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Virus dynamics in the presence of synaptic transmission

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Abstract

Traditionally, virus dynamics models consider populations of infected and target cells, and a population of free virus that can infect susceptible cells. In recent years, however, it has become clear that direct cell-to-cell transmission can also play an important role for the in vivo spread of viruses, especially retroviruses such as human T lymphotropic virus-1 (HTLV-1) and Human immunodeficiency virus (HIV). Such cell-to-cell transmission is thought to occur through the formation of virological synapses that are formed between an infected source cell and a susceptible target cell. Here we formulate and analyze a class of virus dynamics models that include such cell-cell synaptic transmission. We explore different "strategies" of the virus defined by the number of viruses passed per synapse, and determine how the choice of strategy influences the basic reproductive ratio, R_0 , of the virus and thus its ability to establish a persistent infection. We show that depending on specific assumptions about the viral kinetics, strategies with low or intermediate numbers of viruses transferred may correspond to the highest values of R_0 . We also explore the evolutionary competition of viruses of different strains, which differ by their synaptic strategy, and show that viruses characterized by synaptic strategies with the highest R_0 win the evolutionary competition and exclude other, inferior, strains.

1. Introduction

Mathematical models have played a central part in advancing our understanding of the in vivo dynamics of viral infections. For reviews, see [1, 2, 3]. The basic model structure is related to the epidemiological literature [4] and typically contains three variables, the susceptible cells, infected cells and free virus. It aims to capture in the simplest terms the most essential processes in the viral life-cycle: infected cells produce offspring virus, which is subsequently released into the extracellular environment. If a free virus particle encounters a susceptible cell, it has a chance to infect the cell, enabling the virus to spread through its target cell population. The basic model of virus dynamics is a generic framework that can be potentially applied to a wide variety of viral infections. It has been the basis for the development of many more elaborate models that take into account further biological complexities, usually in the context of specific viral infections, e.g. [5, 1, 2, 6, 7, 8]. Human

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immunodeficiency virus (HIV) has been a particular focus for this research [1, 2]. Apart from the high level of biomedical significance, many detailed clinical and experimental data are available that document the amount of virus over time in patients or animal models of the infection (such as monkeys infected with simian immunodeficiency virus), allowing models to be applied to data for the purpose of validation [9, 10, 11, 12]. Much of this work has been formulated in terms of ordinary differential equations, and is reviewed for example in [1, 2].

Most mathematical models of virus dynamics have been based on the assumption that in vivo virus spread through the target cell population occurs via the release of free virions that infect susceptible cells. It has become clear, however, that direct cell-to-cell transmission also plays an important role for the in vivo spread of the virus, especially in the case of retroviruses. Such cell-to-cell transmission is thought to occur through the formation of virological synapses that are formed between an infected source cell and a susceptible target cell [13, 14, 15, 16]. Many viruses can potentially pass through this connection. A predominant example is Human T cell leukemia virus HTLV-1 [16]. In this case, it is thought that the virus does not spread via free virus alone and that spread to susceptible target cells occurs only through virological synapses. Recently, virological synapses have also gained a lot of attention in the context of HIV [13, 14, 15, 17, 18, 19]. It has become clear that besides cell-free virus transmission, the virus can spread via virological synapses. In fact, it has been observed that this is an extremely efficient process on a per cell basis, leading to the transfer of tens to hundreds of virus per synapse. This in turn can greatly promote the infection of cells with multiple copies of virus. These viruses can be either genetically identical if a cell became infected via the connection with only one source cell, or they can potentially be genetically different if synaptic connections were established with several source cells containing different viral variants. Synaptic transmission is thought to be particularly important in the tissue environments where cells are packed relatively densely. Data indicate an average number of 3-4 viruses per infected cell in the spleen [20]. On the other hand, infected cells in the blood tend to be singly infected [21], presumably because the increased degree of mixing of cells inhibits the efficient formation of synaptic connections.

Multiple infections of target cells have been studied previously in the literature [22, 23], in particular in the context of viral recombination [24, 25, 26, 27]. The first model of multiple infection by means of cell-cell transmission was developed by Dixit and Perelson [28], where the rate of infection was calculated assuming only free-virus transfer and both free-virus transfer and cell-cell transmission. The resulting probability distributions of the number of viral particles per infected cells' genome were fitted to the data on the multiplicity of infection from [20]. It was found that roughly 10% of infections were transmitted by cell-free virions and the rest were transmitted by infected cells and that every infectious cell-cell contact results in the average transmission of 3.4 viral genomes.

The present paper provides a detailed mathematical analysis of an ODE model of virus dynamics that explicitly takes into account virus spread via virological synapses. The model is constructed and analyzed specifically with HIV in mind, where both free-virus and synaptic pathways are known to play a role. We investigate basic virus dynamic properties

in this model, such as the basic reproductive ratio of the virus and virus load at equilibrium. We ask evolutionary questions in the context of the efficiency of different “synaptic transmission strategies” defined by the number of viruses passed per synapse. We show that depending on specific assumptions about the viral kinetics, strategies with low or intermediate numbers of viruses transferred may correspond to the highest values of R_0 . We also take these concepts further and explore the evolutionary competition of viruses of different strains, which differ by their synaptic strategy, and show that viruses characterized by synaptic strategies with the highest R_0 win the evolutionary competition and exclude other, inferior, strains.

The rest of this paper is organized as follows. In Section 2 we formulate the mathematical model and show how various assumptions can lead to reductions of the system, allowing for an analytical solution for the steady state. In Sections 3 and 4 we study synaptic transmission under two assumptions: first, we assume that the viral kinetics are independent of the number of viruses infecting the host cell, and subsequently, we explore what happens if the virus production becomes dependent on the number of resident viruses. We calculate the basic reproductive ratio of the virus depending on the synaptic strategy. Based on these calculations, we determine which strategy is the most effective (that is, has the highest basic reproductive ratio). In Section 5 we explore evolutionary dynamics of competition among different strains. Section 6 is reserved for discussion and conclusions.

