# Control Strategies for HIV Infected systems

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# HIV and Immune Response

HIV (Human Immunodeficiency Virus) attacks CD4+ T helper 1 (TH1) lymphocytes

TH1 has a central function in adaptive immune response → the activation of the antigen-specific CD8 cytotoxic T lymphocytes (CTL)

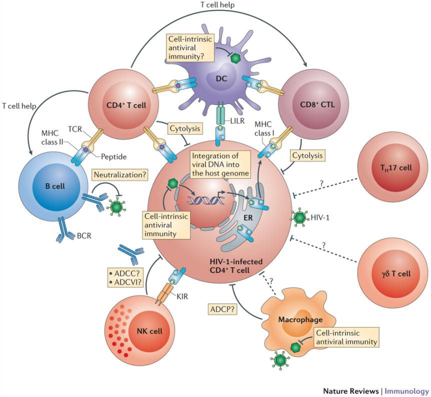



Figure: from Walker and Yu, 2013

# Timeline of HIV Infection

HIV infection causes a decline in TH1 activity, which eventually leads to symptomatic stage of infection known as AIDS.

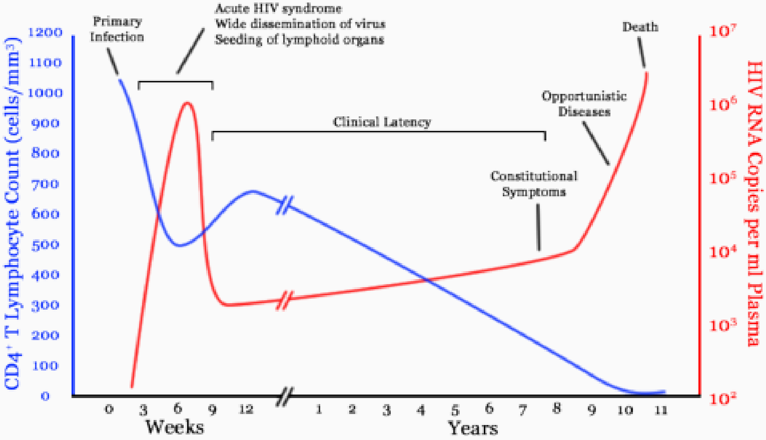



Figure: from Pantaleo, Graziosi, and Fauci, 1993

# HIV Theraphy and Interrupted Treatment

HAART (Highly Active Antiretroviral Therapy) → multiple drugs that act on different viral targets

Structured Treatment Interruption (STI) → A strategy in which the patients are cycled on and off therapy in hope of allowing them to maintain immune control of virus in the absence of treatment

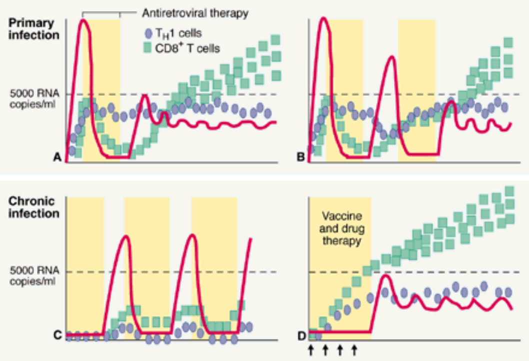



Figure: from Autran and Carcelain, 2000

# Objective

Goal: Choose treatment strategy $u(t)$ to drive system into a healthy steady state where viral population can be kept below the threshold value by immune system alone.

# Approaches to solving the problem

In optimal control theory, an objective function is constructed that when maximized (or minimized) achieves a desired result. For continuous problems, the general form of this functional can be written as

$$J[u] = \phi(x(t_f), t_f) + \int_{t_0}^{t_f} L(x(t), u(t), t)$$

or in a discrete form as

$$J[u] = \phi(x(t_f), t_f) + \sum_{i=1}^{n} L(X_i, u_i)$$

subject to the constraints of the problem.

# How to choose a control strategy?

Choice of control must be in accordance with real-world capabilities. While many variations exist, our work will focus on two common variants:

