Mathematical models for in-host dynamics of infectious diseases

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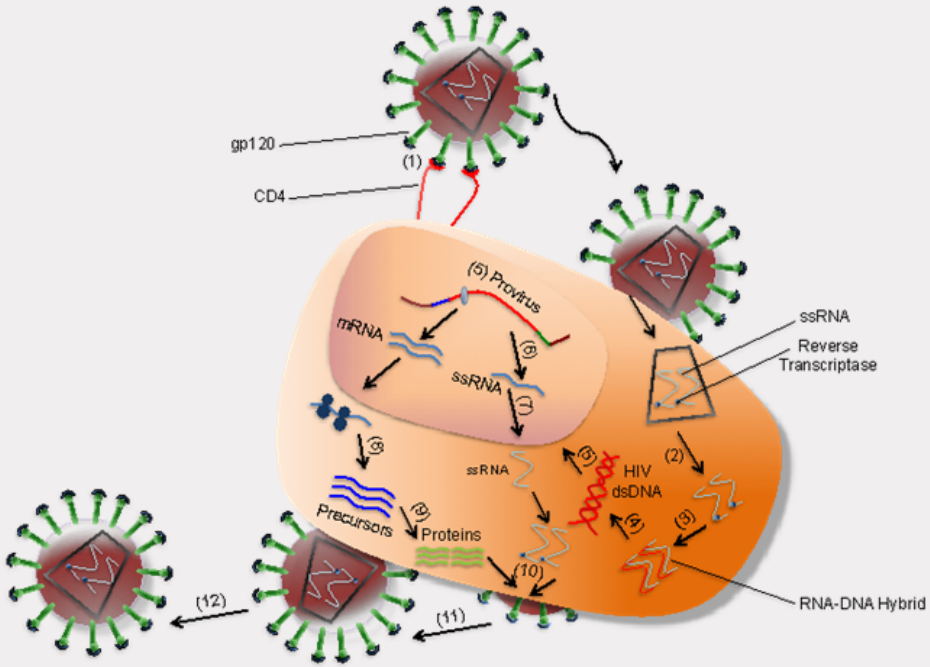
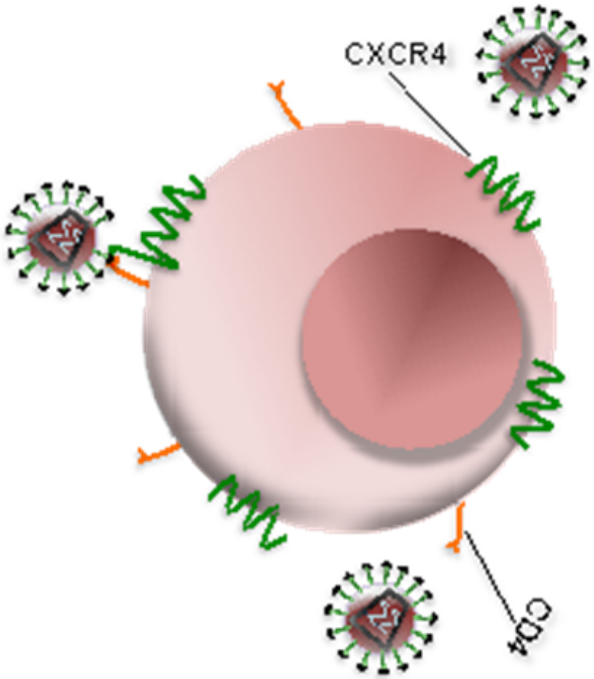
What is our interest?

- To understand the general principles of pathogen infection and immune system response mechanisms.

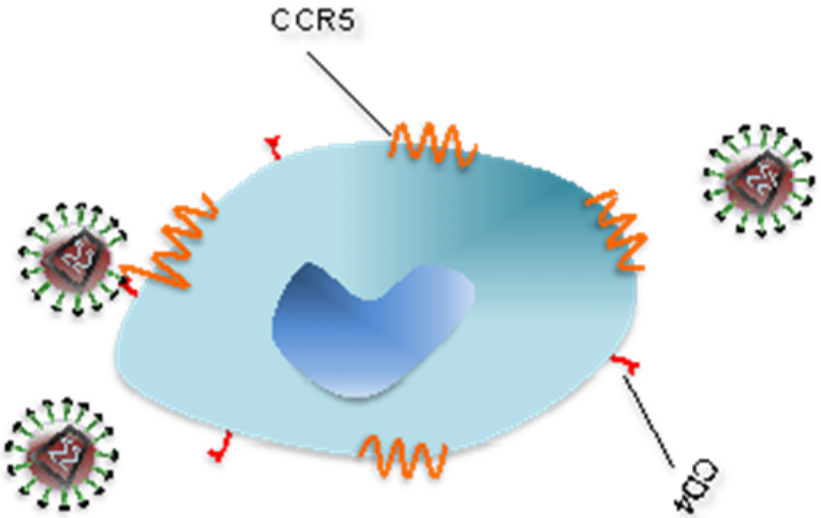
Pathogen infection mechanism (e.g. HIV)



Pathogen infection co-receptors (e.g. HIV)



T cell



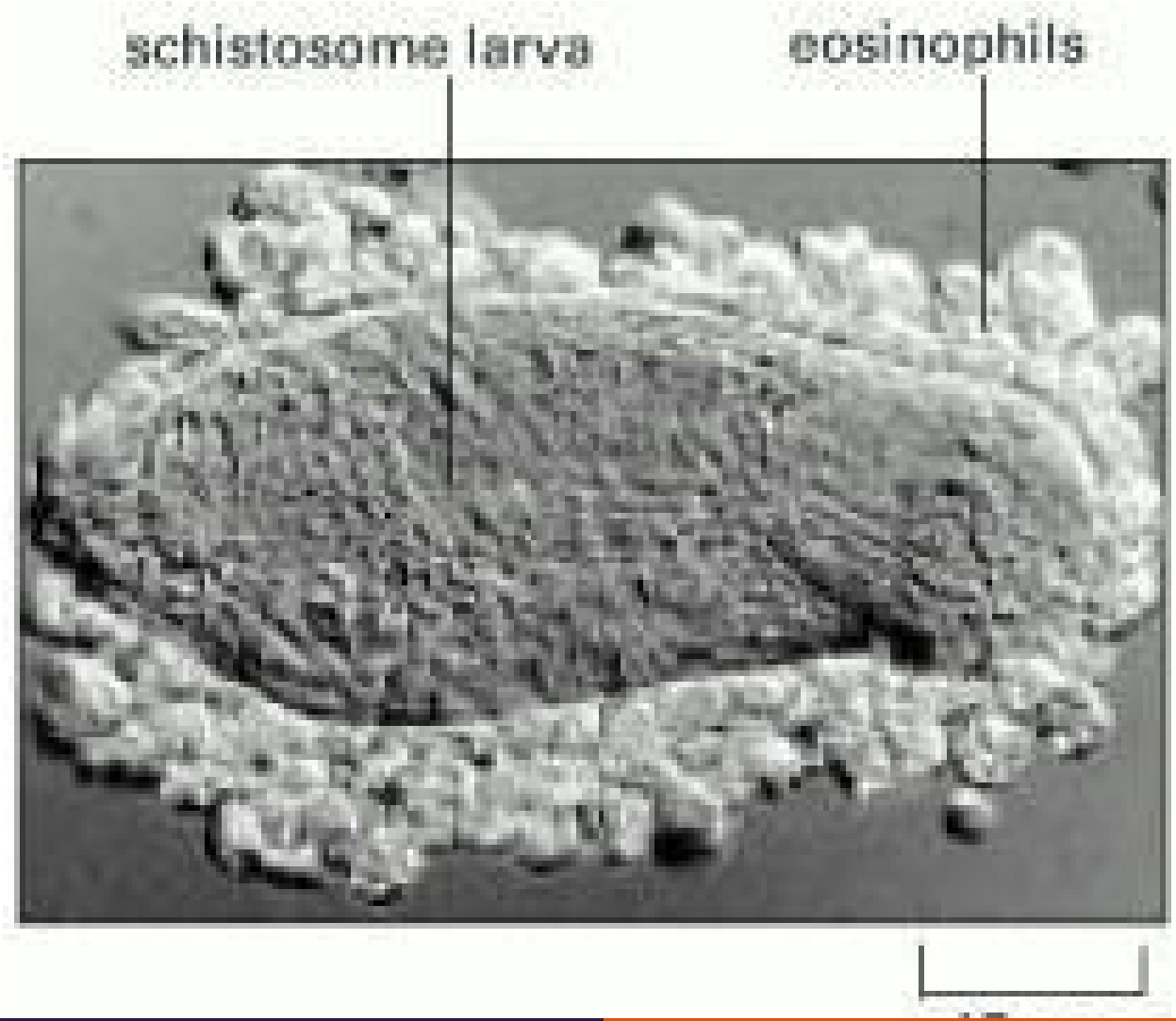
Monocyte

Basic Immune system response to pathogen

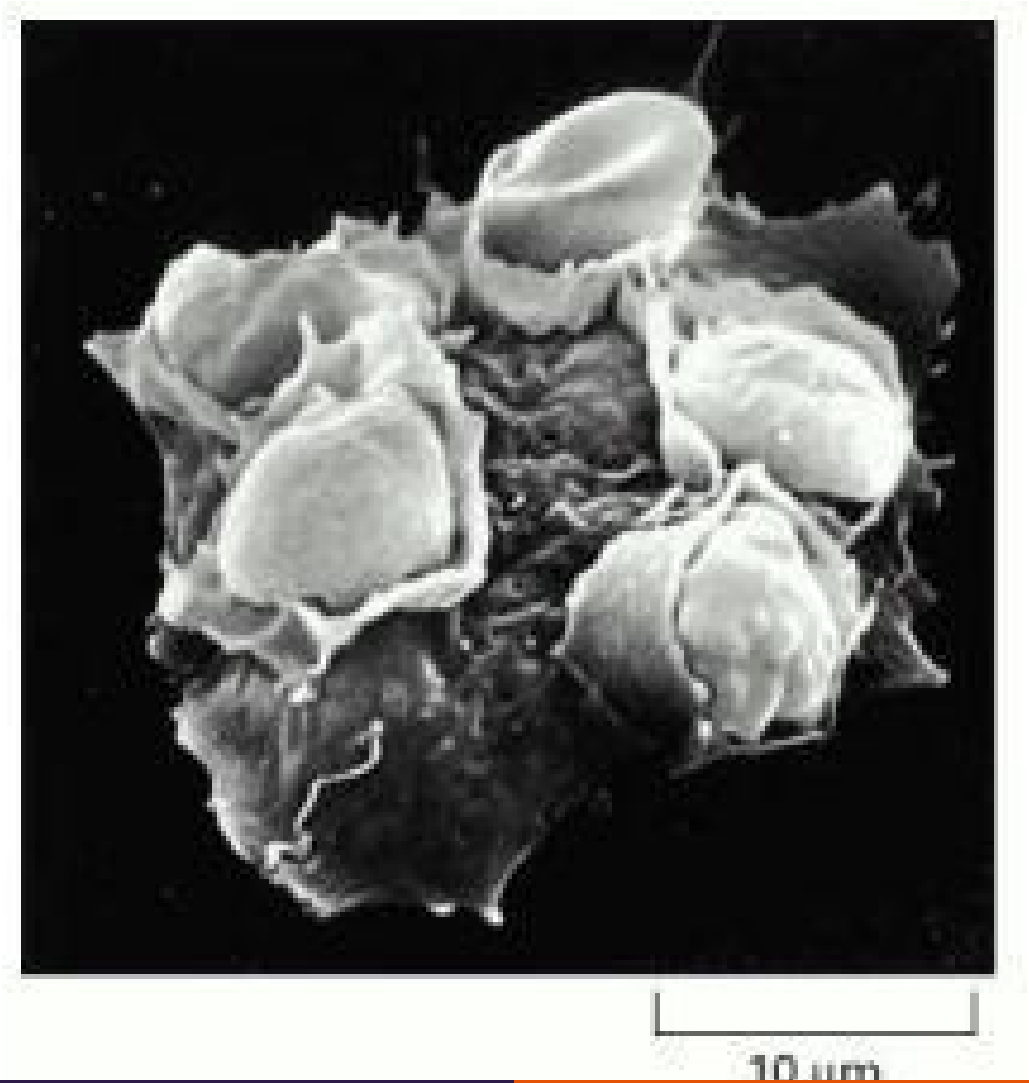
Innate (nonspecific) immune response

1. Innate (nonspecific) immune system response - first line response.
   - physical barriers - the skin,
   - change in body environment - fever
   - immmune cells - Macrophages, eosinophils, dentritic cells, Natural Killer cells.
2. **Cannot specifically recognize the physical structure of the pathogen sense and react to the presence of an invader.**
3. Slow down initial growth pathogen but insufficient to clear an infection.

