Appendix to "Competition-colonization dynamics in an RNA virus"

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December 23, 2009

1 Mathematical model of virus dynamics

1.1 Virus dynamics in cell culture

The basic model of virus dynamics in cell culture describes the abundances of uninfected cells, x, infected cells, y, and free virus, v, over time as

$$\begin{aligned} \dot{x} &= -\beta x v \\ \dot{y} &= \beta x v - a y \\ \dot{v} &= k y - u v \end{aligned} \tag{S1}$$

with initial conditions $x(0) = x_0$, $y(0) = 0$, and $v(0) = v_0$.

This ordinary differential equations (ODE) system describes uninfected cells being infected with efficiency β, infected cells dying and releasing viral offspring at rate a, and free virus being produced at rate k and inactivated at rate u.

Note that in contrast to the basic model that was developed for virus dynamics *in vivo* [3], in cell culture there is no further supply of uninfected cells. We denote by $\lambda = v_0/x_0$ the multiplicity of infection, i.e., the initial density of viruses per cell.

The dynamics of this model are shown in Figure S1. For generic parameters, uninfected cells become infected and produce progeny viruses during lysis. This process leads to the eventual extinction of viruses and of both uninfected and, after a peak, infected cells. If we neglect clearance of free virus and set $u = 0$, then the cell dynamics are almost identical, while the number of free viruses saturates at a maximal abundance of $v^* = v_0 + (k/a)x_0$. This final yield of viruses increases with the multiplicity of infection:

$$v^* = \left(\lambda + \frac{k}{a}\right) x_0. \tag{S2}$$

1.2 Two competing viruses in cell culture

Let us now consider two different viruses with abundances v_1 and v_2, respectively, that are competing for the cell pool of size x. We have singly infected cells of abundances y_1 and y_2, and a subset of superinfected (doubly infected) cells of size y_{12}. The model parameters are indexed accordingly. We make the following general assumptions about the parameters:

Parameter	Description	Virus 1 (competitor)	Virus 2 (colonizer)	Unit
r_0	initial viral growth rate	1.43	1.94	h^{-1}
R_0	basic reproductive number	69.5	69.5	1
a	death rate of infected cells	0.14	0.25	h^{-1}
u	clearance rate of free virus	0.28	0.28	h^{-1}
$K = k/a$	burst size	250	250	1
k	production rate of free virus	34.6	62.5	h^{-1}
β	rate of infection	$7.8 \cdot 10^{-8}$	$7.8 \cdot 10^{-8}$	$ml \cdot h^{-1}$
c	prob. of type 1 viral offspring	0.62	$1 - c$	

Table S1: Parameters of the basic model of virus dynamics in cell culture.

- equal infection efficiencies, $\beta_1 = \beta_2 = \beta_{12} = \beta_{21} =: \beta$,
- equal viral clearance rates, $u_1 = u_2 =: u$.

Our experimental results (Table S1) further specify the parameters to

- equal death rates of cells infected by virus 1 and those doubly infected, $a_1 = a_{12}$,
- equal burst sizes, $K := k_1/a_1 = k_2/a_2 = k_{12}/a_{12}$.

These two constraints also imply the equality $k_{12} = k_1$ of viral production rates. In other words, the experimental findings summarized in Table S1 assert that a coinfected cell behaves like a cell infected only by virus 1 with the exception that it produces both types of viruses.

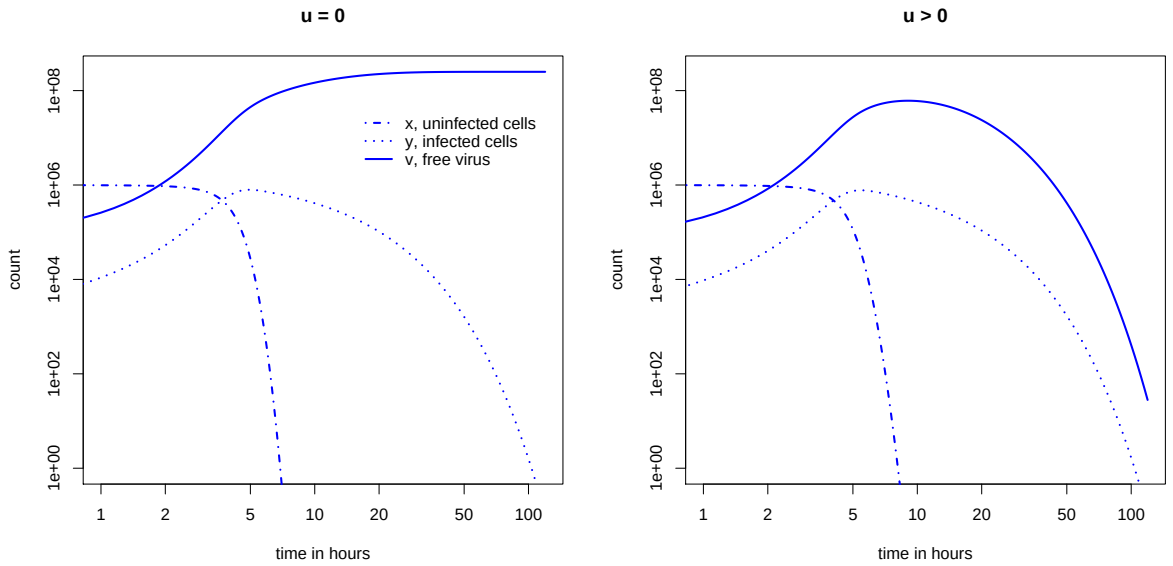

Figure S1: Dynamics of the basic cell culture model (S1) assuming no clearance of free virus ($u = 0$, left) and a positive death rate of free viruses ($u > 0$, right). Shown are the abundances of uninfected cells (x, dash-dot line), infected cells (y, dotted line), and free virus (v, solid line).

