\tau' \right] + \mu_h I(t) \tag{17}$$

$$\frac{dI(t)}{dt} = S(t) \left[ \beta_0 I_0 e^{-\mu_h t} + \int_0^t \beta(t - \tau') i(t, \tau') d\tau' \right] - \mu_h I(t). \tag{18}$$

$$i(t, \tau) = S(\tau) \left[ \beta_0 I_0 e^{-\mu_h \tau} + \int_0^\tau \beta(\tau - \tau') i(\tau, \tau') d\tau' \right] e^{-\mu_h(t-\tau)}. \tag{19}$$

Note that in equations (17)–(19) there are infected individuals that enter the system before  $t = 0$ .

To see how equations (14) and (15) reduce to the more usual form we assume that the infected individuals before  $t = 0$  are all concentrated at  $t = 0$ . Thus, we can assume that  $i(t, \tau) = 0$  for  $\tau < 0$ . Furthermore, we assume that at  $t = 0$  there is a number of susceptible individuals  $N - I_0$  and  $I_0$  infected individuals. We have

$$\int_{-\infty}^0 \beta(t - \tau') i(t, \tau') d\tau' = 0, \tag{20}$$

Hence, equations (14) and (15) reduce to

$$\frac{dS(t)}{dt} = -S(t) \int_0^t \beta(t - \tau') i(t, \tau') d\tau' + \mu_h I(t), \quad t > 0 \tag{21}$$

$$\frac{dI(t)}{dt} = S(t) \int_0^t \beta(t - \tau') i(t, \tau') d\tau' - \mu_h I(t) \quad t > 0 \tag{22}$$

that must be solved with the initial conditions  $I(0) = I_0$  and  $S(0) = N - I_0$ .

We can obtain an integral equation for  $i(\tau, \tau)$ . To do this, we replace  $t$  by  $\tau$  and  $S(\tau)$  by  $S(\tau) = N - I(\tau)$  in equation (19) and using equation (3), we obtain

$$i(\tau, \tau) = \left[ N - I_0 e^{-\mu_h \tau} - \int_0^\tau i(\tau', \tau') e^{-\mu_h(\tau-\tau')} d\tau' \right] \times \left[ \beta_0 I_0 e^{-\mu_h \tau} + \int_0^\tau \beta(\tau - \tau') i(\tau', \tau') e^{-\mu_h(\tau-\tau')} d\tau' \right]. \tag{23}$$

Equation (23) can be solved iteratively using a self-consistent iterative algorithm as follows. Choose as initial value  $i(\tau' = 0, \tau' = 0) = 0$  and iterate. After each step, compare the value of  $i(\tau', \tau')$  with its previous step value; when the difference is less than a given  $\varepsilon$  (chosen as  $\varepsilon = 10^{-8}$ ), we assume that convergence is achieved. Integrals were calculated numerically using the trapezoidal rule.

Once  $i(\tau, \tau)$  is obtained,  $i(t, \tau)$  is given by equation (3). From  $i(t, \tau)$ , we can calculate  $I(t)$  as follows

$$I(t) = \int_{-\infty}^t i(t, \tau) d\tau = \int_{-\infty}^0 i(t, \tau) d\tau + \int_0^t i(t, \tau) d\tau. \tag{24}$$

As  $\int_{-\infty}^0 i(t, \tau) d\tau$  is unknown, we replace it by  $I(0)e^{-\mu_h t}$ , obtaining

$$I(t) = I(0)e^{-\mu_n t} + \int_0^t i(\tau, \tau) e^{-\mu_n(t-\tau)} d\tau. \quad (25)$$

The first term of equation (25) represents individuals that were infected before  $t = 0$  and this term, as can be seen, decays with time. On the other hand, the second term represents individuals that were infected after  $t = 0$ .

To check the solution, we can now solve equations (17) and (18) with initial conditions  $S(0) = N - I_0$  and  $I(0) = I_0$ . Note that we are interested only in individuals that were infected after  $t = 0$ . Alternatively, we can check analytically that equation (25) satisfies equation (19).

## 2.2. The equations at the individual level: determination of $\beta(t - \tau)$

In this Section, we consider the internal development (within each individual) of the disease, upon which  $\beta(t - \tau)$  depends (Sasaki & Gilchrist, 2002). This internal competition depends on the type of infectious disease considered.

In this paper we consider two types of disease: bacterial-like infections and viral-like infections (Antia, Levin, & May, 1994).

### 2.2.1. Bacterial-like infections

Let  $V(t)$  be the number of bacteria within a “typical” individual.

We consider that  $V(t)$  obeys a logistic-like growth

$$\frac{dV(t)}{dt} = rV(t) \left( 1 - \frac{V(t)}{K} \right), \quad (26)$$

where  $r$  is the bacteria growth rate within the host and  $K$  is the carrying capacity of the host (Britton, 2003). Note that equation (26) includes death rate and birth rate. See details in Barlow, Kean, and Briggs (1997). We are ignoring, for simplicity, innate and adaptive immunity that would modify the assumed logistic dynamics.

This equation may be easily solved, and the solution is given by

$$V(t) = \frac{V(0)K}{V(0) + (K - V(0))e^{-rt}}. \quad (27)$$

In order to couple the internal process just described with the population dynamics, we assume that

$$\beta(t - \tau) = \beta_1 \left( 1 - e^{-\frac{V(t-\tau)}{B}} \right), \quad (28)$$

where  $\beta_1$  and  $B$  are parameters controlling the infectiousness of the infected hosts.

We can also use instead for the coupled function (equation (28)) a saturated function as proposed by Shen et al. (2015).

$$\beta_S(t - \tau) = \frac{\beta_1 V(t - \tau)}{1 + \alpha_0 V(t - \tau)}, \quad (29)$$

where  $\beta_1 > 0$  and  $\alpha_0 \geq 0$  are saturated coefficients. The effect of this change is shown in the numerical calculations.