→ "bang-bang" control

Switch-like control, i.e. either full treatment or none at all

→ Continuous control

Control parameter can be any value in a specified range

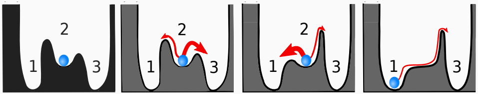



Figure: from Wells, Kath, and Motter, 2015

# Representing an HIV infected system

$$
\begin{aligned}
\dot{\mathbf{x}} &= \lambda - d\mathbf{x} - \beta(1-\eta u)\mathbf{x}\mathbf{y} \\
\dot{\mathbf{y}} &= \beta(1-\eta u)\mathbf{x}\mathbf{y} - a\mathbf{y} - p_1\mathbf{z_1}\mathbf{y} - p_2\mathbf{z_2}\mathbf{y} \\
\dot{\mathbf{z_1}} &= c_1\mathbf{z_1}\mathbf{y} - b_1\mathbf{z_1} \\
\dot{\mathbf{w}} &= c_2\mathbf{x}\mathbf{y}\mathbf{w} - c_2 q\mathbf{y}\mathbf{w} - b_2\mathbf{w} \\
\dot{\mathbf{z_2}} &= c_2 q\mathbf{y}\mathbf{w} - h\mathbf{z_2}
\end{aligned}
$$

where $\mathbf{x} =$ healthy T cells, $\mathbf{y} =$ infected T cells,
$\mathbf{z_1} =$ helper-independent. CTL, $\mathbf{w} =$ CTL precursors,
$\mathbf{z_2} =$ helper-dependent CTL. $u$ - treatment, 1 or 0.

# Developing a Treatment Strategy

The control problem can be rephrased as a minimization of the cost function

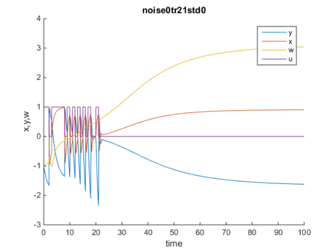
$$V(X_k, U) = \sum_{i=k}^{k+N-1} l(X_i, u_i) + F(X_{k+N})$$

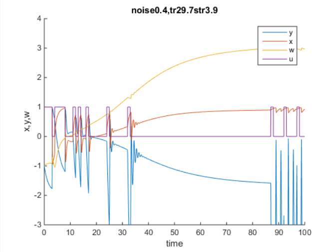
$$l(X_i, u_i) = \alpha_1 (x_i - \hat{x})^2 + \alpha_2 (w_i - \hat{w})^2 + \alpha_3 |u_i|$$
$$F(X_k) = \alpha_1 (x_k - \hat{x})^2 + \alpha_2 (w_k - \hat{w})^2$$

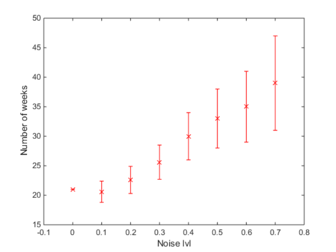
→ Use exhaustive search to find the set of *U* that minimizes cost function for the next 6 weeks

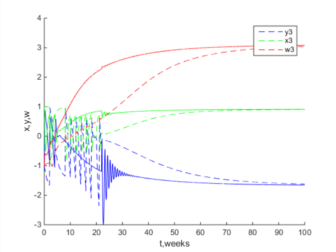
→ Step forward just 1 week, then redo the procedure

# Results for deterministic system

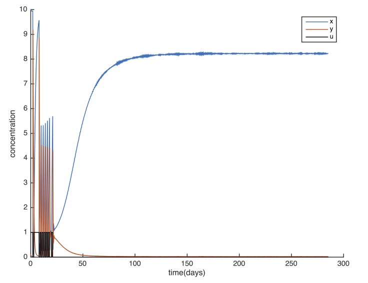


# Results for stochastic system



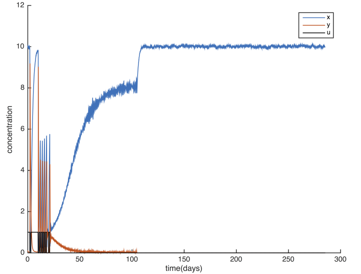




Figure: Increasing particles in the system leads to approximately deterministic behavior (left), while fewer particles allow for potential removal of virus (right)

# Calculating a continuous control

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T + T^* + T^{**}}{T_{max}}\right) - k_1 VT$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**}$$

$$\frac{dV}{dt} = u(t) N \mu_b T^{**} - k_1 VT - \mu_V V$$

Where $T =$ healthy T cells, $T^* =$ latently infected T cells, $T^{**} =$ actively infected T cells, and $V =$ viral load.

# Developing a Treatment Strategy

We aim to maximize the cost function

$$J(u) = \int_{tstart}^{tfinal} T(t) - \frac{1}{2}B(1 - u(t))^2 dt$$

- → Use Euler-Lagrange Equations to find $u(t)$ that maximizes $J$
- → Steady states depend on u

# Lagrangian approach

We take the Lagrangian to be:

$$
\begin{aligned}
L(T, T^*, T^{**}, V, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4) &= T(t) - \frac{1}{2}B(1-u(t))^2 \\
&+ \lambda_1\left(\frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T + T^* + T^{**}}{T_{max}}\right) - k_1 VT\right) \\
&+ \lambda_2(k_1 VT - \mu_T T^* - k_2 T^*) + \lambda_3(k_2 T^* - \mu_b T^{**}) \\
&+ \lambda_4(u(t) N \mu_b T^{**} - k_1 VT - \mu_V V) + \omega_1(t)u(t) + \omega_2(t)(1-u(t))
\end{aligned}
$$