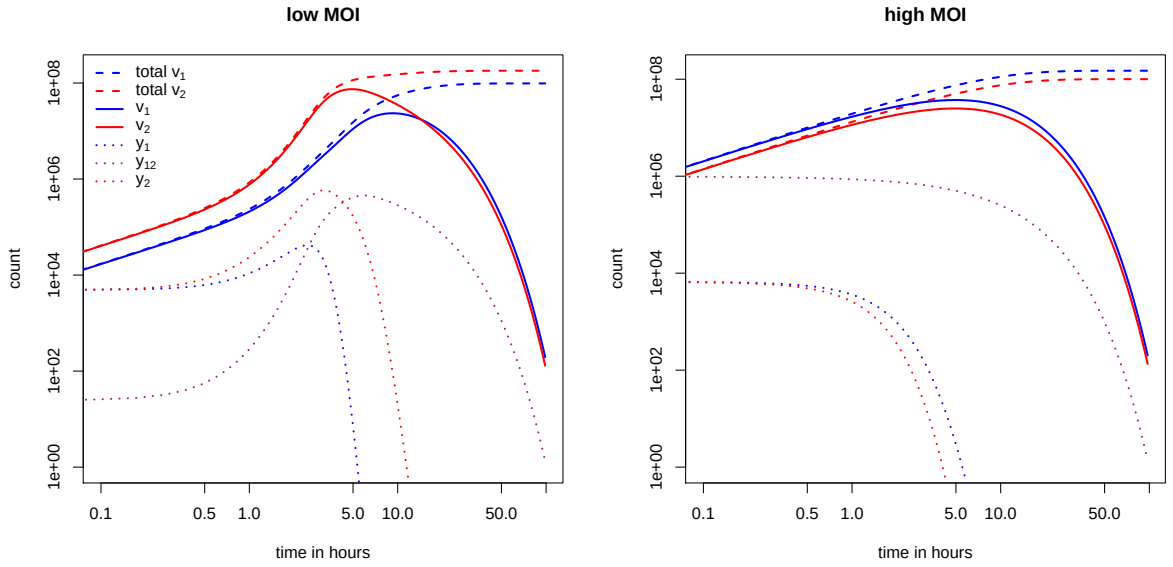

Figure S2: Dynamics of two competing viruses in cell culture (Equations (S3)) with low (left) and high (right) multiplicity of infection. Dashed lines denote the total amount of virus, dead or alive.

For the two-virus system, we obtain the equations

$$\begin{aligned}
\dot{x} &= -\beta x v_1 - \beta x v_2 \\
\dot{y}_1 &= \beta x v_1 - \beta y_1 v_2 - a_1 y_1 \\
\dot{y}_{12} &= \beta y_1 v_2 + \beta y_2 v_1 - a_1 y_{12} \\
\dot{y}_2 &= \beta x v_2 - \beta y_2 v_1 - a_2 y_2 \\
\dot{v}_1 &= k_1 y_1 + c k_1 y_{12} - u v_1 \\
\dot{v}_2 &= k_2 y_2 + (1-c) k_1 y_{12} - u v_2
\end{aligned} \tag{S3}$$

The additional parameter c denotes the probability that a virus produced by a multiply infected cell is of type 1. We have $0 \leq c \leq 1$.

The two experimentally analyzed viruses display differences in cell killing and in producing offspring in superinfected cells (Table S1):

- Virus 1 produces more offspring in coinfected cells, $c > \frac{1}{2}$,
- Virus 2 is spreading faster, $a_1 < a_2$.

The first virus is a competitor, which is more effective within coinfected cells, whereas the second virus is a colonizer, which is faster at cell killing and releasing new virus particles. Competitors produce more offspring when competing for resources within cells, whereas colonizers are more efficient in spreading infection. The dynamics of the two-virus model are shown in Figure S2 for the competitor and the colonizer defined by the parameters in Table S1.

1.3 *In silico* versus *in vitro* dynamics

To compare model predictions with experimental results, we have to make small adjustments to the basic model presented above.

1.3.1 Initial conditions

To control the amount of virus that is added to a cell culture, the first stages of infection are carried out as in a virus titration assay. A volume of medium containing a known amount of virus is added to the culture. One hour later, the virus inoculum is removed and fresh medium is added to the culture. For this technical reason, in the first infection we deal with infected cells in absence of free virus. Thus, we calculate the number of infected cells in this single round of infection and use this value, rather than the initial number of viruses, as the starting solution of the ODE system.

