Dynamics of Recurrent Viral Infection – Supplementary Material

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1 Effects of Viral Infectivity

We explored the effect of antibody efficacy, \( k \), on the period of recurrence, \( T \), for viruses with different infectivities, \( \beta \). We numerically determined the length of the period, \( T \), for a range of values of \( \beta \) and \( k \). Figure 1 demonstrates that \( T \) increases as the infectivity decreases; the period is longer for viruses that infect new cells less efficiently. We also see that if the infectivity is relatively low and the antibody efficacy is high, the period between recurrences can be long. In particular, we can prove that the period approaches infinity if we make the assumption that the virus does not decay \((q = 0); this assumption is mathematically convenient but physiologically unjustified.\)

Mathematically, although we omit the proof here, when \( q = 0 \) the leading eigenvalue at the Hopf bifurcation described in the paper is also equal to zero. This "zero-frequency" Hopf bifurcation (or Takens-Bogdanov bifurcation (Perko 2001)) occurs at a critical value of the infectivity \( \beta_c \); for \( \beta < \beta_c \) the virus will be cleared. As \( \beta \) approaches \( \beta_c \) from above, however, the period \( T \) approaches infinity. Thus \( T \) can be arbitrarily long and can certainly be longer than the lifespan of the host. For the more realistic case when \( q > 0 \), the period is bounded (does not approach infinity), but numerical results indicate that \( T \) can be very long in this case as well.

We also examine the interaction between CTL efficacy, \( p \), and viral infectivity, \( \beta \). Figure 2 illustrates that \( T \) gradually decreases with increasing CTL response, and decreases markedly with increasing infectivity. If both infectivity and CTL efficacy are low, the period between recurrences can be long.

Finally, we demonstrate that the effect of the memory response on \( T \) is robust across a range of viral infectivities, \( \beta \). This result is illustrated in Figure 3. Thus, our model predicts, perhaps counter-intuitively, that a larger population of memory T cells results in more frequent, less severe recurrent infections. When \( z_M \) is increased further, recurrent episodes are no longer observed, and the system remains in a virus-persistent equilibrium state.
Figure 1: The period between recurrences depends on the infectivity of the virus ($\beta$) and the efficacy of the antibody response ($k$). Other parameters are as provided for Figure 1 in the main paper.

Figure 2: The period between recurrences depends on the infectivity of the virus ($\beta$) and the efficacy of the CTL response ($p$). Other parameters are as provided for Figure 1 in the main paper.
Figure 3: The period between recurrences, $T$, decreases when the memory T cell population, $z_M h$, increases. The change in $T$ is robust across a range of viral infectivities, $\beta$. Other parameters are as provided for Figure 1 in the main paper.

2 Fluctuations in host health can trigger recurrence.

We model the overall effects of fluctuations in host health by adding a stochastic component to one or more of the populations in our basic model during numerical integration. For example, we let $z(t)$ be $z(t) + \sigma n(t)$, where $n(t)$ is an additive white noise term (that is, $n(t) \in [0, 1]$, the expected value of $n(t) = 0.5$ and $< n(t) n(t') > = \delta(t-t')$). Thus $n(t)$ models random reductions in the CTL population due to exogenous factors, and $\sigma$ scales the magnitude of the fluctuations. Similarly, we perturb the population of infected cells such that $y(t)$ becomes $y(t) + \sigma n(t)$.

Typical results obtained after the inclusion of the noise term are displayed in Fig. 4. The solid line illustrates the noise-free behaviour, with recurrent episodes happening at exactly regular intervals. In contrast, when a small amount of random noise is added to the system (dotted line), recurrent episodes happen more frequently, and with less regularity. It is also interesting to note that these episodes, when triggered, are less severe.

3 Alternative Model Assumptions

A number of the assumptions in our model may have other plausible alternatives. We must therefore establish the extent to which the main results and predictions of our model are sensitive to these
Figure 4: The population of infected cells, with (dotted line) and without (solid line) additive random noise. (a) Infected cells are additively perturbed in the form $y + \sigma n$ and (b) CTLs are perturbed in the form $z + \sigma n$; in both cases $\sigma = 10^{-4}$. The other parameter values are as for Fig. 1 in the main paper, except that $k = 10^{-4}$ particle$^{-1}$ $\mu$L day$^{-1}$.

assumptions. We investigated a series of alternative models, as described in detail below. In every case we observed: (a) recurrent infection without the need for an exogenous trigger; (b) the period of recurrence increases with increasing antibody efficacy; (c) the period of recurrence decreases with increasing CTL efficacy.