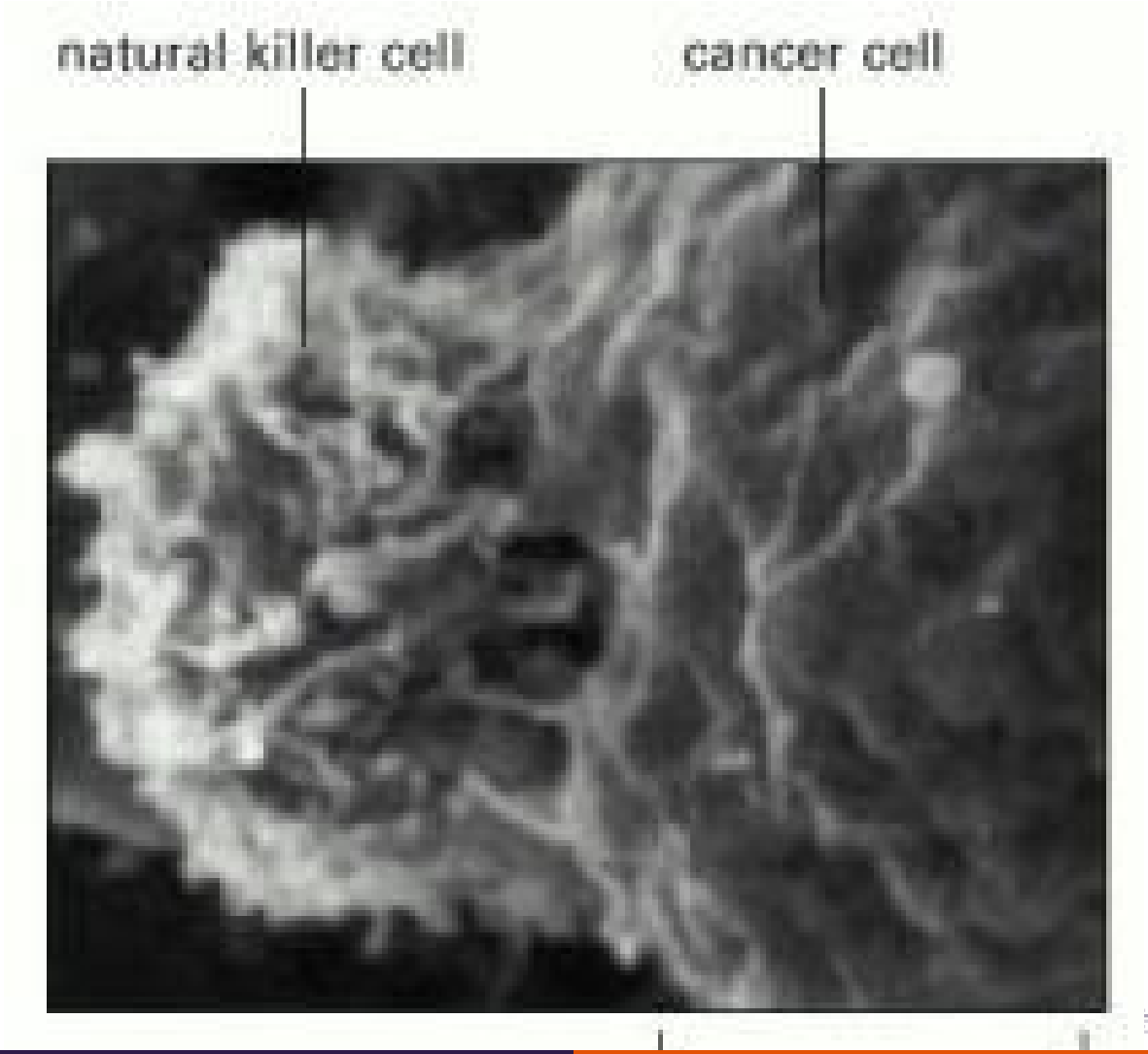
Innate Immune response - eosinophils



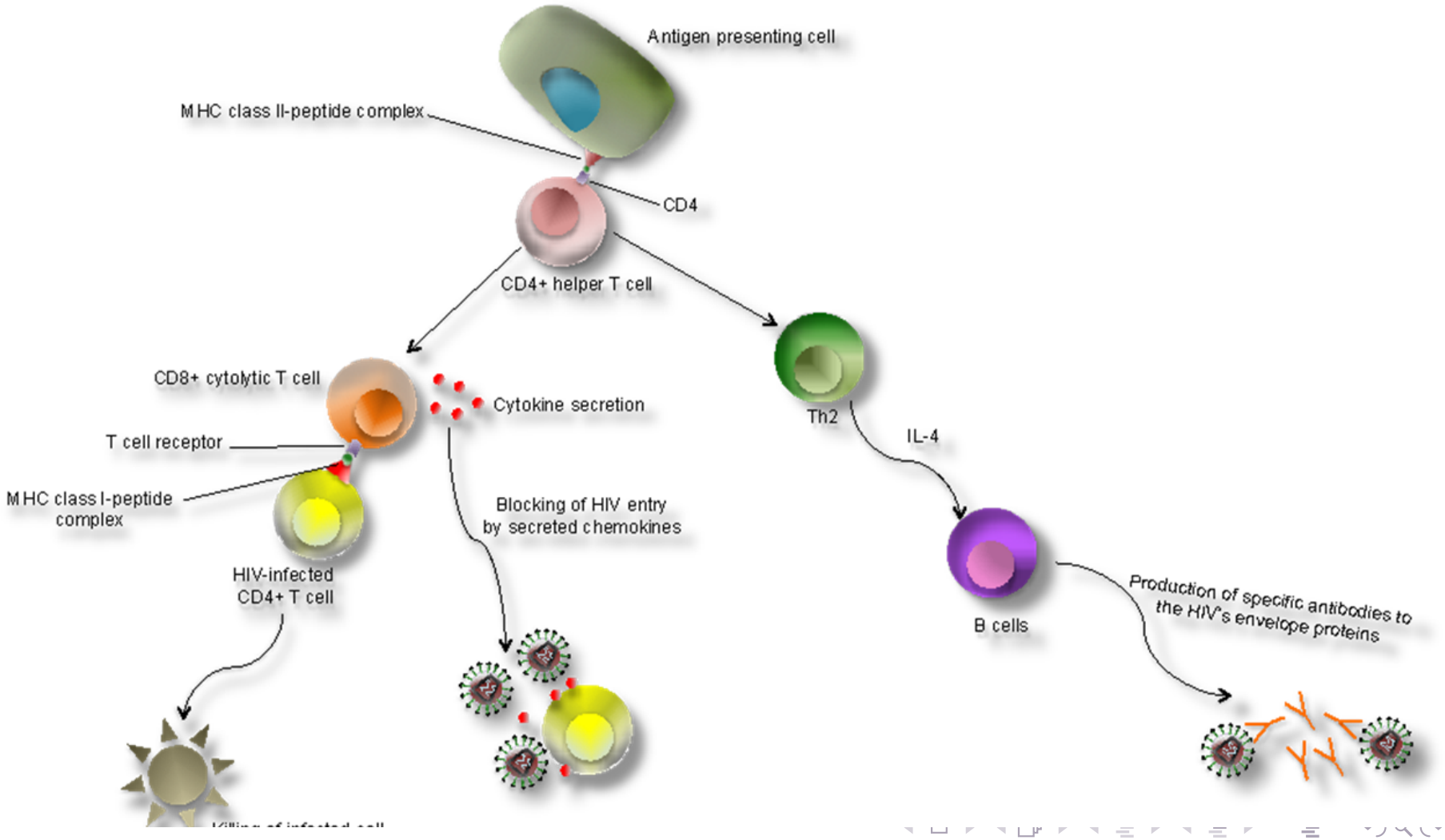
Innate Immune response - phagocytosis



Innate Immune response - Natural Killer cell



Adaptive Immune response



Basic Immune system response to pathogen

Adaptive (specific) immune response

1. Adaptive (specific) immune response - second line response
2. Immune cells have receptors to recognize physical structure of pathogen
3. Immune cells divide and expand - effectively fight the pathogen - clearance may occur.
   - $CD4^+$ T cells - regulatory (helper)
   - $CD8^+$ T cells- effector response - directly fight pathogen.
   - B Cells - effector response - Neutralising antibodies - directly fight pathogen.
4. Pathogens - have epitopes recognized by immune cell receptors - pathogen may have several epitopes.
5. Multiple adaptive responses may be required for one pathogen.

What is our interest?

- To understand the general principles, assumptions and basic techniques used in mathematical models for infectious diseases within the host, appreciate the value and limits of mathematical models and explore the behavior of different models.

Mathematical model

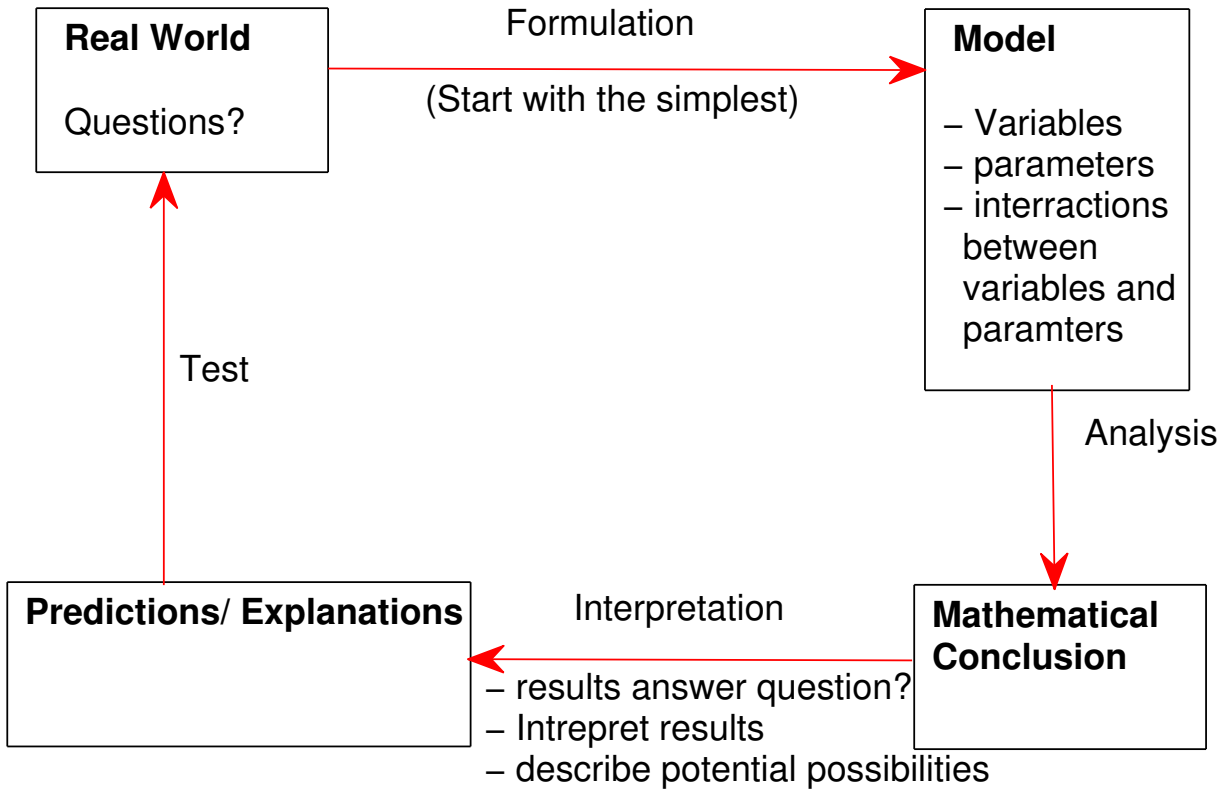
- **Mathematical model**- a conceptual tool that uses the language of mathematics to produce a more refined and precise description of a system.
- - a set of equations describing the structure and interaction of individuals in an area or region.
- Used to analyze experimental results and provide predictions and suggestions for follow-up experiments.
- Can attempt to synthesize existing knowledge and provide a theoretical framework for the interpretation of existing paradigms.
- use of mathematical models instrumental in deepening our understanding of infection.

Model types

Influenced by the scientific question of concern - research question?

- Deterministic models
- Stochastic models
- Statistical models
- many more
- The more assumptions put into the model, the harder it is to be confident about the conclusions
- A well designed model can test different assumptions and provide important new insights into questions that cannot be readily answered experimentally.

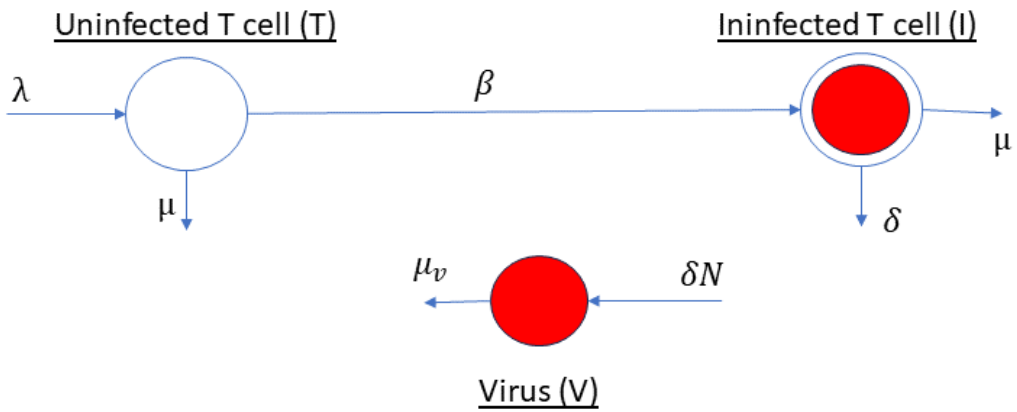
Process of modelling

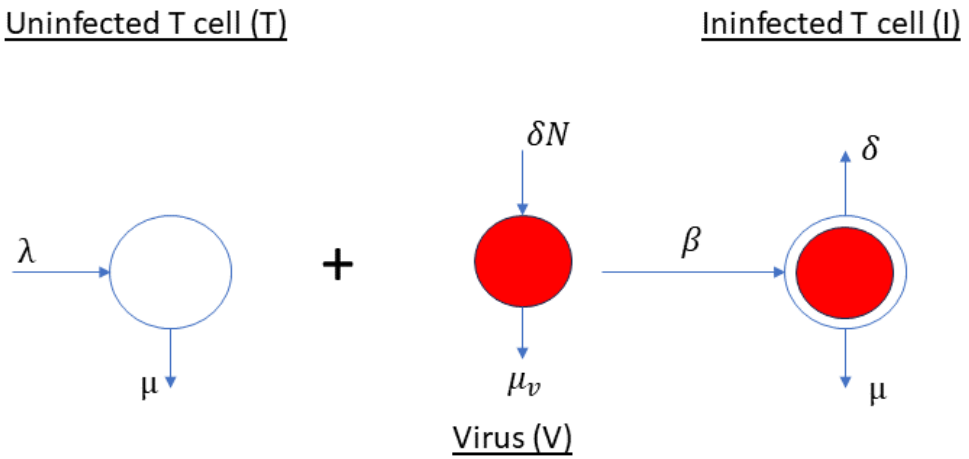


Designing an in-host model

1. Specify the State variables
2. Specify the processes affecting the state variables.
3. Specify the process rates of the state variables.
4. Produce the dynamic equation specifying the state variables' change over time.