Let us first consider a single virus at initial multiplicity of infection $\lambda = v/x_0$. The probability of finding a k-fold infected cell, denoted $X = k$, after one round of infection is given by the Poisson distribution [2]

$$\text{Prob}(X = k) = \frac{\lambda^k e^{-\lambda}}{k!},$$

if we assume a large number of cells and independent viruses. Thus, the probability of a cell being infected by at least one virus particle is

$$\text{Prob}(X \geq 1) = 1 - \text{Prob}(X = 0) = 1 - e^{-\lambda}.$$

For two viruses with $\lambda_1 = v_1/x_0$ and $\lambda_2 = v_2/x_0$, let $X_i = k$ denote a k-fold infection with virus i, $i = 1, 2$. Assuming that infections are independent, we find

$$\begin{aligned}
p_{00} &= \text{Prob}(X_1 = 0,\, X_2 = 0) &&= e^{-(\lambda_1+\lambda_2)} \\
p_{01} &= \text{Prob}(X_1 = 0,\, X_2 \geq 1) &&= e^{-\lambda_1}\left(1 - e^{-\lambda_2}\right) \\
p_{10} &= \text{Prob}(X_1 \geq 1,\, X_2 = 0) &&= \left(1 - e^{-\lambda_1}\right) e^{-\lambda_2} \\
p_{11} &= \text{Prob}(X_1 \geq 1,\, X_2 \geq 1) &&= \left(1 - e^{-\lambda_1}\right)\left(1 - e^{-\lambda_2}\right)
\end{aligned}$$

and use the following initial conditions for the ODE system:

$$x(0) = p_{00}x_0, \quad y_1(0) = p_{10}x_0, \quad y_2(0) = p_{01}x_0, \quad y_{12}(0) = p_{11}x_0, \quad v_1(0) = v_2(0) = 0 \quad \text{(S4)}$$

1.3.2 Counting viruses

As a comparative measure of success of two competing viruses in cell culture, we quantify their abundances at the end of the infection experiment. Because the experimental read-out can not distinguish infectious from non-infectious virus particles, in the mathematical model, we also have to account for inactivated viruses. The abundances of inactivated viruses, w_1 and w_2, follow the additional equations

$$\begin{aligned}
\dot{w}_1 &= uv_1 \\
\dot{w}_2 &= uv_2.
\end{aligned}$$

We define t^* as the earliest time point at which the number of infected cells is less than one,

$$t^* = \inf\{t \geq 0 \mid y_1(t) < 1,\, y_2(t) < 1,\, y_{12}(t) < 1\},$$

and write $v(t^*) = v^*$, etc. The computational read-out is the relative fitness advantage of virus 2, the colonizer, over virus 1, the competitor,