Throughout sections 3.1 through 3.4, we will for convenience refer to the model investigated in detail in the paper as “Model 1”:

$$
\begin{align*}
\dot{x} &= \lambda - dx - \beta xv \\
\dot{y} &= \beta xv - ay - pyz \\
\dot{z} &= cyz - bz + hyz_M \\
\dot{u} &= \xi z - \eta u - kwv \\
\dot{v} &= cy - kwv - \gamma xv - qv
\end{align*}
$$

Here $x$, $y$, $z$, $u$, $v$ are the populations of uninfected cells, infected cells, CTLs, antibodies and free virions respectively.

### 3.1 CTL proliferation

In Model 1 we use the term $cyz$ to model the proliferation of activated CTL. While this form has been suggested by other authors, several alternative assumptions have also been proposed in the
literature. In “Model 2”, we assume density-dependent CTL proliferation, following DeBoer et al. (1995).

\[
\begin{align*}
\dot{x} & = \lambda - dx - \beta xv \\
\dot{y} & = \beta xv - ay - pyz \\
\dot{z} & = \frac{c_1y_0z}{c_2 + y + z} - bz + hyz_M \\
\dot{u} & = \xi z - \eta u - kuw \\
\dot{v} & = ey - kuv - \gamma xv -qv
\end{align*}
\] (2)

Results for this model are illustrated in Figures 5 and 6. These figures illustrate that observations (a), (b) and (c) described above are clearly unaffected by this change in the model assumptions. In Figure 7, we show that the period between recurrent episodes, T, and the peak infected cell population, \(y_{\text{max}}\), differ only slightly between Model 1 and Model 2.

![Diagram](image)

**Figure 5:** The period between recurrent episodes decreases with infectivity of the virus (\(\beta\)) and increases with efficacy of the antibody response (\(k\)). Results from Model 2, with \(c_1 = 15\text{day}^{-1}\) and \(c_2 = 10^3\) cells/\(\mu\text{L}\). Other parameters are as provided for Figure 4 in the paper.

We also investigated the dependence of this behaviour on the choice of parameters, paying particular attention to \(c_2\) in Model 2. This parameter reflects the richness of the resource required for proliferation (e.g. how “stiff” the competition for cytokines may be). We observed recurrent episodes whenever \(c_2\) was sufficiently large; when \(c_2\) is very small (few cytokines available), we instead observe the virus-persistent equilibrium (data not shown). This is not surprising since in this case an insufficient CTL response allows the virus to persist.

Finally, we investigated an alternate model of CTL proliferation, as suggested by Wodarz et al.
Figure 6: The period between recurrent episodes decreases with the efficacy of the CTL response ($p$). Model 2, parameters as provided for Figure 5.

Figure 7: (a) The period between recurrent episodes, $T$, and (b) the peak number of infected cells, $y_{\text{max}}$, are fairly insensitive to the terms used to describe CTL proliferation. Solid lines are results predicted by Model 1, broken lines for Model 2.
(1999):
\[
\begin{align*}
\dot{x} & = \lambda - dx - \beta xv \\
\dot{y} & = \beta xv - ay - pyz \\
\dot{z} & = \frac{c_1wz}{c_2 + z} - bz + hyz_M \\
\dot{u} & = \xi z - \eta u - kuv \\
\dot{v} & = ey - kuv - \gamma xv - qv
\end{align*}
\] 

Results for Model 3 were again very similar to those observed for Model 2. As an example we show the dependence of the period of recurrence on the efficacy of the antibody response in Figure 8.

Figure 8: The period between recurrent episodes decreases with infectivity of the virus ($\beta$) and increases with efficacy of the antibody response ($k$). Results from Model 3, with $c_1 = 15 \text{day}^{-1}$ and $c_2 = 10^3 \text{cells/\mu L}$. Other parameters are as provided for Figure 4 in the paper.

### 3.2 Uninfected cell proliferation

The simplest possible assumption regarding target cell production is that cells are produced at a constant rate $\lambda$ from some pool of precursors. We investigated the sensitivity of our results to this assumption by adding target cell proliferation at a density-dependent rate, where the density in question is given by the total population of uninfected and infected target cells. This gives Model
The production and proliferation term is in the form suggested by Wodarz et al. (1999).

\[
\begin{align*}
\dot{x} &= (\lambda + gx)(1 - \frac{x+y}{N}) - dx - \beta xv \\
\dot{y} &= \beta xv - ay - pyz \\
\dot{z} &= cyz - bz + hyz_M \\
\dot{u} &= \xi z - \eta u - kuv \\
\dot{v} &= ey - kuv - \gamma xv - qv
\end{align*}
\]

(4)

Once again we observe recurrent viral episodes separated by long periods of relative quiescence. Figures 9 and 10 demonstrate that the main conclusions of our study are insensitive to the precise model of target cell proliferation.

