Statistical and Mathematical Modeling in HIV: Estimation and Control

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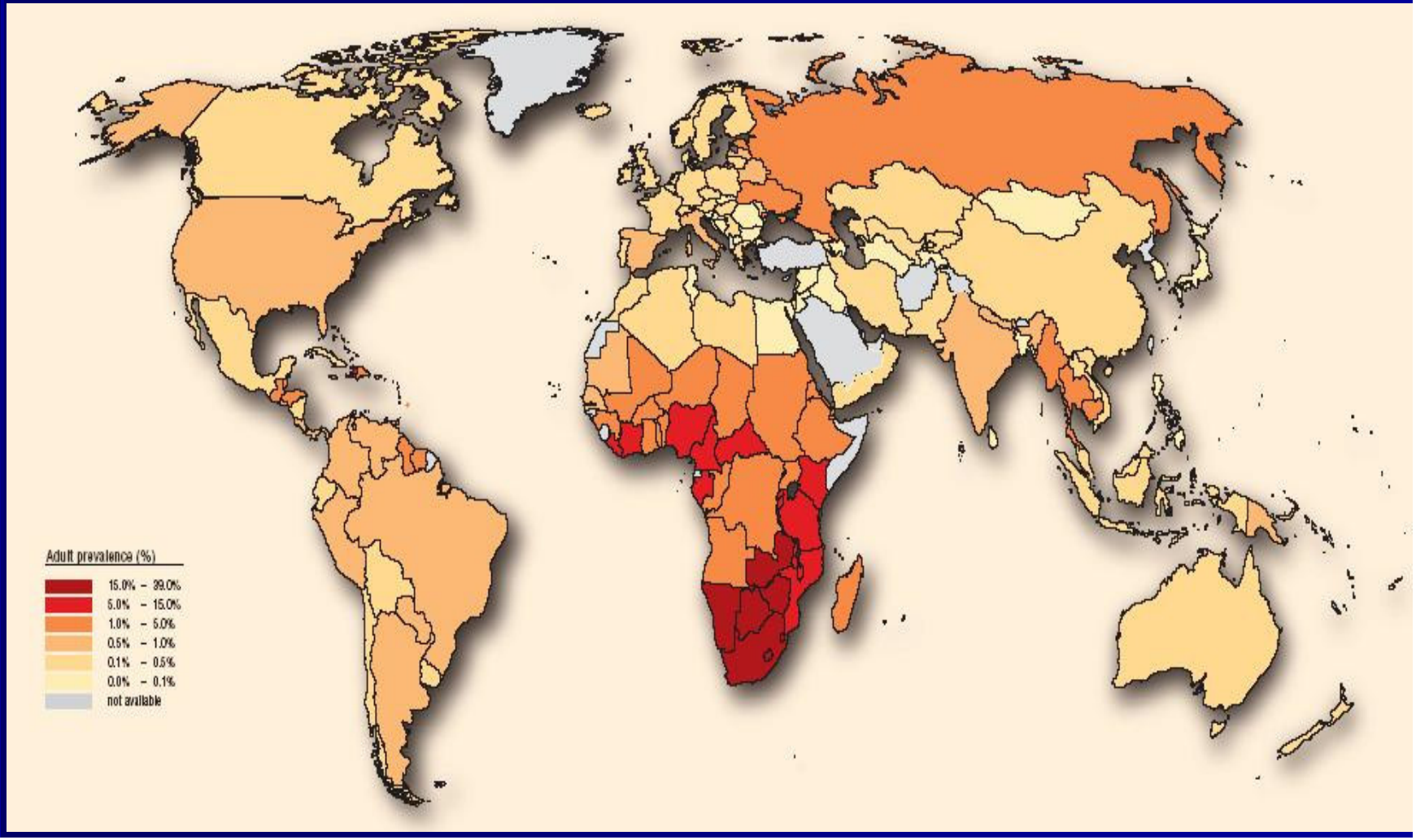
HIV – An Overview

Human immunodeficiency virus (HIV)

~38 million infected as of 2003 (WHO/UNAIDS)



