

Synopses

A Mathematical Model and CD4+ Lymphocyte Dynamics in HIV Infection

Appendix

The model considers immature and mature CD4+ (\bar{P} and P cells) and CD8+ lymphocytes (\bar{R} and R cells). As normal values of R cells equal about two thirds of those of P cells, it is assumed that normal \bar{R} values correspond in a similar way to $2/3$ of \bar{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).

$$\frac{d\bar{P}(t)}{dt} = \frac{I_P + f[(P_0 - P(t)) + (R_0 - R(t))]}{d(t)} - \tau_P \bar{P}(t) - \bar{c} P a(t) C(t) \bar{P}(t), \quad \bar{P}(0) = \bar{P}_0 \quad (1)$$

$$\frac{dP(t)}{dt} = \tau_P \bar{P}(t) - \tau_P P(t) - c P a(t) C(t) P(t), \quad P(0) = P_0 \quad (2)$$

$$\frac{d\bar{R}(t)}{dt} = \frac{2}{3} \frac{I_P + f[(P_0 - P(t)) + (R_0 - R(t))]}{d(t)} - \tau_R \bar{R}(t), \quad \bar{R}(0) = \frac{2}{3} \bar{P}_0 \quad (3)$$

$$\frac{dR(t)}{dt} = \tau_R \bar{R}(t) - (\tau_R - \rho_R) R(t), \quad R(0) = \frac{2}{3} P_0 \quad (4)$$

$$\frac{da(t)}{dt} = a(t) [\theta - \zeta - \gamma C(t)], \quad a(0) = a_0 \quad (5)$$

$$\frac{dC(t)}{dt} = \lambda a(t) [\epsilon I_c + \alpha C(t)] \left(\frac{P(t)}{P_0} \right)^v - (\tau_c - \rho_c) C(t), \quad C(0) = C_0 \quad (6)$$

where the influx-constraining function was

$$d(t) = \begin{cases} 1 & \text{if } \ln \frac{a(t)}{a_0} < L \\ h \ln \frac{a(t)}{a_0} & \text{if } \ln \frac{a(t)}{a_0} \geq L \end{cases} \quad (7)$$

Here I_P is the influx of \bar{P} cells, i.e., the rate (all rates are in days⁻¹) of differentiation of \bar{P} cells from stem cells, $\bar{\tau}_P$ is the rate of maturation of \bar{P} cells into P cells, and τ_P is the rate of natural death of P cells; the quantities $\bar{\tau}_R$ and τ_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 \bar{P} and \bar{R} cells at time t .

The quantity $\bar{e}_P a(t) C(t)$ 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, $c_P a(t) C(t)$ is the rate of elimination of P cells. The value a_0 is the function of the infectious dose of HIV, θ characterizes the growth rate of HIV, and γ 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, ϵ their maturation rate, α the proliferation rate of C cells under the antigenic stimulation by HIV products and helper T cell influence, and τ_C their natural death rate. Helper T cell effect on maturation and proliferation of C cells is expressed by the ratio $\bar{P}(t)/\bar{P}_0$; the coefficient ν 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: ζ - HIV elimination rate by AZT or passive immunization, λ - immune response-enhancing factor, and ρ_R - and ρ_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: $\bar{\tau}_P = 0.2$, $\tau_P = 0.01$, $\bar{\tau}_R = 0.2$, $\tau_R = 0.01$, $\tau_C = 0.01$, $I_P = 1.0$, $I_C = 0.2$, $\bar{P}_0 = 5.0$, $P_0 = 100.0$, $\bar{R}_0 = 3.33$, $R_0 = 66.7$, $C_0 = 0.0$, $a_0 = 0.0005$, $f = 0.01$, $\alpha = 0.7$, $\epsilon = 0.512$, $\gamma = 0.3$, $\theta = 0.02$, $\nu = 1.6$, $h = 3.5$, $L = 3.0$. Only mature CD4+ lymphocytes were assumed to be susceptible to HIV products, i.e. $\bar{e}_P = 0.0$,

$\rho = 20.0$. 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.