$$f = \frac{v_2^* + w_2^*}{v_1^* + w_1^*}.$$

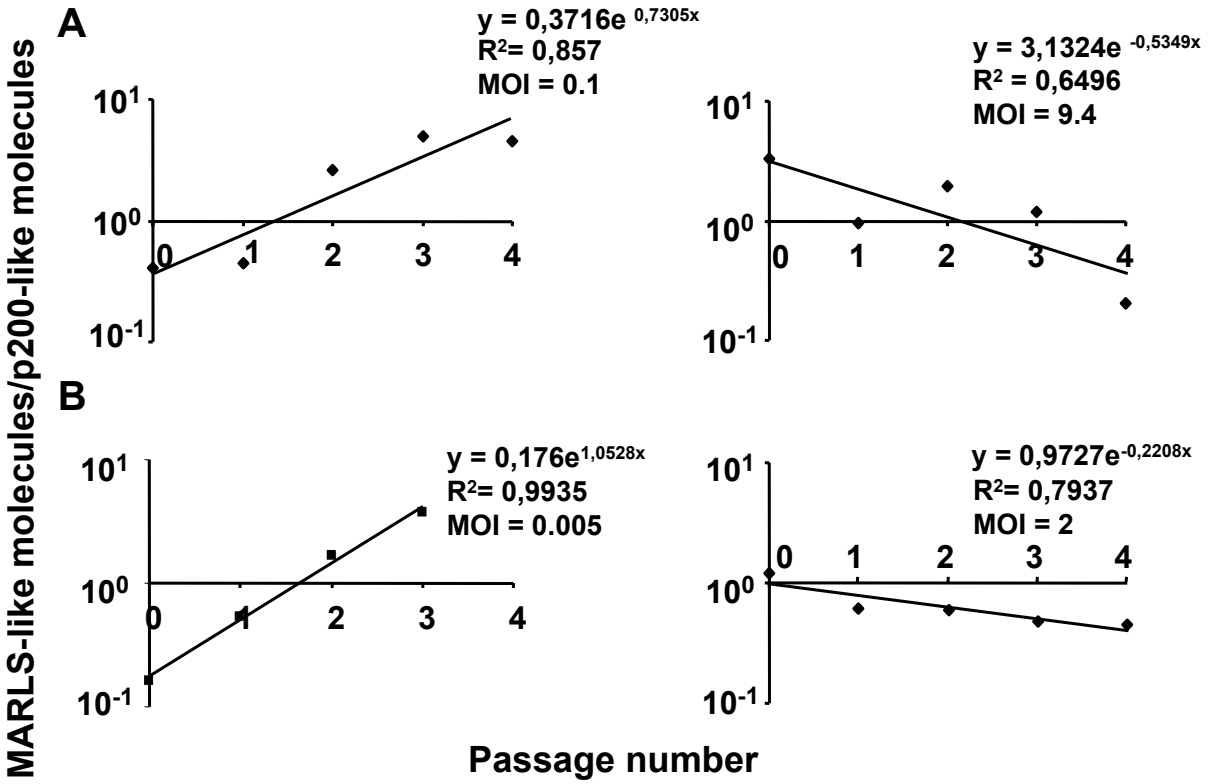

Figure S3: Competition experiments between MARLS and p200 viruses at different MOI. The competitions and quantifications of viral RNA were carried out as specified in the Methods section. Each point represents the number of MARLS genomic RNA molecules divided by the number of p200 genomic RNA molecules. Data have been fitted by linear regression; Regression equation, R^2 value, and MOI used are indicated in each plot. A) Competition between populations p200 and p200p5d (MARLS). B) Competition between two p200 representative clones (240c1, 240c13), and two MARLS representative clones (p240c2, p240c12). All viruses were mixed using equal number of PFU. As a relative fitness measure we used the slope of each graph which is the increase in frequency of each genotype per passage.

The experimental assessment of the final relative abundances of both viruses was performed in competition assays (Figure S3) for different initial viral densities

$$\lambda = \frac{v_{0,1} + v_{0,2}}{x_0}. \tag{S5}$$

Figure S2 illustrates that, according to the model, the winner of the competition can be either the competitor or the colonizer, depending on the initial multiplicity of infection. In Figure 2 of the main text, this model prediction is validated by comparing predicted and observed relative viral abundances.

2 Experimental measurements

2.1 Origin of viral strains

We first describe the experimental procedures that were employed to obtain the two different viral subpopulations.

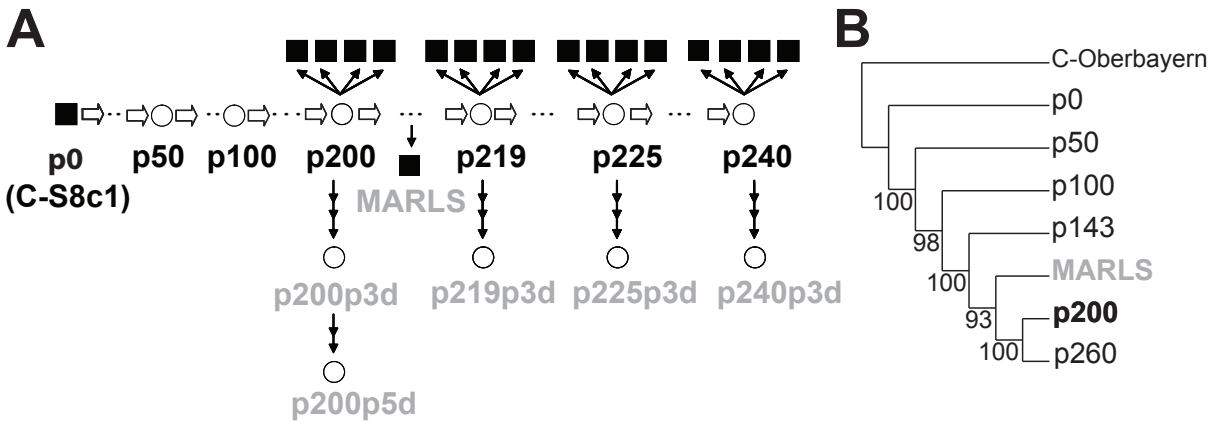

Figure S4: Genetic diversification of a biological clone of FMDV in cell culture. (A) Schematic representation of passages of clone C-S8c1 (p0) in BHK-21 cells. Biological clones are depicted as filled squares and populations as empty circles. Thick arrows indicate high-MOI passages (1 to 20 PFU/cell), sequential thin arrows indicate low-MOI infections (0.006 to 0.02 PFU/cell), and single thin arrows represent isolation of biological clones. Viral populations are labelled by passage number (e.g., p200 at passage 200). Populations with suffix p3d and p5d were derived by three and five low-MOI passages, respectively. MARLS is a monoclonal antibody-escape clone isolated at passage 213. Viruses resembling MARLS and p200 are labelled in grey and black, respectively. B) Phylogenetic reconstruction based on whole genome consensus nucleotide sequences of populations derived from biological clone p0. The sequence of C-Oberbayern is included as outgroup. The tree was constructed by maximum likelihood using the Tamura-Nei substitution model with Gamma distributed rates (TN-8Γ). Confidence values higher than 80% are shown at the corresponding branching points.

Serial infections of BHK-21 cells at high MOI were carried out with the biologically pure clone of FMDV C-S8c1 (Figure S4A). Evolutionary history of the consensus sequences at consecutive passages was reconstructed by maximum likelihood phylogenetic analysis (Figure S4B). The phylogenetic tree reflected the successive evolution of the virus and showed that C-S8c1 diversified into MARLS between passage 143 and passage 200.

2.2 Model parameters

We have performed several experiments and employed theoretical considerations in order to obtain the parameter values displayed in Table S1.