### 2.2.2. Viral-like infections

The difference between virus infection and the bacteria infection treated above is that virus uses the organism cell to multiply themselves (Gilchrist & Coombs, 2006; Nowak & May, 2004). Thus the dynamics of viral infections is more complicated than the dynamics of bacteria described above. The difference will be particularly notable for the case when we have two or more virus infecting a single patient because in this case as we will see in the model for two infectious agents (Section 3), the competitive exclusion principle (Amaku, Coutinho, Chaib, & Massad, 2013; Bremermann & Thieme, 1989; Dib, Bitam, Tahri, Bensouilah, & De Meeüs, 2008) holds.

Let  $S_c(t)$  be the number of susceptible cells in one individual or in one individual organ if the virus attack only the organ.

Let  $V(t|\tau)d\tau$  be the number of infected cells within an individual that was infected between  $\tau$  and  $\tau + d\tau$  at time  $t$ . Note that we are assuming the infection that occur at a time  $\tau'$  so that  $\tau < \tau' < t$  does not influence the process, that is, secondary infections are not taken into account. So we have

$$\frac{dS_c(t)}{dt} = -\beta_c S_c(t) V(t|\tau) - \mu_{V_c} S_c(t) + \Lambda_c(t) \quad (30)$$

$$\frac{dV(t|\tau)}{dt} = \beta_c S_c(t)V(t|\tau) - \mu_V V(t|\tau). \tag{31}$$

We also assume that infected cells infect susceptible cells in a mass-action transmission process, thus we do not consider the infection age within cells. Equations (30) and (31) are actually a simplified version of the dynamics that, in principle, should include virions. However, the inclusion of the virions would not affect our main results and would complicate unnecessarily our arguments. For a preliminary study of the influence of including virions in the dynamics, see Amaku et al. (2010a) and Nowak and May (2004, p.92), where it is shown that virions can be eliminated from the equations if their dynamics is fast.

We set  $\Lambda_c(t)$  as

$$\Lambda_c(t) = \mu_V S_c(t) + \mu_V V(t|\tau), \tag{32}$$

The term  $\mu_V V(t|\tau)$  was added to equation (32) to compensate the death rate of infected cells so that the population remains constant by some mechanism on the individual. Note that the term  $\mu_V V(t|\tau)$  does not mean that infected cells divide into susceptible cells.

Defining the total number of cells as  $N_c = S_c(t) + V(t|\tau)$ , we can write (31) as

$$\frac{dV(t|\tau)}{dt} = -\beta_c V^2(t|\tau) + (\beta_c N_c - \mu_V)V(t|\tau), \tag{33}$$

whose solution is

$$V(t|\tau) = \frac{(\beta_c N_c - \mu_V)V(\tau|\tau)e^{(\beta_c N_c - \mu_V)(t-\tau)}}{[\beta_c N_c - \mu_V - \beta_c V(\tau|\tau)]} \times \left[ 1 + \frac{\beta_c V(\tau|\tau)e^{(\beta_c N_c - \mu_V)(t-\tau)}}{\beta_c N_c - \mu_V - \beta_c V(\tau|\tau)} \right]^{-1}. \tag{34}$$

We assumed that  $V(\tau|\tau) = pS(\tau)$ , that is, at the infection event, a fraction  $p$  of susceptible cells are infected. This is a simplification because the initial number of infected cells may depend on the state of the individual from whom the infection was acquired. However, this is a reasonable biological simplification.

The maximum value for  $V(t|\tau)$ , obtained by letting  $t \rightarrow \infty$  for a fixed  $\tau$ , is

$$\lim_{t \rightarrow \infty} V(t|\tau) = N_c - \frac{\mu_V}{\beta_c}.$$

This maximum viral load may be used to calculate the maximum effect of the infection on the human (host) population.

### 2.3. Approximate thresholds

From equation (18), dropping the term  $\beta_0 I_0 e^{-\mu_h t} S(t)$ , we obtain

$$\frac{dI(t)}{dt} = S(t) \int_0^t \beta(t - \tau') i(t, \tau') d\tau' - \mu_H I(t) \leq I(t)(N \max[\beta(t - \tau')] - \mu_H) \tag{35}$$

where  $\max[\beta(t - \tau')] = \beta_{\max}$  is the maximum value of  $\beta(t - \tau')$  for  $0 < \tau' \leq t$ . Therefore, if  $(N\beta_{\max} - \mu_H) < 0$  then  $I(t) \rightarrow 0$  as  $t \rightarrow \infty$ .

The basic reproduction number  $R_0$ , the number of cases one infected individual generates on average over the course of her/his infectious period in a susceptible population, is associated with the threshold condition  $\frac{dI(t)}{dt} < 0$ . If  $R_0 < 1$ , then  $I(t) \rightarrow 0$  as  $t \rightarrow \infty$ . Thus, we have obtained an upper limit for the basic reproduction number of this system, that is,

$$R_0 \leq \frac{N\beta_{\max}}{\mu_H}. \tag{36}$$

*Conjecture.* Consider equation (18)

$$\frac{dI(t)}{dt} = S(t) \left[ \beta_0 I(0) e^{-\mu_h t} + \int_0^t \beta(t - \tau') i(t, \tau') d\tau' \right] - \mu_h I(t).$$

Note that with our assumptions regarding the within-host evolution of the disease,  $\beta(t - \tau')$  is maximum ( $\beta_{\max}$ ) when  $t \rightarrow \infty$  and is  $\beta_1 \left(1 - e^{-\frac{t}{B}}\right)$  for bacteria infections and  $\beta_1 \left(1 - e^{-\frac{1}{B} \left(N_c - \frac{\mu V}{\beta_c}\right)}\right)$  for viral infections. Note also that for  $t = 0$ ,  $\frac{dI(t)}{dt}|_{t=0} > 0$  if  $N\beta_0 - \mu_h > 0$ . If this does not happen, we conjecture that the system will have a non-trivial solution if there is a  $t^*$  such that  $S(t^*) \int_0^{t^*} \beta(t^* - \tau') i(t^*, \tau') d\tau' - \mu_h I(t^*) > 0$ .

### 2.4. Numerical solution

As mentioned before, equations (23) and (25) with  $\beta(t - \tau')$  given by equation (28) and  $V(t - \tau)$  given by equations (27) and (34) for bacterial-like and virus-like infections, respectively, can be integrated numerically. The parameters involved were chosen arbitrarily and are given in Table 1.

