Supporting Information

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SI Text

S1. The Model for Two Viral Variants

We consider in detail a model for two cross-immunoreacting viral variants u and v with different replication rates f_u, f_v and with the CRN shown in Fig. 3*A*. In these settings the system [**1**] and [**2**] has the following form:

$$\dot{x}_u = f_u x_u - p x_u r_u, \qquad \textbf{[S1]}$$

$$\dot{x}_v = f_v x_v - p x_v (\beta r_u + r_v), \qquad \textbf{[S2]}$$

$$\dot{r}_u = c x_u + c \frac{\alpha r_u}{\alpha r_u + r_v} x_v - b r_u, \qquad \textbf{[S3]}$$

$$\dot{r}_v = c \frac{r_v}{\alpha r_u + r_v} x_v - b r_v. \qquad \textbf{[S4]}$$

S1.1. Stationary States and Their Stability. Without cross-reactivity (i.e., $\alpha = \beta = 0$), the system converges to the equilibrium solution

$$x_u^\circ = \frac{b f_u}{cp}, \quad x_v^\circ = \frac{b f_v}{cp}, \quad r_u^\circ = \frac{f_u}{p}, \quad r_v^\circ = \frac{f_v}{p} \qquad \textbf{[S5]}$$

(Fig. S1), which was used as a benchmark for comparison with solutions corresponding to the cases with cross-immunoreactivity.

Further, we assume that $\alpha > \beta \geq 0$. The Jacobian of the system is given by

$$J(x_u, x_v, r_u, r_v) = \begin{pmatrix} f_u - p r_u & 0 & -p x_u & 0 \\ 0 & f_v - p(\beta r_u + r_v) & -p\beta x_v & -p x_v \\ c & \frac{\alpha c r_u}{\alpha r_u + r_v} & \frac{c\alpha r_v x_v}{(\alpha r_u + r_v)^2} - b & -\frac{c\alpha r_u x_v}{(\alpha r_u + r_v)^2} \\ 0 & \frac{c r_v}{\alpha r_u + r_v} & \frac{-c\alpha r_v x_v}{(\alpha r_u + r_v)^2} & \frac{c\alpha r_u x_v}{(\alpha r_u + r_v)^2} - b \end{pmatrix}.$$

The system [**S1**]–[**S4**] has the following stationary solutions:

i)

$$x_u^* = \frac{b}{c}\frac{(1-\alpha) f_u}{p}, \quad x_v^* = \frac{b}{c}\frac{(\alpha-\beta) f_u + f_v}{p}, \quad r_u^* = \frac{f_u}{p}, \quad r_v^* = \frac{f_v - \beta f_u}{p}, \qquad \textbf{[S6]}$$

where $f_v - \beta f_u > 0$ and $\alpha < 1$ (Fig. S2). This solution describes antigenic cooperation between variants u and v. Here $x_v^* - x_v^\circ = (b/c)(\alpha - \beta)h$, so v converges to the higher population size than in solution [**S5**] by using the response r_u. This effect is associated with reduction of the equilibrium population of u with respect to solution [**S5**].

We will prove that solution [**S6**] is stable when $f_u = f_v = f$. The characteristic polynomial of $J(x_u^*, x_v^*, r_u^*, r_v^*)$ has the form $P(\lambda) = \lambda^4 - S_1\lambda^3 + S_2\lambda^2 - S_3\lambda + S_4$, where S_i is the sum of all principal i minors of $J(x_u^*, x_v^*, r_u^*, r_v^*)$ (1). Using direct calculations, we have $S_1 = b((2(\beta-1) - \alpha\beta)/(\alpha - \beta + 1))$, $S_2 = bf(2 + \alpha\beta - \alpha - \beta) + b^2(((1-\alpha)(1-\beta))/(\alpha - \beta + 1))$, $S_3 = -b^2 f(((1-\alpha)(1-\beta)(2 + \alpha - \beta))/(\alpha - \beta + 1))$, $S_4 = b^2 f^2 (1-\alpha)(1-\beta)$. By the Routh–Hurwitz criterion (1), solution [**S6**] is stable, if the following conditions hold: $S_2, S_4 > 0$, $S_1, S_3 < 0$, $\Delta_1 = -S_1 S_2 + S_3 > 0$, $\Delta_2 = S_1 S_2 S_3 - S_1^2 S_4 - S_3^2 > 0$.