Basic reproductive number, R_0. The basic reproductive number of a virus, R_0, is defined as the number of secondary infections, i.e., the number of infections that result from a single infected cell, when all cells are uninfected. If $R_0 > 1$, each cell produces on average more than one virus and the virus population will initially grow exponentially as $v(t) \propto e^{r_0 t}$. The growth rate, r_0, is the largest root of the equation

$$r_0^2 + (a+u)r_0 + au(1-R_0) = 0 \tag{S6}$$

[3]. From this equation, we can derive the basic reproductive number, R_0. The intial growth rate of each virus, $r_{0,i}$, has, in turn, been determined experimentally by averaging the slope of the virus growth curves depicted in Figure S5

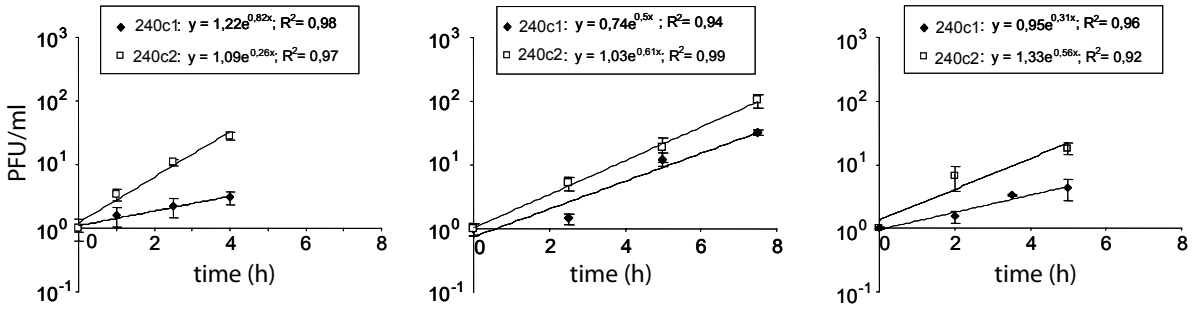

Figure S5: Viral growth curves. The initial exponential growth of the MARLS clone, 240c2, and the p200 clone, 240c1, was monitored by titration at several time points of the supernatant of cells infected independently by each clone. The growth rates $r_{0,i}$ correspond to the average slopes of each experiment represented in the individual panels.

Virus[a]	**Subpopulation**	**Progeny production (PFU/ml)**[b]
240c1	p200, competitor	$2.95 \times 10^7 \pm 9.84 \times 10^6$
240c13	p200, competitor	$3.43 \times 10^7 \pm 4.41 \times 10^6$
240c2	MARLS, colonizer	$3.74 \times 10^7 \pm 5.49 \times 10^6$
240c12	MARLS, colonizer	$6.90 \times 10^7 \pm 2.78 \times 10^7$

[a] The origin of clones is described in the Materials and Methods Section, in Section 2.1, and in Figure S4

[b] Each titration was determined at least in triplicate. Two independent infections were carried out with each clone to determine the virus yield.

Table S2: Progeny production of MARLS and p200 clones. BHK-21 cells were infected with equal amounts of specified virus clones. After 1h of adsorption to the cells, the inoculum was removed, cells were washed, and fresh medium was added. When complete cytopathic effect was reached, infectivity was determined by titration of the cell culture supernatant.

Death rate of infected cells, a. To obtain the differences in a, the time that the slow virus takes to kill one cell (a_2) was measured by monitoring cell viability with the trypan blue staining technique (see Methods section in the main text). This procedure does not allow to determine, with sufficient accuracy, the death rate of fast viruses that kill host cells in a few hours. For this reason, we use Equation S6 to derive a_1 in a precise fashion.

Clearance rate of free virus, u. FMDV infectivity decays exponentially with time [1]. We assume uniform inactivation rates $u_1 = u_2 = u$ (cf. Sec 1.2) and take the mean value of $u = 0.28$ h^{-1}, which corresponds to the standard observation in our laboratory of the inactivation rate of FMDV at 37°C.

Burst size, $K = k/a$. Production of MARLS and p200 viruses was very similar as shown by titration of individual viral clones and reported in Table S2. Dividing these virus titers by the number of infected cells, one obtains $K = k_1/a_1 = k_2/a_2 = k_{12}/a_{12}$.

Efficiency of infection, β. We assume uniform infection efficiencies $\beta_1 = \beta_2 = \beta_{12} = \beta_{21} = \beta$ (cf. Sec 1.2) and obtain a numerical estimate from the equation $R_0 = \beta k x_0/au$ for the basic reproductive number [3].

Probability of producing type 1 viral offspring, c. As described for the calculation of the burst size, the viral progeny production in a viral infection at high multiplicity of infection (MOI) represents an average of the production by each individual cell. The advantage of p200 viruses in coinfected cells was calculated by averaging the results of the serial competitive infections used to determine relative fitness and confirmed by three additional individual infections carried out at high MOI.