2. Modeling cell-to-cell transmission

Let us suppose that a susceptible cell can be infected by up to N viruses (that is, up to N viral genomes can be incorporated into a cell's genome). We denote by x_i the number of cells infected by i viruses, $0 \leq i \leq N$, and refer to the number i as the cells' *multiplicity of infection*. In this notation, x_0 is the number of uninfected cells. The equations describing synaptic virus transmission are:

$$\dot{x}_0 = \lambda - dx_0 - \sum_{m=1}^N x_m \sum_{j=1}^N \gamma_j^{(m)} x_0, \quad (1)$$

$$\dot{x}_i = \sum_{m=1}^N x_m \left(\sum_{j=1}^i \gamma_j^{(m)} x_{i-j} - x_i \sum_{j=1}^{N-i} \gamma_j^{(m)} \right) - a^{(i)} x_i, \quad 1 \leq i \leq N, \quad (2)$$

where $\gamma_j^{(m)}$ is the probability for a cell infected with m viruses to transmit j viruses per synapse. Since $\gamma_j^{(m)}$ is a probability, we have $\sum_{j=0}^N \gamma_j^{(m)} = 1$ for all $1 \leq m \leq N$. Note that in equation (2) when $i = N - 1$, the summation in the out-going term goes from 1 to 1, that is, there is only one term in that sum. When $i = N$, the summation formally goes from 1 to 0, which means that there are no terms in that sum. In other words, for $i = N$, there is no out-going term. The quantity $\gamma_j^{(m)}$ contains all the information about the virus production and synapse formation. The rate of successful infection is given by

$$\beta^{(m)} = \sum_{j=1}^N \gamma_j^{(m)}.$$

2.1. Including free-virus transmission

Let us assume for the moment that only one virus can be transmitted per synapse.

Mathematically this leads to setting $\gamma_k^{(m)} = 0$ for all $2 \leq k \leq N$. Then the system reduces in the following way:

$$\dot{x}_0 = \lambda - dx_0 - x_0 \sum_{m=1}^N x_m \gamma_1^{(m)}, \quad (3)$$

$$\dot{x}_i = \sum_{m=1}^N x_m \gamma_1^{(m)} (x_{i-1} - x_i) - a^{(i)} x_i. \quad (4)$$

One can easily see that this system formally corresponds to the coinfection equations in the context of free-virus transmission, see e.g. [29, 30, 23], where the equation for free virus is given by $\dot{v} = \sum_{m=1}^N x_m \gamma_1^{(m)} - v$, and the virus population is assumed to be in steady state, $v = \sum_{m=1}^N x_m \gamma_1^{(m)}$. Therefore, free-virus transmission mode is implicitly included in system (1-2), and all the mathematical methods developed for system (1-2) will hold for a system that explicitly includes free-virus transmission. The only difference lies in the numerical values of the coefficients $\gamma_1^{(m)}$, which should include a contribution from both free-virus and synaptic pathways.

2.2. Transmission and death independent of the multiplicity of infection

Let us assume that the probability to transmit virus for a cell does not depend on how many viruses the cell contains, that is, $\gamma_j^{(m)} = \gamma_j$ does not depend on m (symmetric transmission assumption). Additionally, we assume that $a^{(i)}$ do not depend on $1 \leq i \leq N$ (symmetric death assumption). Then the equations become,

$$\dot{x}_0 = \lambda - dx_0 - x_0 \sum_{m=1}^N x_m \sum_{s=1}^N \gamma_s, \quad (5)$$

$$\dot{x}_i = \sum_{m=1}^N x_m \left(\sum_{s=1}^i \gamma_s x_{i-s} - \sum_{s=1}^{N-i} \gamma_s x_i \right) - ax_i. \quad (6)$$

We can obtain two closed equations for the variables $y = \sum_{m=1}^N x_m$ and $x = x_0$:

$$\dot{x} = \lambda - dx - \beta xy, \quad (7)$$

$$\dot{y} = \beta xy - ay, \quad (8)$$

where we denoted $\beta = \sum_{j=1}^N \gamma_j$. To see this, we add all equations (6) for $1 \leq i \leq N$ to obtain

$$\dot{y} = y \left(\sum_{i=1}^N \sum_{s=1}^i \gamma_s x_{i-s} - \sum_{i=1}^N \sum_{s=1}^{N-i} x_i \gamma_s \right) - ay.$$

We note that

$$\sum_{i=1}^N \sum_{s=1}^i \gamma_s x_{i-s} = \sum_{s=1}^N \sum_{i=s}^N \gamma_s x_{i-s} = \sum_{s=1}^N \sum_{k=0}^{N-s} \gamma_s x_k,$$

and

$$\sum_{i=1}^N \sum_{s=1}^{N-i} x_i \gamma_s = \sum_{s=1}^N \sum_{i=1}^{N-s} x_i \gamma_s.$$

Some simple algebra then yields equations (7-8).

System (7-8) has two steady states. One is given by

$$x = \frac{\lambda}{d}, \quad y = 0, \quad (9)$$

which corresponds to a virus-free population. The other steady state is

$$x = \frac{a}{\beta}, \quad y = \frac{\lambda}{a} - \frac{d}{\beta}, \quad (10)$$

which is the state of infection for a two-component virus dynamics system. The parameter R_0 , the basic reproductive ratio of the virus, is given by

$$R_0 = \frac{\lambda \beta}{ad}.$$

If $R_0 < 1$, infection cannot be established, and solution (9) is globally stable. If $R_0 > 1$, the system converges to solution (10) with a nonzero number of infected cells. The components of this solution $x_1, \dots, x_N$ are found explicitly below.

2.3. Steady-state solution for the symmetric case

One can write down an explicit formula for the steady-state solution of equations (6). We have a recursive solution,

$$x_i = \frac{\sum_{s=1}^i \gamma_s x_{i-s}}{\tilde{a} + p_i}, \quad 1 \leq i < N, \quad (11)$$

where we introduced the notations $\tilde{a} = a/y$ with y given by equation (10), and $p_i = \sum_{s=1}^{N-i} \gamma_s$, the probability to accept virus particles. An explicit solution for x_i can be constructed. Let us fix an integer i , and consider sequences of positive integers,

$$\{k_1, \dots, k_l\},$$

such that $k_1 < \dots < k_l$ and $k_l = i$. The length of a sequence, l , satisfies $1 \leq l \leq i$. Let us denote the set of all such sequences as $\mathcal{S}_i$. Further, for each such sequence, we form the corresponding sequence of increments,

$$\{r_1, \dots, r_l\},$$

where $r_1 = k_1$ and $r_s = k_s - k_{s-1}$ for $2 \leq s \leq l$. Then the number of cells infected with i viruses is given by

$$x_i = x \sum_{\mathcal{S}_i} \prod_{s=1}^l \frac{\gamma_{r_s}}{\tilde{a} + p_{k_s}}, \quad 1 \leq i < N, \quad (12)$$

where x is given by equation (10) and $x_N = y - \sum_{i=1}^{N-1} x_i$. In the case where transmission only happens by means of a free virus, we have

$$x_i = x \left(\frac{\gamma_1}{\tilde{a} + \gamma_1} \right)^i, \quad 1 \leq i < N. \quad (13)$$

Solution (12) is illustrated in Section 3 by using a specific model for distribution $\{\gamma_j\}$.

3. Transmission strategies independent of the multiplicity of infection

In this section we will continue to use the assumption that virus transmission and the cell death are independent of the cells' multiplicity of infection. This assumption will be relaxed later on.