For Δ_1 we have $\Delta_1 = (b^2 f/(\alpha - \beta + 1)) g_1(\alpha, \beta) + g_2(\alpha, \beta)$, where $g_1(\alpha, \beta) = \alpha^2\beta^2 + (1-\beta)(2\alpha\beta + 2 - \beta) - \alpha(1-\alpha)(1-2\beta)$ and $g_2(\alpha, \beta) = b^3(((\alpha\beta + 2(1-\beta))(1-\alpha)(1-\beta))/(\alpha - \beta + 1)^2)$; we have $g_2(\alpha, \beta) \geq 0$. To show that $g_1(\alpha, \beta) \geq 0$, note that $g_1(\alpha, \beta) \geq (1-\beta)(2\alpha\beta + 2 - \beta) - \alpha(1-\alpha)(1-\beta) = (1-\beta)(2\alpha\beta + 2 - \beta - \alpha(1-\alpha)) = g_3(\alpha, \beta) \geq 0$. Moreover, $g_3(\alpha, \beta) = 0$ if and only if $\beta = 1$. Then, with $\beta = 1$ we have $g_1(\alpha, \beta) = 0$, if and only if $\alpha = 0$. According to the assumption $\alpha > \beta$, it is impossible, and so we have $\Delta_1 > 0$.

For Δ_2 we have $\Delta_2 = b^4 f^2 (((1-\alpha)(1-\beta))/(\alpha - \beta + 1)^2)$ $g_4(\alpha, \beta)$, where $g_4(\alpha, \beta) = (2 + \alpha\beta - 2\beta)(2 + \alpha\beta - \alpha - \beta + (b/f)$ $(((1-\alpha)(1-\beta))/(\alpha - \beta + 1)))(2 + \alpha - \beta) - (2 + \alpha\beta - 2\beta)^2 - (1-\alpha)$ $(1-\beta)(2 + \alpha - \beta)^2 \geq (2 + \alpha\beta - 2\beta)(2 + \alpha\beta - \alpha - \beta)(2 + \alpha - \beta) -$ $(2 + \alpha\beta - 2\beta)^2 - (1-\alpha)(1-\beta)(2 + \alpha - \beta)^2 = (1 + \alpha - \beta)((1-\alpha)$ $(1-\beta) - 1)^2 = g_5(\alpha, \beta) \geq 0$. Moreover, $g_5(\alpha, \beta) = 0$ if and only if $\alpha = 0, \beta = 1$, or $\alpha = \beta = 0$. The first case is impossible according to the assumption $\alpha > \beta$, and in the second case $\Delta_2 = 4b^5 f > 0$. So we have $\Delta_2 > 0$. The stability of solution [**S6**] is proved.

ii) The family of solutions parameterized by h

$$x_u^* = 0, x_v^* = \frac{b}{c}\left(\frac{f_v}{p} + (1-\beta)h\right), \quad r_u^* = h, r_v^* = \frac{f_v}{p} - \beta h, \qquad \textbf{[S7]}$$

where $h > 0$ depends on the initial conditions and the parameters of [**S1**]–[**S4**] (Fig. S4). These solutions exist only when $\alpha = 1$ and describe the stronger form of altruistic cooperation. The variant u is completely eliminated, but with the same initial conditions the population of v achieves an exponentially higher equilibrium level with respect to the solution [**S6**] (Fig. S3) (according to [**S6**], for $\alpha < 1$ the value of x_v^* grows linearly with α, but for $\alpha = 1$ the exponential leap of x_v^* is observed).