Model diagram - T helper cells only

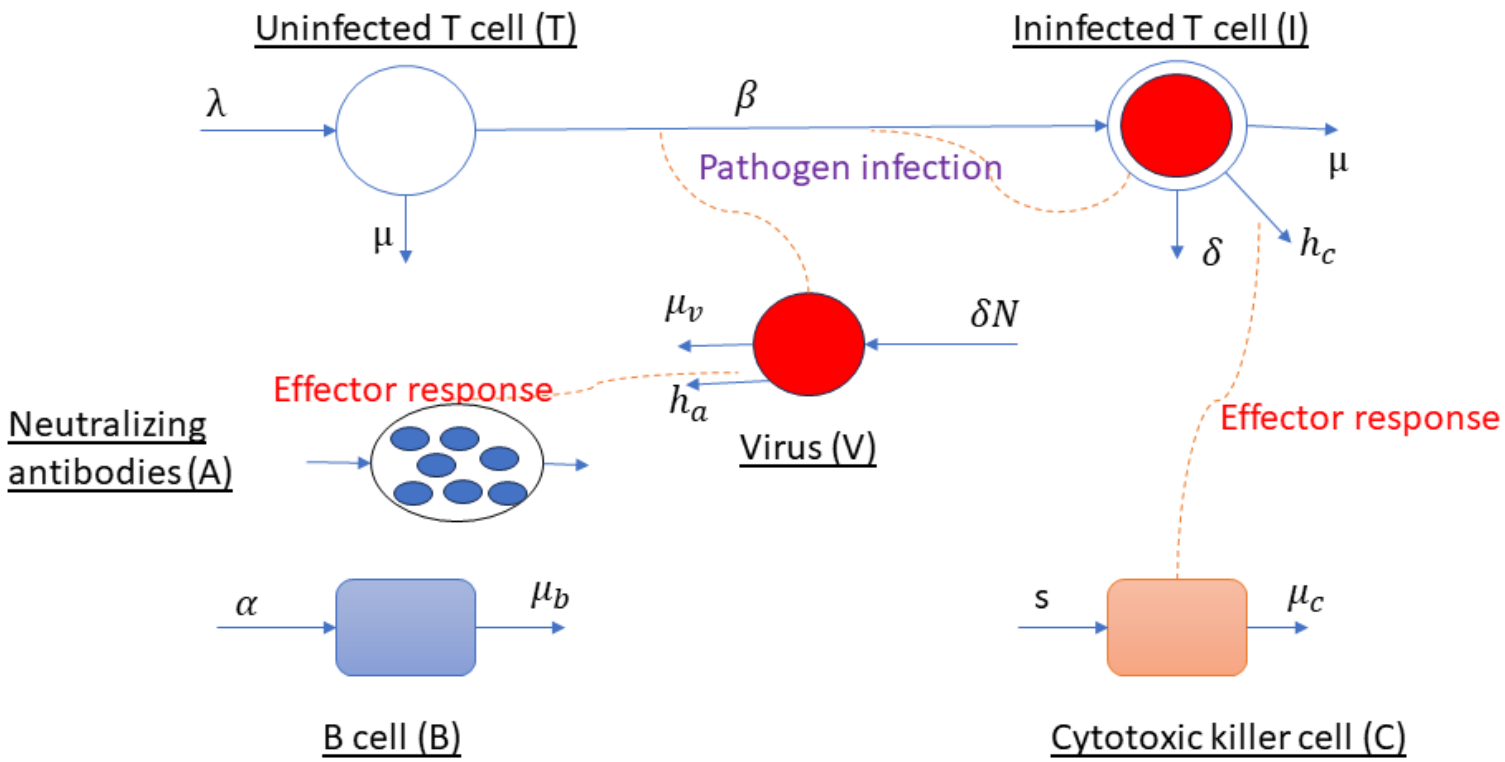




In-host model with T helper cells only (e.g. HIV)

$$\begin{aligned}
\dot{T} &= \pi - \mu T - \beta_1 TV, \\
\dot{I} &= \beta_1 TV - (\mu + \alpha) I, \\
\dot{V} &= N\alpha I - \beta_1 TV - \mu_V V.
\end{aligned}$$

Model diagram - T Helper cells + effector response



In-host model with T helper cells + Effector response (e.g. HIV)

1. Cytotoxic T Lymphocytes (CTLs) proliferate - stimulated by the pathogen.
2. CTLs - fights the virus population (killing infected cells).
3. Virus - CTLs interraction similar to **predator-prey** dynamics in ecology.
4. CTLs (predator) and pathogen (prey).

$$\begin{aligned}
\dot{T} &= \pi - \mu T - \beta_1 TV, \\
\dot{I} &= \beta_1 TV - (\mu + \alpha) I - h_c IC, \\
\dot{V} &= N\alpha I - \beta_1 TV - \mu_V V, \\
\dot{C} &= a_c IC - \mu_c C.
\end{aligned}$$

In-host model with T helper cells + Effector response (e.g. HIV)

1. CTL expansion saturates as the number of CTL grows to relatively high numbers.

$$\dot{T} = \pi - \mu T - \beta_1 TV, \quad (1)$$

$$\dot{I} = \beta_1 TV - (\mu + \alpha)I - \frac{h_c IC,}{\epsilon C + 1} \quad (2)$$

$$\dot{V} = N\alpha I - \beta_1 TV - \mu_V V, \quad (3)$$

$$\dot{C} = \frac{a_c IC}{\epsilon C + 1} - \mu_c C. \quad (4)$$

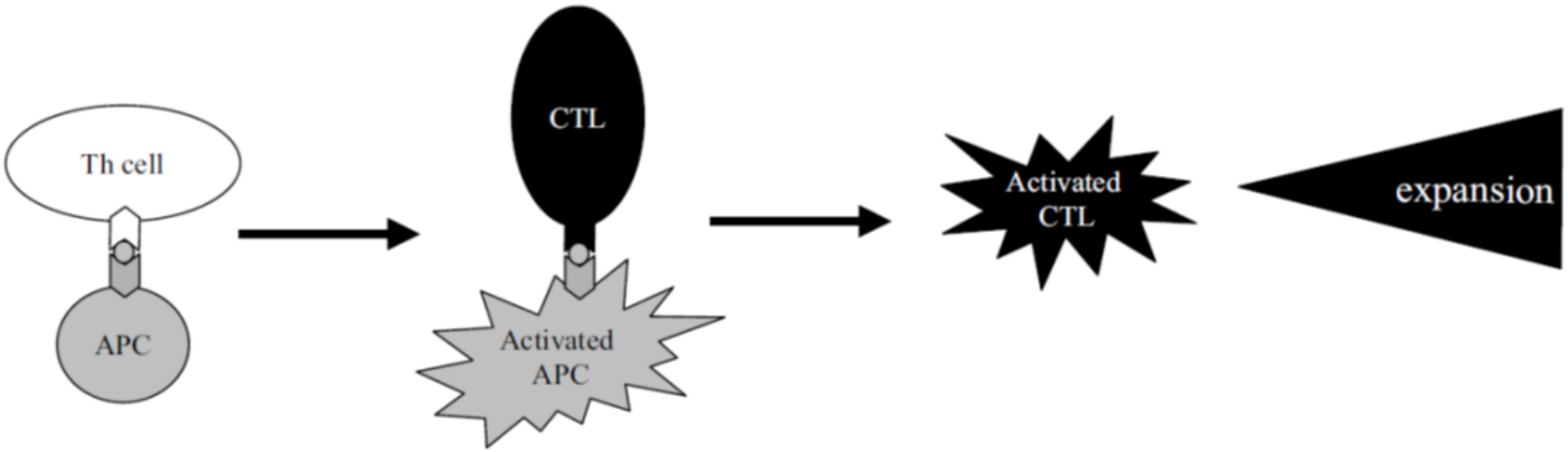
2. Saturation already occurs at lower numbers of CTL

$$\dot{I} = \beta_1 TV - (\mu + \alpha)I - h_c IC, \quad (5)$$

$$\dot{C} = h_c IC - \mu_c C. \quad (6)$$

Modeling CD4 T cell help: CD4-APC-CTL pathway.

1. $CD4^+$ T cell plus APCs = activated APCs.
2. Activated APCs + CTLs = Activated CTLs $\Longrightarrow$ clonal expansion of CTLs.



CD4-APC-CTL pathway reaction scheme

Let $Th-$CD4 T helper cells, $A-$APCs, $T8-$CTLs, $^*-$activated state, k_i-reaction constants and $n-$number of new CTLs.

$$Th + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ThA, \tag{7}$$

$$ThA \xrightarrow{k_3} Th + A^*, \tag{8}$$

$$T8 + A^* \underset{k_5}{\overset{k_4}{\rightleftharpoons}} T8A^*, \tag{9}$$

$$T8A^* \xrightarrow{k_6} (n+1)T8 + A^*, \tag{10}$$

$$A^* \xrightarrow{k_7} A. \tag{11}$$

CD4-APC-CTL pathway reaction scheme kinetics

Let []−concentrations of cell types.

$$\begin{aligned}
\frac{d[A]}{dt} &= -k_1[A][Th] + k_2[ThA] + k_7[A^*], \\
\frac{d[A^*]}{dt} &= k_3[ThA] - k_4[A^*][T8] + k_5[T8A^*] + k_6[T8A^*] - k_7[A^*], \\
\frac{d[Th]}{dt} &= -k_1[A][Th] + k_2[ThA] + k_3[ThA], \\
\frac{d[T8]}{dt} &= -k_4[A^*][T8] + k_5[T8A^*] + k_6(n+1)[T8A^*], \\
\frac{d[ThA]}{dt} &= k_1[A][Th] - k_2[ThA] - k_3[ThA], \\
\frac{d[T8A^*]}{dt} &= k_4[A^*][T8] - k_5[T8A^*] - k_6[T8A^*].
\end{aligned}$$

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

- Kinetics of complexes $[ThA]$ and $[T8A^*]$ are fast compared to the other reactions - they go to their quasi-steady states

$$
\begin{aligned}
[ThA] &= \frac{k_1}{k_2 + k_3}[A][Th], \\
[T8A^*] &= \frac{k_4}{k_5 + k_6}[A^*][T8],
\end{aligned}
$$

reducing the reaction kinetics to

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

$$
\begin{aligned}
\frac{d[A]}{dt} &= -k_1[A][Th] + \frac{k_1 k_2}{k_2 + k_3}[A][Th] + k_7[A^*], \\
\frac{d[A^*]}{dt} &= \frac{k_1 k_3}{k_2 + k_3}[A][Th] - k_4[A^*][T8] + \frac{k_4(k_5 + k_6)}{k_5 + k_6}[A^*][T8] \\
&\quad -k_7[A^*], \\
\frac{d[Th]}{dt} &= -k_1[A][Th] + \frac{k_1(k_2 + k_3)}{k_2 + k_3}[A][Th], \\
\frac{d[T8]}{dt} &= -k_4[A^*][T8] + \frac{k_4(k_5 + k_6(n+1))}{k_5 + k_6}[A^*][T8],
\end{aligned}
$$

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

$$
\begin{aligned}
\frac{d[A]}{dt} &= -\frac{k_1 k_3}{k_2 + k_3}[A][Th] + k_7[A^*], \\
\frac{d[A^*]}{dt} &= \frac{k_1 k_3}{k_2 + k_3}[A][Th] - k_7[A^*], \\
\frac{d[Th]}{dt} &= 0, \\
\frac{d[T8]}{dt} &= n\frac{k_4 k_6}{k_5 + k_6}[A^*][T8],
\end{aligned}
$$

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

- Note that $[Th]$ is constant
- Let $T = [Th] + [ThA]-$ total number of CD4 T helper cells.
- Number of helper cells in $[ThA]$ much smaller than number of free $[Th]$ so that $T = [Th] + [ThA]$

$$\begin{aligned}
\frac{d[A]}{dt} &= -\frac{k_1 k_3 T}{k_2 + k_3}[A] + k_7[A^*], \\
\frac{d[A^*]}{dt} &= \frac{k_1 k_3 T}{k_2 + k_3}[A] - k_7[A^*], \\
\frac{d[T8]}{dt} &= n\frac{k_4 k_6}{k_5 + k_6}[A^*][T8],
\end{aligned}$$

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

- Note also that at quasisteady state

$$[ThA] = \frac{k_1 T}{k_2 + k_3}[A],$$
$$[T8A^*] = \frac{k_4}{k_5 + k_6}[A^*][T8],$$

- Let $A_c = [A] + [A^*] + \frac{k_1 T}{k_2+k_3}[A] + \frac{k_4}{k_5+k_6}[A^*][T8]-$ total number of APCs.

$$[A^*] = \frac{k_1 k_3 T A_c}{k_7(k_2 + k_3) + k_1 k_3 T\left(1 + \frac{k_4[T8]}{k_5+k_6}\right) + k_1 k_7 T}$$

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

$$[A^*] = \frac{\epsilon T A_c}{1 + \epsilon T (1 + \sigma[T8]) + \rho T}$$

- $\epsilon = \frac{k_1 k_3}{k_2 + k_3}$ – net reaction constant of APC activation.
- $\sigma = \frac{k_4}{k_5 + k_6}$ –proportionality constant for CTL-APC complex
- $\rho = \frac{k_1}{k_2 + k_3}$ –proportionality constant for TH-APC complex

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

- Let $C = [T8] + [T8A^*]$−total number of CTLS.
- The number of CTL in $[T8A^*]$ is negligible, then $C = [T8]$
- Proliferation rate of CTL's is given by

$$\frac{\gamma \epsilon T A_c C}{1 + \epsilon T (1 + \sigma C) + \rho T}$$

- $\gamma = n \frac{k_4 k_6}{k_5 + k_6}$−net reaction constant for CTL activation.

CD4-APC-CTL pathway reaction scheme kinetics simplifyting assumptions

- Assume that amount of CD4 help is constant, i.e. T is constant. The proliferation function reduces to

$$\frac{\alpha_1 A_c C}{\alpha_2 + C}$$

- Assume that amount of CD4 help is small and vanishes. The proliferation function reduces to

$$\gamma \epsilon T A_c C$$

- Using the quasi-steady state assumption $k_2 + k_3 >> k_1$ and $k_5 + k_6 >> k_4$, we can ignore σ and ρ. The proliferation function reduces to $\frac{\gamma \epsilon T A_c C}{1 + \epsilon T}$

HIV infection in CD4$^+$ T cells and Other immune cells

- Langerhans cells - the skin epidermis, the anal and vaginal mucosa, and the male foreskin.
- capture and destroy HIV or can get infected by HIV.

$$\dot{L} = \lambda_l - \mu_l L - \frac{\beta_1 V}{A+L} L - \frac{\beta_2 L(L_i + T_i)}{A+L}, \quad (12)$$

$$\dot{T} = \pi - \mu T - \beta_3 L_i T - \beta_4 T I - \beta_5 T V, \quad (13)$$

$$\dot{L_i} = \frac{\beta_1 V}{A+L} L + \frac{\beta_2 L(L_i + T_i)}{A+L} - \mu_l L_i, \quad (14)$$

$$\dot{I} = \beta_3 L_i T + \beta_4 T I + \beta_5 T V - (\mu + \alpha) I, \quad (15)$$

$$\dot{V} = N\alpha I - \frac{\phi V L}{A+L} - \mu_V V. \quad (16)$$

Threshold analysis

$$\Re_1^2 = \frac{T_0\left(\beta_5\alpha N(\mu_l-\beta_2\Psi)+\beta_2\beta_3\Psi(\mu_v+\phi\Psi)+\beta_1\beta_3\alpha\Psi N\right)}{(\mu_v+\phi\Psi)(\mu_l-\beta_2\Psi)(\mu+\alpha-\beta_4T_0)}.$$

:pand $\Re_1^2$ and write it as

$$\Re_1^2 = \Re_{T_i\to V\to T_i}+\Re_{T_i\to L_i\to T_i}+\Re_{T_i\to V\to L_i\to T_i},$$

$$\Re_{T_i\to V\to T_i} = \frac{T_0\beta_5\alpha N}{(\mu_v+\phi\Psi)(\mu+\alpha-\beta_4T_0)},$$

$$\Re_{T_i\to L_i\to T_i} = \frac{T_0\beta_2\beta_3\Psi}{(\mu_l-\beta_2\Psi)(\mu+\alpha-\beta_4T_0)},$$

$$\Re_{T_i\to V\to L_i\to T_i} = \frac{T_0\beta_1\beta_3\alpha\Psi N}{(\mu_v+\phi\Psi)(\mu_l-\beta_2\Psi)(\mu+\alpha-\beta_4T_0)}.$$

Threshold analysis

$$\frac{\partial \Re_1^2}{\partial \alpha} = \frac{T_0\left(\mu - \beta_4 T_0\right)\left(\beta_1\beta_3\Psi + \beta_5\left(\mu_l - \beta_2\Psi\right)\right)\left(N - N_1^c\right)}{\Re_1\left(\mu_v + \phi\,\Psi\right)\left(\mu_l - \beta_2\Psi\right)\left(\mu + \alpha - \beta_4 T_0\right)^2},$$

where

$$N_1^c = \frac{\beta_2\beta_3\Psi\ \left(\mu_v + \phi\,\Psi\right)}{\left(\mu - \beta_4 T_0\right)\left(\beta_1\beta_3\Psi + \beta_5\left(\mu_l - \beta_2\Psi\right)\right)}. \tag{3.11}$$

The reciprocal of the expression $\mu - \beta_4 T_0$ is the average infectious period for T_i cells in the absence of viral lysis (i.e., $\alpha = 0$), so we assume that $\mu - \beta_4 T_0 > 0$. We formulate a theorem on N and N_1^c as follows.