3.1. General definition of synaptic strategies

We will adopt a more detailed model of infection. Let us assume that infected cells have a given probability distribution to pass on a number of viruses, given by q_i , with $\sum_{i=0}^N q_i = 1$. The probability distribution, $\{q_i\}$, defines a *strategy* for cell-to-cell transmission.

Suppose that each virus has a probability to establish a successful infection, r , or fail with probability $1 - r$. The probability to produce i viruses which successfully infect another cell is then

$$\gamma_j = \sum_{i=j}^N q_i \binom{i}{j} r^j (1-r)^{i-j}.$$

The mean number of viruses passed by the cell per synapse (the rate of synaptic viral transfer) is given by

$$k = \sum_{i=1}^N q_i i. \quad (14)$$

The mean number of *successful* viruses produced by the cell is

$$V = \sum_{i=1}^N \sum_{j=i}^N q_j \binom{j}{i} r^i (1-r)^{j-i} i = \sum_{j=0}^N q_j \sum_{i=0}^j \binom{j}{i} r^i (1-r)^{j-i} i = \sum_{j=0}^N q_j j r = k r,$$

where we interchanged the order of summation and then used the formula for the mean of the binomial distribution. The probability of successful infection is

$$\beta = 1 - \gamma_0 = 1 - \sum_{j=0}^N q_j (1-r)^j. \quad (15)$$

3.2. Strategies with a fixed transmission number

For simplicity we will consider the probability distributions of the form,

$$q_0 = 1 - q, \quad q_s = q, \quad q_k = 0 \quad k \neq 0, \quad k \neq s.$$

In other words, a cell either passes s viruses or 0 viruses. For such a cell, we have

$$\gamma_j = q \binom{s}{j} r^j (1-r)^{s-j}, \quad 0 \leq j \leq s, \quad \gamma_j = 0, \quad j > s. \quad (16)$$

Further,

$$k = qs, \quad V = qsr, \quad \beta = (1 - (1-r)^s)q.$$

Each strategy is characterized by two numbers: q , the probability to transmit, and s , the number of viruses transmitted. These numbers are not independent if we assume certain patterns about the virus production and synapse transmission for various strategies. In this paper we will concentrate on the following model [31]:

$$q = \frac{Q}{s+z}, \quad (17)$$

where Q is a constant. Given a relationship between q and s , each strategy is characterized by just one parameter, s , which we will call the cell's *strategy*. There are two cases we would like to distinguish:

- In the simplest case, where $z = 0$ in formula (17), we assume that all cells are characterized by the same number of viruses transmitted, regardless of their strategy:

$$k = qs = \frac{Q}{s} s = Q.$$

Cells with high values of s form synapses infrequently, but when they do so, they transmit a large number of viral particles at once. On the other hand, cells with small values of s can transmit a small amount of virus by means of a synapse, but the rate at which they attempt to form synapses is relatively high.

- More generally, $z > 0$ in formula (17). In this case, the rate of synaptic transmission is given by

$$k = \frac{Qs}{s+z},$$

an increasing function of s . In particular, the rate of transmission is the lowest for low values of s . This is a consequence of the following biological considerations. For small values of s , a cell would have to form synapses at a very high rate to keep up the same intensity of transfer as cells with high values of s . This however may not be possible because each synapse takes a certain amount of time to be formed,

and further, as cells in a spatial setting have only a small number of neighbors, there is a limit to how many different synapses a cell can form. Therefore, a nonzero value of z accounts for the fact that the synapse formation cannot grow in intensity inversely proportional to the strategy value, s .

The functions γ_j , formulas (16) and (17) are illustrated in figure 1 for three different values of strategy s . We can see that the maximum of the one-humped functions γ_j is near $j = rs = 0.5s$.

3.3. The basic reproductive ratio

Let us suppose that the cells differ by their strategies with regards to how many viruses they pass (the parameter s). We ask, which strategies correspond to higher rates of successful synapse formation? In order to answer this question, we consider the basic reproductive ratio, R_0 , which is different for different strategies:

$$R_0 = \frac{\lambda\beta}{ad} = \frac{\lambda Q}{ad} \frac{1 - (1-r)^s}{s+z}. \quad (18)$$

Infection cannot be established when $R_0 < 1$. To find the infection threshold, we solve the inequality $R_0 > 1$ and obtain that for a given strategy, s , a successful infection can be established if

$$r > r_c(s) \equiv 1 - \left(1 - \frac{da(s+z)}{\lambda Q}\right)^{1/s}. \quad (19)$$

To investigate the behavior of R_0 analytically, let us denote

$$P = \frac{(1 - (1-r)^s)}{s+z} \leq 1.$$

It is easy to see that $\frac{\partial R_0}{\partial r} \propto \frac{\partial P}{\partial r} \geq 0$. Let us further denote

$$A = \frac{ad}{Q\lambda}.$$

We have $R_0 = P/A$. We require that $A < 1$, such that for the strongest viral strategy with $P = 1$, $R_0 > 1$. Otherwise, no strategy can establish successful infection. We further note that infection cannot in principle be established for strategies with

$$s > s_c = \frac{1}{A} - z.$$

If $s > s_c$, we have $R_0 < 1$ even for $r = 1$, the best case scenario.

Let us study the behavior of R_0 as a function of strategy s . First we note that dR_0/ds has the same sign as dP/ds . Evaluating dP/ds yields

$$\frac{dP}{ds} = C_1(f_2 - f_1), \quad C_1 > 0, \quad f_2 = 1 + |\ln(1 - r)| (s + z), \quad f_1 = (1 - r)^{-s}. \quad (20)$$

For $s = 0$, we have $f_1 = f_2$ with the equality corresponding to $z = 0$. As s increases, f_2 grows exponentially while f_1 grows linearly. We distinguish two cases, $z = 0$ and $z > 0$, below.

The case $z = 0$. For $z = 0$, we have $f_2 = f_1$. In other words, for the $z = 0$ model, $dP/ds = 0$, that is, the basic reproductive ratio is a monotonically decreasing function of s . The strategy corresponding to the highest infection level is $s_m = 1$. Figure 2(a) shows the levels of the basic reproductive ratio, R_0 , as a function of the infectivity, r , and strategy, s . We can see that for each fixed value of r it is a decaying function of s . Intuitively, each viral particle transmitted by a synapse, has a certain chance to result in a successful infection. Therefore, to maximize the total number of infections, it would make sense to send one particle per synapse, and form more synapses to maximize the total number of infections. Therefore, in the case where synapses are “cheap” ($z = 0$), the strategy with $s = 1$ is the most efficient transmission strategy.