If $\beta > 0$, then $h \leq f_v/(\beta p)$, and thus the size of the equilibrium population of variant v is bounded by $(b/c)(f_v/\beta p)$. When $\beta = 0$, the equilibrium solution has the form

$$x_u^* = 0, \quad x_v^* = \frac{b}{c}\left(\frac{f_v}{p} + h\right), \quad r_u^* = h, \quad r_v^* = \frac{f_v}{p}, \qquad \textbf{[S8]}$$

and x_v^* can be arbitrarily high (Fig. S4).

The Jacobian $J(x_u^*, x_v^*, r_u^*, r_v^*)$ has the following eigenvalues: $\lambda_1 = f_u - ph$, $\lambda_2 = (1/2)(-b - \sqrt{b^2 - 2cp\beta x_v - 2p(1-\beta)br_v})$, $\lambda_3 = (1/2)(-b + \sqrt{b^2 - 2cp\beta x_v - 2p(1-\beta)br_v})$, $\lambda_4 = 0$. It implies that the solution is unstable, if $h < f_u/p$. So, at the stable equilibrium, the immune response associated with u is supported by v at a sufficiently high level.

iii) $x_u^\bullet = (b/c)(f_u/p)$, $x_v^\bullet = 0$, $r_u^\bullet = f_u/p$, $r_v^\bullet = 0$.
This solution describes a situation, when the mechanism of antigenic cooperation was not involved, and variant u persisted, whereas v was eliminated (Fig. S5). The matrix $J(x_u^\bullet, x_v^\bullet, r_u^\bullet, r_v^\bullet)$ has the following eigenvalues: $\lambda_1 = (1/2)(-b - \sqrt{b^2 - 4bf_u})$, $\lambda_2 = (1/2)(-b + \sqrt{b^2 - 4bf_u})$, $\lambda_3 = -b$, $\lambda_4 = f_v - \beta f_u$. We have $Re(\lambda_1), Re(\lambda_2), Re(\lambda_3) < 0$. The solution is stable, if $f_u > (1/\beta) f_v$ (i.e., the replication rate of u is sufficiently

high to outcompete v and overcome the effect of cross-reactivity), and unstable, if $f_u > (1/\beta)f_v$. In particular, this equilibrium is unstable, if $\beta = 0$.

iv)

$$x_u^\circ = 0, \quad x_v^\circ = \frac{b}{c}\frac{f_v}{p}, \quad r_u^\circ = 0, \quad r_v^\circ = \frac{f_v}{p}. \qquad \textbf{[S9]}$$

In this case $\lambda_1 = f_u > 0$ is an eigenvalue of $J(x_u^\circ, x_v^\circ, r_u^\circ, r_v^\circ)$, and therefore the solution is unstable.

v)

$$x_u^\circ = h, \quad x_v^\circ = \frac{b}{c}\frac{f_u}{p} - h, \quad r_u^\circ = \frac{f_u}{p}, \quad r_v^\circ = 0, \qquad \textbf{[S10]}$$

where $0 < h < (b/c)(f_u/p)$ is a parameter depending on the initial conditions and parameters of **[S1]**–**[S4]**. This solution exists only if $f_v = \beta f_u$.

The eigenvalues of $J(x_u^\circ, x_v^\circ, r_u^\circ, r_v^\circ)$ are the following: $\lambda_1 = 0$, $\lambda_2 = (1/2)(-b - \sqrt{b^2 - 4(\beta b f_u + (1-\beta)phc)})$, $\lambda_3 = (1/2)(-b + \sqrt{b^2 - 4(\beta b f_u + (1-\beta)phc)})$, $\lambda_4 = (((1-\alpha)bf_u - cph)/\alpha f_u)$. $Re(\lambda_2)$, $Re(\lambda_3) < 0$. The solution is unstable, if $h < (1-\alpha)(b/c)(f_u/p)$.