# Costate equations

By Pontryagin's Maximum Principle, the optimization problem can be rephrased as a solving the original system along with

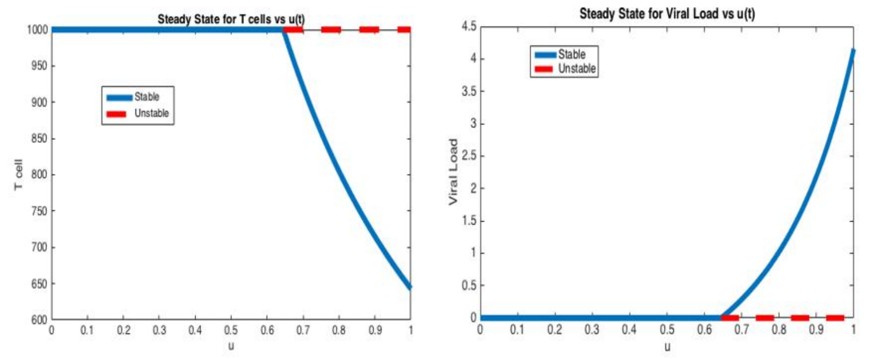
$$\lambda_1' = -\frac{\partial L}{\partial T} = -\left[1 + \lambda_1\left(-\mu_T + r\left(1 - \frac{T + T^* + T^{**}}{T_{max}}\right) - r\frac{T}{T_{max}} - k_1 V\right)\right.$$

$$\lambda_2' = -\frac{\partial L}{\partial T^*} = -\left[-r\frac{\lambda_1 T}{T_{max}} - \lambda_2(\mu_T + k_2) + \lambda_3 k_2\right]$$

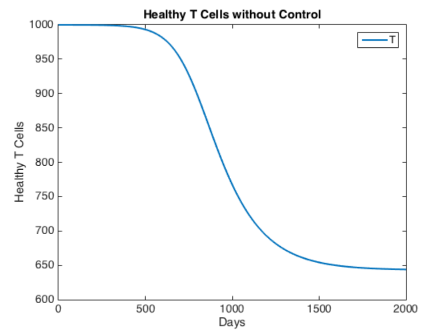
$$\lambda_3' = -\frac{\partial L}{\partial T^{**}} = -\left[-r\frac{\lambda_1 T}{T_{max}} - \lambda_3\mu_b + \lambda_4 u(t)\right]$$

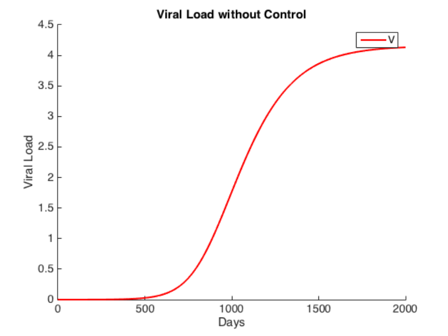
$$\lambda_4' = -\frac{\partial L}{\partial V} = -\left[-\frac{\lambda_1 s}{(1+V)^2} - \lambda_1 k_1 T + \lambda_2 k_1 T + \lambda_4(-k_1 T - \mu_V)\right]$$

# Steady State

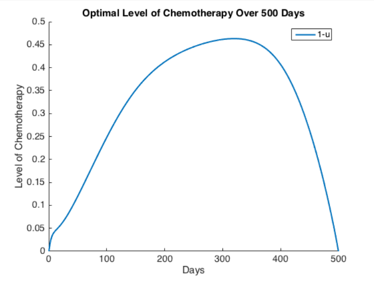


# Behavior without control

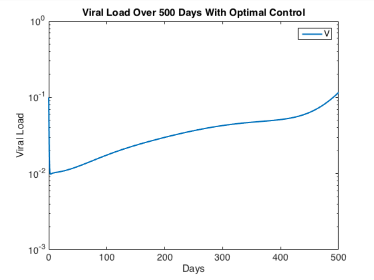


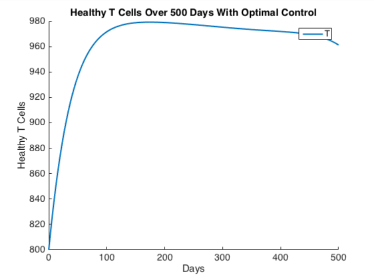



# Optimal deterministic control




Computed control helps system to recover, allowing for a healthy T Cell population



# Any Questions?

Thank you for listening. (Y'all better not ask any questions.)

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