3 Mathematical analysis

For our mathematical analysis of the ODE system describing two competing viruses in cell culture, we rewrite the equations using $K = k_1/a_1 = k_2/a_2$,

$$\begin{aligned}
\dot{x} &= -\beta x v_1 - \beta x v_2 \\
\dot{y}_1 &= \beta x v_1 - \beta y_1 v_2 - a_1 y_1 \\
\dot{y}_{12} &= \beta y_1 v_2 + \beta y_2 v_1 - a_1 y_{12} \\
\dot{y}_2 &= \beta x v_2 - \beta y_2 v_1 - a_2 y_2 \\
\dot{v}_1 &= K a_1 y_1 + c K a_1 y_{12} - u v_1 \\
\dot{v}_2 &= K a_2 y_2 + (1-c) K a_1 y_{12} - u v_2 \\
\dot{w}_1 &= u v_1 \\
\dot{w}_2 &= u v_2 .
\end{aligned}$$

3.1 Conservation law

Slightly abusing notation we set, for $i = 1, 2$, $v_i^* = v_i(\infty)$ and $w_i^* = w_i(\infty)$. The sum

$$\phi = x + y_1 + y_{12} + y_2 + \frac{v_1 + w_1 + v_2 + w_2}{K}$$

is a conserved quantity of the system, i.e., $\dot{\phi} = 0$. For the initial conditions (S4), we obtain from $\phi(0) = \phi(\infty)$ the equation

$$v_1^* + w_1^* + v_2^* + w_2^* = K x_0 .$$

This relation does not determine the final numbers of both viruses, but defines a constraint on them. This restriction does not depend on β (even if we would not have assumed that all infection rates are equal). Similarly, for the initial conditions

$$x(0) = x_0, \quad y_1(0) = y_2(0) = y_{12}(0) = 0, \quad v_1(0) = v_{1,0}, \;\; v_2(0) = v_{2,0}$$

we have

$$v_1^* + w_1^* - v_{1,0} + v_2^* + w_2^* - v_{2,0} = K x_0 ,$$

Using Eq. S5 we obtain an expression similar to Eq. S2,

$$v_1^* + w_1^* + v_2^* + w_2^* = (K + \lambda) x_0 .$$

3.2 Parameter space

We introduce the following linear change of coordinates,

$$\hat{t} = a_1 t,\ \hat{x} = \frac{\beta K}{a_1} x,\ \hat{y}_1 = \frac{\beta K}{a_1} y_1,\ \hat{y}_{12} = \frac{\beta K}{a_1} y_{12},\ \hat{y}_2 = \frac{\beta K}{a_1} y_2,$$
$$\hat{v}_1 = \frac{\beta}{a_1} v_1,\ \hat{v}_2 = \frac{\beta}{a_1} v_2,\ \hat{w}_1 = \frac{\beta}{a_1} w_1,\ \hat{w}_2 = \frac{\beta}{a_1} w_2,$$

to obtain the simplified ODE system (where we drop the hats)

$$\begin{aligned}
\dot{x} &= -xv_1 - xv_2 \\
\dot{y}_1 &= xv_1 - y_1 v_2 - y_1 \\
\dot{y}_{12} &= y_1 v_2 + y_2 v_1 - y_{12} \\
\dot{y}_2 &= xv_2 - y_2 v_1 - a y_2 \\
\dot{v}_1 &= y_1 + c y_{12} - \mu v_1 \\
\dot{v}_2 &= a y_2 + (1-c) y_{12} - \mu v_2 \\
\dot{w}_1 &= \mu v_1 \\
\dot{w}_2 &= \mu v_2
\end{aligned}$$

This system has only three parameters, namely $a := a_2/a_1$, c, and $\mu := u/a$. We have eliminated the direct dependencies on β, K, and a_1. The competitor and the colonizer described in Table S1 differ only in two of the three remaining parameters, namely a and c.

In order to explore the complete parameter space of the model it is enough to consider the case where $\beta = 1$, $K = 1$, and $a_1 = 1$. We are interested whether the relative fitness

$$f = \frac{v_2^* + w_2^*}{v_1^* + w_1^*} = \frac{(1+\lambda)x_0}{v_1^* + w_1^*} - 1$$

is greater or less than 1 for any given values of a, c, and μ.

Figure S6 explores this quantity by plotting the sign of its logarithm in the a-c plane for three different multiplicities of infection and three different values of μ. Positive values ($f > 1$) indicate that colonizers win the competition and are displayed in red, whereas at negative values ($f > 1$) competitors win.

For values of c below $1/2$, colonizers will always win, whereas for $c > 1/2$ and small values of a, competitors will always outcompete colonizers. However, for $c > 1/2$ and $a > 1$, the outcome of the competition depends on the initial multiplicity of infection: colonizers win under low-density conditions, but competitors win under high-density conditions.

The rows of Figure S6 show that this effect is largely independent of the viral inactivation rate μ. We therefore assume $\mu = 0$ for the following analytical analysis of the model. The ODE system then simplifies to

$$\begin{aligned}
\dot{x} &= -xv_1 - xv_2 \\
\dot{y}_1 &= xv_1 - y_1 v_2 - y_1 \\
\dot{y}_{12} &= y_1 v_2 + y_2 v_1 - y_{12} \\
\dot{y}_2 &= xv_2 - y_2 v_1 - a y_2 \\
\dot{v}_1 &= y_1 + c y_{12} \\
\dot{v}_2 &= a y_2 + (1-c) y_{12}
\end{aligned} \tag{S7}$$