The case $z > 0$. For positive values of z , the two functions f_1 and f_2 in (20) have one intersection for $s > 0$. Assuming that $rs \ll 1$, we can find the point of intersection approximately,

$$s_m \approx \sqrt{\frac{2z}{r}}.$$

A quick check reveals that $s_m r \ll 1$ for small values of r . The strategy with $s = s_m$ corresponds to the highest basic reproductive ratio. Next, for given parameters A , r , and z we have to establish whether s_m is a viable strategy, that is, if $P(s_m) > A$. We get a simple condition in the case when $r \ll 1/z$: for given values of A , r , and z , if

$$r > A,$$

then we have at least one viable strategy with $s = s_m$.

In figure 2(b) we show the contours of the quantity R_0 as a function of infectivity, r , and strategy, s . As before, R_0 increases with r . Unlike in the case Where $z = 0$, now the basic reproductive ratio R_0 can be a one-humped function of the strategy, s , with the maximum corresponding to intermediate values of the strategy parameter.

3.4. The number of infected cells

Next, let us consider the number of infected cells at steady state.

The case $z = 0$. Figure 3(a) plots the dependence of the number of infected cells on parameter r for different strategies, s , according to formula (10). We can see that small values of s correspond to the largest infection loads, and $y(r)$ is an increasing function of r . It is clear that the total number of infected cells is the highest for low values of s . In fact, the infection cannot be established for very high- s strategies. The particular parameter values chosen in the figure allow viral strategies with $1 \leq s \leq 13$ to establish a successful infection. For $s > 13$, $R_0 < 1$, $y < 0$, and the infection fails. For smaller values of r , fewer strategies are possible.

The steady-state solution formula, equation (12), is illustrated in figure 3(b), where we plot the components x_i of the solution (to make the interpretation easier, we connected them by a continuous line). Each line corresponds to one value s of the strategy, and 10 such solutions are presented. We can see that for each s , the maximum of the solution corresponds to $i = rs = 0.5s$, and secondary modes are observed for higher values of i . For $i \gg s$ we observe an exponential decay of the solution components. This can be seen immediately from the analytical expression for $s = 1$, given by formula (13), and solutions with $s > 1$ approach this line for high values of i .

The case $z > 0$. In figure 4, we plot the total number of infected cells, y , at the equilibrium as a function of parameters r and s . We can see that similar to the function R_0 , this quantity has a maximum corresponding to some intermediate value of the strategy parameter, s . This can be seen by the same argument as we used to study the behavior of R_0 in the $z > 0$ case, because the sign of the derivative dy/ds is the same as that for dP/ds .

4. Transmission strategies depend on the multiplicity of infection

Now let us suppose that the probability distribution, $q_i^{(m)}$, depends on the index m , the number of viruses in the transmitting cell, by assuming that the total number of viruses transferred is a function of the cell's multiplicity of infection. At present, it is not known whether the multiplicity of infection modifies the virus production/synapse formation of an infected cell. The null-assumption that all the kinetics are independent of the multiplicity of infection was studied in Section 3. Here we explore the assumption that the infection kinetics depend on the cells' multiplicity. Let us consider the simplest choice of strategies, such as

$$q_i^{(m)} = \begin{cases} 1 - Q^{(m)}/s, & i=0, \\ Q^{(m)}/s, & i=s, \\ 0, & \text{otherwise.} \end{cases}$$

We assume that $Q^{(m)}$ is a non-decreasing function of m . This model is a generalization of model (17), where we set $z = 0$. In other words, we will concentrate on the effects of the multiplicity of infection, but ignore the rate-limiting effects of synapse formation ($z > 0$)

considered in Section 3. Combining the two effects can be done in a straightforward way by using the methodology developed here.

4.1. The limit of large infectivity, $r = 1$

Let us solve equations (1-2) in the limit where $r = 1$, that is, when the infection event is a certainty. We have

$$\gamma_i^{(m)} = \begin{cases} 1 - Q^{(m)}/s, & i=0, \\ Q^{(m)}/s, & i=s, \\ 0, & \text{otherwise.} \end{cases}$$

Therefore, at steady state we will only have types that contain the number of viruses which is a multiple of s . Let us denote by K the integer part of N/s ,

$$K = \lfloor N/s \rfloor.$$

Then equations (1-2) can be rewritten as

$$\dot{x}_0 = \lambda - dx_0 - Zx_0, \quad (21)$$

$$\dot{x}_{is} = Z(x_{(i-1)s} - x_{is}) - ax_{is}, \quad 1 \leq i \leq K-1, \quad (22)$$

$$\dot{x}_{Ks} = Zx_{(K-1)s} - ax_{Ks}, \quad (23)$$

where we introduced the notation

$$Z = \frac{1}{s} \sum_{i=1}^K k^{(is)} x_{is}.$$

System (21-23) can be solved in terms of Z :

$$x_0 = \frac{\lambda}{d+Z}, \quad x_i = \frac{x_0}{(1+a/Z)^i}, \quad 1 \leq i \leq K-1, \quad x_K = \frac{x_0 Z}{a(1+a/Z)^{K-1}}.$$

The quantity Z satisfies the following close-form equation,

$$Z = \frac{\lambda}{(d+Z)s} \left(\sum_{i=1}^{K-1} \frac{Q^{(is)}}{(1+a/Z)^i} + \frac{Q^{(sK)} Z}{a(1+a/Z)^{K-1}} \right). \quad (24)$$

We are interested in the quantity y ,

$$y = \sum_{i=1}^K x_{is} = \frac{Z\lambda}{a(d+Z)}, \quad (25)$$

where we performed the summation of the geometric progression. Equation (25) shows, in particular, that the number of viruses, y , is an increasing (decreasing) function of s iff the function Z defined by equation (24) is an increasing (decreasing) function of s .

In particular, if $K = 1$ (which corresponds to $s > N/2$), we have

$$Z = \frac{\lambda Q^{(s)}}{as} - a, \quad y = Q^{(s)} x_s = \frac{Zs}{Q^{(s)}} = \frac{\lambda}{a} - \frac{ds}{Q^{(s)}}.$$

If $s/Q^{(m)}$ is an increasing function of s , then Z decays with s . We can see that in this case, y is a strictly decreasing function of s . That is, for high values of r and high values of s , the number of infected cells is smaller for higher strategy indexes.

In general, equation (24) can be rewritten in a more convenient form,

$$\frac{(d+Z)a}{\lambda} = \sum_{i=0}^{K-1} \frac{Q^{(is+s)} - Q^{(is)}}{s} q^i, \quad q \equiv \frac{Z}{Z+a}, \quad (26)$$

where we formally set $Q^{(0)} = 0$. We need to investigate how the solution of this equation, Z , changes with s . The left hand side is a linear function of Z with a positive slope, which does not depend on s . The right hand side is a constant if $K = 1$, and for $K > 1$ it is a monotonically increasing function of Z which equals $Q^{(m)}/s$ for $Z = 0$ and approaches $Q^{(Ks)}/s$ as $Z \rightarrow \infty$ (and $q \rightarrow 1$). This limiting value follows from collapsing the telescoping sum. If $Q^{(m)} > (da)/\lambda$, the two curves are guaranteed to have one intersection. The intersection point will shift to the left as s increases, as long as the right hand side is a decreasing function of s . The latter is guaranteed if the function $Q^{(m)}$ grows slower than s ,

such that its chords have decreasing slopes, $\frac{Q^{(is+s)} - Q^{(is)}}{s}$ for $i \in \{0, 1, \dots, K-1\}$.

