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Modeling multiple infection of cells by viruses: Challenges and insights

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ABSTRACT

The multiple infection of cells with several copies of a given virus has been demonstrated in experimental systems, and has been subject to previous mathematical modeling approaches. Such models, especially those based on ordinary differential equations, can be characterized by difficulties and pitfalls. One such difficulty arises from what we refer to as multiple infection cascades. That is, such models subdivide the infected cell population into sub-populations that are carry i viruses, and each sub-population can in principle always be further infected to contain $i + 1$ viruses. In order to study the model with numerical simulations, the infection cascade needs to be cut artificially, and this can influence the results. This is shown here in the context of the simplest setting that involves a single, homogeneous virus population. If the viral replication rate is sufficiently fast, then most infected cells will accumulate in the last member of the infection cascade, leading to incorrect numerical results. This can be observed even with relatively long infection cascades, and in this case computational costs associated with a sufficiently long infection cascade can render this approach impractical. We subsequently examine a more complex scenario where two virus types/strains with different fitness are allowed to compete. Again, we find that the length of the infection cascade can have a crucial influence on the results. Competitive exclusion can be observed for shorter infection cascades, while coexistence can be observed for longer infection cascades. More subtly, the length of the infection cascade can influence the equilibrium level of the populations in numerical simulations. Studying the model in a parameter regime where an increase in the infection cascade length does not influence the results, we examine the effect of multiple infection on the outcome of competition. We find that multiple infection can promote coexistence of virus types if there is a degree of intracellular niche separation. If this is not the case, the only outcome is competitive exclusion, similar to equivalent models that do not take into account multiple infection of cells. We further find that multiple infection has a reduced ability to allow coexistence if virus spread is spatially restricted compared to a well-mixed system. These results provide important insights when analyzing and interpreting multiple infection models.

1. Introduction

Investigating the dynamics of virus spread through target cell populations has produced a better understanding of the principles underlying virus dynamics and evolution, and has provided insights into in vivo processes that contribute to the development of disease from a variety of human pathogens, such as human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV). Mathematical models have played an important role in this respect [1–3]. A relatively underexplored area in virus dynamics is the multiple infection of cells, i.e. the simultaneous infection of a cell with more than one copy of a virus. This can occur in different infections. For example, adenoviruses are thought to infect cells with several viral copies, and interesting dynamics have been observed that appear related to multiple infection and that warrant further investigation with mathematical models [4]. Some of the better documented data come from human immunodeficiency virus (HIV). A collection of in vitro and ex vivo studies clearly showed that more than one virus can enter the same cell [5–8]. For in vivo scenarios, patient data have been reported that showed an average of 3–4 proviruses per infected cell in the spleen [9]. Other studies, however, argued that the great majority of infected cells in HIV-infected patients in the blood and tissues are singly infected [10,11]. This discrepancy might be due to the particular T cell subsets examined in the respective studies, although the reason is not understood. The occurrence of viral recombination in vivo, however, further indicates an important role of multiple infection, since recombination would otherwise not be possible [7,9,12].

Virus dynamics in the presence of multiple infection has been examined mathematically in a few studies. Basic dynamics were investigated with ordinary differential equations and integro-differential equations by Dixit and Perelson [13,14], and subsequently investigated further in references [15,16], using ordinary differential

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equations and agent-based models. The effect of recombination, which requires multiple infection, has been modeled, e.g. [17–19]. Competition was also incorporated into multiple infection models [20,21]. The ordinary differential equations models that have been reported are similar in structure compared to those in the field of epidemiology, where multiple pathogens are assumed to infect hosts [22–28].

Those models can be characterized by certain difficulties and pitfalls, especially when investigating simplified formulations in terms of ODEs. ODEs that describe multiple infection generally divide the population of infected cells in subpopulations that are infected with one, two, three etc. viruses. We refer to this as the "multiple infection cascade". In principle, this cascade can be infinite. In practical terms, the number of cells infected with a multiplicity that lies above a certain threshold will be negligible, and thus the infection cascade can be truncated. It is, however, unclear how exactly the truncation of the cascade can affect the results. In the presence of competition, it has been shown that certain truncated and simplified model forms can lead to pathological outcomes, where the assumption of two identical (and thus competitively neutral) pathogens can lead to a unique equilibrium [27].

In this paper, we examine in more detail ODE modeling approaches to study the multiple infection of cells with viruses. We start by investigating how the truncation of the multiple infection cascade can affect the outcome in different parameter regions in the context of basic dynamics. We then expand the multiple infection models to investigate the competition between two virus strains, taking into account both competition for target cells (as in standard virus competition models) and the competition for intracellular resources.

This analysis will be performed in the most general setting, without considering one specific infection. The aim of this work is to gain a better understanding of how model structure can influence outcome in models that describe the multiple infection of cells by viruses. This can form the basis for future work that applies this type of model to specific infections, which will require careful consideration of assumptions that are specific to the virus in question.