In Fig. 1, we show the results of the simulations for the number of individuals infected by bacteria as a function of time for different growth rates and also for the saturated function (29). The effect of the history of the infection is to modify the initial growth rate of the infection in the population in the early stages. If the infection develops slowly within the host, the infection propagates slowly in the population as expected (Fig. 1).

In Fig. 2, we show the number of individuals infected by bacteria as a function of time for different values of  $B$ , the parameter related to the infectiousness of the infected hosts. The higher the value of  $B$ , the lower the number of infected individuals at the steady state. Note that the curve for the saturated function (29) reaches a higher plateau in both Figs. 1 and 2.

To explore the effect of treatment, we have simulated the number of infected individuals for different  $\beta_c$  (Fig. 3). When we decrease the transmission rate within host  $\beta_c$ , what would be equivalent to treating infected individuals, the transmission rate between host  $\beta$  is reduced, so that treatment decreases  $I(t)$ .

## 3. Model for two infectious agents

### 3.1. Within-host competition and the competitive exclusion principle

Let  $V_1(t|\tau_1)$  be the number of cells infected at time  $t$  that were infected with strain 1 between  $\tau_1$  and  $\tau_1 + d\tau_1$  and  $V_2(t|\tau_2)$  be the number of cells infected at time  $t$  that were infected with strain 2 between  $\tau_2$  and  $\tau_2 + d\tau_2$ . We assume that  $0 < \tau_1 < \tau_2$  and consider the solution in the following time intervals.

- 1) For  $t < \tau_1 < \tau_2$ , the solutions obviously are  $V_1(t|\tau_1) = V_2(t|\tau_2) = 0$ .
- 2) For  $\tau_1 < t < \tau_2$ , as deduced in equation (34), the solution for  $V_1(t|\tau_1)$  for a viral-like infection is a logistic given by

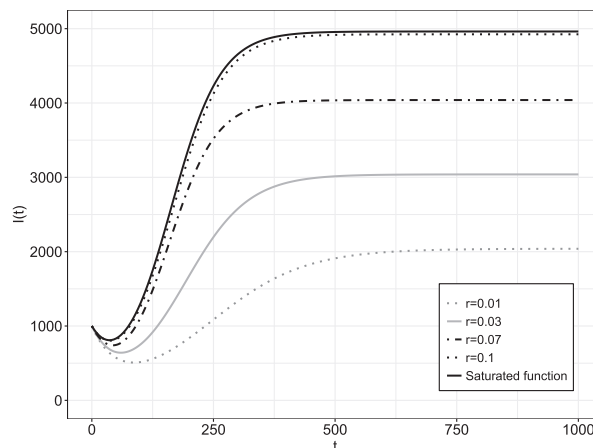
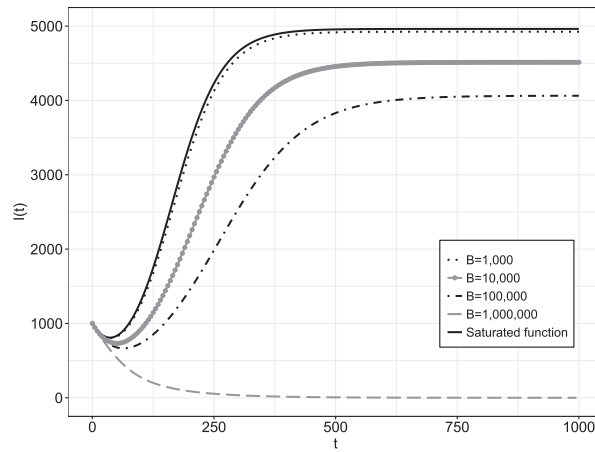
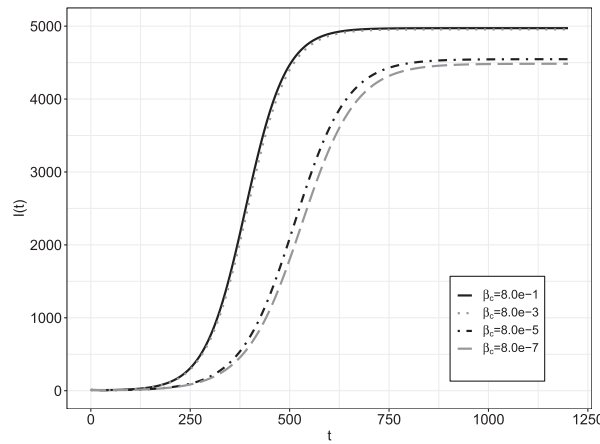


Fig. 1. Number of individuals infected by bacteria as a function of time for different growth rates ( $r$ ) using equation (28) and also for the saturated function (equation (29)).

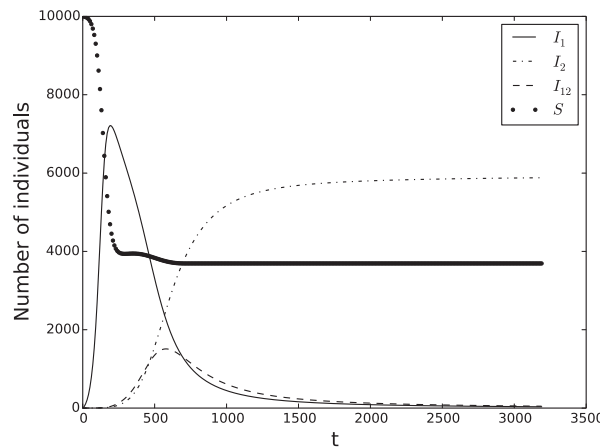




**Fig. 2.** Number of individuals infected by bacteria as a function of time for different values of  $B$ , the parameter related to the infectiousness of the infected hosts, using equation (28) and also for the saturated function (equation (29)).