![Figure 9: The period between recurrent episodes decreases with infectivity of the virus ($\beta$) and increases with efficacy of the antibody response ($k$). Results from Model 4, with proliferation rate $g = 4d$ and carrying capacity $N = 10^{-3}\text{cells}uL^{-1}$. Other parameters are as provided for Figure 4 in the paper.](image-url)
Figure 10: The period between recurrent episodes decreases with the efficacy of the CTL response \((p)\). Model 4, parameters as provided for Figure 9 above.

3.3 B cells

We also investigated the possibility of including B cells explicitly in the model, with antibody production proportional to the total B cell population:

\[
\begin{align*}
\dot{x} &= \lambda - dx - \beta xv \\
\dot{y} &= \beta xv - ay - pyz \\
\dot{z} &= ayz - bz + hyzM \\
\dot{u} &= \xi B - \eta u - kuv \\
\dot{B} &= c_{3y}B - b_{1}B + h_{1}yB_{M} \\
\dot{v} &= ey - kuv - \gamma xv - qv
\end{align*}
\]  

Here \(B\) is the population of activated B cells. These die at constant per capita rate \(b_{1}\), and proliferate at a rate proportional to the population of infected cells. In Model 5 above, we assume that any decay in the population of memory B cells, \(B_{M}\), over the time period of interest is negligible. Thus \(B_{M}\), like \(z_{M}\), is a constant, and this population of memory B cells becomes activated at a rate proportional to the population of infected cells, \(h_{1}y\). (For alternative assumptions regarding memory B and T cells, see the next section.)

The explicit inclusion of B cells in Model 5 did not change our observation of recurrent episodes, nor did it change the relations between CTL efficacy, antibody efficacy and the period of recurrence. Results obtained for Model 5 are shown in Figures 11 and 12.
Figure 11: The period between recurrent episodes increases with the efficacy of the antibody response \((k)\). Model 5, with \(h = 10^{-4}\text{day}^{-1}, \ h_1 = 0.8h, \ c_3 = 0.8c\) and \(b_1 = 1.2b\); other parameters as provided for Figure 1 in the paper.

Figure 12: The period between recurrent episodes decreases with the efficacy of the CTL response \((p)\). Model 5, parameters as provided for Figure 11 above.
3.4 Memory T and B cells

Model 1 assumes that memory T and B cells exist at constant levels throughout the time period of interest. These memory cells are activated at a rate proportional to the population of infected cells. We thus neglect the natural death rate of the memory cells, and also the decrease in the memory cell population as memory cells are activated during recurrent viral episodes. To capture these effects, we examined Model 6:

\[
\begin{align*}
\dot{x} &= \lambda - dx - \beta xv \\
\dot{y} &= \beta xv - ay - pyz \\
\dot{z} &= cyz - bz + hyz_M \\
\dot{z}_M &= -f_1z_M - hyz_M \\
\dot{u} &= \xi B - \eta u - kuv \\
\dot{B} &= c_1yB - b_2B + h_2yB_M \\
\dot{B}_M &= -f_2B_M - h_2yB_M \\
\dot{v} &= ey - kuv - \gamma xv - qv
\end{align*}
\] (6)

Here $z_M$ and $B_M$ are the memory T and B cells, respectively. To model primary infection, these populations are both set to zero. To model recurrent infection, we start with a large initial population of memory T and B cells. This population gradually declines over the lifetime of the patient, through natural death rates $f_1$ and $f_2$, which may be very small (i.e. the lifetime of the memory cells can be long, as long as the lifetime of the host). The memory cell populations are also diminished as the memory cells differentiate into CTL and activated B cells.

Like the other simpler models we have considered, Model 6 exhibits recurrent viral episodes, punctuated by long periods of relative quiescence. For Model 6, however, the system exhibits “quasi-periodic oscillations”, meaning that both the period $T$ and the peak number of infected cells, $y_{max}$ are not constant but either slightly increase or slightly decrease over time.

In Figure 13, we demonstrate the average length of the period between recurrent episodes, as a function of the decay rate of the memory T and B cell populations.

Model 6 is somewhat cumbersome; we have increased to eight populations and nineteen parameters. This model however still neglects the possibility that new memory B and T cells may be produced during the apoptosis events at the end of each recurrent episode.