2. Results

2.1. Basic ODE models of multiple infection

Mathematical models of virus dynamics are often based on ordinary differential equations, and this approach has also been used to describe the infection of cells by multiple copies of the same virus (multiple infection). Denoting the population of susceptible cells by S, free virus by V, and the population of cells infected with i viruses by I_i, the model is given as follows.

$$\begin{aligned}
\frac{dS}{dt} &= \lambda - dS - \beta SV \\
\frac{dI_1}{dt} &= \beta SV - a_1 I_1 - \beta I_1 V \\
\frac{dI_i}{dt} &= \beta I_{i-1} V - a_i I_i - \beta I_i V \\
&\cdots \\
\frac{dI_n}{dt} &= \beta I_{n-1} V - a_n I_n \\
\frac{dV}{dt} &= \sum_{i=1}^{n} k_i I_i - uV
\end{aligned} \tag{1}$$

This is an extension of basic virus dynamics models [1–3], and has been described first by Dixit and Perelson [13], with extensions published subsequently [2,3]. Susceptible target cells are produced with a rate λ and die with a rate d. Infection of susceptible cells by virus occurs with a rate β, generating cells infected with a single copy of the virus. These cells can be infected by further virus particles with a rate β, generating cells infected with i copies of the virus. This process can continue until the end of the infection cascade, I_n, is reached. Cells in this population cannot be infected any further. Infected cell populations die with a rate a_i and produce virus with a rate k_i. Free virus decays with a rate u. In this formulation, the rate of virus production, k, and the rate of infected cell death, a, can depend on the multiplicity of infection, i, although it does not have to. In the simplest form, these parameters do not depend on the multiplicity of infection, as described by Dixit and Perelson [13]. In this case, virus production is determined predominantly by cellular factors, keeping the overall amount of virus produced constant and independent of the number of viruses in the cell. Alternatively, it is possible that the rate of virus production and the death rate of infected cells can increase to a certain degree in multiply infected cells, a scenario considered in [16]. In models that have been applied to HIV infection, it has also been assumed that the ability of a cell to become infected can be lost over time, as a result of e.g. receptor down-modulation [13]. This will not be considered in the present context.

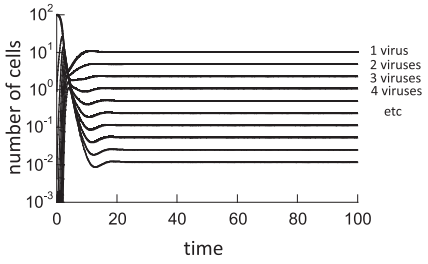

Fig. 1. Distribution of the number of cells infected with i viruses, according to model (1) where the rate of virus production does not depend on infection multiplicity. Singly infected cells are most abundant, and the number of cells containing higher infection multiplicities is successively lower. Parameters were chosen as follows. $\lambda = 10$; $d = 0.1$; $a = 1$; $\beta = 0.1$; $k = 1$; $u = 1$; $\varepsilon = 0$. Infection cascade length $n = 100$.

One aspect we would like to explore here is the dependency of the dynamics on model structure. In particular, the ODE formulation requires an arbitrary end to the infection cascade, I_n. The larger the value of n, the more computationally expensive simulations of this system become. The value of n, however, can impact the dynamics that are observed in this model, and this will be investigated in the following sections. First, it will be assumed that virus parameters are independent of the infection multiplicity. Subsequently, we will assume that multiply infected cells produce more virus during their life-span than singly infected cells.

2.1.1. Virus parameters are independent of infection multiplicity

This system has been studied analytically before, and the reader is referred to these analyses for details [13,16]. If the basic reproductive ratio of the virus is greater than one, the virus and cell populations converge to an internal, stable equilibrium, which has been defined [13,16]. Here, we concentrate on the distribution of cells infected with different multiplicities. The most abundant infected cell population are singly infected cells, I_1, and the abundance of multiply infected cells, I_i, are successively lower (Fig. 1). The population size of the infected cell sub-populations decline exponentially with increasing multiplicities of infection (Fig. 2a), and the rate of this exponential decline is given by $\ln(\frac{\beta\lambda - ad}{\beta\lambda - ad - a^2})$, and hence depends on the parameters that determine the basic reproductive ratio of the virus. The faster the basic reproductive ratio of the virus, the slower the rate of decline. In other words, the singly infected cells become less dominant and the distribution becomes more even for faster viral replication kinetics. In the extreme case where the basic reproductive ratio of the virus is very large, all infected cell sub-populations are almost equally abundant.

If the decline of the successive infected cell sub-populations is relatively slow, the modeling approach discussed here can become difficult. If the length of the multiple infection cascade, n, is not sufficiently large, the majority of the infected cells will accumulate in the