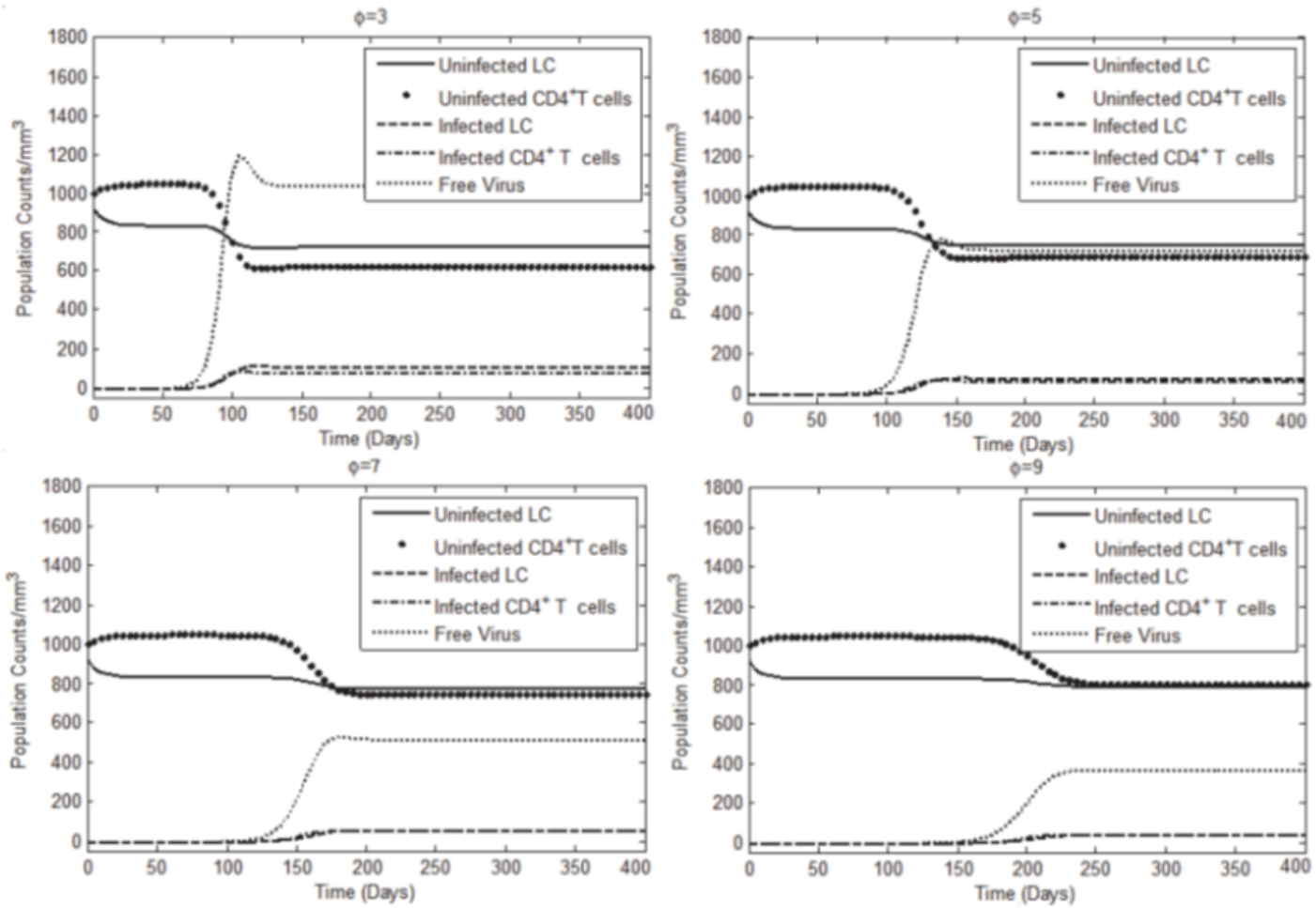
THEOREM 3.3. *There is a threshold number N_1^c, such that the following hold:*

(i) *If $N < N_1^c$, $\Re_1$ decreases with respect to α.*
(ii) *If $N > N_1^c$, $\Re_1$ increases with respect to α.*
(iii) *If $N = N_1^c$, $\Re_1$ is constant with respect to α.*

Differentiating $\Re_1^2$ with respect to ϕ we obtain

$$\frac{\partial \Re_1^2}{\partial \phi} = -\frac{T_0\alpha\Psi N\left(\beta_5(\mu_l - \beta_2\Psi) + \beta_1\beta_3\Psi\right)}{\left(\mu_v + \phi\,\psi\right)^2\left(\mu_l - \beta_2\psi\right)\left(\mu + \alpha - \beta_4 T_0\right)}.$$

Simulations



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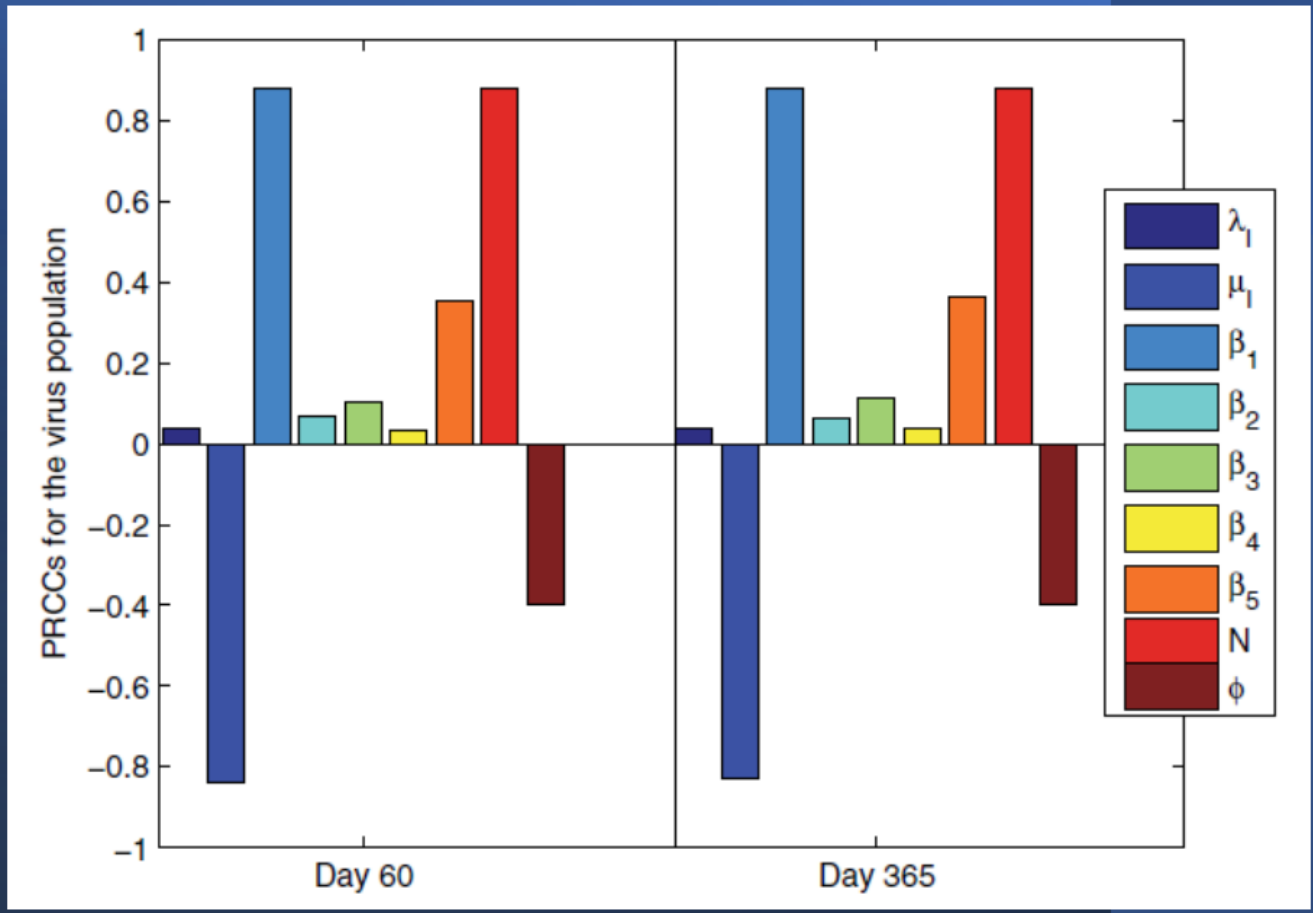


Summary

1. Established three subreproduction ratios,
   (i) cycle from infected CD4+ T cells to free virus and back to infected CD4+ T cells,
   (ii) cycle from infected CD4+ T cells to infected Langerhans cells and back to infected CD4+ T cells, and
   (iii) cycle from infected CD4+ T cells to free virus to infected Langerhans cells and back to infected CD4+ T cells.
2. Degradation effects of Langerhans cells are countered by the opposing viral lysis effects.
3. Focus on strategies that reduce the cell-free infection towards both Langerhans cells and CD4+ T cells as well as boost the degradation mechanisms of the Langerhans cells towards the free virus.

Incorporating constant treatment in HIV in-host models

$$
\begin{aligned}
\dot{L} &= \lambda_l - \mu_l L - \frac{\beta_1 V}{A+L} L - \frac{\beta_2 L(L_i+T_i)}{A+L} - \sigma_1 L, \\
\dot{T} &= \pi - \mu T - \beta_3 L_i T - \beta_4 T I - \beta_5 T V - \sigma_2 T, \\
\dot{L_d} &= \sigma_1 L - \mu_l L_d - \frac{\beta_1(1-\delta\epsilon_R)V}{A+L_d} L_d - \frac{\beta_2(1-\delta\epsilon_R)L_d(L_i+T_i)}{A+L_d}, \\
\dot{T_d} &= \sigma_2 T_d - \mu T_d - (1-\epsilon_R)(\beta_3 L_i + \beta_4 I + \beta_5 V) T_d, \\
\dot{L_i} &= \frac{\beta_1 V}{A+L} L + \frac{\beta_2 L(L_i+T_i)}{A+L} + \frac{\beta_1(1-\delta\epsilon_R)V}{A+L_d} L_d \\
&\quad + \frac{\beta_2(1-\delta\epsilon_R)L_d(L_i+T_i)}{A+L_d} - (\mu_l+\rho)L_i,
\end{aligned}
$$

Incorporating constant treatment in HIV in-host models

$$\dot{I} = (\beta_3 L_i + \beta_4 I + \beta_5 V)(T + (1 - \delta\epsilon_R)T_d) - (\mu + \alpha)I,$$

$$\dot{V} = N(1 - \epsilon_p)\alpha I + M(1 - \epsilon_p)\rho L_i - \frac{\phi V(L + L_d)}{A + L + L_d} - \mu_V V.$$

Threshold analysis

$$\Re_1^2 = \Re_{T_i \to V \to T_i} + \Re_{T_i \to L_i \to T_i} + \Re_{T_i \to V \to L_i \to T_i} + \Re_{T_i \to L_i \rightleftarrows V \to T_i},$$

where $\Re_{T_i \to V \to T_i} = \frac{(1-\epsilon_{PI}) N \alpha \Theta_4 \beta_5}{\Theta_1 (\phi \Phi_2 + \mu_v)}$, $\Re_{T_i \to V \to L_i \to T_i} = \frac{\beta_3 \beta_1 \alpha N (1-\epsilon_{PI}) \Theta_4 \Theta_3}{\Theta_2 \Theta_1 (\phi \Phi_2 + \mu_v)}$,

$\Re_{T_i \to L_i \to T_i} = \frac{\Theta_3 \beta_2 \beta_3 \Theta_4}{\Theta_2 \Theta_1}$, $\Re_{T_i \to L_i \rightleftarrows V \to T_i} = \frac{(1-\epsilon_{PI}) \Theta_3 \rho M (\Theta_4 \beta_2 \beta_5 + \Theta_1 \beta_1)}{\Theta_2 \Theta_1 (\phi \Phi_2 + \mu_v)}$.

where, $\Theta_3 = (1-\delta \epsilon_{RTI}) \Phi_1 + \Phi$, $\Theta_4 = T_1 + (1-\epsilon_{RTI}) T_{d_1}$,

$\Theta_1 = \mu + \alpha - \beta_4 (1-\epsilon_{RTI}) T_{d_1} - \beta_4 T_1$, $\Theta_2 = \mu_l + \rho - \beta_2 (1-\delta \epsilon_{RTI}) \Phi_1 - \beta_2 \Phi$,

$\Phi = \frac{L_1}{A + L_1}$, $\Phi_1 = \frac{L_{d_1}}{A + L_{d_1}}$, $\Phi_2 = \frac{L_1 + L_{d_1}}{A + L_1 + L_{d_1}}$, $L_1 = \frac{\lambda_l}{\mu_l + \sigma_1}$, $T_1 = \frac{\pi}{\mu + \sigma_2}$

Incorporating time-varying treatment in HIV in-host models

1. Pharmacokinetics - the kinetics of absorption, distribution and elimination of drugs inside the body
   - Minimum and maximum concentration of the drug
   - dosage rate, half-life, time to max concentration
2. Drug concentration at the site of action is the most important aspect but not feasible to routinely measure clinically
3. Plasma/blood concentration widely used - linear relationship between plasma concentration and site-of-action concentration.