vi)

$$x_u^\circ = 0, \quad x_v^\circ = \frac{b}{c}\frac{f_v}{\beta p}, \quad r_u^\circ = \frac{f_v}{\beta p}, \quad r_v^\circ = 0, \qquad \textbf{[S11]}$$

where $\beta > 0$. The Jacobian $J(x_u^\circ, x_v^\circ, r_u^\circ, r_v^\circ)$ has the following eigenvalues: $\lambda_1 = f_u - f_v/\beta$, $\lambda_2 = b/\alpha - b$, $\lambda_3 = (-b + \sqrt{b^2 - 4bf_v})/2$, $\lambda_4 = (-b + \sqrt{b^2 - 4bf_v})/2$. So, the solution is unstable, if $\alpha < 1$ or $\beta > f_v/f_u$. The solution may be stable, only if $\alpha = 1$ and β is sufficiently small.

S1.2. Effect of Initial Population Size and Replication Rate. The equilibrium solution **[S8]** is a parametric family depending on the parameter h, which is determined by the initial conditions and parameters of the system **[S1]**–**[S4]**. Interesting biological conclusions could be made by analyzing dependencies between the equilibrium population size x_v^*, initial population size $x_v(0)$, and replication rate f_v (with other parameters being fixed).

The relation between equilibrium population x_v^* and initial value $x_v(0)$ is shown in Fig. S6. Interestingly, x_v^* is a monotonically decreasing function of $x_v(0)$.

Fig. S7 illustrates the relation between x_v^* and replication rate f_v and shows that when f_v is bounded, then v achieves a maximum equilibrium population size with sufficiently low replication rate.

The aforementioned observations indicate that a small replication rate and initial population size may be beneficial for a variant with an advantageous position in the CRN. It can be explained by the observation that longer persistence of a larger population of u is beneficial for v, because it allows the greater level of the immune response r_u and convergence of r_u to the higher equilibrium, which, according to **[S8]**, results in higher value of x_v^*. The ability of v to stimulate r_u implies that faster replication or larger initial population of v causes faster development of r_u and earlier decline or elimination of u.

S1.3. CR and the Population Bottleneck. Every viral variant after the initial exponential growth rapidly declines to a very low level under the elicited immune response, which is usually followed by the convergence to an equilibrium in damped oscillations (Figs. S1, S2, and S4). At the end of that initial rapid decline, each variant experiences a population bottleneck, which suggests that, due to the discreteness of viral populations, at that moment the variant has high chances to be completely eliminated. It is interesting to note that variant v, which has an advantageous position in the CRN, has higher chances to survive a bottleneck than the variants in the system without cross-reactivity (Fig. S8); in particular, the value of x_v at the bottleneck is 179.9 times higher for $\alpha = 1, \beta = 0$ and 13.6 times higher for $\alpha = 0.8, \beta = 0.2$ than for $\alpha = \beta = 0$.

S2. Robustness of the Model Prediction to Variation of Parameters

To evaluate robustness of the model predictions to slight variation of parameters other than K, the model described by Eqs. **1** and **2** with CR-matrices **[4]** was simulated on 240 random CRNs with $n = 500, \ldots, 1{,}000$ vertices; $K = 10$; initial conditions $x_i(0) = 0.01$, $r_i(0) = 0.0001$; and the parameters f, p, c, b, α, γ randomly chosen from ranges $f \in \{2.25, 2.5, 2.75\}$, $p \in \{1.75, 2.0, 2.25\}$, $c \in \{0.1, 0.3, 0.5\}$, $b \in \{0.01, 0.05, 0.1\}$, $\alpha \in \{0.4, 0.5, 0.6\}$, $\gamma \in \{1.3, 1.5, 1.7\}$ with uniform probabilities. Viral variants and immune responses were assumed abolished once their values computed in the model fell below their initial conditions.

For test cases with low immune response decay rate ($b = 0.01$) all viral variants were eliminated by the immune system, indicating that constant generation of new variants escaping immune responses is required for the virus to survive in this case.

For higher immune response decay rates AC was observed in 95.8824% of cases. The parameters obtained in these simulations are similar to those reported in Table 1 (Table S1). For the remaining 4.1176% of cases elimination of all viral variants was observed, indicating a role of complex combinations of parameters and/or topologies of CRNs in the predicted infection outcome.

