SUPPLEMENTARY INFORMATION

(Appendices A, B, and C)

Cumulative viral load, an indicator of virulence, is controlled by the host's immune response.

Yoh Iwasa, Akane Hara, and Shihomi Ozone

Appendix A.

Formula for the cumulative viral load

The basic model Eqs. (1a), (1b), and (1c) include six parameters. Here we derive an approximate formula for the cumulative viral load, defined as the time integral of the viral abundance until its clearance from the body.

In the initial state, $V(0) = \varepsilon$, where $\varepsilon > 0$ is a very small positive number, and $H(0) = 0$, $M(0) = 0$ hold. The solution depends on the choice of ε, but we focus on the limit when ε is very small ($\varepsilon \to 0$). Then, we have a single solution that depends only on six parameters in the model (a, b, c, r, ρ, and u). To reduce the number of parameters in the dynamical system, we introduce four modified variables: $\bar{V}$, $\bar{H}$, $\bar{M}$, and τ defined as follows:

$$\bar{V} = k_v V,\ \bar{H} = k_h H, \bar{M} = k_m M, \text{and } \tau = k_t t. \tag{A.1}$$

After some calculations, Eq. (1) can be rewritten as follows using Eq. (A.1).

$$\frac{d\bar{V}}{d\tau} = \frac{r}{k_t}\bar{V} - \frac{b}{k_t k_h}\bar{V}\bar{H} \tag{A.2a}$$

$$\frac{d\bar{H}}{d\tau} = \frac{ak_h}{k_v k_t}\bar{V} + \frac{qk_h}{k_m k_t}\bar{M} - \frac{c}{k_t}\bar{H} \tag{A.2b}$$

$$\frac{d\bar{M}}{d\tau} = \frac{uk_m}{k_v k_t}\bar{V} \tag{A.2c}$$

By choosing k_v, k_h, k_m, and k_t in the following manner, the number of parameters is reduced from six to two.

$$k_t = r,\ k_h = \frac{b}{r},\ k_m = \frac{qb}{r^2}\ \text{, and}\ k_v = \frac{qub}{r^3} \tag{A.3a}$$

$$\alpha = \frac{ak_h}{k_v k_t} = \frac{ar}{qu}\text{, and}\ \beta = \frac{c}{k_t} = \frac{c}{r} \tag{A.3b}$$

Using these parameters, Eq. (A.2) becomes Eq. (4) in text.

The time-integral of viral abundance is

$$\varphi = \int_0^\infty V(t)dt = \frac{1}{k_v k_t}\int_0^\infty \bar{V}(\tau)d\tau = \frac{r^2}{qub}\int_0^\infty \bar{V}(\tau)d\tau = \frac{r^2}{qub}\bar{M}(\infty) \quad . \tag{A.4}$$

Because Eq. (4) includes only two parameters, α and β, as defined in Eq. (A.3b), the value of $\bar{M}(\infty)$ should depend only on α and β. It can be written as $\bar{M}(\infty) = \psi(\alpha, \beta)$. Eq. (A.4) becomes

$$\varphi = \frac{r^2}{qub}\psi\left(\frac{qu}{ar}, \frac{c}{r}\right) \tag{A.5}$$

which is the formula for the cumulative viral load.

Appendix B

Simple formulas valid in four parameter regions

We consider the dynamics given by Eq. (4) in text. In the initial state, $\bar{H}(0) = \bar{M}(0) = 0$ hold, and $\bar{V}(0) = \bar{\varepsilon}$ is a small positive number. In the following, we are interested in the limit of $\bar{\varepsilon} \to 0$. The time integral of the virus number is

$$\int_0^\infty \bar{V}(\tau)d\tau = \bar{M}(\infty) = \psi(\alpha, \beta) \quad \text{(B.1)}$$

We would like to derive an approximate formula for this quantity. Because the model includes two parameters: α and β, it should be a function of these two parameters only. Because c is the mortality rate of cytotoxic T cells and its inverse $1/c$ is the mean longevity of cytotoxic T cells. A large c shortens the longevity of cytotoxic T cells and weakens immune reactions. We expect that the cumulative viral load should be an increasing function of $\beta = c/r$.

We can derive simplified formulas $\psi(\alpha, \beta)$ holding in four extreme cases: when α is very large or very small, and when β is very large or very small.