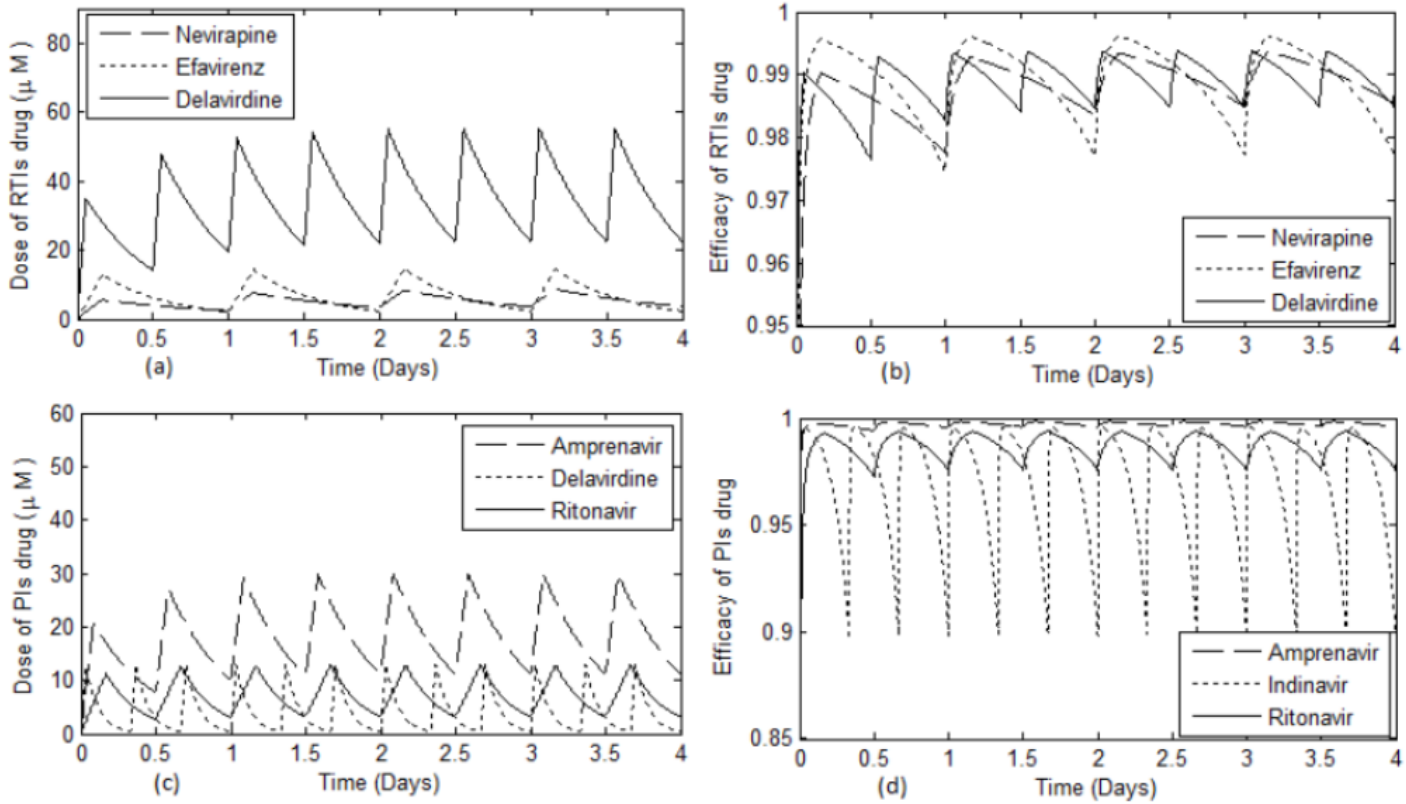
Drug concentration

$$C(t) = \begin{cases} C_{min} + \frac{(C_{max} - C_{min})(1 - e^{-t})}{1 - e^{-T_{max}}}, & t \in [t_i, T_{max}], \\ C_{max} e^{-k(t - T_{max})}, & t \in [T_{max}, \tau + t_i]. \end{cases}$$

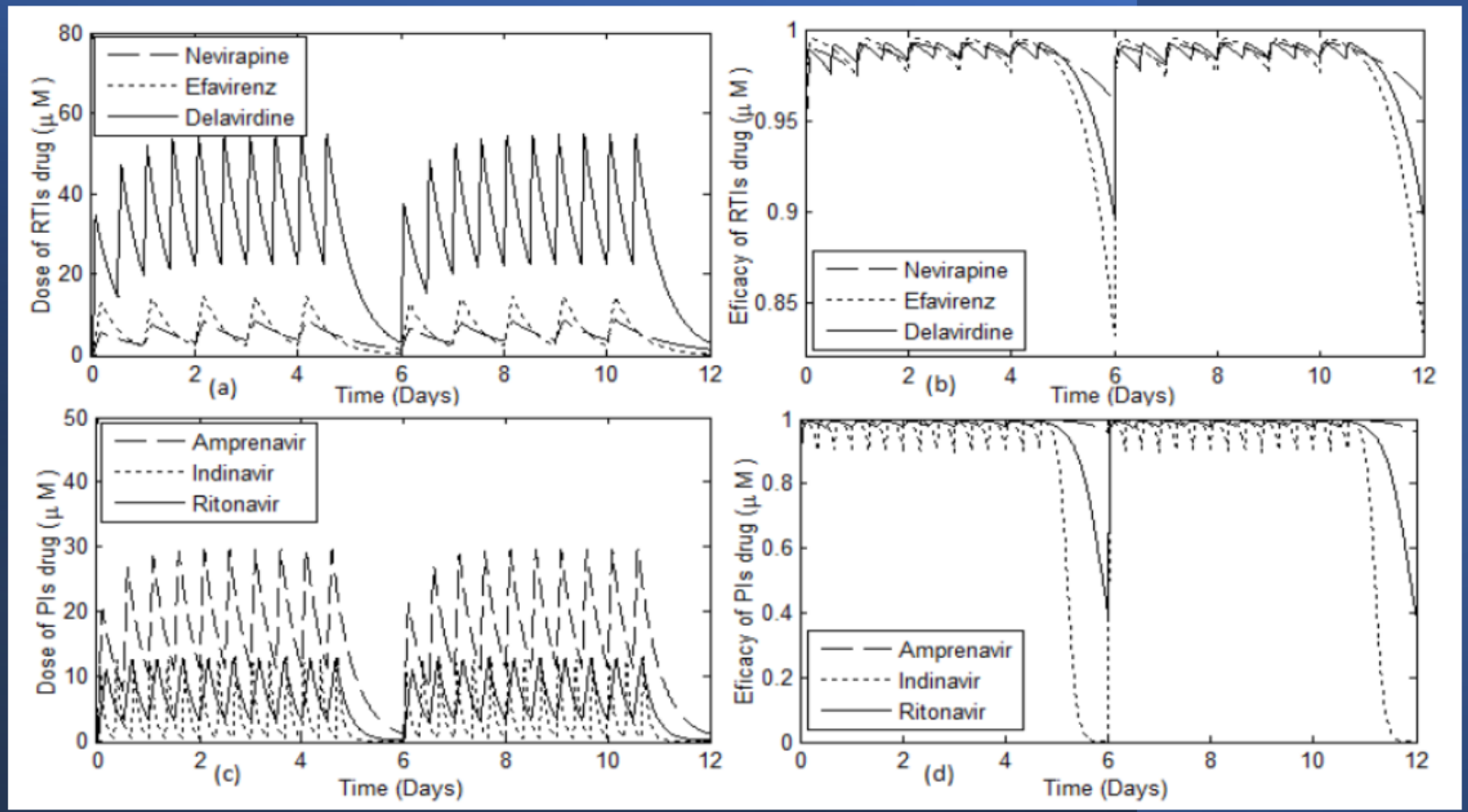
Efficacy functions

$$\epsilon(t) = \frac{C(t)}{IC_{50} + C(t)}$$

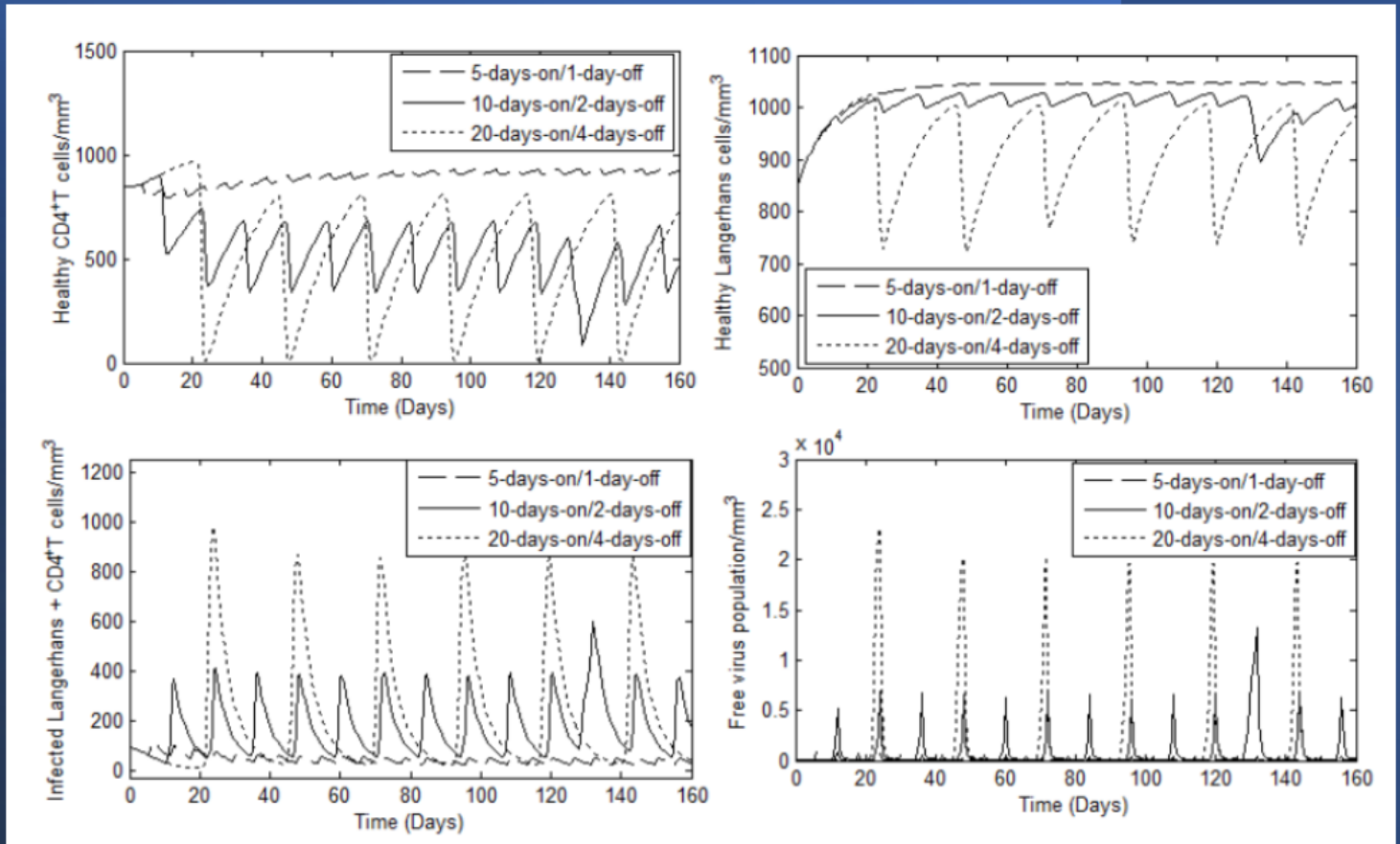
Numerical experimentation



Numerical experimentation



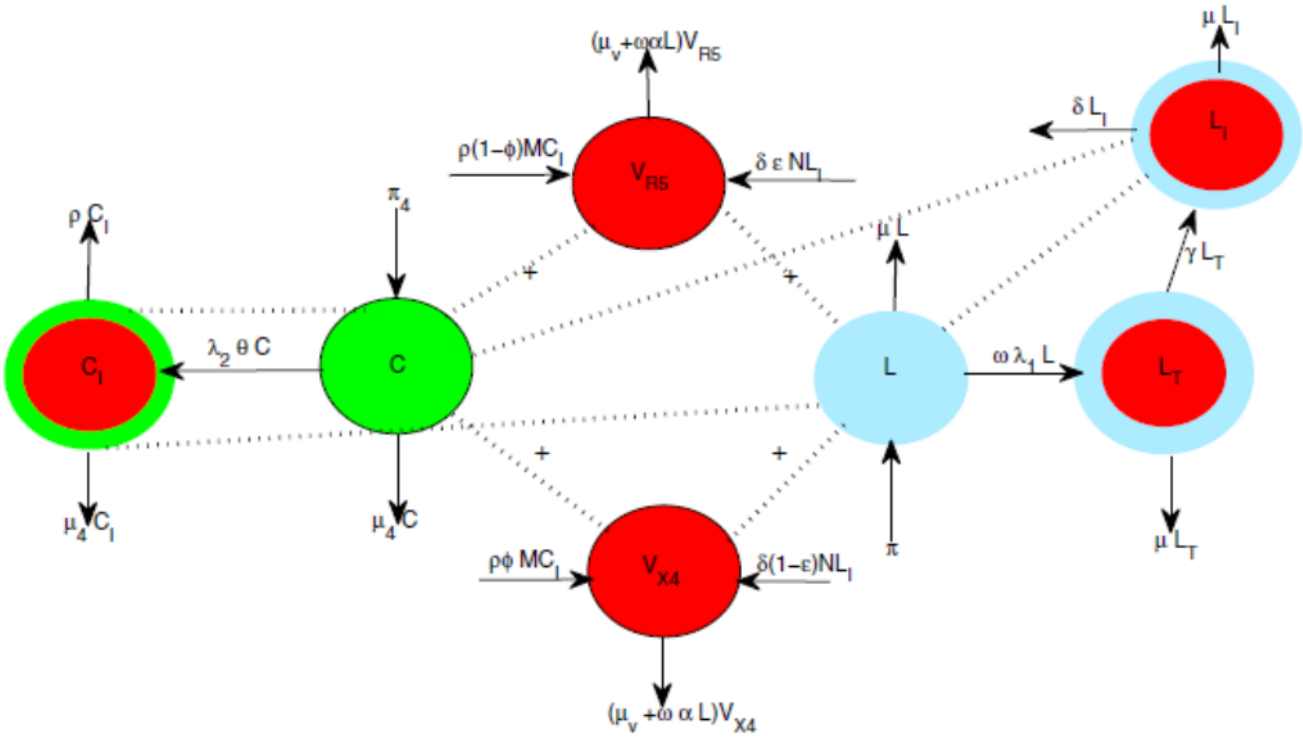
Numerical experimentation



Summary

1. Periodic drug holidays are more effective if the time duration of the drug holidays is shorter

Some connection of HIV in-host model and population dynamics



Full linked model

$$
\begin{aligned}
\frac{dL}{dt} &= \pi - (\omega\lambda_1 + \mu)L, \\
\frac{dL_T}{dt} &= \omega\lambda_1 L - (\mu + \gamma)L_T, \\
\frac{dL_I}{dt} &= \gamma L_T - (\mu + \delta)L_I, \\
\frac{dC}{dt} &= \pi_4 - (\lambda_2 + \mu_4)C, \\
\frac{dC_L}{dt} &= \lambda_2 C - (\mu_4 + \gamma_4)C_L, \\
\frac{dC_I}{dt} &= \gamma_4 C_L - (\mu_4 + \rho)C_I,
\end{aligned}
$$