**Fig. 3.** Number of individuals infected by virus as a function of time for different values of  $\beta_c$ .



**Fig. 4.** Number of individuals in the four classes:  $S$ ,  $I_1$ ,  $I_2$  and  $I_{12}$ . Note that strain 2 replaces strain 1.

$$V_1(t|\tau_1) = \frac{(\beta_{c1}N_c - \mu_1)V_1(\tau_1|\tau_1)e^{(\beta_{c1}N_c - \mu_1)(t - \tau_1)}}{[\beta_{c1}N_c - \mu_1 - \beta_{c1}V_1(\tau_1|\tau_1)]} \times \left[ 1 + \frac{\beta_{c1}V_1(\tau_1|\tau_1)e^{(\beta_{c1}N_c - \mu_1)(t - \tau_1)}}{\beta_{c1}N_c - \mu_1 - \beta_{c1}V_1(\tau_1|\tau_1)} \right]^{-1}, \tag{37}$$

where  $\beta_{c1}$  is a contact rate between cells for strain 1 and  $N_c$  is the total number of cells.

We assume that  $V_1(\tau_1|\tau_1) = p_1 S_c(\tau_1)$ , in words, at the infection event, a fraction  $p_1$  of susceptible cells are infected by strain 1. Note that we are assuming that the initial infection is independent of the state of infectiousness from which the host acquire the infection. This simplification is certainly acceptable except when the infection of the host that transmits the infection is in its very early stages.

3) Solution for  $t > \tau_2 > \tau_1$ . The equations for  $V_1(t|\tau_1)$  and  $V_2(t|\tau_2)$  are

$$\frac{dV_1(t|\tau_1)}{dt} = \beta_{c1} S_c(t) V_1(t|\tau_1) - \mu_1 V_1(t|\tau_1) \tag{38}$$

$$\frac{dV_2(t|\tau_2)}{dt} = \beta_{c2} S_c(t) V_2(t|\tau_2) - \mu_2 V_2(t|\tau_2). \tag{39}$$

We may write equations (38) and (39) as

$$\frac{1}{\beta_{ci}} \frac{dV_i(t|\tau_i)}{V_i(t|\tau_i)} + \frac{\mu_i}{\beta_{ci}} dt = S_c(t) dt, \quad i = 1, 2 \tag{40}$$

or, equivalently,

$$\frac{1}{\beta_{c1}} \frac{dV_1(t|\tau_1)}{V_1(t|\tau_1)} + \frac{\mu_1}{\beta_{c1}} dt = \frac{1}{\beta_{c2}} \frac{dV_2(t|\tau_2)}{V_2(t|\tau_2)} + \frac{\mu_2}{\beta_{c2}} dt. \tag{41}$$

The previous equation may be rewritten as

$$\frac{d}{dt} \left[ \log(V_1(t|\tau_1))^{1/\beta_{c1}} + \frac{\mu_1}{\beta_{c1}} t \right] = \frac{d}{dt} \left[ \log(V_2(t|\tau_2))^{1/\beta_{c2}} + \frac{\mu_2}{\beta_{c2}} t \right] \tag{42}$$

Integrating from  $\tau_2$  to  $t$ , we obtain

$$\frac{[V_1(t|\tau_1)]^{1/\beta_{c1}}}{[V_2(t|\tau_2)]^{1/\beta_{c2}}} = e^{\left(\frac{\mu_2}{\beta_{c2}} - \frac{\mu_1}{\beta_{c1}}\right)(t - \tau_2)} e^A, \tag{43}$$

where

$$A = \log \left[ \frac{V_1(\tau_2|\tau_1)^{1/\beta_{c1}}}{V_2(\tau_2|\tau_2)^{1/\beta_{c2}}} \right]. \tag{44}$$

Substituting  $S_c(t) = N_c - V_1(t|\tau_1) - V_2(t|\tau_2)$  in equation (38), we obtain the differential equation

$$\frac{dV_1(t|\tau_1)}{dt} = -\beta_{c1} V_1^2(t|\tau_1) + (\beta_{c1} N_c - \mu_1) V_1(t|\tau_1) - \beta_{c1} V_1(t|\tau_1) V_2(t|\tau_2) \tag{45}$$

that may be solved numerically, using  $V_2(t|\tau_2)$  derived from equation (43), that is,

$$V_2(t|\tau_2) = [V_1(t|\tau_1)]^{\beta_{c2}/\beta_{c1}} e^{-\beta_{c2} \left(\frac{\mu_2}{\beta_{c2}} - \frac{\mu_1}{\beta_{c1}}\right)(t - \tau_2) - \beta_{c2} A}. \tag{46}$$

The continuity condition is such that, for  $t < \tau_2$ ,

$$V_1(\tau_2|\tau_1) + S_c(\tau_2^-) = N_c \tag{47}$$

and, for  $t > \tau_2$ ,

$$V_1(\tau_2|\tau_1) + V_2(\tau_2|\tau_2) + S_c(\tau_2^+) = N_c, \tag{48}$$

where

$$S_c(\tau_2^+) = S_c(\tau_2^-) - p_2 S_c(\tau_2^-) = (1 - p_2) S_c(\tau_2^-).$$

Note that  $V_2(\tau_2|\tau_2) = p_2 S_c(\tau_2^-)$ , that is, at the infection event, a fraction  $p_2$  of susceptible cells are infected with strain 2. We are again assuming that the initial infection is independent of the state of infectiousness from which the host acquire the infection.

Analysing expression (43), we note that the ratio  $\frac{V_1(t|\tau_1)^{1/\beta_{c1}}}{V_2(t|\tau_2)^{1/\beta_{c2}}}$  increases if  $\frac{\mu_2}{\beta_{c2}} > \frac{\mu_1}{\beta_{c1}}$ , and decreases, vanishing for large  $t$  if  $\frac{\mu_2}{\beta_{c2}} < \frac{\mu_1}{\beta_{c1}}$ . Therefore, if  $R_{0,2} = \frac{\beta_{c2} N_c}{\mu_2}$  is greater than  $R_{0,1} = \frac{\beta_{c1} N_c}{\mu_1}$ , strain 2 invades the cells even if the organism is previously infected with strain 1. On the other hand, if the host is infected with strain 2, strain 1 cannot invade it.