4.2. The bifurcation analysis

We investigate the bifurcation of the no-infection solution of system (1-2),

$$x_0 = \frac{\lambda}{d}, \quad x_i = 0, \quad 1 \leq i \leq N. \quad (27)$$

Let us consider r to be the control parameter. As the infectivity grows, infection gets established. We want to find the value $r = r_c$ for which solution (27) loses stability. This

corresponds to an eigenvalue of the Jacobian, J , of (1-2) evaluated at solution (27) having a zero real part. Let us denote by I the unit matrix of size $N \times N$. We have

$$J = -aI + \begin{pmatrix} a-d & -\frac{\lambda}{d} \sum_{k=1}^N \gamma_k^{(1)} & -\frac{\lambda}{d} \sum_{k=1}^N \gamma_k^{(2)} & \dots & -\frac{\lambda}{d} \sum_{k=1}^N \gamma_k^{(N)} \\ 0 & \frac{\lambda}{d} \gamma_1^{(1)} & \frac{\lambda}{d} \gamma_1^{(2)} & \dots & \frac{\lambda}{d} \gamma_1^{(N)} \\ 0 & \frac{\lambda}{d} \gamma_2^{(1)} & \frac{\lambda}{d} \gamma_2^{(2)} & \dots & \frac{\lambda}{d} \gamma_2^{(N)} \\ \dots & \dots & \dots & \dots & \dots \\ 0 & \frac{\lambda}{d} \gamma_s^{(1)} & \frac{\lambda}{d} \gamma_s^{(2)} & \dots & \frac{\lambda}{d} \gamma_s^{(N)} \\ 0 & \dots & \dots & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & \dots & \dots & \dots & 0 \end{pmatrix}$$

The first eigenvalue of this matrix is equal to $d - 0$. We also have the eigenvalue a of multiplicity $N - s$. To find the rest of the eigenvalues, consider the $s \times s$ matrix $J = \{m_{ij}\}$, whose entries are given by

$$m_{ij} = \frac{\lambda}{d} \gamma_i^{(j)} = \frac{\lambda}{d} r^i (1-r)^{s-i} \frac{Q^{(j)} s!}{s! (s-i)!} \equiv \mu_i \nu_j.$$

The remaining eigenvalues of the matrix J are related to eigenvalues of the matrix $\tilde{J}$ by $\Lambda - a$, where Λ is an eigenvalue of $\tilde{J}$. Matrix $\tilde{J}$ has the eigenvalue 0 with multiplicity $s - 1$, which corresponds another $s - 1$ eigenvalues of size a for matrix J . Finally, we have

$\Lambda = \sum_{i=1}^s \mu_i \nu_i$. Therefore, the expression for the last eigenvalue of J is

$$\frac{\lambda}{d} \sum_{i=1}^s r^i (1-r)^{s-i} \frac{Q^{(i)} s!}{s! (s-i)!} - a.$$

Equating this expression to zero we obtain the equation for the bifurcation threshold parameter, or the basic reproductive ratio of this system,

$$R_0 = \frac{\lambda}{ad} \sum_{i=1}^s r^i (1-r)^{s-i} \frac{Q^{(i)} s!}{s! (s-i)!}. \quad (29)$$

The virus-free equilibrium is unstable if $R_0 > 1$. The equation $R_0 = 1$ solved for r gives us the threshold value r_c such that for $r > r_c$ solution (27) loses stability.

It is interesting that the system with synaptic transmission where the parameters depend on the multiplicity of infection exhibits bistability. There is a region in the parameter space where both the viral-free equilibrium and the virus equilibrium are stable, and the long-term outcome of the dynamics depends on the initial conditions. A similar result was obtained in a system with coinfection [23], and a detailed analysis of this phenomenon is work in

progress. Here we note that as long as the basic reproductive ratio defined by formula (29) satisfies $R_0 > 1$, virus infection is the only possible outcome.

4.3. Multiplicity-dependent case: analysis of R_0

Let us study the properties of the basic reproductive ratio given by expression (29). If $Q^{(m)} = Q$, we obtain

$$R_0 = \frac{\lambda Q}{ad} \sum_{i=1}^s \frac{r^i (1-r)^{s-i}}{s} \frac{s!}{i!(s-i)!} = \frac{\lambda Q}{ad} \frac{1 - (1-r)^s}{s}, \quad (30)$$

see expression (18). This is a growing function of r which is equal to r for $s = 1$, and is a saturating function for $s > 1$, with the value of $1/s$ at $r = 1$. As s grows, this function decreases. Therefore, if $Q^{(s)} = 1$, the intersection of this function with the constant function 1 shifts to the right. This means that for constant $Q^{(m)}$, r_c is a growing function of s . It is harder for larger s to establish a successful infection.

This trend can potentially be reversed if $Q^{(m)}$ grows with m . Next we show sufficient requirements on the function $Q^{(m)}$ to guarantee that R_0 grows with s , thus making it easier for high s to establish successful infection. Consider the class of functions $Q^{(m)}$,

$$Q^{(m)} = Q \left(1 + \frac{g(m-1)(1+\eta)}{m-1+\eta} \right). \quad (31)$$

The parameter g tells us how quickly the rate of virus transmission increases with the multiplicity of infection, m , and parameter η is responsible for the saturation of this function for high values of m . The simplest case when $\eta \rightarrow \infty$ corresponds to the absence of saturation,

$$Q^{(m)} = Q(1 + g(m-1)). \quad (32)$$

The value $g = 0$ corresponds to the model of constant Q . The regime with $g < 1$ corresponds to subadditive effect of coinfection. This is because for $g < 1$, we have $Q^{(m1+m2)} < Q^{(m1)} + Q^{(m2)}$. This inequality is reversed if we have $g > 1$, which corresponds to superadditive, or cooperative, behavior of coinfection. The special case $g = 1$ describes an additive effect of coinfection. We can calculate the parameter R_0 in the case where the rate of virus transmission size is given by formula (32):

$$R_0 = \frac{\lambda Q}{ad} \left(gr + \frac{(1-g)(1 - (1-r)^s)}{s} \right).$$

We can see that $g = 0$ corresponds to the constant- Q formula, (30). The case $g = 1$ gives $R_0 = \lambda Q r / (ad)$, that is, the basic reproductive ratio is independent of the strategy, s , and is proportional to the probability of viruses to infect a cell. For any $0 < g < 1$, the function R_0 is

a decaying function of s , because the function $\frac{1 - (1 - r)^s}{s}$ is a decaying function of s . Finally, for all $g > 1$, R_0 grows with s , and saturates at a constant level, $\lim_{s \rightarrow \infty} R_0 = gr$. In other words, starting from a certain values of s , all high- s strategies are more or less equally effective.