Case 1: β is very large and α is very small

When α is very small, we can neglect the term $\alpha\bar{V}$ in Eq. (4b) in text. Then according to Eq. (4b), $\bar{H}$ converge to the following value.

$$\bar{H} = \frac{\bar{M}}{\beta} \quad \text{(B.2)}$$

which is small but positive in magnitude. Using this value, Eqs. (4a) and (4c) become

$$\frac{d\bar{V}}{d\tau} = \bar{V} - \bar{V}\frac{\bar{M}}{\beta} \quad \text{(B.3a)}$$

$$\frac{d\bar{M}}{d\tau} = \bar{V} \quad \text{(B.3b)}$$

respectively. We consider the two-dimensional dynamics Eqs. (B.3a) and (B.3b). The trajectories on a $(\bar{V}, \bar{M})$-plane are as follows:

$$\frac{d\bar{V}}{d\bar{M}} = \frac{\frac{d\bar{V}}{d\tau}}{\frac{d\bar{M}}{d\tau}} = 1 - \frac{\bar{M}}{\beta} \tag{B.4}$$

We integrate this equation by $\bar{M}$ from $\bar{M}(0) = 0$ to $\bar{M}(\tau)$. We have:

$$\bar{V}(\tau) - \varepsilon = \bar{M} - \frac{\bar{M}^2}{2\beta} \tag{B.5}$$

In Eq. (3), in the limit when $\tau \to \infty$, $\bar{V}(\tau) \to 0$ holds. Hence, Eq. (B.5) indicates $\bar{M}(\tau) \to 2\beta$ for a very small ε. Hence, we have

$$\int_0^\infty \bar{V}(\tau) d\tau = \bar{M}(\infty) = 2\beta \tag{B.6}$$

This implies $\psi(\alpha, \beta) = 2\beta$.

Case 2: When β is very small, and α is larger than 1, it is not very large (compared with $1/\beta$)

Under these conditions, Eqs. (4a) and (4b) become

$$\frac{d\bar{V}}{d\tau} = \bar{V} - \bar{V}\bar{H} \tag{B.7a}$$

$$\frac{d\bar{H}}{d\tau} = \alpha\bar{V} \tag{B.7b}$$

We consider the two-dimensional dynamics Eqs. (B.7a) and (B.7b). We obtain the trajectory on an $(\bar{H}, \bar{V})$-plane that satisfies the following differential equation:

$$\frac{d\bar{V}}{d\bar{H}} = \frac{1}{\alpha} - \frac{1}{\alpha}\bar{H}. \tag{B.8}$$

Integration of Eq. (B.8) leads to

$$\bar{V} = \varepsilon + \frac{1}{\alpha}\bar{H} - \frac{1}{2\alpha}\bar{H}^2. \tag{B.9}$$

From this, we have $\bar{H}(\infty) = 2$, if the initial dose of the virus is small ($\varepsilon \to 0$). By integrating Eq. (B.7b), we obtain

$$\bar{H}(\infty) = \alpha \int_0^\infty \bar{V}(\tau) d\tau \quad , \tag{B.10}$$

which leads to

$$\int_0^\infty \bar{V}(\tau) d\tau = \frac{2}{\alpha} \quad . \tag{B.11}$$

This implies $\psi(\alpha, \beta) = \frac{2}{\alpha}$.

Case 3: Both β and α are large.

Under this condition, the dynamics of cytotoxic T cells, given by Eq. (4b), is very fast. They can suppress the excess increase in the peak viral abundance in the host. However, the increase in memory T cells is slower. Hence, we expect that $\bar{V}$ and $\bar{H}$ would converge to the quasi-equilibrium by the fast dynamics while $\bar{M}$ does not change much. The quasi-equilibrium can be obtained by setting Eq. (3a) and (3b) equal to zero.

$$0 = \bar{V} - \bar{V}\bar{H} \tag{B.12a}$$

$$0 = \alpha\bar{V} + \bar{M} - \beta\bar{H} \tag{B.12b}$$

which leads to $\bar{H} = 1$, $\bar{V} = \frac{1}{\alpha}(\beta - \bar{M})$. For each value of $\bar{M}$, the other two variables are determined. Then from Eq. (4c), the slow dynamics of $\bar{M}$ are given by

$$\frac{d\bar{M}}{d\tau} = \frac{1}{\alpha}(\beta - \bar{M}) \tag{B.13}$$

Eq. (B.13) shows that $\bar{M}(t)$ increases and converges to the following value:

$$\bar{M}(\infty) = \beta \tag{B.14}$$

This implies $\psi(\alpha, \beta) = \beta$.

Case 4: When both α and β are small.

