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New virus dynamics in the presence of multiple infection

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HIGHLIGHTS

- Virus dynamics and equilibrium structure change in the presence of coinfection.
- Conditions are found for infection to be established even for $R_0 < 1$.
- For this, the rate of virus production must increase with multiplicity of infection.
- These trends redefine the notion of R_0 in the presence of coinfection.

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ABSTRACT

While most aspects of virus dynamics are well understood in standard models, the phenomenon of multiple infection (or coinfection) can change the properties of the dynamics, and this has so far not been fully explored. An important parameter in determining the properties of the model is the virus output from multiply infected cells compared to that from singly infected cells. If the amount of virus produced by infected cells during their life-span is independent of the infection multiplicity, then multiple infection does not change the dynamics. If, however, multiply infected cells produce more virus during their life-span than singly infected cells, then the properties of the dynamics can change fundamentally. This paper presents a detailed mathematical analysis of this scenario. We demonstrate that under some realistic conditions, the equilibrium structure of the solutions acquires novel properties. In particular, infection can persist even for values of the basic reproductive number, R_0, smaller than unity. In this regime, we observe the phenomenon of bistability, when two stable equilibria are present simultaneously, and the outcome is determined by the initial conditions. The two possible solutions are the virus-free equilibrium, which is exactly the same as the one observed in the absence of multiple infection, and a novel infection equilibrium. In the presence of this outcome, it is clear that the meaning of the parameter R_0 changes, as it no longer simply indicates the possibility of successful infection. This adds to our understanding and interpretation of R_0 in virus dynamics models, and also provides further insights about conditions that can lead to virus extinction rather than persistence. It turns out that conditions for bistability depend (in a fully specified way) on the model structure, particularly on the way the infection term is formulated. We provide a general condition that informs us whether or not bistability occurs, and define what needs to be measured when examining the dynamics of multiple infection in specific biological systems.

1. Introduction

Standard models of virus dynamics traditionally assume that each cell is infected with a single copy of the virus, see e.g. Nowak and May (2000), Perelson (2002), Perelson and Ribeiro (2013), De Boer and Perelson (1998), and Wodarz and Nowak (2002). With this assumption, the basic reproductive ratio, R_0, can be calculated by standard methods, which determines whether or not the virus can establish an infection in the host. Namely, if $R_0 > 1$, successful infection can be established, and if $R_0 < 1$, virus goes extinct independent of the initial viral load (Anderson and May, 1991; Nowak and May, 2000; Heffernan et al., 2005).

It has been proposed, however, that in different infections, multiple viruses can infect the same cell. This is thought to occur in adenovirus infections, and this has been suggested to be a factor

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that can drive the dynamics of virus growth (Hofacre et al., 2012). In HIV infection, the occurrence of multiple infection of cells has been clearly shown to occur in vitro (Levy et al., 2004; Dang et al., 2004; Chen et al., 2005). In vivo, it has also been suggested to occur, with infected cells harboring on average 3–4 viruses in the spleen of patients (Jung et al., 2002; Dang et al., 2004). Further, recombination, which requires multiple infection, is thought to contribute to genetic diversity in vivo (Jung et al., 2002; Neher and Leitner, 2010). Other data, on the other hand, argue that most cells in HIV infected patients are singly infected (Josefsson et al., 2011, 2013), although this might be influenced by the particular subtypes of T cells examined.

In the light of this complexity, it becomes important to gain a better understanding of the consequences of multiple infection for basic virus dynamics. The first coinfection model was proposed by Dixit and Perelson (2004, 2005), which assumes that adding more virus to the cell reduces the replicative output of the individual viruses, such that multiply infected cells produce the same number of virus as singly infected cells. The properties of this model are very similar to those of the basic model in the absence of multiple infection. In this case also, conditions for successful infection are provided by basic reproductive ratio R_0, which is the same as in the models with no coinfection.

In Cummings et al. (2012), an opposite assumption is made. It is postulated that multiply infected cells produce more virus than singly infected cells. As a consequence of this assumption, the basic properties of virus dynamics are found to be significantly altered. In this case the basic reproductive ratio alone is not enough to determine whether or not successful infection will be established. In particular, it was found that if $R_0 > 1$, then infection can be established similar to the standard models. For $R_0 < 1$, however, persistence of virus also depends on the initial viral load, with higher virus loads promoting successful infection. Mathematically, this behavior is explained by the existence of two equilibria in the system which are stable simultaneously, for the same parameter values. This phenomenon is referred to as "bistability". Bistability is not observed in the standard model of virus dynamics, but can be part of the model explored in Cummings et al. (2012). The existence of bistability depends on the replication rate of the virus in multiply infected cells. Namely, bistability is observed if the addition of a virus to the cell increases the overall viral output by a sufficiently large margin, although this phenomenon was not studied mathematically in Cummings et al. (2012).