Full linked model continued

$$
\begin{aligned}
\frac{dV_{R5}}{dt} &= (1-(\zeta_c+\zeta_I))p(I+\eta_0 A)+\rho(1-\phi)MC_I \\
&\quad +\delta\epsilon NL_I-(\mu_V+\omega\alpha L)V_{R5}, \\
\frac{dV_{X4}}{dt} &= (\zeta_c+\zeta_I)p_c(I+\eta_0 A)+\rho\phi MC_I+\delta(1-\epsilon)NL_I \\
&\quad -(\mu_V+\omega\alpha L)V_{X4}, \\
\frac{dS}{dt} &= \Lambda_0-\lambda_3 S-d_0 S, \\
\frac{dI}{dt} &= \lambda_3 S-(d_0+\gamma_0)I, \\
\frac{dA}{dt} &= \gamma_0 I-(d_0+\delta_0)A,
\end{aligned}
$$

Full linked model continued

$$\lambda_1 = \beta_1(V_{R5} + \eta_3 V_{X4} + \eta_2 C_I + \eta_1 L_I),$$

$$\lambda_2 = \beta_2(V_{X4} + \sigma_3 V_{R5} + \sigma_2 C_I + \sigma_1 L_I),$$

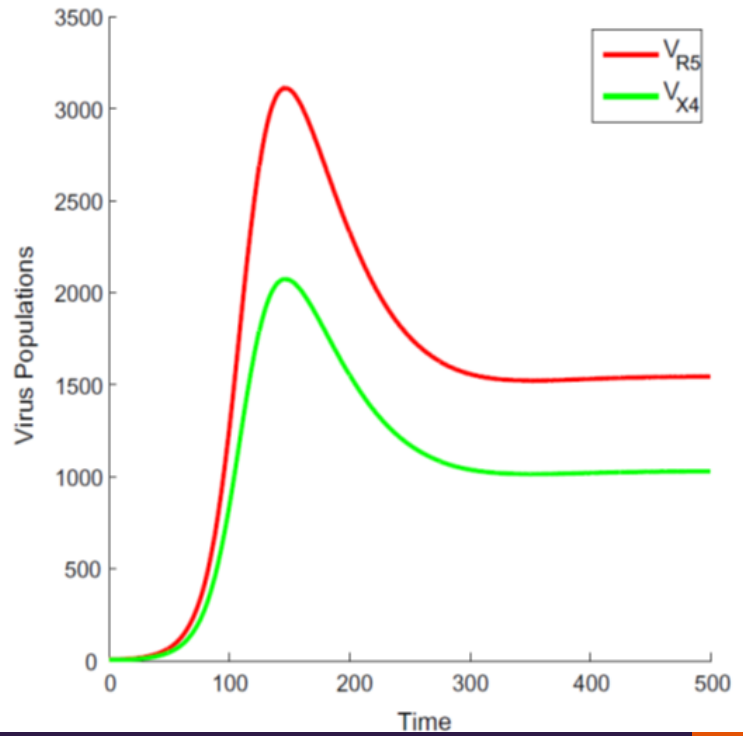
$$\lambda_3 = \frac{\beta_3(\eta_b V_{X4} + (1-\eta_b) V_{R5})(I + \eta_0 A)}{N_0}.$$

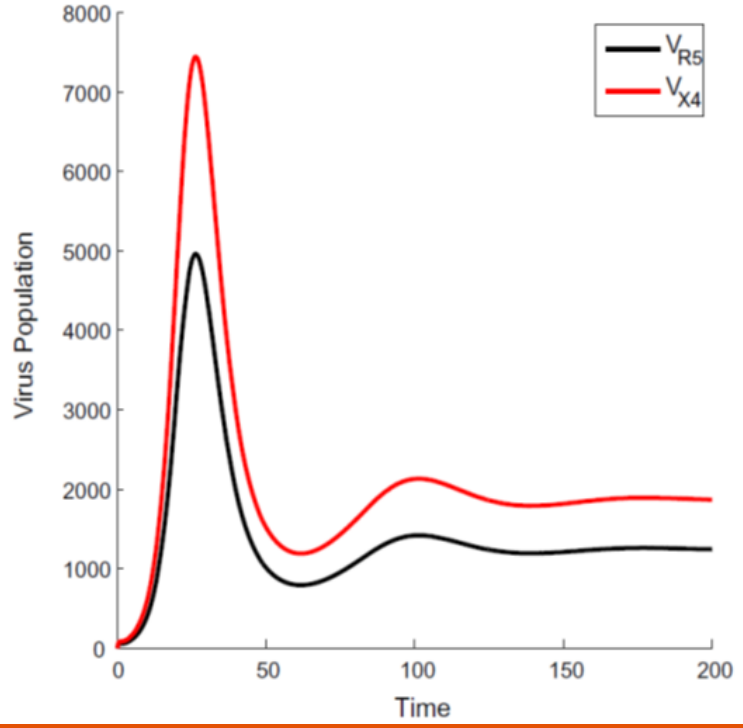
Balanced time scales for within host dynamics and population dynamics

Equations with respect to fast dynamics	Equations with respect to slower time τ_b
$\dot{L} = \pi - (\omega\lambda_1 + \mu)L$	$\varepsilon_b L' = \pi - (\omega\lambda_1 + \mu)L$
$\dot{L_T} = \lambda_1 L - (\mu + \gamma)L_T$	$\varepsilon_b L'_T = \lambda_1 L - (\mu + \gamma)L_T$
$\dot{L_I} = \gamma L_T - (\mu + \delta)L_I$	$\varepsilon_b L'_I = \gamma L_T - (\mu + \delta)L_I$
$\dot{C} = \pi_4 - (\lambda_2 + \mu_4)C$	$\varepsilon_b C' = \pi_4 - (\lambda_2 + \mu_4)C$
$\dot{C_L} = \lambda_2 C - (\mu_4 + \gamma_4)C_L$	$\varepsilon_b C'_L = \lambda_2 C - (\mu_4 + \gamma_4)C_L$
$\dot{C_I} = \gamma_4 C_L - (\mu_4 + \rho)C_I$	$\varepsilon_b C'_I = \gamma_4 C_L - (\mu_4 + \rho)C_I$
$\dot{V_{R5}} = \varepsilon_b(1 - (\zeta_c + \zeta_l))p (I + \eta_0 A) + \rho(1 - \phi)MC_I + \delta\varepsilon NL_I - (\mu_v + \omega\alpha L)V_{R5}$	$\varepsilon_b V'_{R5} = (1 - (\zeta_c + \zeta_l))p(I + \eta_0 A) + \rho(1 - \phi)MC_I + \delta\varepsilon NL_I - (\mu_v + \omega\alpha L)V_{R5}$
$\dot{V_{X4}} = \varepsilon_b(\zeta_c + \zeta_l)p(I + \eta_0 A) + \rho\phi MC_I + \delta(1 - \varepsilon)NL_I - (\mu_v + \omega\alpha L)V_{X4}$	$\varepsilon_b V'_{X4} = (\zeta_c + \zeta_l)p(I + \eta_0 A) + \rho\phi MC_I + \delta(1 - \varepsilon)NL_I - (\mu_v + \omega\alpha L)V_{X4}$
$\dot{S} = \varepsilon_b\left(\tilde{\Lambda_0} - \tilde{\lambda_3}S - \tilde{d_0}S\right)$	$S' = \Lambda_0 - \lambda_3 S - d_0 S$
$\dot{I} = \varepsilon_b\left(\tilde{\lambda_3}S - (\tilde{d_0} + \tilde{\gamma_0})I\right)$	$I' = \lambda_3 S - (d_0 + \gamma_0)I$
$\dot{A} = \varepsilon_b\left(\tilde{\gamma_0}I - (\tilde{d_0} + \tilde{\delta_0})A\right)$	$A' = \gamma_0 I - (d_0 + \delta_0)A$

Simulations before and after linking

Simulations before and after linking





Summary

1. Results suggest that ignoring the differences in time scales may lead to underestimation of the impact of the infection.
2. Within the host - there is potential to increase the viral load whilst decreasing the CD4 count within the host.
3. At population level- members of infected and AIDS individuals increase.
4. The direct linking can also be used for all infectious diseases that can be transmitted directly.

HIV Mutation within the host

1. HIV known for error-prone replication - mutation - partial/full resistance to drugs.
2. Mutation results from (i) - copying errors, (ii) - taking antiretroviral drugs

HIV model with mutation

HIV model with competing strains

$$\dot{T} = s - \mu_T T - \sum_{i=1}^{n} k_i \left(1 - \frac{1}{n} \sum_{j=1, j \neq i}^{n} \frac{I_j}{C_{I_j}}\right) T V_i.$$

$$\dot{I}_i = k_i \left(1 - \frac{1}{n} \sum_{j=1, j \neq i}^{n} \frac{I_j}{C_{I_j}}\right) T V_i - \mu_{I_i} I_i.$$

$$\dot{V}_i = r_i \left(1 - \frac{V_i}{C_i}\right) V_i + N_i \mu_{w_i} I_i - \mu_{V_i} V_i,$$

Necessary conditions

Theorem 2.1. *The uninfected steady-state of the system (1)–(3) is locally asymptotically stable for* $N_i < N^{V_i}_{crit}$ *and unstable for* $N_i > N^{V_i}_{crit}$.

Sufficient conditions

Sufficient conditions

$$N^{s}_{crit} = \frac{\mu_I(\mu_V - r)}{k\mu_w T_0},$$

$$N^{n}_{crit} = \max\left\{\frac{\mu_{I_i}\mu_T(\mu_{V_i} - r_i)}{k_i s\mu_{w_i}}\right\}$$

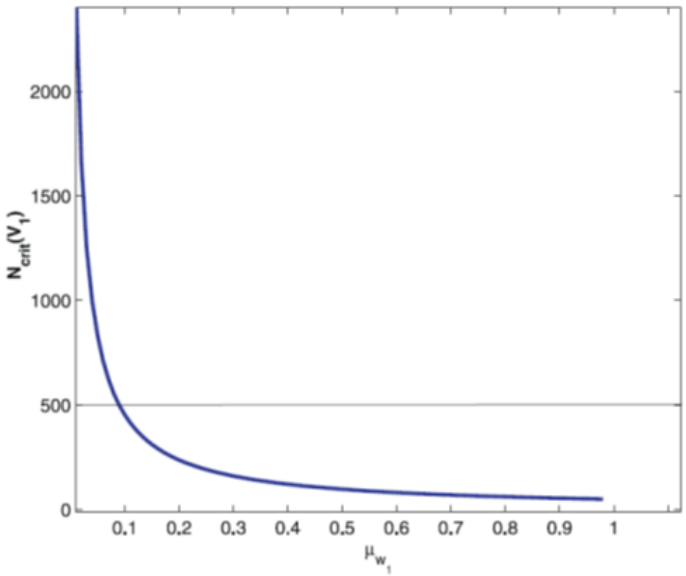
$$\frac{\mu_I(\mu_V - r)}{k\mu_w T_0} \geq \frac{\sum_{i=1}^{n}\mu_{I_i}(\mu_{V_i} - r_i)\prod_{j=1\, j\neq i}^{n}\mu_{w_j}}{\prod_{i=1}^{n}k_i\mu_{w_i}}.$$

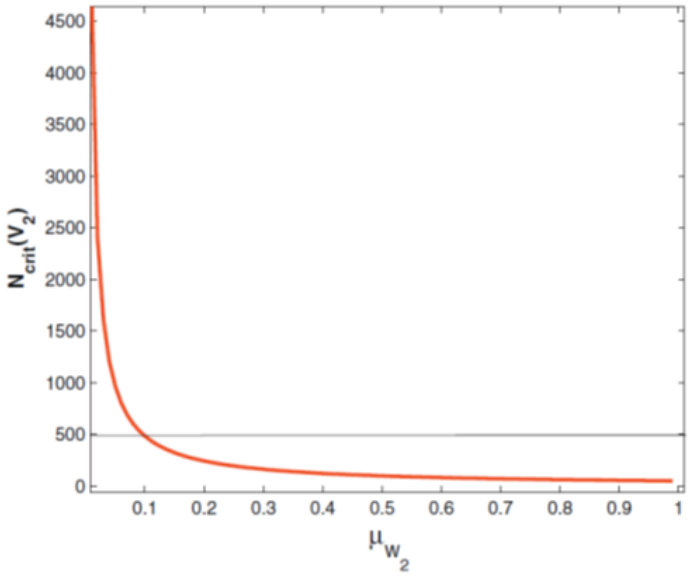
Sufficient conditions

Theorem 2.2. *The uninfected steady-state of the system of Eqs. (1)–(3) is locally asymptotically stable and remains sero-negative for* $N_i < N^n_{crit} < N^s_{crit}$.