Under this condition, Eq. (4b) becomes $d\bar{H}/dt = \bar{M}$. This, combined with Eqs. (4a) and (4c), provides a dynamical system without parameters. We performed the numerical integration of these dynamics, and we obtained

$$\psi(\alpha, \beta) = \bar{M}(\infty) \sim 1.306 \tag{B.15}$$

Appendix C

Regression analysis of parameter sensitivity

We performed a sensitivity analysis of φ, the time-integral of viral abundance, on six parameters (a, r, b, c, q, and u), using Python package scikit-learn 0.23.1 (Pedregosa et al., 2011), function sklearn.linear_model.LinearRegression. Because $\varphi = \frac{r^2}{qub}\psi\left(\frac{ar}{qu}, \frac{c}{r}\right)$ holds, the parameter dependence is known from the effect via factor $\frac{r^2}{qub}$, and additionally the effect through $\frac{ar}{qu}$ and through $\frac{c}{r}$. Hence, the sensitivity to a particular parameter could be different if $\alpha = \frac{ar}{qu}$ and $\beta = \frac{c}{r}$ are different. We chose the range of α and β as wide as possible. To be specific, we adopted $\alpha = 2^{2i}$ and $\beta = 2^{2j}$ $(i, j = -3, -2, -1, 0, 1, 2, 3)$. Hence, we have $log_2\alpha = 2i$ and $log_2\beta = 2j$ $(i, j = -3, -2, -1, 0, 1, 2, 3)$. To realize these combinations, there are many ways to chose six parameters (a, r, b, c, q, and u). We here chose the following manner as one example:

$log_2 a = \frac{1}{2}i$, $log_2 r = \frac{1}{2}i$, $log_2 q = -\frac{1}{2}i$, $log_2 u = -\frac{1}{2}i$. and $log_2 c = \frac{1}{2}i + 2j$

Then we have

$$log_2\alpha = log_2 a + log_2 r - log_2 q - log_2 u = 2i$$

$$log_2\beta = log_2 c - log_2 r = \frac{1}{2}i + 2j - \frac{1}{2}i = 2j$$

This is the way to generate the standard vales used in Fig. 4.

The parameter sensitivity of the cumulative viral load is represented in terms of elasticity; elasticity to parameter k is defined as $c_k = \partial ln\varphi/\partial lnk = (k/\varphi)(\partial\varphi/\partial k)$. Elasticity differs between the parameter regions (specifically, α and β). Fig. 4 illustrates the values of elasticity for different combinations of α and β, obtained numerically by multivariate analysis (see the text for explanation). These

results are close to those predicted by the four explicit formulas for the cumulative viral load.

However, the elasticity for an intermediate parameter values is not the one intermediate between the extreme values (see text for details). Fig. S1 clearly illustrates this pattern.

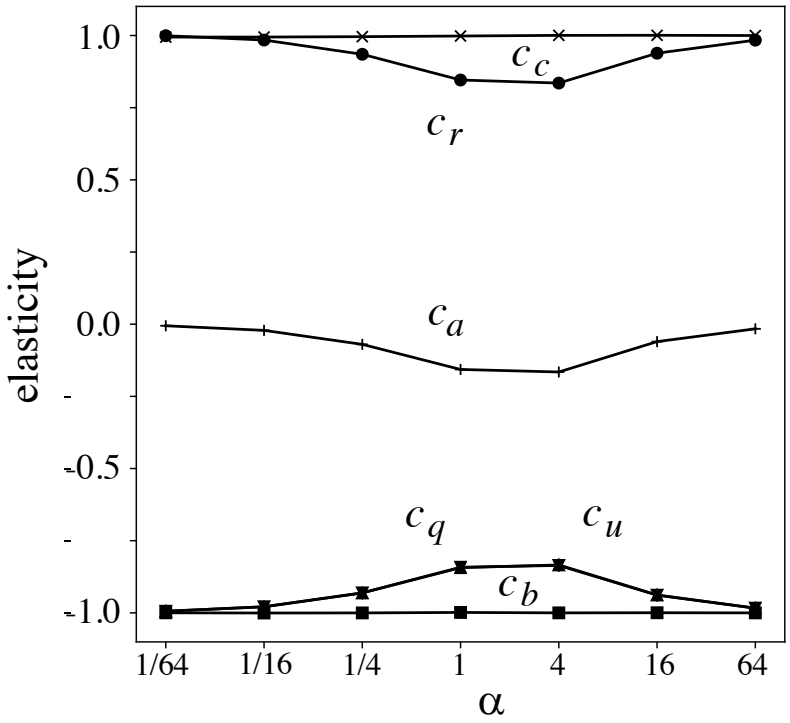

Figure S1 Elasticity of φ to six different parameters, obtained numerically by regression in a close neighborhood of a standard parameter set. They depend on the choice of α and β, corresponding to the standard parameter set. Horizontal axis is for the value of α. Elasticity is close to the one predicted by four formulas (very large or very small α), but they may show nonmonotonic dependence on α. We fixed $\beta = 64$.

Reference of Supplementary Information:

[SI-1] Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., & Duchesnay, É. (2011). Scikit-Learn: machine learning in Python. J. Mach. Learn. Res., 12, 2825–2830.