These observations are consistent with experimental facts, which indicate that, although arrival to negative selection at late stages is the most frequent outcome of HCV infection, virus can be cleared at an early stage of infection (2–4). The simulation outcomes suggest an important role of intrahost factors represented by parameters of the model. Comprehensive analysis of parameter space warrants further investigation.

1. Gantmacher F (2000) *Matrix Theory* (Am Math Soc, Providence, RI).
2. Wang CC, et al. (2007) Acute hepatitis C in a contemporary US cohort: Modes of acquisition and factors influencing viral clearance. *J Infect Dis* 196(10):1474–1482.
3. Yeung LTF, To T, King SM, Roberts EA (2007) Spontaneous clearance of childhood hepatitis C virus infection. *J Viral Hepat* 14(11):797–805.
4. Micallef JM, Kaldor JM, Dore GJ (2006) Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. *J Viral Hepat* 13(1): 34–41.

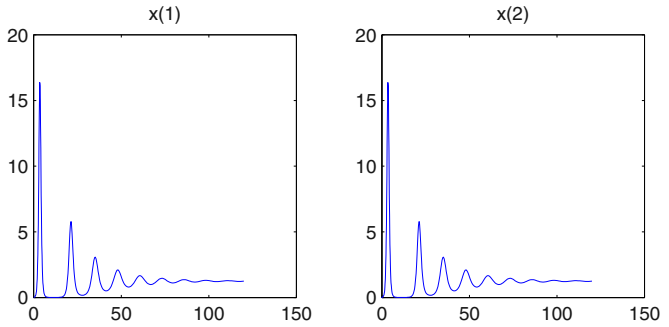

Fig. S1. Populations of variants u and v without cross-reactivity. $\alpha=\beta=0$, $f_u=f_v=2.5$, $p=2$, $c=0.1$, $b=0.1$.

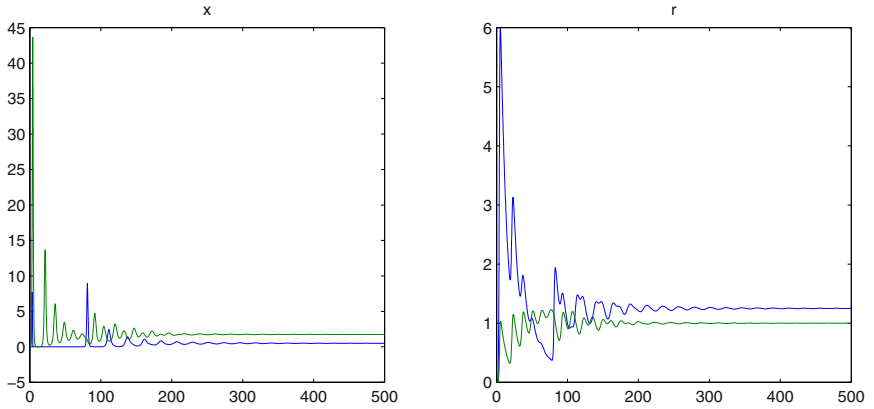

Fig. S2. Antigenic cooperation. $\alpha=0.6$, $\beta=0.2$, $f_u=f_v=2.5$, $p=2$, $c=0.1$, $b=0.1$.