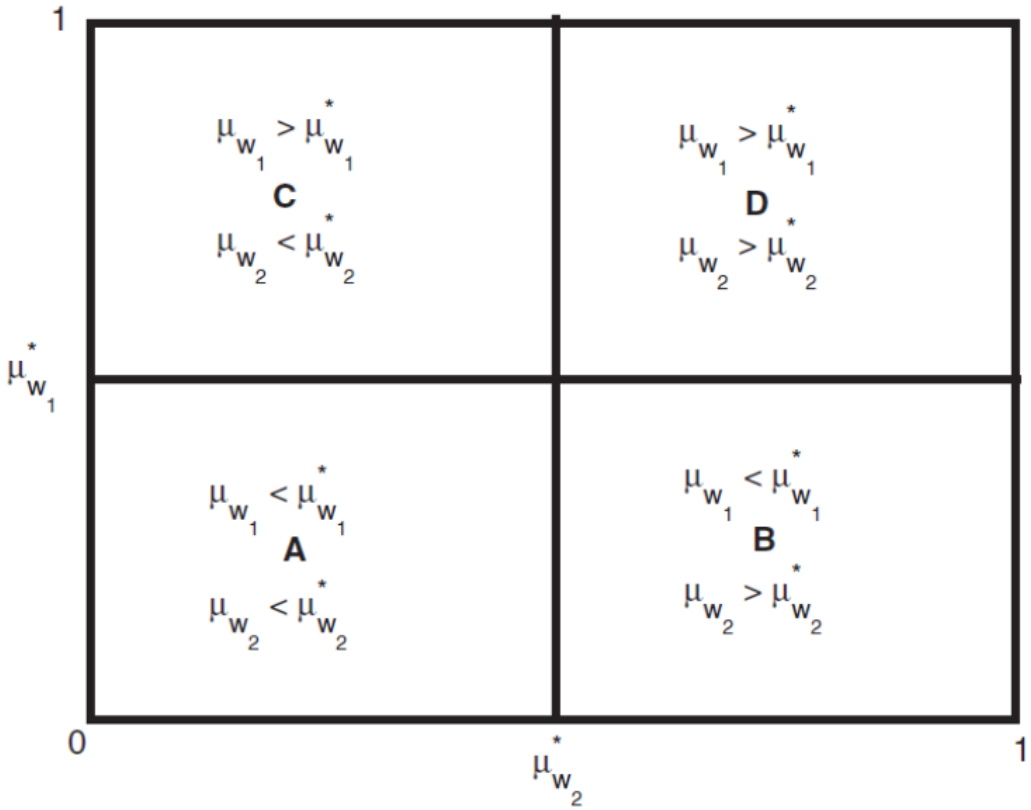
Numerical thresholds for viral fitness

Two strain numerical thresholds



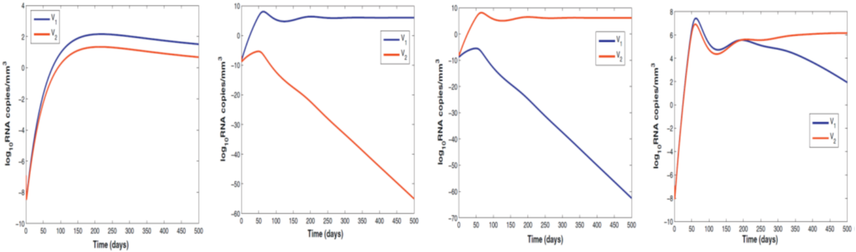


Numerical thresholds for viral fitness



Numerical thresholds for viral fitness

Region specific simulations



Summary

1. Mutation implications regarding treatment - treatment of one strain may promote selective pressure of the other one as well as replicative fitness.
2. Wild type virus can co-exist with the mutant virus in a switching dominance manner

Feasibe region

$$\dot{T} = \pi - \mu T - \beta_1 TV, \quad (17)$$
$$\dot{I} = \beta_1 TV - (\mu + \alpha)I, \quad (18)$$
$$\dot{V} = N\alpha I - \beta_1 TV - \mu_V V. \quad (19)$$

- Feasible region

$$\Omega = \{(T, I, V) \in \mathbb{R}^3_+ | 0 < T + I \leq \frac{\pi}{\mu}, 0 \leq V \leq \frac{N\alpha\pi}{\beta_1\pi + \mu\mu_V}\}.$$

Theorem

The positive orthant Ω is positively invariant for the system (20) and solutions are bounded.

Feasible region

- No solution paths leave through any boundary
- right sides of the model are smooth, so that initial value problems have solutions that exist on maximal intervals
- Since paths cannot leave Ω, solutions exist for all positive time.
- the model is mathematically and biologically meaningful.

The concept of positive invariance ensures that positive solutions are preserved both mathematically and biologically. Cell populations under consideration are always positive or nonnegative and thus mathematical solutions from the model will have a biological meaning and predictions from mathematical solutions can be biologically validated.

Equilibria analysis

$$
\begin{aligned}
E_0 &= (T_0, 0, 0), T_0 = \frac{\pi}{\mu}, \\
E^* &= (T^*, I^*, V^*), \\
T^* &= \frac{\mu T_0}{\mu + \beta_1 \nu_1 (\Re_0 - 1)(\mu_V + \beta_1 T_0)}, \\
I^* &= \frac{\beta_1 \mu (\Re_0 - 1) T_0 (\mu_V + \beta_1 T_0)}{\mu + \beta_1 \nu_1 (\Re_0 - 1)(\mu_V + \beta_1 T_0)}, \\
V^* &= \nu_1 (\Re_0 - 1)(\mu_V + \beta_1 T_0).
\end{aligned}
$$

Equilibria analysis

$$
\begin{aligned}
E_0 &= (T_0, 0, 0), T_0 = \frac{\pi}{\mu}, \\
E^* &= (T^*, I^*, V^*), \\
T^* &= \frac{\mu T_0}{\lambda^* + \mu}, \quad I^* = \frac{\mu T_0 \lambda^*}{(\mu + \delta)(\lambda^* + \mu)}, \\
V^* &= \left(\frac{\mu T_0 \delta}{\mu_V (\mu + \delta)} (N - N_{crit}) + \frac{\mu_V (\delta + \mu)}{\beta_1 T_0 \delta} \right) \frac{\lambda^*}{(\lambda^* + \mu)}, \\
\lambda^* &= \frac{\mu \beta_1 \delta T_0}{\mu_V (\mu + \delta)} (N - N_{crit}).
\end{aligned}
$$

Threshold analysis: Next generation operator method

1. Procedure - Classify the classes into
   - X- uninfected
   - Y- infected but noninfectious
   - Z- infected

   $X = \{T\}, \quad Y = \{\emptyset\}, \quad Z = \{I, V\}.$
2. Solve $\frac{dY}{dt} = 0$ to get $Y^*(Z)$ and substitute $Y^*(Z)$ into $\frac{dZ}{dt}$. Since Y is an empty set, we just go straight to $\frac{dZ}{dt}$ system.

$$\begin{aligned} \dot{I} &= \beta_1 TV - (\mu + \alpha)I, \\ \dot{V} &= N\alpha I - \beta_1 TV - \mu_V V. \end{aligned}$$

Threshold analysis: Next generation operator method

3. Let $J = \left(\frac{\partial}{\partial Z}\left(\frac{dZ}{dt}\right)\right)|_{DFE}$.

$$J = \begin{pmatrix} -\delta - \mu & \beta_1 T_0 \\ \delta N & -(\beta_1 T_0 + \mu_V) \end{pmatrix}$$

4. Decompose $J = M - D, \quad M \geq 0, \ D \geq 0, \quad D$-Diagonal matrix.

$$J = \begin{pmatrix} 0 & \beta_1 T_0 \\ \delta N & 0 \end{pmatrix} - \begin{pmatrix} \delta + \mu & 0 \\ 0 & (\beta_1 T_0 + \mu_V) \end{pmatrix},$$

$$M = \begin{pmatrix} 0 & \beta_1 T_0 \\ \delta N & 0 \end{pmatrix}, \quad D = \begin{pmatrix} \delta + \mu & 0 \\ 0 & (\beta_1 T_0 + \mu_V) \end{pmatrix},$$

Threshold analysis: Next generation operator method

5. $\Re_0$ is the dorminant eigenvalues of MD^{-1}.

$$D^{-1} = \begin{pmatrix} \frac{1}{\delta+\mu} & 0 \\ 0 & \frac{1}{(\beta_1 T_0+\mu_V)} \end{pmatrix}, \quad MD^{-1} = \begin{pmatrix} 0 & \frac{\beta_1 T_0}{(\beta_1 T_0+\mu_V)} \\ \frac{\delta N}{\delta+\mu} & 0 \end{pmatrix},$$

$$\Re_0 = \rho MD^{-1} = \sqrt{\frac{\delta N \beta_1 T_0}{(\delta+\mu)(\beta_1 T_0+\mu_V)}}$$

- Compare results with the computation using the next genearation matrix method

Threshold analysis

The computation using the next generation matrix method yields

$$\Re_0 = \frac{\alpha\beta_1 N T_0}{(\mu+\alpha)(\mu_V+\beta_1 T_0)}, \quad T_0 = \frac{\pi}{\mu},$$

If $\Re_0 = 1$ we get an equivalent critical Threshold

$$N_{crit} = \frac{(\mu+\alpha)(\mu_V+\beta_1 T_0)}{\alpha\beta_1 T_0},$$

$$N_{crit} = \frac{N}{\Re_0}.$$

Recall

$$
\begin{aligned}
E_0 &= (T_0, 0, 0), T_0 = \frac{\pi}{\mu}, \\
E^* &= (T^*, I^*, V^*), \\
T^* &= \frac{\mu T_0}{\mu + \beta_1 \nu_1 (\Re_0 - 1)(\mu_V + \beta_1 T_0)}, \\
I^* &= \frac{\beta_1 \mu (\Re_0 - 1) T_0 (\mu_V + \beta_1 T_0)}{\mu + \beta_1 \nu_1 (\Re_0 - 1)(\mu_V + \beta_1 T_0)}, \\
V^* &= \nu_1 (\Re_0 - 1)(\mu_V + \beta_1 T_0).
\end{aligned}
$$

Recall

$$
\begin{aligned}
E_0 &= (T_0, 0, 0),\ T_0 = \frac{\pi}{\mu}, \\
E^* &= (T^*, I^*, V^*), \\
T^* &= \frac{\mu T_0}{\lambda^* + \mu}, \quad I^* = \frac{\mu T_0 \lambda^*}{(\mu+\delta)(\lambda^*+\mu)}, \\
V^* &= \left(\frac{\mu T_0 \delta}{\mu_V(\mu+\delta)}(N - N_{crit}) + \frac{\mu_V(\delta+\mu)}{\beta_1 T_0 \delta} \right) \frac{\lambda^*}{(\lambda^*+\mu)}, \\
\lambda^* &= \frac{\mu \beta_1 \delta T_0}{\mu_V(\mu+\delta)}(N - N_{crit}).
\end{aligned}
$$

Existence and Stability of Equilibria

Theorem

1. E_0 *exists for all* $\Re_0$.
2. E^* *exists only for* $\Re_0 > 1$.

Equivalently,

Theorem

1. E_0 *exists for all* N
2. E^* *exists only for* $N > N_{crit}$.

Existence and Stability of Equilibria

Theorem

1. *E_0 is locally asymptotically stable when $\Re_0 < 1$ and unstable when $\Re_0 > 1$.*
2. *E^* is locally asymptotically stable when $\Re_0 > 1$.*

Equivalently,

Theorem

1. *E_0 is locally asymptotically stable when $N < N_{crit}$ and unstable when $N > N_{crit}$.*
2. *E^* is locally asymptotically stable when $N > N_{crit}$.*

Stability of E_0

Proof.

The Jacobian matrix is given by

$$J(E) = \begin{pmatrix} -V\beta - \mu & 0 & -T\beta \\ V\beta & -\delta - \mu & T\beta \\ -V\beta & N\delta & -T\beta - \mu_V \end{pmatrix}$$

Evaluate at $E = E_0$

$$J(E_0) = \begin{pmatrix} -\mu & 0 & -T\beta \\ 0 & -\delta - \mu & \beta T_0 \\ 0 & N\delta & -\beta T_0 - \mu_V \end{pmatrix}$$

□

Stability of E_0

Proof.

The Characteristic equation

$$(\lambda+\mu)(\lambda^2+(\delta+\mu+\beta T_0+\mu_v)\lambda+(\delta+\mu)(\beta T_0+\mu_v)(1-\Re_0)=0,$$

$$\Re_0 = \frac{\beta\delta N T_0}{(\delta+\mu)(\beta T_0+\mu_v)}.$$

OR

$$(\lambda+\mu)(\lambda^2+(\delta+\mu+\beta T_0+\mu_v)\lambda+\beta\delta T_0(N_{crit}-N)=0,$$

$$N_{crit}=\frac{(\delta+\mu)(\beta T_0+\mu_v)}{\beta\delta T_0}$$

□

Stability of E_0

Proof.

The Eigenvalues

$$\begin{aligned}\lambda_1 &= -\mu, \quad \lambda_2 = \frac{-a_1 + \sqrt{a_1^2 - 4a_0}}{2}, \quad \lambda_3 = \frac{-a_1 - \sqrt{a_1^2 - 4a_0}}{2},\\ a_1 &= \delta + \mu + \beta T_0 + \mu_v, \quad a_0 = (\delta + \mu)(\beta T_0 + \mu_v)(1 - \Re_0)\end{aligned}$$

OR

$$\begin{aligned}\lambda_1 &= -\mu, \quad \lambda_2 = \frac{-a_1 + \sqrt{a_1^2 - 4a_0}}{2}, \quad \lambda_3 = \frac{-a_1 - \sqrt{a_1^2 - 4a_0}}{2},\\ a_1 &= \delta + \mu + \beta T_0 + \mu_v, \quad a_0 = \beta\delta T_0(N_{crit} - N)\end{aligned}$$

Stability of E_0

Proof.

For stability, we require $\lambda_i < 0$ or $Re(\lambda_i) < 0$.

$$\begin{aligned} \lambda_1 &= -\mu < 0, \\ \lambda_{2,3} &= \frac{-a_1 \pm \sqrt{a_1^2 - 4a_0}}{2} < 0 \; Re(\lambda_{2,3}) < 0 \end{aligned}$$

provided $a_0 > 0$, that is, $\Re_0 < 1$.
OR

$$\lambda_{2,3} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_0}}{2} < 0 \; Re(\lambda_{2,3}) < 0$$

provided $a_0 > 0$, that is, $N < N_{crit}$

Stability of E_0

Proof.

Note that if $\Re_0 > 1$.

$$\lambda_2 = \frac{-a_1 + \sqrt{a_1^2 - 4a_0}}{2} > 0$$

and E_0 becomes unstable.
OR
if $N > N_{crit}$

$$\lambda_2 = \frac{-a_1 + \sqrt{a_1^2 - 4a_0}}{2} > 0$$

and E_0 becomes unstable. □

Stability of E^*

Proof.

The Jacobian matrix evaluated at E^*

$$J(E^*) = \begin{pmatrix} -\beta V^* - \mu & 0 & -\beta T^* \\ \beta V^* & -\delta - \mu & \beta T^* \\ -\beta V^* & N\delta & -\beta T^* - \mu_V \end{pmatrix}$$

Characteristic equation of $J(E^*)$

$$X^3 + c_2 X^2 + c_1 X + c_0 = 0,$$

where

□

Stability of E^*

Proof.

$$
\begin{aligned}
c_2 &= \frac{a_2\left(a_4\beta\lambda + (\lambda+\mu)(\mu+\mu v)\right) + a_1\left(a_2\beta + \lambda + \mu\right)}{a_2(\lambda+\mu)},\\
c_1 &= \frac{a_2\mu v\left(a_4\beta\lambda + \mu(\lambda+\mu)\right) + a_1^2\beta + a_1\left(a_4\beta\lambda + a_2\beta(\mu - \delta N1) + (\right.}{a_2(\lambda+\mu)}\\
c_0 &= \frac{a_1\left(\mu v\left(a_4\beta\lambda + \mu(\lambda+\mu)\right) + a_1\beta\mu - a_2\beta\delta\mu N1\right)}{a_2(\lambda+\mu)},\\
a_1 &= \mu T_0, \quad a_2 = \frac{a_1}{\mu+\delta},\\
a_3 &= \frac{\delta}{\mu v}(N - N_{crit}) + \frac{\mu\mu_V}{\delta\beta_1}, \quad a_4 = a_3 a_2.
\end{aligned}
$$

□

Stability of E^*; Use the R-Huwitz criterion

Proof.