Numerical integration shows that, if  $R_{0,2} > R_{0,1}$ , strain 2 replaces strain 1 (Figs. 4 and 5). On the other hand, if  $R_{0,2} < R_{0,1}$ , strain 1 cannot invade a host infected with strain 2 even if  $R_{0,2}$  is not much greater than  $R_{0,1}$ . In this case, the initial amount of strain 1 virus decreases exponentially.

### 3.2. Between-host dynamics

In this Subsection, we assume that  $R_{0,2} > R_{0,1}$ . Therefore, in the population, individuals infected with strain 2 cannot be infected by strain 1. So, the between-hosts model consists of four classes of individuals:  $S(t)$ , representing the number of individuals susceptible to both strains of virus, at time  $t$ ;  $I_1(t)$  and  $I_2(t)$ , representing individuals infected with strain 1 or 2, respectively; and  $I_{12}(t)$ , representing individuals infected with both strains but who acquired strain 1 first. Note that individuals cannot get simultaneously infected by both strains, since this would be a second-order effect. The variables and parameters of the model for two infectious agents are in Table 2.

The governing equations that will be explained later are

$$\begin{aligned} \frac{dS(t)}{dt} &= -[\lambda_1(t) + \lambda_2(t) + \lambda_{12 \rightarrow 1}(t) + \lambda_{12 \rightarrow 2}(t)]S(t) - \mu_h S(t) + \Lambda(t) \\ \frac{dI_1(t)}{dt} &= [\lambda_1(t) + \lambda_{12 \rightarrow 1}(t)]S(t) - [\lambda_2(t) + \lambda_{12 \rightarrow 2}(t)]I_1(t) - \mu_h I_1(t) \\ \frac{dI_2(t)}{dt} &= (\theta(t - \tau_2))([\lambda_2(t) + \lambda_{12 \rightarrow 2}(t)]S(t) - \mu_h I_2(t)) \\ \frac{dI_{12}(t)}{dt} &= (\theta(t - \tau_2))([\lambda_2(t) + \lambda_{12 \rightarrow 2}(t)]I_1(t) - \mu_h I_{12}(t)). \end{aligned} \tag{49}$$

The equations for  $\lambda_i(t)$  ( $i = 1, 2$ ) and  $\lambda_{12 \rightarrow k}(t)$  ( $k = 1, 2$ ) require some further definitions, given below, and we set  $\Lambda(t) = \mu_h(S(t) + I_1(t) + I_2(t) + I_{12}(t))$  to keep the population constant. Note also that we are assuming that the infections do not affect the mortality of the individuals, for simplicity.

Let  $i_1(t, \tau_1)$  represent the number of individuals at time  $t > \tau_1$  infected between  $\tau_1$  and  $\tau_1 + d\tau_1$  with strain 1, and  $i_2(t, \tau_2)$  represent the number of individuals at time  $t > \tau_2$  infected between  $\tau_2$  and  $\tau_2 + d\tau_2$  with strain 2. In addition, let  $i_{12}(t, \tau_1, \tau_2^*)$  ( $t > \tau_2^* > \tau_1$ ) represent individuals at time  $t$  that were infected between  $\tau_1$  and  $\tau_1 + d\tau_1$  and between  $\tau_2^*$  and  $\tau_2^* + d\tau_2^*$  with strains 1 and 2, respectively.

The relation between the variables of equation (49) and the quantities defined above are as follows.

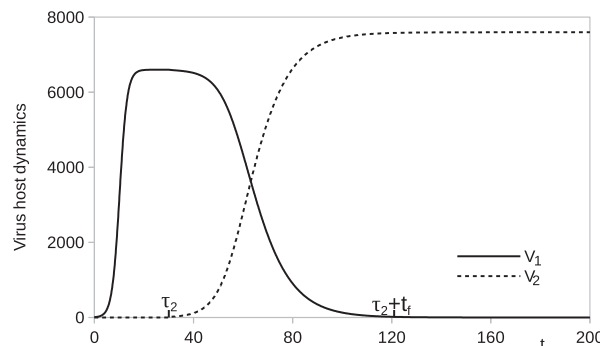


Fig. 5. Virus dynamics in the host, showing that strain 2 (dashed line) replaces strain 1 (solid line).

**Table 2**  
Summary of the variables, parameters and initial conditions of the model for two infectious agents.

Variable	Description	Value
$I_1(t)$	Individuals infected by strain 1	<i>Initial condition</i> $I_1(0) = 0.001$
$I_2(t)$	Individuals infected by strain 2	$I_2(0) = 0.001$
$I_{12}(t)$	Individuals infected by both strains who acquired strain 1 first	$I_{12}(0) = 0.0014$
$S_c(t)$	Susceptible cells in the host	$S_c(0) = 8000$
$V_1(t \tau_1)$	Number of cells infected by strain 1 at time $\tau_1$	
$V_2(t \tau_2)$	Number of cells infected by strain 2 at time $\tau_2$	
<i>Parameter</i>		<i>Value</i>
$B$	Parameter that controls the infectiousness of infected hosts	1000
$\beta_1^{eff}$	Effective contact rate	$2.0 \times 10^{-5} \text{days}^{-1}$
$\beta_{01}$	Contact rate for the transmission of strain 1 (HCV)	$4.0 \times 10^{-8} \text{days}^{-1}$
$\beta_{02}$	Contact rate for the transmission of strain 2 (HAV)	$4.01 \times 10^{-8} \text{days}^{-1}$
$\mu_h$	Human (host) death rate	$3.9 \times 10^{-5} \text{days}^{-1}$
$K$	Host carrying capacity	10000
$\mu_1$	Death rate of cells infected by strain 1 (HCV)	$2.0 \times 10^{-2} \text{days}^{-1}$
$\mu_2$	Death rate of cells infected by strain 2 (HAV)	$1.2 \times 10^{-2} \text{days}^{-1}$
$\beta_{c1}$	Contact rate within the host for strain 1 (HCV)	$1.0 \times 10^{-4} \text{days}^{-1}$
$\beta_{c2}$	Contact rate within the host for strain 2 (HAV)	$1.0 \times 10^{-4} \text{days}^{-1}$
$p_1$	Fraction of susceptible cells infected at the infection event by strain 1	0.001
$p_2$	Fraction of susceptible cell infected at the infection event by strain 2	0.002