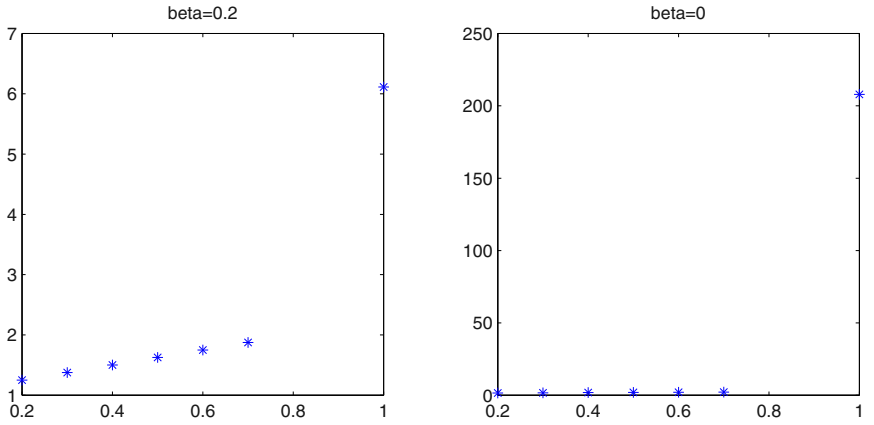

Fig. S3. Relation between x_v^* and α. $\beta=0$ and 0.2, $f_u=f_v=2.5$, $p=2$, $c=0.1$, $b=0.1$, $x_u(0)=x_v(0)=0.01$, $r_u(0)=r_v(0)=0.0001$.

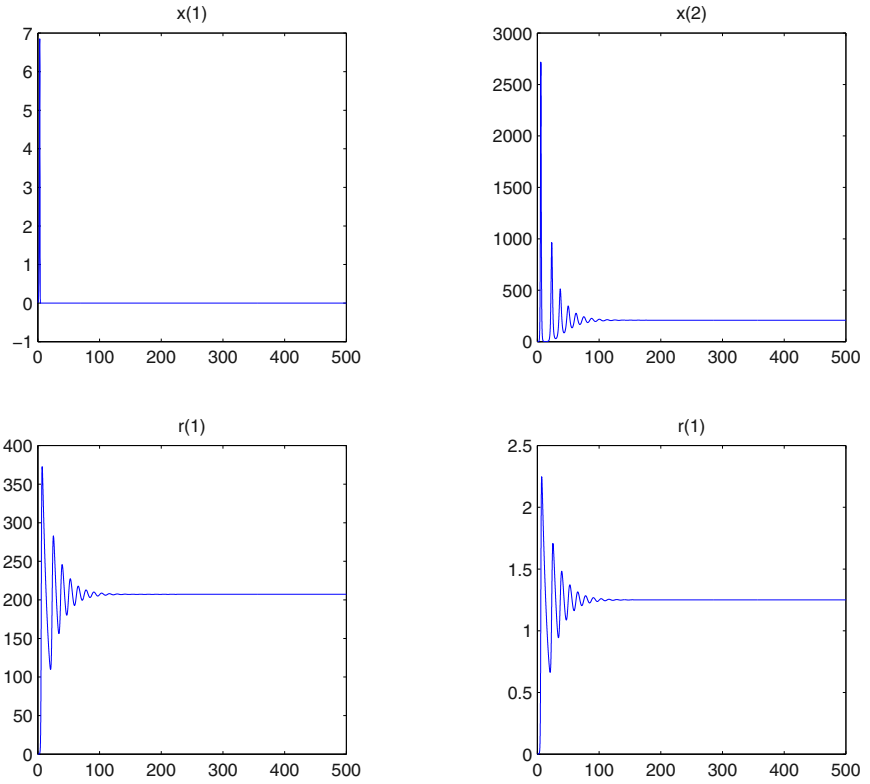

Fig. S4. Strong antigenic cooperation. $\alpha = 1$, $\beta = 0$, $f_u = f_v = 2.5$, $p = 2$, $c = 0.1$, $b = 0.1$.