In all of the models described above, we assume that CTLs differentiated from memory T cells are indistinguishable from those deriving from the activation of naïve T cells. We tested the effects of
Figure 13: The average period between recurrent episodes either increases or decreases slightly with the decay of memory B and T cells. Results from Model 6, with $h_2 = h = 10^{-4} \mu$Lcell$^{-1}$day$^{-1}$, $c_1 = 1.2c$, $b_2 = 0.8b$ and the initial value of $z_M = B_M = 100$cells$\mu$L$^{-1}$. The other parameters are as provided for Figure 1 in the paper.

this assumption in Model 7:

$$
\begin{align*}
\dot{y} &= \beta xy - ay - py(z + z_m) \\
\dot{z} &= cyz - bz \\
\dot{z}_m &= c_my_zm(1 - \frac{z_m}{K_z}) - b_1z_m \\
\dot{u} &= \xi(B + B_m) - \eta u - kwv \\
\dot{B} &= c_1yB - b_2B \\
\dot{B}_m &= c_2yB_m(1 - \frac{B_m}{K_B}) - b_3B_m
\end{align*}
$$

(7)

Here $z_m$ and $B_m$ are activated T and B cells which have been produced by differentiation from memory T and B cells respectively. For the parameters, we take $c_m = c_2 = 2c$ so that the reactivation of memory cells is much faster than the naive CTL and B cells, and $b_1 = b_3 = 0.8b$ so that the lifespan of activated cells differentiated from memory cells is a little longer than that of activated cells differentiated from naive T and B cells. We also set $c_1 = 0.8c$ and $b_2 = 1.2b$ so that activated B cells will be fewer than activated CTLs; this is likely because recurrence often happens in B-cell or antibody immunodeficiency. The proliferation rates of $z_m$ and $B_m$ are resource-limited; this may reflect a number of possible limitations on the growth of these populations, including a limited number of memory T and B cells. $K_z$ and $K_B$ are the carrying capacities of $z_m$ and $B_m$ respectively. We set $K_z = K_B = 5$ because the maximum population of CTL without the contribution of memory cells is around 100 cells/$\mu$L and the maximum population of memory
cells is about 10% of this peak. We assume that the maximum population of CTL and B cells
differentiated from these memory cells must be less than this value.

Figures 14 and 15 demonstrate that once again, recurrency exists and the period $T$ is a little
shorter than that observed in Model 1. We note, however, that when either $K_B$ or $K_z$ are very
large, recurrency disappears (data not shown). This supports the clinical observation that recurrent
episodes are more likely to occur when memory cells are deficient.

We also note from Figure 15 that the period between recurrent episodes decreases with CTL efficacy
in Model 7, agreeing with previous results, as long as the the infectivity $\beta$ is not too low. When
$\beta$ is very small, however, we observe an increase in period with increasing $p$. This is presumably
related to the fact that in this parameter range, CTL differentiated from memory T cells play an
ever increasing role in host defense. We have assumed that such cells are longer-lived than CTL
differentiated from naive T cells, thus the period may increase slightly as the contribution of $z_M$
increases. Since the increases in the period are very small, however (less than 5%), the biological
relevance of this scenario is unclear.

![Graph](image)

Figure 14: The period between recurrent episodes increases with efficacy of the antibody response
($k$). Results from Model 7, with parameters as described in the text and in Figure 4 of the paper.

4 Discussion

The predictions of our model are also supported by some recent anecdotal results. Larghi et al.
(2003) report an intriguing case of hepatitis B virus (HBV) reactivation 8 years after kidney trans-
plantation. Although patients who have recovered from primary HBV infection usually obtain
Figure 15: The period between recurrent episodes decreases with the efficacy of the CTL response ($p$). Model 7, parameters as provided for Figure 14.

lifetime immunity, in this case the recurrence after 8 years of quiescence proved fatal. Although anecdotal, this case is clearly consistent with our model, suggesting that (i) the primary HBV infection was not completely cleared, and the patient was likely in some state of virus-persistent equilibrium before the transplant operation (ii) large perturbations to the immune system (in this case, immune suppression for a transplant operation) may have decreased immunological pressure and moved the system from a stable virus-persistent equilibrium to a state exhibiting cycles of viral production with a long (8 year) period (iii) the recurrent episode which occurred after this long period was extremely severe.

Finally, given Figure 6 in the main paper, we can speculate regarding the existence of two different defense strategies for the host: if perpetual low-grade viral production can be tolerated, then more frequent, less severe recurrent episodes would be preferable (left-hand side of the figure); alternatively, immunological pressure could be increased such that the interval between recurrent episodes is extended beyond the host lifespan. Similarly, higher peak levels of viral shedding may be advantageous to many viruses, allowing renewal of the latent virus pool and transmission to new hosts. Other viruses, however, may maximize their overall transmission through more frequent, less severe viral episodes.
References