The case of a subadditive effect of coinfection is illustrated in figure 5. There, R_0 is a decaying function of s , and high- s strategies are less effective in establishing the infection than low- s strategies. In figure 5 we consider two examples of subadditive function $Q^{(m)}$, formula (31), with $g = 1/2$, without (a) and with (b) saturation. We plot the number of infected cells at the equilibrium. We can see that low s -strategies perform better in the entire domain of r . In the presence of saturation (finite values of the parameter η in formula (31)), the picture in the subadditive or additive cases does not change qualitatively.

In order for the function R_0 to grow with s , coinfection must exhibit a certain degree of cooperation among viruses, such that the effect of coinfection is superadditive. In this case it is possible that R_0 increases with s , and it is easier for the high- s strategies to establish infection. This is illustrated in figure (6), where we plot the number of infected cells at equilibrium as a function of r , for the function $Q^{(m)}$ given by formula (31) with $g = 2$, with (a) and without (b) saturation. We can see that for low values of r , high- s strategies are more efficient at establishing infection compared to low- s strategies. For $r \approx 1$, low- s strategies are more efficient.

A more systematic study of the behavior of the basic reproductive ratio is presented in figure 7, which shows how R_0 depends on the parameters r , the infectivity and s , the synaptic strategy of the virus. In the case of figure 7(a), we used a subadditive version of formula (31). We can see that for all values of r , R_0 decays with s . In figure 7(b) we used a superadditive law and demonstrated that R_0 is a one-humped function of the strategy with a maximum achieved for an intermediate value of s .

An example of a different type of dependence of $Q^{(m)}$ on m is presented in figure 8. There, the function $Q^{(m)}$ is given by $Q^{(m)} = \tanh^7(10m/N)$ and has a superadditive region, see figure 8(a). In figure 8(b) we plot the basic reproductive ratio, R_0 , as a function of r . For low values of r , the basic reproductive ratio is an increasing function of strategy s . For higher values of r the basic reproductive ratio R_0 experiences a maximum at $s = 3$, and decays as s increases.

5. Evolutionary competition of viral strategies

So far we concentrated on virus dynamics where all the viruses had the same strategy, s . In other words, all infected cells attempted to transmit the same number of viral particles per synapse. We have seen that the basic reproductive ratio, R_0 , and the viral load at equilibrium, y , both depended on the synaptic strategy. In particular, in the case where viral strategies were independent of the multiplicity of infection and synapse formation did not impose a constraint ($z = 0$), the largest R_0 corresponded to low values of s . In the case where the multiplicity of infection played a role in the rate of viral transfer, or if synapse formation imposed a constraint ($z > 0$), the basic reproductive ratio was maximized for intermediate

values of s . The question is whether the value of R_0 can be associated with the evolutionary fitness of different strategies.

In this section we explore the following related problem. If two viral strategies, s_1 and s_2 , are characterized by different basic reproductive ratios, can we predict the result of their evolutionary competition? In order to address this question, we need to formulate the virus dynamics equations, (1-2), in the presence of two different, competing types of virus.

Suppose the first strategy is s_1 and the second strategy is s_2 . Then we let the variable x_{ij} denote the number of cells with i s_1 -type viruses and j s_2 -viruses. Further, the parameter γ_{qp}^{mk} is the probability that a cell with m s_1 -viruses and k s_2 -viruses successfully transmits q s_1 -viruses and p s_2 -viruses. A generalization of system (1-2) to the two-species case is as follows:

$$\begin{aligned}\dot{x}_{00} &= \lambda - dx_{00} - x_{00} \sum_{m=0}^N \sum_{\substack{k=0 \\ m+k>0}}^{N-m} x_{mk} \sum_{q=0}^N \sum_{\substack{p=0 \\ p+q>0}}^{N-q} \gamma_{qp}^{mk}, \\ \dot{x}_{ij} &= \sum_{m=0}^N \sum_{\substack{k=0 \\ m+k>0}}^{N-m} x_{mk} \left(\sum_{q=0}^i \sum_{\substack{p=0 \\ p+q>0}}^j x_{i-q,j-p} \gamma_{qp}^{mk} - x_{ij} \sum_{q=0}^{N-i} \sum_{\substack{p=0 \\ p+q>0}}^{N-i-j-q} \gamma_{qp}^{mk} \right) - ax_{ij},\end{aligned}\quad (33)$$

where in the second equation we assume $i+j > 0$ and $i+j \leq N$, and in all of the double summations the two indices are not zero simultaneously.

All the information about viral strategies is contained in the function γ_{qp}^{mk} . We will assume that if a cell is only infected with s_1 viruses, then γ_{q0}^{m0} is identical to the probability distribution given by formula (16), and no viruses of type s_2 are transmitted. Similarly, if only s_2 viruses are present in a cell, no viruses of s_1 type are transmitted, and γ_{0p}^{0k} is identical to that defined by equation (16).

A more complicated modeling question arises if a cell is infected by both types of viruses simultaneously. In this paper we assume that such mixed-strategy cells infected by m copies of the s_1 virus and k copies of the s_2 virus adopt a single strategy, s_{mk} , which can be defined based on the composition of the viruses infecting the cell, m and k . Below are three alternative ways in which this mixed strategy can be defined.

- a. The average strategy: $s_{mk} = \left\lceil \frac{ms_1 + ks_2}{m+k} \right\rceil$, where the square brackets indicate rounding to the nearest integer;
- b. The strategy of the majority: $s_{mk} = s_1$ if $m \geq k$, and $s_{mk} = s_2$ otherwise;
- c. The maximum strategy: define $s_{max} = \max\{s_1, s_2\}$ and $s_{min} = \min\{s_1, s_2\}$; then $s_{mk} = s_{max}$ as long as the cell is infected with at least one virus carrying that strategy; we have $s_{mk} = s_{min}$ otherwise.