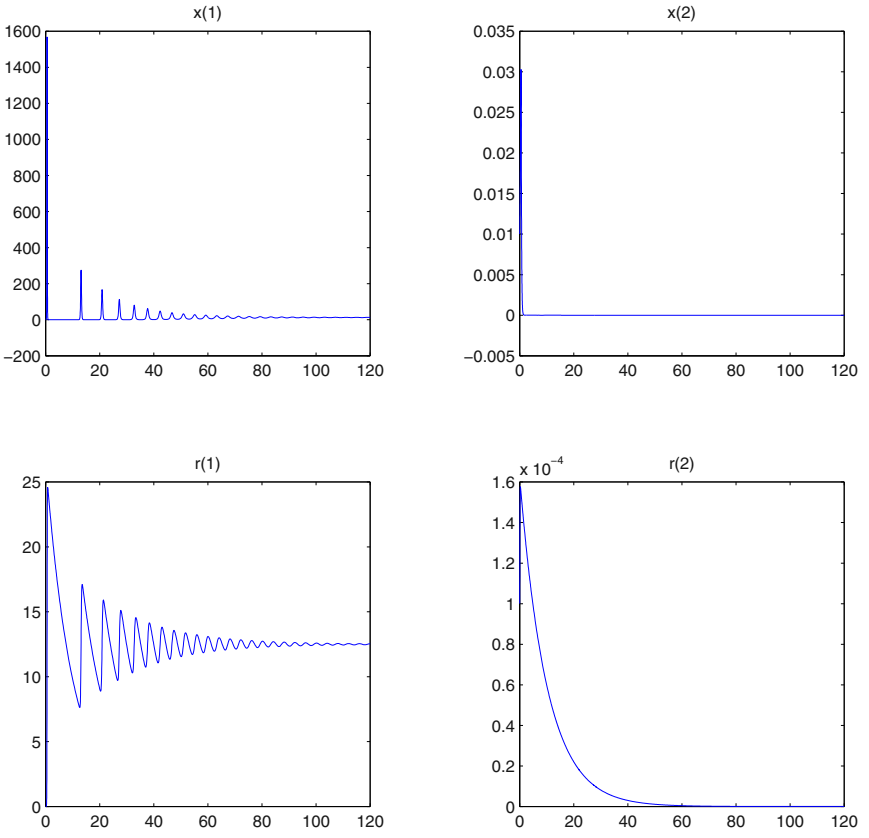

Fig. S5. Absence of antigenic cooperation. $\alpha = 0.8$, $\beta = 0.2$, $f_u = 25$, $f_v = 2.5$, $p = 2$, $c = 0.1$, $b = 0.1$.

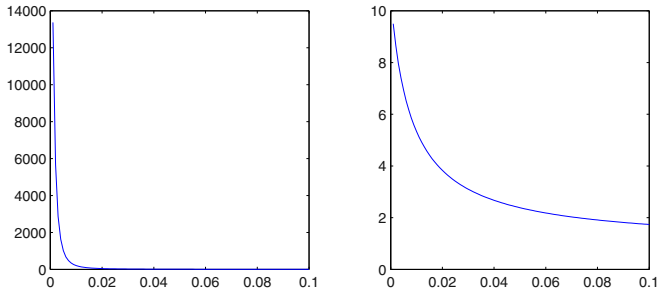

Fig. S6. x_v^* as a function of $x_v(0)$ in standard scale (*Left*) and logarithmic scale (*Right*). $\alpha = 1$, $\beta = 0$, $f_u = f_v = 2.5$, $p = 2$, $c = 0.1$, $b = 0.1$, $x_u(0) = 0.01$.

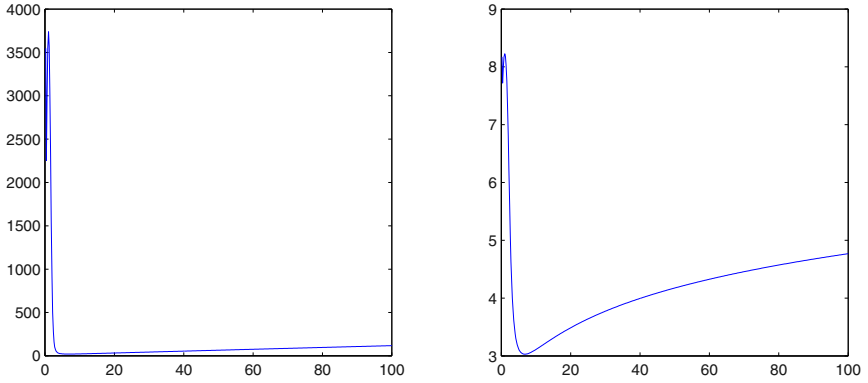

Fig. S7. x_v^* as a function of f_v in standard scale (*Left*) and logarithmic scale (*Right*). $\alpha = 1$, $\beta = 0$, $f_u = 2.5$, $p = 2$, $c = 0.1$, $b = 0.1$, $x_u(0) = x_v(0) = 0.01$.