$$\begin{aligned}
 I_i(t) &= \int_{-\infty}^t i_i(t, \tau'_i) d\tau'_i = \int_{-\infty}^0 i_i(t, \tau'_i) d\tau'_i + \int_0^t i_i(t, \tau'_i) d\tau'_i \\
 &= I_i(0)e^{-\mu_h t} + \int_0^t i_i(t, \tau'_i) d\tau'_i \quad (i = 1, 2)
 \end{aligned}
 \tag{50}$$

$$\begin{aligned}
 I_{12}(t) &= \int_{-\infty}^t \int_{-\infty}^t i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 \\
 &= \int_{-\infty}^0 \int_{-\infty}^0 i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 + \int_{-\infty}^0 \int_0^t i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 \\
 &\quad + \int_0^t \int_{-\infty}^0 i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 + \int_0^t \int_0^t i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 \\
 &= I_{12}(0)e^{-\mu_h t} + \int_0^t \int_0^t i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2
 \end{aligned}
 \tag{51}$$

Note that we are assuming that infected individuals (the terms  $I_1(0)$ ,  $I_2(0)$  and  $I_{12}(0)$ ) can enter the population only if infected before the time  $t = 0$ . In particular, in equation (51), we assumed that the terms referring to individuals infected at various times before  $t = 0$  were taken into consideration in the term  $I_{12}(0)e^{-\mu_h t}$ .

The definition for the force of infection  $\lambda_i(t)$  ( $i = 1, 2$ ) is given by

$$\lambda_i(t) = \int_{-\infty}^t \beta_i(t - \tau'_i) i_i(t, \tau'_i) d\tau'_i = \int_{-\infty}^0 \beta_i(t - \tau'_i) i_i(t, \tau'_i) d\tau'_i + \int_0^t \beta_i(t - \tau'_i) i_i(t, \tau'_i) d\tau'_i
 \tag{52}$$

where  $\beta_i(t - \tau'_i)$  ( $i = 1, 2$ ) is the probability that  $i_i(t, \tau'_i)$  transmits the infection per unit of time.

The contact rate functions  $\beta_i(t - \tau'_i)$  ( $i = 1, 2$ ) are assumed to be related to the virus densities as follows

$$\begin{aligned} \beta_1(t) &= \beta_{01}\phi_1(t) \\ \beta_2(t) &= \beta_{02}\phi_2(t) \end{aligned} \tag{53}$$

where

$$\begin{aligned} \phi_1(t) &= \frac{V_1(t)}{V_1(t) + V_2(t)} \left[ 1 - e^{-V_1(t)/k_1} \right] \\ \phi_2(t) &= \frac{V_2(t)}{V_1(t) + V_2(t)} \left[ 1 - e^{-V_2(t)/k_2} \right] \end{aligned} \tag{54}$$

and  $\beta_{0i}$  ( $i = 1, 2$ ) is the contact rate common to all individuals in the population times the probability of getting the infection that can differ from strain to strain. Note that the terms  $\phi_1(t)$  and  $\phi_2(t)$  imply that this probability should be multiplied by the density of the pathogen within individuals.

Since we do not know the distribution of infected hosts before  $t = 0$ , we have to introduce an empirical assumption (see the comments after equation (16))

$$\beta_i^{eff} I_i(0)e^{-\mu_h t} = \int_{-\infty}^0 \beta_i(t - \tau'_i) i_i(t, \tau'_i) d\tau'_i \tag{55}$$

and rewrite equation (52) as

$$\lambda_i(t) = \beta_i^{eff} I_i(0)e^{-\mu_h t} + \int_0^t \beta_i(t - \tau'_i) i_i(t, \tau'_i) d\tau'_i \tag{56}$$

Analogously,  $\lambda_{12 \rightarrow k}(t)$  ( $k = 1, 2$ ) is given by

$$\begin{aligned} \lambda_{12 \rightarrow k}(t) &= \int_{-\infty}^t \int_{-\infty}^t \beta_k(t - \tau'_k) i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 \\ &= \int_{-\infty}^0 \int_{-\infty}^0 \beta_k(t - \tau'_k) i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 + \int_{-\infty}^0 \int_0^t \beta_k(t - \tau'_k) i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 \\ &\quad + \int_0^t \int_{-\infty}^0 \beta_k(t - \tau'_k) i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 + \int_0^t \int_0^t \beta_k(t - \tau'_k) i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2 \\ &= \beta_{12 \rightarrow k}^{eff} I_{12}(0)e^{-\mu_h t} + \int_0^t \int_0^t \beta_k(t - \tau'_k) i_{12}(t, \tau'_1, \tau'_2) d\tau'_1 d\tau'_2. \end{aligned} \tag{57}$$

The kernels  $i_i(t, \tau_i)$  ( $i = 1, 2$ ) and  $i_{12}(t, \tau_1, \tau_2^*)$  are obtained as follows.

$$\begin{aligned} i_i(t, \tau_i) &= e^{-\mu_h(t-\tau_i)} i_i(\tau_i, \tau_i) \\ &= S(\tau_i) [\lambda_i(\tau_i) + \lambda_{12 \rightarrow i}(\tau_i)] e^{-\mu_h(t-\tau_i)}. \end{aligned} \tag{58}$$

$$\begin{aligned} i_{12}(t, \tau_1, \tau_2^*) &= e^{-\mu_h(t-\tau_2^*)} i_{12}(\tau_2^*, \tau_1, \tau_2^*) \\ &= i_1(\tau_2^*, \tau_1) [\lambda_2(\tau_2^*) + \lambda_{12 \rightarrow 2}(\tau_2^*)] e^{-\mu_h(t-\tau_2^*)}. \end{aligned} \tag{59}$$

Equations (58) and (59) may be solved iteratively, using equations (56) and (57). The populations  $I_1(t)$ ,  $I_2(t)$  and  $I_{12}(t)$  can be calculated from equations (50) and (51).