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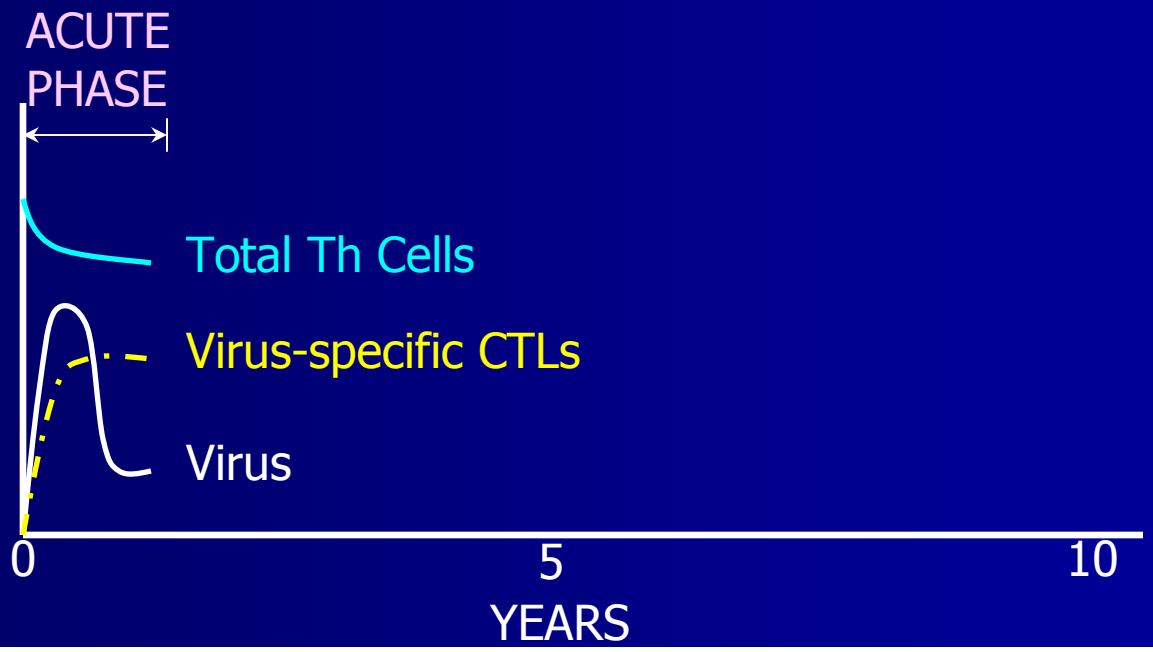
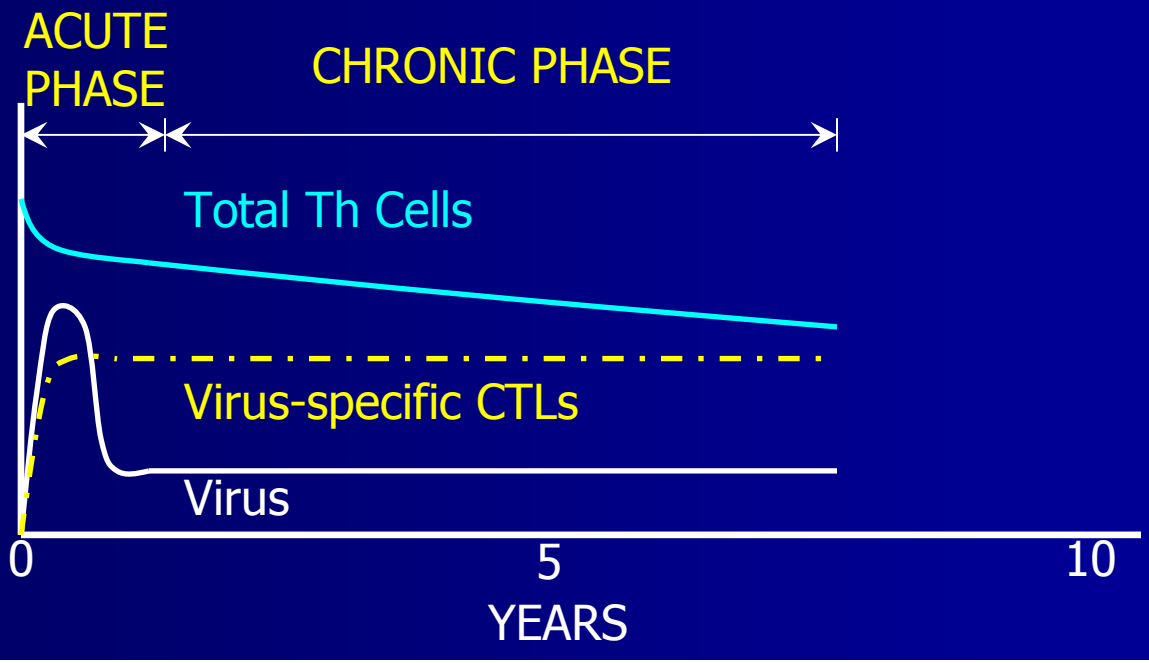
Dynamics of HIV Infection

- Viruses enter cells, and use the cell's biosynthetic machinery to make many more copies of the virus
- Newly made viruses then burst out of the cell, and go on to infect other cells
- After a week or so, the virus-specific B cells, helper T cells (General), and killer T cells (cytotoxic lymphocytes – CTL, soldier) are activated, proliferate, and begin to attack the virus-infected cells