The observed phenomenon of bistability is a strong indicator that points to fundamental differences in the virus dynamics with and without multiple infection, in the case of increased viral output from multiply infected cells. In particular, the presence of multiple infection can change the structure of the equilibria such that infection becomes possible to maintain even below the $R_0 = 1$ threshold. In this paper, we examine the phenomenon of bistability in more detail. We extend the particular coinfection model presented in Cummings et al. (2012) and consider a very general class of virus dynamics models. An important parameter turns out to be the virus production rate, k_i, of cells with multiplicity of infection i. We present a detailed mathematical analysis of several specific cases, and then give the general conditions for the existence of bistability for virus dynamics systems in the presence of multiple infection.

These considerations require a more detailed discussion of the basic reproductive ratio of the virus, R_0, and its definition. R_0 is typically defined as the average number of newly infected cells produced by one infected cell during its life-span, when placed into a large pool of uninfected cells. In this setting, the occurrence of multiply infected cells is extremely unlikely. Even if we start off with a multiply infected cell, most offspring will be singly infected cells under these circumstances. A central focus of this paper is the finding that if we start from a number of infected cells that is large relative to the number of uninfected cells, then establishment of infection can occur even if R_0, as defined above, is less than one. This indicates that the concept of R_0 may have limited use in such cases as an indicator whether a persistent infection is established or not. Note that the definition of R_0 does not apply to a situation where we start with an initial number of infected cells that is large compared to the number of uninfected cells, since then target cell limitation is in place. These concepts are explored mathematically throughout the paper, and it is shown that the expression for R_0 in the multiple infection model where the rate of virus output increases with infection multiplicity is basically the same as in the simpler virus dynamics models that do not take into account multiple infection. This is shown in the context of different methods to calculate R_0, including the next generation matrix method.

The rest of this paper is organized as follows. In Section 2 we formulate the basic model of virus dynamics in the presence of multiple infection and recast some preliminary results. In Section 3 we consider a simple system where only three types of virus population are considered: target cells, cells infected with one virus, and cells infected with two viruses. This simple case paves the way for the more general system with N infected populations, considered in Section 4. We study three different functional dependencies of the virus production rate, k_i, on the multiplicity of infection, and find conditions on the function k_i to guarantee bistability. Finally, in Section 5 we extend the analysis to models with a general infection term. Discussion is presented in Section 6.

2. The modeling framework

2.1. Model formulation

In this paper we use the term "multiple infection" to refer to cells that contain more than one copy of a given virus (regardless of how far apart in time they have entered the cell). We model the effects of multiple infection on basic viral dynamics by using ordinary differential equations, which describe the average population sizes of infected and uninfected cells. We take into account $N+1$ populations: uninfected cells, x_0, and cells infected with i copies of the virus, x_i, with $1 \le i \le N$, where N is the maximum multiplicity of infection. The variable v describes the amount of virus in the system. Instead of a single model, we perform the analysis on a very general class of models, which are described as follows:

$$\begin{aligned}
\dot{x}_0 &= \lambda - dx_0 - \beta x_0 G_0 v \\
\dot{x}_i &= \beta x_{i-1} G_{i-1} v - \beta x_i G_i v - a_i x_i, \quad 1 \le i \le N-1 \\
\dot{x}_N &= \beta x_{N-1} G_{N-1} v - a_N x_N,
\end{aligned} \tag{1}$$

where the virus is described by equation

$$\dot{v} = \sum_{i=1}^{N} \tilde{k}_i x_i - uv. \tag{2}$$

Below we explain various components of this system.

Infection terms: The functions $G_i = G_i(x_0, \ldots, x_N)$ describe the rate at which cells having i copies of the virus get infected with an additional virus. These functions can take a variety of forms. For example, in the simplest case, we have $G_i = 1$, such that the probability of infection is simply proportional to the abundance of target cells and the number of free viruses, v. The coefficient β in front of the infection term represents the infectivity of the virus. This simple formulation is used very widely, see e.g. Nowak and May (2000). We will refer to this model as a "no-saturation" model.

As the number of target cells increases, the simple model with $G_i = 1$ assumes that the rate of infection will continue to increase