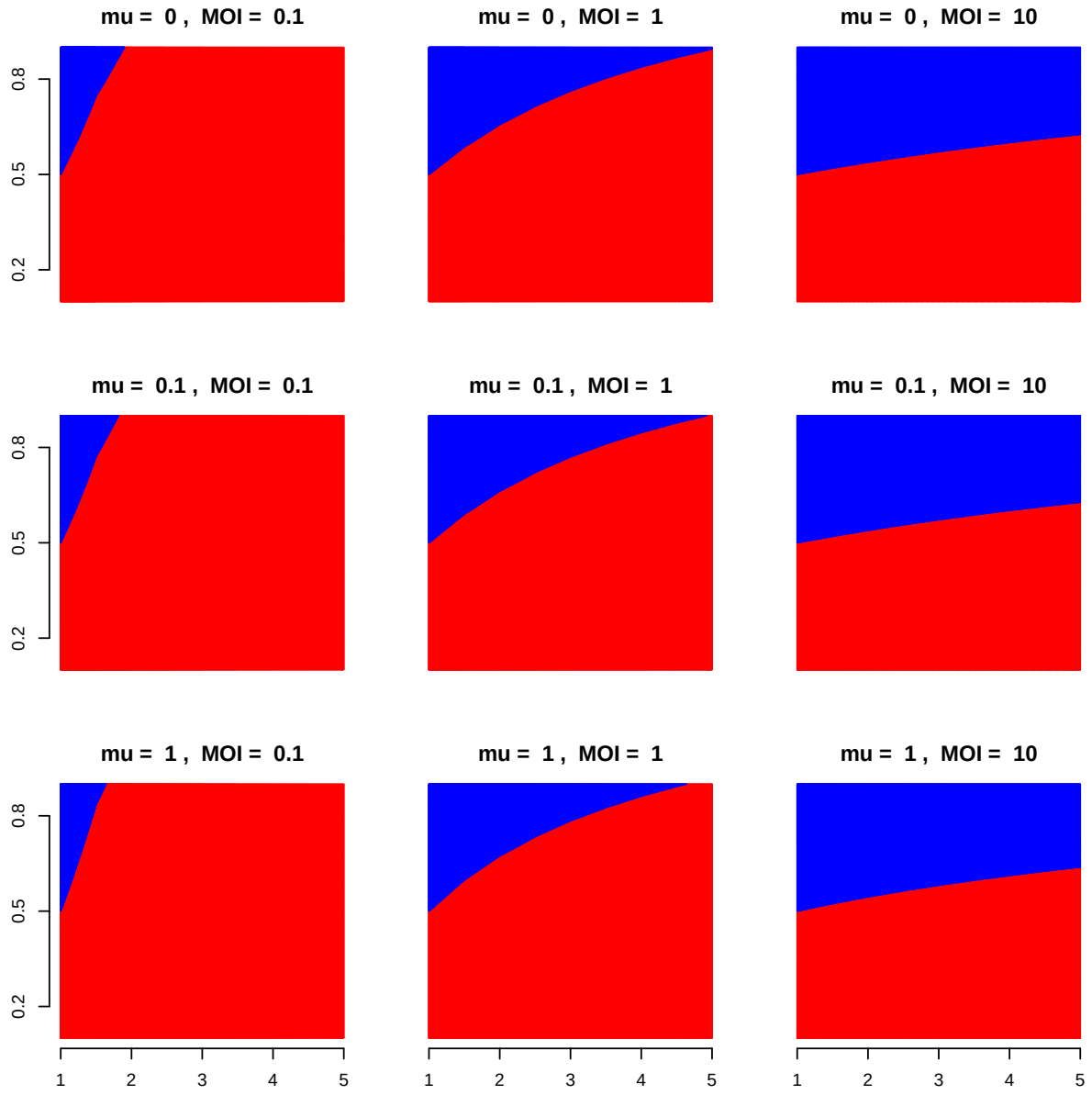

Figure S6: Viral competition outcome. Each plot indicates the winner of the competition experiment (blue: competitor wins; red: colonizer wins) over the parameter subspace defined by the cell killing ratio $a = a_2/a_1$ (x-axis) and the intracellular advantage c (y-axis). Subfigures correspond, from left to right, to increasing multiplicities of infection (MOI), λ, and, from top to bottom, to increasing viral inactivation rates, μ.

and it depends exactly on the two parameters a and c in which the competitors and colonizers of Table S1 differ.

3.3 Large initial virus load limit

Analytic treatment of the nonlinear ODE system (S7) is quite challenging. In order to obtain the final virus densities, we need to find the complete time dependent solution; the stationary solution is not enough. We can find a solution of (S7) in the limit of large initial virus density (MOI). Since the rate of infection is proportional to the virus load, for large virus loads the slow effect of virus inactivation can be neglected. We assume

that $v_1(0), v_2(0) \gg u/\beta$, and hence we take $u = 0$ as in (S7).

If the initial virus density is large, its relative change will be small during the entire process. Hence we will assume that the virus densities are constant during the process, $v_1 = v_1(0)$ and $v_2 = v_2(0)$, which makes the first four equations of (S7) linear. Then by letting the virus densities depend on time again, we can integrate the fifth and sixth equations of (S7) to obtain the total virus production. Let us now follow this outline.

We concentrate on the initial value problem $x(0) = x_0$ and $y_1(0) = y_{12}(0) = y_2(0) = 0$. The first four equations of (S7) remain unchanged if we measure all densities x, y_1, y_{12}, and y_2 in units of x_0. Hence the final virus production will be proportional to x_0 and, for simplicity, we can set $x(0) = x_0 = 1$.

