A Mathematical Model and CD4+ Lymphocyte Dynamics in HIV Infection

Appendix

The model considers immature and mature CD4+ (R and P cells) and CD8+ lymphocytes (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).

\[
\frac{d\bar{P}(t)}{dt} = I_P + f[(P_0 - \bar{P}(t)) + (R_0 - \bar{R}(t))] \frac{\bar{P}(t) - \gamma a(t)C(t)\bar{P}(t)}{d(t)} - \frac{\bar{P}(0) = \bar{P}_0}{d(t)}
\]

\[
\frac{dP(t)}{dt} = \frac{\bar{P}(t) - \bar{P}(t)}{d(t)} - \frac{\bar{P}(0) = \bar{P}_0}{d(t)}
\]

\[
\frac{d\bar{R}(t)}{dt} = 2 \frac{I_P + f[(P_0 - \bar{P}(t)) + (R_0 - \bar{R}(t))]}{d(t)} - \frac{2}{\gamma} \frac{\bar{R}(t)}{d(t)}
\]

\[
\frac{d\bar{R}(t)}{dt} = \frac{I_P + f[(P_0 - \bar{P}(t)) + (R_0 - \bar{R}(t))]}{d(t)} - \frac{2}{\gamma} \frac{\bar{R}(t)}{d(t)}
\]

\[
\frac{da(t)}{dt} = \frac{a(t)[\theta - \zeta \gamma C(t)]}{d(t)} - \frac{a(0) = a_0}{d(t)}
\]

\[
\frac{dC(t)}{dt} = \lambda a(t)[\sigma + \alpha C(t)] \left( \frac{P(t)}{P_0} \right)^v - (\tau_c - \rho_c)C(t), \quad C(0) = C_0
\]

where the influx-constraining function was

\[
d(t) = \begin{cases} 
1 & \text{if } \ln \left(\frac{a(t)}{a_0}\right) < L \\
\ln \left(\frac{a(t)}{a_0}\right) & \text{if } \ln \left(\frac{a(t)}{a_0}\right) \geq L
\end{cases}
\]
Here $I_p$ is the influx of $\bar{P}$ cells, i.e., the rate (all rates are in $\text{days}^{-1}$) of differentiation of $\bar{P}$ cells from stem cells, $\tau_p$ is the rate of maturation of $\bar{P}$ cells into $P$ cells, and $\tau_R$ is the rate of natural death of $\bar{P}$ cells; the quantities $\tau_R$ and $\tau_C$ are defined in a fully analogical way. Further, $f$ is the amplifying coefficient of the linear feedback effect of $\bar{P}$ and/or $R$ cell decrease on the influx of $\bar{P}$ and $\bar{R}$ cells at time $t$.

The quantity $\bar{c}_{pa}(t)C(t)$ is the rate of elimination of $\bar{P}$ cells due to the amount of HIV products $a(t)$ and the number of cytotoxic T cells $C(t)$ at time $t$. Analogously, $\bar{c}_{pa}(t)C(t)$ is the rate of elimination of $P$ cells. The value $\alpha_0$ is the function of the infectious dose of HIV, $\beta$ 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, $\sigma$ their maturation rate, $\alpha$ the proliferation rate of $C$ cells under the antigenic stimulation by HIV products and helper T cell influence, and $\tau_C$ their natural death rate. Helper T cell effect on maturation and proliferation of $C$ cells is expressed by the ratio $\rho_0/\rho_0$; the coefficient $v$ is introduced to characterize the intensity of this helper effect. The value $h$ characterizes HIV-constraining intensity on the $\bar{P}$ and $\bar{R}$ 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 $R_{pR}$- and $R_{pC}$-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: $\tau_p = 0.2$, $\nu_p = 0.01$, $\tau_R = 0.2$, $\tau_C = 0.01$, $\tau_C = 0.01$, $I_p = 1.0$, $I_C = 0.2$, $\rho_0 = 5.0$, $\rho_0 = 100.0$, $\rho_0 = 3.33$, $\rho_0 = 66.7$, $C_0 = 0.0$, $a_0 = 0.0005$, $f = 0.01$, $\alpha = 0.7$, $\varepsilon = 0.512$, $\gamma = 0.3$, $\beta = 0.02$, $v = 1.6$, $h = 3.5$, $L = 3.0$. Only mature CD4+ lymphocytes were assumed to be susceptible to HIV products, i.e. $\bar{c}_p = 0.0$, $\rho = 20.0$. As a rule, the parameter $e$ was used for final adjustment of the respective simulation run. If no therapeutic interventions are assumed ($\lambda = 1.0$, $\zeta = 0.0$, $\rho_R = 0.0$, $\rho_C = 0.0$), the resulting CD4+ standard curve characterizes best fit of the observed clinical data.