The model was investigated numerically using the parameters shown in Table 2. These parameters are arbitrary, but this was done because we wanted to discuss results that should be found in a number of pathologies, and each pathology could have a different set of parameters. However, the qualitative features obtained illustrate behaviors that we expected can be found in many pathologies.

The solution of this system when virus 1 is introduced at time  $t = 0$  and virus 2 at time  $\tau_1$  is shown in Fig. 4. The number of individuals with only virus 1 decreases and so does  $I_{12}(t)$ , but  $I_2(t)$  increases. From Fig. 4, we can see that there is a fraction of the population that is affected by both viruses. In these individuals, virus 1 is being replaced by virus 2.

Let us examine what happens within each individual of the type  $I_{12}(t)$ . According to equation (43), the amount of virus 1 decreases exponentially within this individual. So it is reasonable to say that, for sufficiently great  $t$ ,  $\frac{V_1(t|0)}{V_2(t|\tau_1)}$  decreases within this individual. When  $\frac{V_1(t|0)}{V_2(t|\tau_1)} = \alpha$  ( $\alpha$  is arbitrary and we choose a small proportion), we can consider that this individual became one of the  $I_2(t)$  individuals, that is, infected only by virus 2.

In the next Subsection, we show how this fact modifies our understanding of the solution of system (49) that describes the propagation of the infection in the human (host) population.

### 3.3. Interpretation of the between host dynamics

Let us consider again the within host dynamics. Assume that virus 1 infects an individual at  $t = 0$  and virus 2 at  $t = \tau_2$ . The internal dynamics is depicted in Fig. 5. In this figure, at time  $\tau_2 + t_f$ , we assume that

$$\frac{V_1(\tau_2 + t_f|0)}{V_2(\tau_2 + t_f|\tau_2)} = \alpha. \tag{60}$$

Using equation (43), we can calculate the time interval  $t^* - \tau_2 = t_f$ , that is, the time it takes for virus 2 to “replace” virus 1.

We will assume that virus 1 infects the system at time  $t = \tau_1$  and virus 2 can infect the system at any time  $\tau_2 > \tau_1$  and so we must calculate  $t_f$  (Fig. 6) as a function of  $\tau_1, \tau_2$  and  $t_f = t_f(\tau_2, \tau_1) = t_f(\tau_2 - \tau_1)$ . This can be done numerically and the result is shown in Fig. 7 for different values of  $\alpha$ .

Therefore we define new compartments as follows:  $S^* = S, I^* = I, I_2^* = I_2 + Y_2$  and  $I_{12}^* = Y_{12}$ , where

$$Y_2(t) = \int_0^t d\tau_1 \int_{\tau_1}^t d\tau_2 \theta\left[\left(t - t_f(\tau_2 - \tau_1)\right) - \tau_2\right] i_{12}(t, \tau_1, \tau_2) \tag{61}$$

and

$$Y_{12}(t) = \int_0^t d\tau_1 \int_0^t d\tau_2 \theta\left[\tau_2 - \left(t - t_f(\tau_2 - \tau_1)\right)\right] i_{12}(t, \tau_1, \tau_2), \tag{62}$$

where  $\theta(x)$  is the Heaviside step function.

The term  $Y_2(t)$  are those  $I_{12}(t)$  where the ratio of the viral load  $\frac{V_1}{V_2}$  is less than  $\alpha$ . On the other hand,  $Y_{12}(t)$  are those  $I_{12}(t)$  where the ratio of the viral load  $\frac{V_1}{V_2}$  is greater than  $\alpha$ . Fig. 8 explains graphically the process.

Consider that virus 1 infects a susceptible individual at time  $t = \tau_1$  and virus 2 infects the individual at any time between  $\tau_1$  and  $t$ . There is a time  $\tau_c$  that, if virus 2 invades between  $\tau_1$  and  $\tau_c$ , there will be no virus 2 left. But if virus 2 infects the individual between  $\tau_c$  and  $t$ , there will be coexistence.

To estimate how fast virus 2 replaces virus 1 in the population, we define a critical time  $t_p$  equivalent to the time it takes for the ratio  $\frac{I_1}{I_2}$  to decrease to an arbitrary ratio  $\Delta$ , i.e.,

$$\frac{I_1(t_p)}{I_2(t_p)} = \Delta. \tag{63}$$

### 3.4. Simulation for the competition between HAV and HCV

Deterding et al. (2006) reported that hepatitis A virus (HAV) infection suppresses hepatitis C virus (HCV) replication and may lead to clearance of HCV. As pointed out by Amaku et al. (2013), the exclusion of HCV by the super-infection with HAV

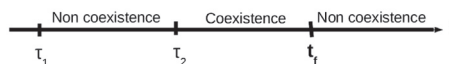
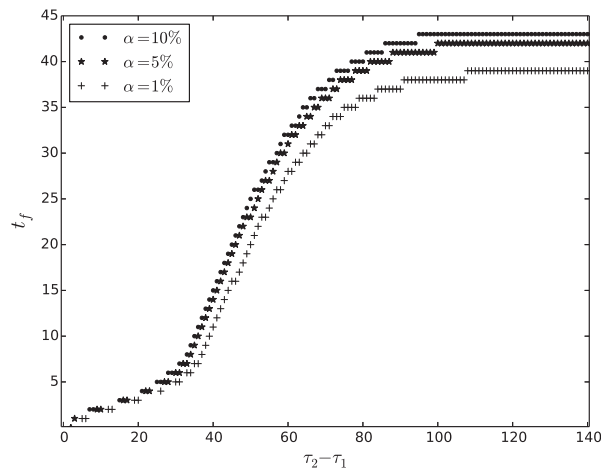
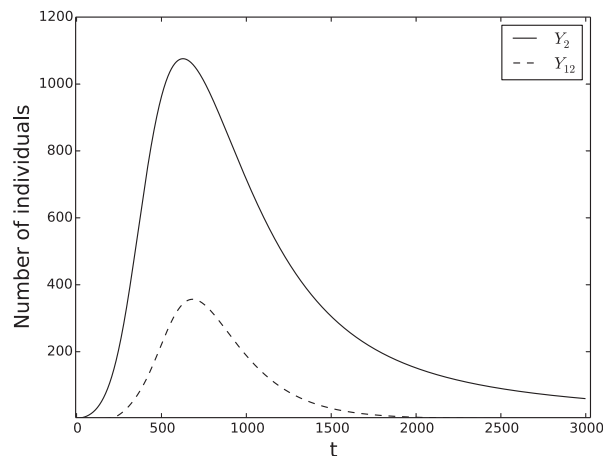


Fig. 6. Virus 1 infects the host at time  $\tau_1$  and the virus 2 infects the host at time  $\tau_2$ . Between  $\tau_1$  and  $\tau_2$ , there is no coexistence. At time  $t_f$ , virus 2 replaces virus 1 and, after  $t_f$ , there is no coexistence again.