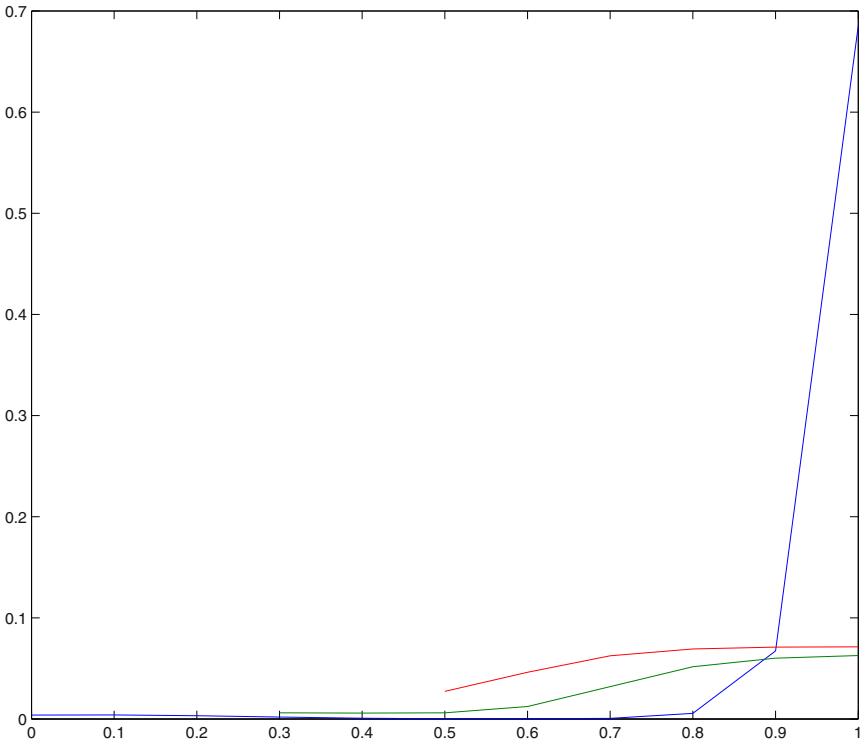

Fig. S8. The relation between x_v at the bottleneck and α. $\beta \in \{0, 0.2, 0.4\}$, $f_u = f_v = 2.5$, $p = 2$, $c = 0.1$, $b = 0.1$. The value for $\beta = 0$ is shown in blue, that for $\beta = 0.2$ in green, and that for $\beta = 0.4$ in red.

Table S1. Results of simulation of the model described by Eqs. 1 and 2 with random parameters

Rows	Average values
a)	9.832 (5.1130)
b)	1.436 (0.4922)
c)	0.056 (0.158)
d)	99.944 (0.158)
e)	18.931 (8.675)
f)	0.008 (0.050)
g)	94.023 (12.256)
h)	99.973 (0.175)
i)	50.871 (7.611)
j)	99.9999 (0.0002)
k)	13.280 (3.504)

Rows *a* and *b*, percentages of persistent and altruistic variants; rows *c* and *d*, total frequencies of immune responses associated with persistent and altruistic variants; rows *e* and *f*, probabilities of persistence for variants adjacent and nonadjacent to altruistic variants; row *g*, percentage of persistent variants without specific immune responses; rows *h* and *i*, percentages of persistent variants and all variants adjacent to altruistic variants; row *j*, total frequency of variants adjacent to altruistic variants; row *k*, ratio of average in-degrees of altruistic and nonaltruistic variants. Values in parentheses are SDs.