With any of these definitions of the mixed strategy, s_{mk} , we define the quantity γ_{qp}^{mk} in the following way: if $p + q > s_{mk}$, we have $\gamma_{qp}^{mk} = 0$, and if $p + q \leq s_{mk}$,

$$\gamma_{qp}^{mk} = \frac{Q}{s_{mk} + z} \frac{(p+q)!}{p!q!} \left(\frac{k}{m+k} \right)^p \left(\frac{m}{m+k} \right)^q \frac{s_{mk}!}{(p+q)!(s_{mk} - p - q)!} r^{p+q} (1-r)^{s_{mk}-p-q}, \quad (34)$$

where we assume the rule $0^0 = 1$ for expressions $(k/(m+k))^p$, $(m/(m+k))^q$. Formula (34) states that if a cell is infected with both s_1 and s_2 viruses, it will attempt to transmit s_{mk} viruses per synapse, and both virus types will be transmitted proportional to their multiplicity in the host cell, m and k . Formula (34) is a direct generalization of the model in Section 3 where virus transmission was assumed to be independent of the multiplicity of infection. The following law serves as a generalization of the model of Section 4 for two virus strains:

$$\gamma_{qp}^{mk} = Q^{(m+k)} \frac{(p+q)!}{p!q!} \left(\frac{k}{m+k} \right)^p \left(\frac{m}{m+k} \right)^q \frac{s_{mk}!}{(p+q)!(s_{mk} - p - q)!} r^{p+q} (1-r)^{s_{mk}-p-q}. \quad (35)$$

5.1. Neutrality of indistinguishable strains

The first step in the analysis of this evolutionary model is to check that it meets the criterion of neutrality when applied to two identical virus populations [32]. This property of neutrality must hold independently of the particular strategy models (34, 35) or the choice of the strategy s_{mk} (a-c) above. Suppose that $s_1 = s_2$. Then in general we must have $\gamma_{qp}^{mk} = \gamma_{cd}^{ab}$ as long as $m + k = a + b$ and $q + p = c + d$. In other words, the exact way in which the virus population is split into two groups is immaterial, and all that matters is the total number of viruses that the cell hosts, and the total number of viruses that gets transferred. This property is definitely satisfied for the particular models given by equations (34, 35) and (a-c) above.

Under these assumptions, we can denote $y_0 = x_{00}$, $y_1 = x_{01} + x_{10}$, $y_2 = x_{02} + x_{11} + x_{20}$, ..., $y_m = \sum_{a+b=m} x_{ab}$. Then, combining equations in system (33) we can derive a closed system of ODEs for the variables y_m , $0 \leq m \leq N$, which is identical to system (1-2). This means that if the two virus strains are identical, the total population behaves like the one described by the one-species system. Moreover, the steady state is fixed for the total populations $y_0, y_1, \dots, y_N$ only, and the exact composition (that is, the distribution between the two identical virus strains) of the virus population at steady state is determined by the initial conditions. We conclude that our model satisfies the neutrality property for identical strains, and proceed with the analysis.

5.2. Competitive exclusion

Next we turn to the studies of the evolutionary dynamics of two viral strains with different strategies, s_1 and s_2 , that correspond to two different basic reproductive ratios, as defined in the previous sections.

Figures 9(a) and 10 illustrate a typical outcome of the evolutionary competition between two strains. In figure 9(a) we show the basic reproductive ratio, R_0 , as a function of s , which was used in the simulations. First we ran the evolutionary competition of strains $s_1 = 1$ and $s_2 = 2$ (figure 10(a)), and then the evolutionary competition of strains $s_2 = 2$ and $s_3 = 3$ (figure 10(b)). The time-dependent solutions of system (33) are presented in the figure. We plot the number of uninfected cells, x_{00} , and two groups of infected cells. The first group of infected cells in figure 10(a) is comprised of all the cells that are infected by s_1 viruses, and possibly other viruses: $\sum_{i=1}^N \sum_{j=0}^{N-i} x_{ij}$, where the first index indicates the number of s_1 viruses and the second index - the number of s_2 viruses. Similarly, the infected population that includes s_2 is given by $\sum_{i=0}^N \sum_{j=1}^{N-i} x_{ij}$.

We can see from figure 10(a) that all the populations that contain viruses of type s_1 go extinct. Similarly in figure 10(b), the populations that contain viruses of type s_3 go extinct. The remaining populations only contain cells infected by virus of type s_2 . This is because this virus has a larger basic reproductive ratio than the other two types considered, see figure 9(a). In general, a virus that has a larger basic reproductive ratio, wins the evolutionary competition leading to a competitive exclusion of the other, weaker strain. This is why it is possible to talk about the function $R_0(s)$ as a “fitness landscape” or “fitness profile”. Types that are higher in this landscape are predicted to win the evolutionary competition.

The results illustrated in figure 10 are very general, and hold for any of the models (a-c) above, as well as for law (35), and for different shapes of the evolutionary landscape. One subtlety that we observed is the dependence of the dynamics on N , the maximum multiplicity of infection of cells. In all the simulations we have to impose a finite N to keep the system finite. It turns out that taking relatively low values of N may lead to a coexistence outcome, where at steady state, two different strains with different R_0 survive. This solution disappears as one increases N , as demonstrated in figure 9(b). We used strains $s_1 = 1$ and $s_4 = 5$, figure 9(a). Figure 9(b) shows the steady state levels of uninfected and two types of infected populations for different values of N . We can see that for $N < 12$, both cells containing strategies s_1 and s_4 coexist at steady state. For $N \geq 12$, this non-biological outcome is no longer observed, and the evolutionary dynamics result in a competitive exclusion. The strain of type s_4 disappears, and only the strongest strain remains in the population.

6. Discussion and conclusions

In this paper we explored virus infection dynamics where the process of infection was assumed to follow the synaptic transmission pathway. Transmission of more than one virus per synapse leads to a different mathematical formulation compared to the traditional models, where infection was assumed to follow the free-virus transmission pathway.

The main results of this study can be summarized as follows.

- We found the analytical steady-state solution for the numbers of cells infected with different numbers of viruses in the case where the infection kinetics were independent of the multiplicity of infection.
- We formulated the notion of synaptic strategy and computed the basic reproductive ratio, R_0 , for different strategies, under several assumptions.
- If synapse formation is fast and the process of infection is independent of the number of resident viruses, the strategy by which only one virus is transmitted per synapse maximizes the basic reproductive ratio.
- More realistically, if synapses cannot be formed arbitrarily quickly, then R_0 is a one-hump function of the number of viruses transferred, and some intermediate strategy maximizes R_0 . In other words, the most efficient transmission mode is to transfer an intermediate number of viruses per synapse.
- Similarly if the multiplicity of infection strongly influences the kinetic of virus production, then R_0 is maximized by an intermediate strategy.
- The value R_0 in the context of synaptic transmission can serve as an effective fitness parameter associated with each strategy, as the strategies with the highest R_0 win the evolutionary competition, leading to competitive exclusion of strategies with lower values of R_0 .