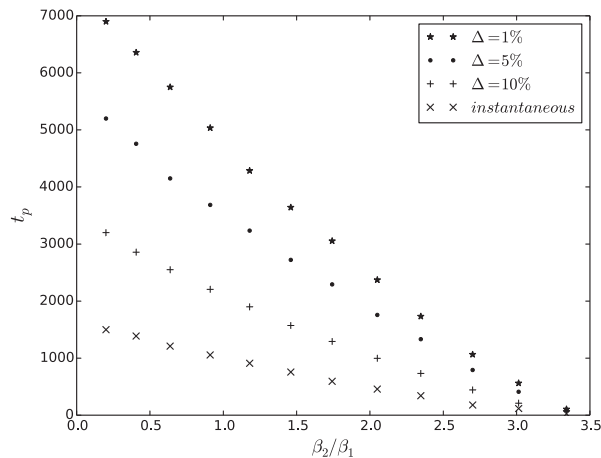
**Fig. 7.** Time it takes for virus 2 to replace virus 1 within the host,  $t_f$ , as a function of the difference between  $\tau_2$ , the time when virus 2 enters the system, and  $\tau_1$ , the time when virus 1 enters the system.



**Fig. 8.** The number of individuals coinfecting with strains 1 and 2,  $I_{12}$ , is split between those still coinfecting by both strains,  $Y_{12}$ , and those infected only by strain 2 after replacing strain 1,  $Y_2$ .

could be explained by the Principle of Competitive Exclusion (Amaku et al., 2010a,b; Bremermann & Thieme, 1989; Burattini et al., 2008). The winning strain (species) is the one with the greatest basic reproduction number.

To give an example of the calculation of the time it takes for virus 2 to replace virus 1 ( $t_p$ ), we developed an example based on the competition between HCV (virus 1) and HAV (virus 2), using parameters of Table 2 but with  $\beta_{01}$  constant and  $\beta_{02}$  varying between  $1.0 \times 10^{-8}$  and  $1.4 \times 10^{-7}$ . These parameters are in a similar range of those used in Amaku et al. (2013). For a given  $\Delta$  (1%, 5% and 10%), we estimated the time  $t_p$  (equation (63)) for several values of the ratio  $\beta_{02}/\beta_{01}$ . The results are shown in Fig. 9. We also simulated the scenario in which the replacement of HCV by HAV within the individual is instantaneous (crosses in Fig. 9). In the instantaneous replacement simulation,  $t_p$  is shorter compared to the case in which the replacement within the infected individuals is not instantaneous. Thus, we have shown that the internal dynamics influence the spread of the infections in the population, affecting the time for replacement of one virus by another. We do not claim that the above model for competition between HCV and HAV is realistic. First, hepatitis is a lytic infection and we assumed (see equation (33)) that the population of cells remains constant. Although the cells die, they are replaced by new ones and we assumed that this process results in a constant cell population. This is surely an approximation, but not a bad one. Second, the parameters shown in Table 2 are arbitrary and may differ from the parameters for HCV and HAV. However, the purpose of this calculation is just to illustrate the calculation of the replacement time when there is an internal viral dynamics compared with the situation where replacement is instantaneous.



**Fig. 9.** Numerical simulation using the parameters shown in Table 2 except for the values of  $\beta_{01}$  and  $\beta_{02}$ . On the x-axis,  $\beta_{01}$  value was kept constant and  $\beta_{02}$  values varied between  $1.0 \times 10^{-8}$  and  $1.4 \times 10^{-7}$  (Amaku et al., 2013).  $\beta_{01}$  represents the transmission rate of hepatocytes infected with HCV, and  $\beta_{02}$  is transmission rate of hepatocytes infected with HAV. On the y-axis,  $t_p$  is the time for the replacement of HCV by HAV in the population. The crosses represent the instantaneous replacement of HCV by HAV in the population.

#### 4. Conclusions

We developed nested or multiscale models for one and two infectious agents, taking into account the coupling between the within-host and the between-host dynamics. These models are a generalization of the model proposed in Amaku et al. (2010a).

In the model for one infectious agent, we analyzed the effect of the age of infection within the host on the disease prevalence in the population. We found that, if the infectious disease is less virulent within the hosts, the endemic steady state in the population is reached more slowly.

In the model for two infectious agents, we found that, when strain 2 has a basic reproduction number  $R_{02}$  greater than the basic reproduction number  $R_{01}$  of strain 1, strain 2 replaces strain 1 in the population. However, if  $R_{02} > R_{01}$  but the values are closer, the replacement does not occur immediately and both strains can coexist for a long time. This model can be generalized for more than two infectious agents.

We applied the model for two infectious agents to simulate the competition between HAV and HCV to infect human liver cells. We showed how short is the time for replacement so that instantaneous replacement could be considered a good approximation. However, we showed cases in which the replacement takes a long time and, therefore, the simpler calculation assuming instantaneous replacement cannot be done. We also showed that the internal dynamics influences the spread of the infectious disease in the population and the time for replacement of one virus by another in a competition scenario is an important element that must be considered.

There are other potential applications for the nested models developed in this paper. For instance, the modelling of the coexistence of different serotypes of dengue virus in the *Aedes aegypti* mosquitoes and also the competition between viruses in plant-pathogens systems.

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