Synopses

**A Mathematical Model and CD4+ Lymphocyte Dynamics in HIV Infection**

Appendix

The model considers immature and mature CD4+ (\( \tilde{P} \) and \( P \) cells) and CD8+ lymphocytes (\( \tilde{R} \) and \( R \) cells). As normal values of \( R \) cells equal about two thirds of those of \( P \) cells, it is assumed that normal \( R \) values correspond in a similar way to 2/3 of \( P \) cells. The sizes of these cell compartments at time \( t \) are described by Eqs. (1)(4). The amount of HIV products at time \( t \) is given by Eq. (5). Finally, Eq. (6) gives the number of cytotoxic T cells specific for HIV (\( C \) cells) at time \( t \). In the model used, these cells both limit proliferation of HIV, as indicated in Eq. (5), and effect destruction of CD4+ cells presenting HIV products according to Eqs. (1)(2).

\[
\begin{align*}
\frac{d\tilde{P}(t)}{dt} &= \frac{I_P + f[(\tilde{P}_0 - \tilde{P}(t)) + (\tilde{R}_0 - \tilde{R}(t))] - \tilde{P} \tilde{P}(t) - \varepsilon \alpha(t)C(t)\tilde{P}(t),}{d(t)} \\
\tilde{P}(0) &= \tilde{P}_0
\end{align*}
\]

(1)

\[
\begin{align*}
\frac{dP(t)}{dt} &= \frac{\tilde{P}\tilde{P}(t) - \varepsilon \tilde{P}(t) - \varepsilon \alpha(t)C(t)\tilde{P}(t),}{d(t)} \\
P(0) &= P_0
\end{align*}
\]

(2)

\[
\begin{align*}
\frac{d\tilde{R}(t)}{dt} &= \frac{2}{3} \frac{I_P + f[(\tilde{P}_0 - \tilde{P}(t)) + (\tilde{R}_0 - \tilde{R}(t))] - \varepsilon \tilde{R}\tilde{R}(t),}{d(t)} \\
\tilde{R}(0) &= \frac{2}{3} \tilde{R}_0
\end{align*}
\]

(3)

\[
\begin{align*}
\frac{d\tilde{R}(t)}{dt} &= \frac{2}{3} \frac{I_P + f[(\tilde{P}_0 - \tilde{P}(t)) + (\tilde{R}_0 - \tilde{R}(t))] - \varepsilon \tilde{R}\tilde{R}(t),}{d(t)} \\
\tilde{R}(0) &= \frac{2}{3} \tilde{R}_0
\end{align*}
\]

(4)

\[
\begin{align*}
\frac{da(t)}{dt} &= a(t)[\theta - \zeta \gamma C(t)], \\
a(0) &= a_0
\end{align*}
\]

(5)

\[
\begin{align*}
\frac{dC(t)}{dt} &= \lambda a(t)[\sigma_c + \alpha C(t)] \left( \frac{P(t)}{P_0} \right)^\gamma - (\tau_c - P_c)C(t), \\
C(0) &= C_0
\end{align*}
\]

(6)

where the influx-constraining function was

\[
d(t) = \begin{cases} 
1 & \text{if } \ln \frac{a(t)}{a(0)} < L \\
\frac{h \ln a(t)}{a_0} & \text{if } \ln \frac{a(t)}{a(0)} \geq L 
\end{cases}
\]

(7)
Here $I_P$ is the influx of $P$ cells, i.e., the rate (all rates are in days$^{-1}$) of differentiation of $P$ cells from stem cells, $r_P$ is the rate of maturation of $P$ cells into $P$ cells, and $r_P$ is the rate of natural death of $P$ cells; the quantities $r_R$ and $r_R$ are defined in a fully analogical way. Further, $f$ is the amplifying coefficient of the linear feedback effect of $P$ and/or $R$ cell decrease on the influx of $P$ and $R$ cells at time $t$.

The quantity $\xi_P a(t)C(t)$ is the rate of elimination of $P$ cells due to the amount of HIV products $a(t)$ and the number of cytotoxic T cells $C(t)$ at time $t$. Analogously, $c_P a(t)C(t)$ is the rate of elimination of $P$ cells. The value $a_0$ is the function of the infectious dose of HIV, $b$ characterizes the growth rate of HIV, and $\gamma$ is the rate of inactivation of HIV products mediated by cytotoxic $C$ cells. The maturation of these cells from their precursors is assumed to be dependent on the encounter with HIV products and the effect of HIV specific helper T cells. $I_C$ is the influx of $C$ cell precursors, $r_C$ their maturation rate, $\alpha$ the proliferation rate of $C$ cells under the antigenic stimulation by HIV products and helper T cell influence, and $r_C$ their natural death rate. Helper T cell effect on maturation and proliferation of $C$ cells is expressed by the ratio $P(t)/P_0$; the coefficient $v$ is introduced to characterize the intensity of this helper effect. The value $h$ characterizes HIV-constraining intensity on the $P$ and $R$ cell influx. Value $L$ defines the level, where such constraining (limiting) effect of $d(t)$ starts. Effects of therapeutic interventions are described by the following parameters: $\zeta$-HIV elimination rate by AZT or passive immunization, $\lambda$-immune response-enhancing factor, and $P_R$ and $P_C$-elimination rates of CD8+ and $C$ cells, respectively, by anti-CD8 antibodies.

If not otherwise stated, the model parameters in simulation runs were selected as follows: $r_P = 0.2$, $\tau_P = 0.01$, $r_R = 0.01$, $\tau_C = 0.01$, $I_P = 1.0$, $I_C = 0.2$, $\xi_P = 5.0$, $P_0 = 100.0$, $R_0 = 3.33$, $\xi_C = 66.7$, $C_0 = 0.0$, $a_0 = 0.0005$, $f = 0.01$, $\alpha = 0.7$, $\varepsilon = 0.512$, $\gamma = 0.3$, $\beta = 0.02$, $v = 1.6$, $h = 3.5$, $L = 3.0$. Only mature CD4+ lymphocytes were assumed to be susceptible to HIV products, i.e. $\xi_P = 0.0$, $p = 20.0$. As a rule, the parameter $e$ was used for final adjustment of the respective simulation run. If no therapeutic interventions are assumed ($\lambda = 1.0$, $\xi = 0.0$, $P_R = 0.0$, $P_C = 0.0$), the resulting CD4+ standard curve characterizes best fit of the observed clinical data.