In the literature, it has been reported that the numbers of viruses that are simultaneously transferred through a single synapse can be as high as $10^2 - 10^3$ [13, 15]. The simplest model, where synapse formation does not impose a temporal/spatial constraint, or where the multiplicity of infection does not play a role in the kinetics of virus production, predicts that $s = 1$ virus transferred by synapse is the optimal strategy. This suggests that this model is probably too simplistic, and other processes, such as viral interactions within the multiply-infected host cell, or constraints during synapse production, play an integral part in the dynamics. Experimental work is needed to investigate this in more detail.

In this paper, we stayed within the realm of ordinary differential equations, continuing a long tradition of modeling virus dynamics [1, 2]. Naturally, this modeling approach does not allow to include spatial effects or stochasticity explicitly. The first natural extension of this model is to consider spatial systems, modeled by PDEs or by using agent-based modeling techniques, see e.g. [30]. In our model, we attempted to mimic at least some effects of space by assuming that synapse formation is limited by the availability of neighbors, formula (17) with $z > 0$. It will be interesting to explore the explicit spatial dynamics of infection and to evaluate if spatial constraints bring out any other qualitative effects. In any case, one cannot hope to understand spatial and stochastic dynamics of the system without first exploring the deterministic, non-spatial model. The present paper undertakes this task.

In our studies of evolutionary dynamics of competition, we observed the weaker strategies to disappear and the strategies with the highest R_0 to establish infection. We however have not examined the time-scale of this process. Once the model is parameterized (which will require accurate measurements of the parameters), one would be able to make a statement about the duration of time it takes for evolution to select for the winner. A time-estimate of

this sort would have to be compared with relevant evolutionary time-scales. At the moment, all we can say is that higher- R_0 strategies would win the evolutionary competition, given enough time.

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- Viruses can spread from cell to cell through virological synapses
- This can influence basic virus dynamics
- This is investigated with a new mathematical model
- Effect on the basic reproductive ratio and virus load are examined
- Competition dynamics of viruses is investigated

Figure 1.

The probability distributions, γ_j , of successfully transferring j viruses per synapse, plotted for three different values of the strategy, s . Other parameters are $Q = 1$, $r = 0.5$, $z = 0$.

Figure 2.

Contour-plots of the basic reproductive ratio, R_0 , as a function of infectivity, r , and strategy, s . The value of R_0 is marked next to the contours. (a) The case $z = 0$ (synapse formation is not a limiting step). Other parameters are $Q = 0.1$, $\lambda/a = 135$. (b) The case $z > 0$ (synapse formation is a limiting step). Parameters are: $z = 4$, $\lambda/a = 135$, $d = 0.3$, $Q = 1$.

Figure 3.

(a) The total number of infected cells at equilibrium, y , as a function of r for different values of s from $s = 1$ to $s = 13$. The other parameters are: $\lambda/a = 135$, $d = 1$, $Q = 0.1$, $z = 0$. (b) The number of infected cells at steady state, x_i , shown as a continuous function of the multiplicity of infection, i . The different curves correspond to the different strategy parameter ranging from $s = 2$ to $s = 20$, with increment 2. Parameters are $Q = 1$, $\lambda = 30$, $a = 1$, $d = 0.6$, $r = 0.5$, $N = 60$, $z = 0$.

Figure 4.

The viral load in the presence of constraints in synapse formation. The total number of infected cells y is plotted as a function of the infectivity r (a), and strategy s (b). The parameters are: $z = 100$, $Q = 1$, $\lambda = 25$, $a = 1$, $d = 0.1$.

Figure 5.

Strategies depending on the multiplicity of infection, in the absence of virus cooperation: the number of infected cells at equilibrium as a function of the parameter r . Graphs are presented for 4 different strategies, $s = 1, 2, 3, 4$. (a) Subadditive effect of coinfection ($g = 1/2$), without saturation ($\eta \rightarrow \infty$), formula (31); $Q = 1/8$, $d = 1$, $a = 2$, $\lambda = 40$, $N = 15$. (b) Same with saturation, $\eta = 10$; $Q = 24/101$, $d = 1.67$, $a = 3.33$, $\lambda = 66.7$, $N = 15$.

Figure 6.

Strategies depending on the multiplicity of infection, in the presence of virus cooperation: the number of infected cells at equilibrium as a function of the parameter r . Graphs are presented for 4 different strategies, $s = 1, 2, 3, 4$. (a) Superadditive effect of coinfection ($g = 2$), without saturation ($\eta \rightarrow \infty$), formula (31); $Q = 1/29$. (b) Same with saturation, $\eta = 10$; $Q = 6/83$. The other parameters are $d = 0.5$, $a = 1$, $\lambda = 20$, $N = 15$.

Figure 7.

Contour-plots of the basic reproductive ratio, R_0 , as a function of infectivity, r , and strategy, s . The value of R_0 is marked next to the contours. The dependence of $Q^{(m)}$ on the multiplicity of infection is given by formula (31). (a) Subadditive case, $g = 0.5$. (b) Superadditive case, $g = 1.5$. Other parameters are $Q = 0.5$, $\eta = 10$, $\lambda = 50$, $d = 0.1$, $a = 1$.

Figure 8.

Strategies depending on the multiplicity of infection. (a) The rate of virus transmission size depends on the viral load, m , as $Q^{(m)} = \tanh^7(10m/N)$. (b) The basic reproductive ratio, R_0 , as a function of r . The horizontal line corresponds to $R_0 = 1$. The other parameters are $d = 0.065$, $a = 0.097$, $\lambda = 0.32$, $N = 15$.

Figure 9.

Competition between strategies. (a) The “fitness profile” - the dependence of the basic reproductive ratio, R_0 , on the strategy s , with four strategies, $s_1 = 1$, $s_2 = 2$, $s_3 = 3$, and $s_4 = 5$ marked by crosses. (b) The steady-state levels of the infected and uninfected cell populations for different values of the maximum multiplicity of infection, N . The two strategies are $s_1 = 1$ and $s_4 = 5$. The other parameters are $Q = 0.5$, $z = 5$, $\lambda/a = 135$, $d = 1$, $r = 0.7$; the formula for γ_{qp}^{mk} is given by equation (34), and the strategy of mixed cells is chosen according to model (a).

Figure 10.

Competitive exclusion as a result of the evolutionary competition of different strains. (a) The competition between strategies s_1 and s_2 (see figure 9(a)). The three lines correspond to the populations of cells as functions of time. The uninfected cells are the variable x_{00} , and the two infected populations are as follows: the infected population which includes s_1 is comprised of all the cells that are infected by s_1 viruses, and possibly other viruses:

$\sum_{i=1}^N \sum_{j=0}^{N-i} x_{ij}$, where the first index indicates the number of s_1 viruses and the second index - the number of s_2 viruses. Similarly, the infected population that includes s_2 is given

by $\sum_{i=0}^N \sum_{j=1}^{N-i} x_{ij}$. (b) The same as (a), but the two strains competing are s_2 and s_3 . The other parameters are as in figure 9.