For constant v_1 and v_2 the time dependent solution of the densities can be obtained by integrating (S7). We find

$$\begin{aligned} x(t) &= e^{-t(v_1+v_2)} \\ y_1(t) &= \frac{v_1}{v_1-1}\left[e^{-t(1+v_2)} - e^{-t(v_1+v_2)}\right] \\ y_2(t) &= \frac{v_2}{v_2-a}\left[e^{-t(a+v_1)} - e^{-t(v_1+v_2)}\right] \end{aligned} \tag{S8}$$

The solution for y_{12} can be obtained by integrating the third equation of (S7), but the result is too cumbersome to include here. Now we can obtain the change in virus densities during the process by integrating the last two equations of (S7),

$$\begin{aligned} \Delta v_1 &= \int_0^\infty y_1(t) + c y_{12}(t)\, dt \;=\; I_1 + cI_{12} \\ \Delta v_2 &= \int_0^\infty a y_2(t) + (1-c) y_{12}(t)\, dt \;=\; aI_2 + (1-c)I_{12} \end{aligned}$$

where

$$\begin{aligned} I_1 &= \int_0^\infty y_1(t)\, dt = \frac{v_1}{(1+v_2)(v_1+v_2)} \\ I_2 &= \int_0^\infty y_2(t)\, dt = \frac{v_2}{(a+v_1)(v_1+v_2)} \\ I_{12} &= \int_0^\infty y_{12}(t)\, dt = \frac{v_1 v_2(1+a+v_1+v_2)}{(a+v_1)(1+v_2)(v_1+v_2)}. \end{aligned} \tag{S9}$$

We are interested in the difference of the final viral densities

$$\begin{aligned} \Delta &= v_2^* - v_1^* \\ &= v_2 + \Delta v_2 - v_1 - \Delta v_1 \\ &= v_2 - v_1 + aI_2 - I_1 + (1-2c)I_{12} \end{aligned}$$

where I_1, I_2, and I_{12} are given above by (S9), and in particular in the case of symmetric initial virus load, i.e., $v := v_1 = v_2$. In that case we obtain

$$\Delta = 1 - 2c - \frac{1-c}{1+v} + \frac{ac}{a+v} \tag{S10}$$

which is a linear function of c. If both viruses equal in cell killing ($a = 1$) and in offspring production ($c = 1/2$), then of course $\Delta = 0$. Also, for any other value of x_0, the difference Δ simply becomes x_0 times larger.

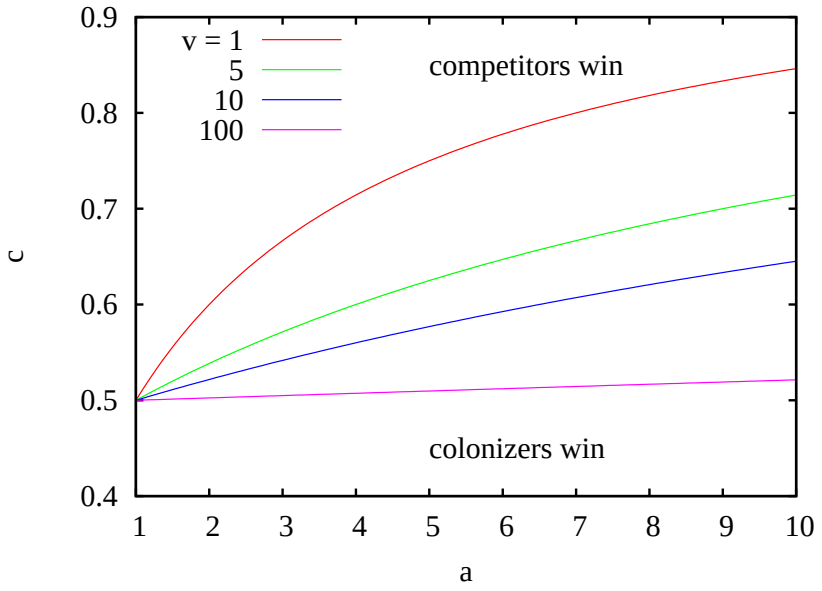

Figure S7: Boundary between regions where colonizers or competitors are favored at different values of initial virus density (v). The lines correspond to the exact solution in the large virus density limit (S11). Low viral density v favors the colonizers (second virus), and larger v favors the competitors (first virus).

Our main question is when the second virus (the competitor) becomes more successful then the first virus (the colonizer), that is when $\Delta > 0$. We find from (S10) that $\Delta > 0$ for $c < c^*$, where the threshold value is

$$c^* = \frac{a + v}{1 + a + 2v} \tag{S11}$$

Competitors are more successful within coinfected cells ($c > 1/2$), whereas colonizers replicate faster ($a = a_2/a_1 > 1$). In the regime of $a > 1$, we indeed have $c^* > 1/2$. For $a > 1$, the critical intracellular competition parameter c^* decreases as v increases, because its rate of change is always negative,

$$\frac{dc^*}{dv} = \frac{1 - a}{(1 + a + 2v)^2} < 0.$$

Hence, we have shown analytically that smaller viral density v favors colonizers, while larger viral density (MOI) favors competitors (Figure S7).

References

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