Exercise: Show that the cubic polynomial satisfy the Routh-Hurwitz criterion.

$$\begin{aligned} c_0 &> 0, \\ c_2 &> 0, \\ c_2 c_1 - c_0 &> 0. \end{aligned}$$

□

Stability using Centre Mainfold theory

$$\begin{aligned}
\dot{T} &= \pi - \mu T - \beta TV, \\
\dot{I} &= \beta TV - (\mu + \alpha) I - hIC, \\
\dot{V} &= pI - cV, \\
\dot{C} &= sI - \mu C.
\end{aligned}$$

Stability using Centre Mainfold theory: Equilibria

$E_0 = (T^*, 0, 0, 0)$, $T^* = \frac{\pi}{\mu}$ and $\bar{E} = (\bar{T}, \bar{I}, \bar{V}, \bar{C})$ where

$$\bar{T} = -\frac{chs\mu - \beta p(\mu+\alpha))}{2\beta^2 p^2} + \sqrt{\left(-\frac{c(hs\mu - \beta p(\mu+\alpha))}{2\beta^2 p^2}\right)^2 + \frac{hsc^2\tau}{\beta^2 p^2 \mu}}$$

$$\bar{I} = \frac{\beta p\mu}{hsc}\left(\bar{T} - \frac{c(\mu+\alpha)}{\beta p}\right),$$

$$\bar{V} = \frac{\beta p^2\mu}{hsc^2}\left(\bar{T} - \frac{c(\mu+\alpha)}{\beta p}\right),$$

$$\bar{C} = \frac{\beta p}{hc}\left(\bar{T} - \frac{c(\mu+\alpha)}{\beta p}\right).$$

Stability using Centre Mainfold theory: Equilibria

Theorem

The uninfected steady state, E_0, exists for all values of R_0 and the infected steady state, $\bar{E}$, exists only when $R_0 > 1$.

Theorem

The infected steady-state, $\bar{E}$, is locally asymptotically stable if $R_0 > 1$.

Stability using Centre Mainfold theory: Equilibria

Proof.

Introduce new variables $x_1 = T,\ x_2 = I,\ x_3 = V,\ x_4 = C$ and rewrite the system of equations (32) - (**??**) as given below

$$\begin{aligned}
\dot{x_1} &= f_1 = \pi - \mu x_1 - \beta x_1 x_3, \\
\dot{x_1} &= f_2 = \beta x_1 x_2 - (\mu + \alpha) x_2 - h x_2 x_4, \\
\dot{x_1} &= f_3 = p x_2 - c x_3, \\
\dot{x_1} &= f_4 = s x_2 - \mu x_4.
\end{aligned}$$

Stability using Centre Mainfold theory: Equilibria

Proof.

The Jacobian at the uninfected steady state

$$J(E_0) = \begin{pmatrix} -\mu & 0 & -\beta T^* & 0 \\ 0 & -(\mu+\alpha) & \beta T^* & 0 \\ 0 & p & -c & 0 \\ 0 & s & 0 & -\mu \end{pmatrix}. \quad (20)$$

Choosing β as a bifurcation parameter when $R_0 = 1$,

$$\beta = \beta^* = \frac{c(\mu+\alpha)}{pT^*}. \quad (21)$$

Stability using Centre Mainfold theory: Equilibria

Proof.

Replace β by β^* in (20)

$$J(E_0^*) = \begin{pmatrix} -\mu & 0 & -\beta^* T^* & 0 \\ 0 & -(\mu+\alpha) & \beta^* T^* & 0 \\ 0 & p & -c & 0 \\ 0 & s & 0 & -\mu \end{pmatrix}. \quad (22)$$

Eigenvalues of $J(E_0^*)$ are $(0, -\mu, -(c+\mu+\alpha), -\mu)$. $\lambda = 0$ is a simple eigenvalue.
Right eigenvector associate with $\lambda = 0$

$$(w_1, w_2, w_3, w_4) = (-\frac{(\mu+\alpha)}{s}, \frac{\mu}{s}, \frac{p\mu}{sc}, 1),$$

Stability using Centre Mainfold theory: Equilibria

Proof.

Right eigenvector associate with $\lambda = 0$

$$(w_1, w_2, w_3, w_4) = (-\frac{(\mu+\alpha)}{s}, \frac{\mu}{s}, \frac{p\mu}{sc}, 1),$$

Left eigenvector associate with $\lambda = 0$

$$(v_1, v_2, v_3, v_4) = (0, \frac{p}{\mu+\alpha}, 1, 0),$$

□

Stability using Centre Mainfold theory: Equilibria

Proof.

The nonzero partial derivatives of f_i in equations (20) - (20), where $i = 1, 2, 3, 4$ are given by

$$\frac{\partial^2 f_1}{\partial x_1 \partial x_3} = \frac{\partial^2 f_1}{\partial x_3 \partial x_1} = -\beta^* T^*, \quad \frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \beta^* T^*,$$

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_2} = -h,$$

$$\frac{\partial^2 f_1}{\partial x_3 \partial \beta^*} = -T^*, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = T^*.$$

Stability using Centre Mainfold theory: Equilibria

Proof.

Compute the parameters that determine the direction of the bifurcation

$$a = 2\beta^* T^* v_2 w_1 w_2 - 2h w_2 w_4 = -2p\mu\left(\frac{p\beta^* T^* \mu}{cds^2} + \frac{h}{\mu+\alpha}\right) < 0,$$

$$b = v_2 w_3 T^* > 0.$$

Since $a < 0$ and $b > 0$, the system exhibits a forward bifurcation and the infected steady-state is locally asymptotically stable whenever $R_0 > 1$ but close to 1. □

Global stability

Proof.

Theorem

The uninfected steady state is Globally asymptotically stable for $R_0 < 1$.

E_0 is the only steady-state that exists when $R_0 < 1$. Then

$$\dot{T} \leq -\mu(T - T^*), \quad \text{for} \quad T > 0, \; V \geq 0.$$

Define

$$T^{\infty} = \lim_{t \to \infty} \sup_{\phi \geq t} T(\phi).$$

Let $T^1(t)$ be an upper solution such that $T^1(t) \geq T(t)$ for all $t \geq 0$

Global stability

Proof.

$T^1(t)$ is a solution to the inequality

$$\dot{T}^1 \leq -\mu(T^1 - T^*), \quad T^1(0) = T^*.$$

$$T^1(t) \leq T^*, \ \forall t > 0.$$

$T^1(t) \to T^*$ as $t \to \infty$. $\forall \epsilon_0 > 0$, $\exists t_0 > 0$ such that $T(t) \leq T^1(t) \leq T^* + \epsilon_0$ for $t \geq t_0$. Thus $T^\infty \leq T^* + \epsilon_0$.

$$T^\infty \leq T^*. \tag{23}$$

Assume T cells is distributed by a small amount ϵ_0. □

Global stability

Proof.

$$\dot{I} \leq \beta(T^* + \epsilon_0)V - (\mu + \alpha)I, \tag{24}$$

$$\dot{V} = pI - cV. \tag{25}$$

In matrix form,

$$\begin{pmatrix} \dot{I} \\ \dot{V} \end{pmatrix} \leq \Theta \begin{pmatrix} \dot{I} \\ \dot{V} \end{pmatrix}, \quad \Theta = \begin{pmatrix} -(\mu + \alpha) & \beta(T^* + \epsilon_0) \\ p & -c \end{pmatrix}. \tag{26}$$

□

Global stability

Proof.

Choose $M \in \mathbf{R}^+$ so that $M > max\{\mu + \alpha, c\}$. The matrix $\Theta + MI_2$, where I_2 is a 2×2 identity matrix, is a strictly positive matrix.

Let $\lambda_1,\ \lambda_2$ be the eigenvalues of Θ, then $\lambda_1 + M, \lambda_2 + M$ are the eigenvalues of $\Theta + MI_2$

Apply the Perron-Frobenious theorem on nonnegative matrices. The matrix $\Theta + MI_2$ has a simple positive eigenvalue equal to the spectral radius and a corresponding positive eigenvector ($\mathbf{e} > 0$) implying that both λ_1 and λ_2 are real. □

Global stability

Proof.

Choose $\lambda_1 + M$ to be the dorminant eigenvalue of $\Theta + MI_2$ implying $\lambda_1 > \lambda_2$, then $\mathbf{e}\Theta = \lambda_1 \mathbf{e}$ and $\lambda_1,\ \lambda_2$ are roots of the equation

$$\lambda^2 + (c + \mu + \alpha)\lambda + c(\mu + \alpha)(1 - R_0(\epsilon_0)) = 0, \quad (27)$$

where

$$R_0(\epsilon_0) = \frac{p\beta(T^* + \epsilon_0)}{c(\mu + \alpha)}.$$

All the coefficients of the quadratic equation (27) are positive when $R_0(\epsilon_0) < 1$, and as $\epsilon_0 \to 0$, we have $R_0 < 1$. □

Global stability

Proof.

Since the eigenvalues λ_1 and λ_2 are real and coefficients of equation (27) are positive so when $R_0 < 1$, then both λ_1 and λ_2 are negative.
For $t \geq t_0$, the inequality

$$\frac{d}{dt}(\mathbf{e} \bullet [I(t), V(t)]) \leq \lambda_1 \mathbf{e} \bullet [I(t), V(t)], \tag{28}$$

holds.
Integrating the inequality yields

$$0 \leq \mathbf{e} \bullet [I(t), V(t)] \leq \mathbf{e} \bullet [I(t), V(t)] e^{\lambda_1 (t - t_1)}, \tag{29}$$

for $t \geq t_1 \geq t_0$. □

Global stability

Proof.

Since $\mathbf{e} > 0$, we conclude that

$$[I(t), V(t)] \quad \rightarrow \quad (0,0) \ \text{ as } \mathrm{t} \rightarrow \infty. \tag{30}$$

For the CTLs population, choose $\epsilon_1 > 0$ sufficiently small so that there exist $t_2 \geq t_1$ such that $I(t) \leq \epsilon_1$ for $t \geq t_2$. Hence,

$$\dot{C(t)} \leq s\epsilon_1 - \mu C,$$

where

$$C(t) \leq \frac{s\epsilon_1}{\mu} + (C(t_2) - \frac{s\epsilon_1}{\mu})e^{\mu(t_2-t)}.$$

As $t \rightarrow \infty$ and letting $\epsilon_1 \rightarrow 0$, $C(t) \rightarrow 0$.

□

Global stability

Proof.

We have so far shown that as $t \to \infty$,
$[I(t), V(t), C(t)] \to (0, 0, 0)$ and $T(t) \to T^*$.
Now choose $\epsilon_2 > 0$ $(\epsilon_2 < \epsilon_1)$ sufficiently small so that for $t > t_2$, $V(t) \leq \epsilon_2$.

$$\dot{T} \geq \pi - \beta\epsilon_2 T - \mu T,$$

and define

$$T_\infty = \lim_{t\to\infty} \inf_{\phi\geq 0} T(\phi).$$

Global stability

Proof.

Solving this inequality gives

$$T_\infty \geq \frac{\pi}{\beta\epsilon_2 + \mu},$$

and letting $\epsilon_2 \to 0$ we obtain that

$$T_\infty \geq T^*. \tag{31}$$

We conclude that $T_\infty = T^\infty = T^*$ which means that $T(t) \to T^*$ as $t \to \infty$. □

Basic within-host HIV dynamics with Immune response: Exercise

$$\dot{T} = \pi - \mu T - \beta_1 TV - \beta_2 TI, \quad (32)$$

$$\dot{I} = (\beta_1 V + \beta_2 I)T - (\mu + \alpha)I - hIT_C, \quad (33)$$

$$\dot{V} = N\alpha I - \mu_V V, \quad (34)$$

$$\dot{T}_C = sI - \mu T_C. \quad (35)$$

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ANALYSIS OF COMBINED LANGERHANS AND CD4+ T CELLS HIV INFECTION*

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Effects of replicative fitness on competing HIV strains

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Modelling Multiple Dosing with Drug Holiday in Antiretroviral Treatment on HIV-1 Infection

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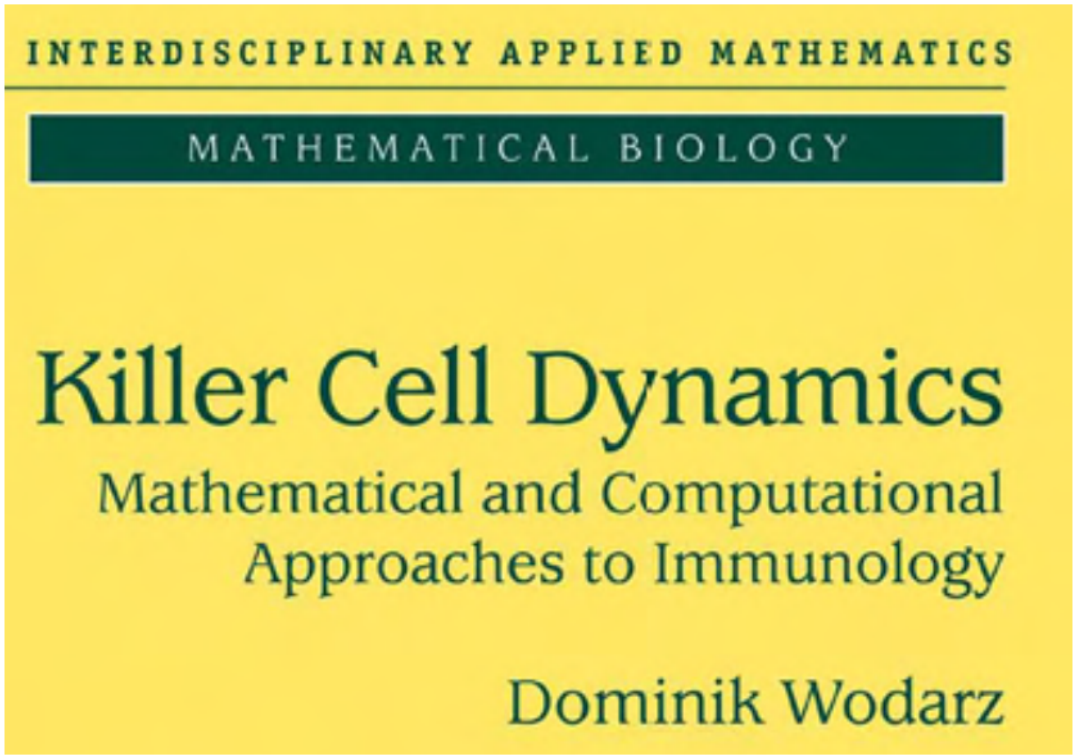
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