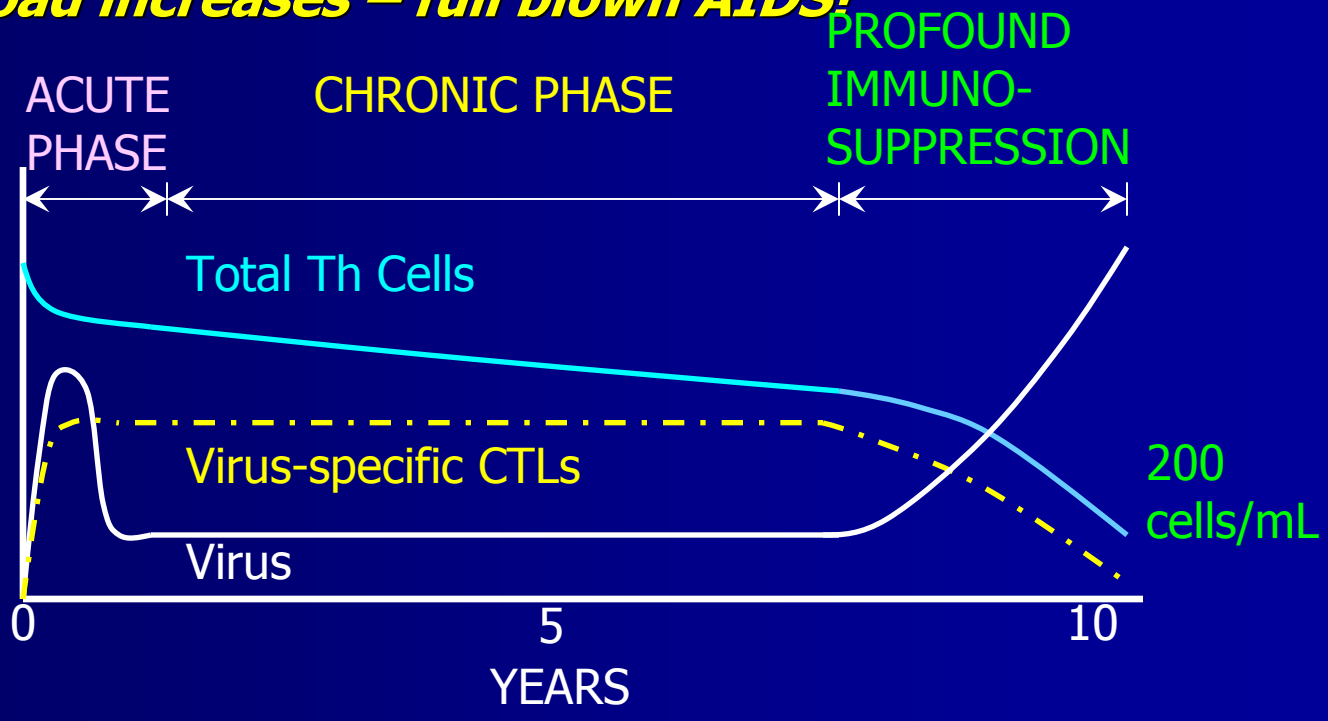
Dynamics of HIV Infection (cont'd)

- With many viruses, the end result of the acute phase of a viral infection is "sterilization" (invading viruses are destroyed), and memory B and T cells are produced to protect against a later infection
- For a very few (lucky individuals), HIV infection may end in sterilization
- Vast majority, HIV infection leads to a chronic phase – fierce battle between the immune system and the AIDS virus



Dynamics of HIV Infection *(cont'd)*

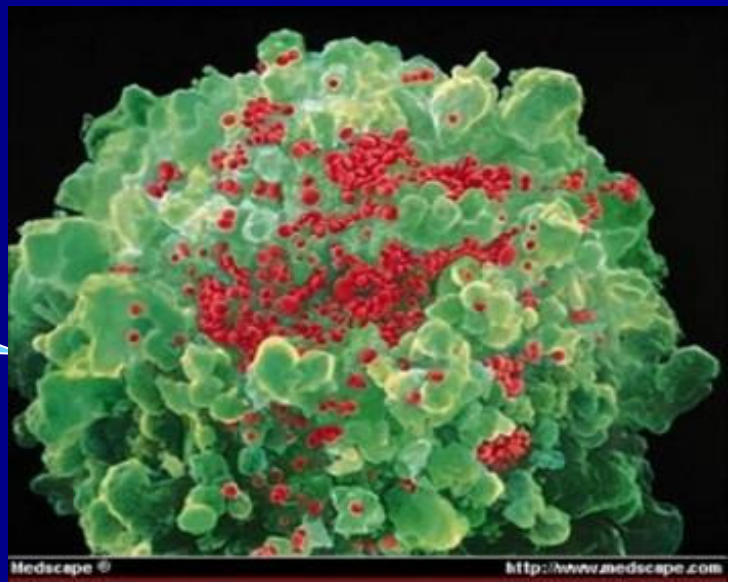
- *As the chronic phase progresses, the Th cells slowly decreases (because these cells are killed by the viral infection)*
- *Eventually, there are not enough Th cells left to provide the help needed by CTLs*
- *When this happens, CTLs also begins to decline*
- *Viral load increases – full blown AIDS!*



What's Happening during the Chronic Phase?

- HIV virus is RNA with a protective coat
  - After it enters a cell, the RNA is copied by an enzyme called reverse transcriptase to make a piece of "copy" DNA (cDNA)
  - Next, the DNA of the cell is cut by an enzyme (integrase) carried by the virus, and the viral cDNA is inserted into the gap in the cellular DNA (retrovirus)
  - Once viral DNA is integrated into cellular DNA, it can just stay there or be transcribed to produce copies of virus

In this latency state, the infected cell cannot be detected by CTLs



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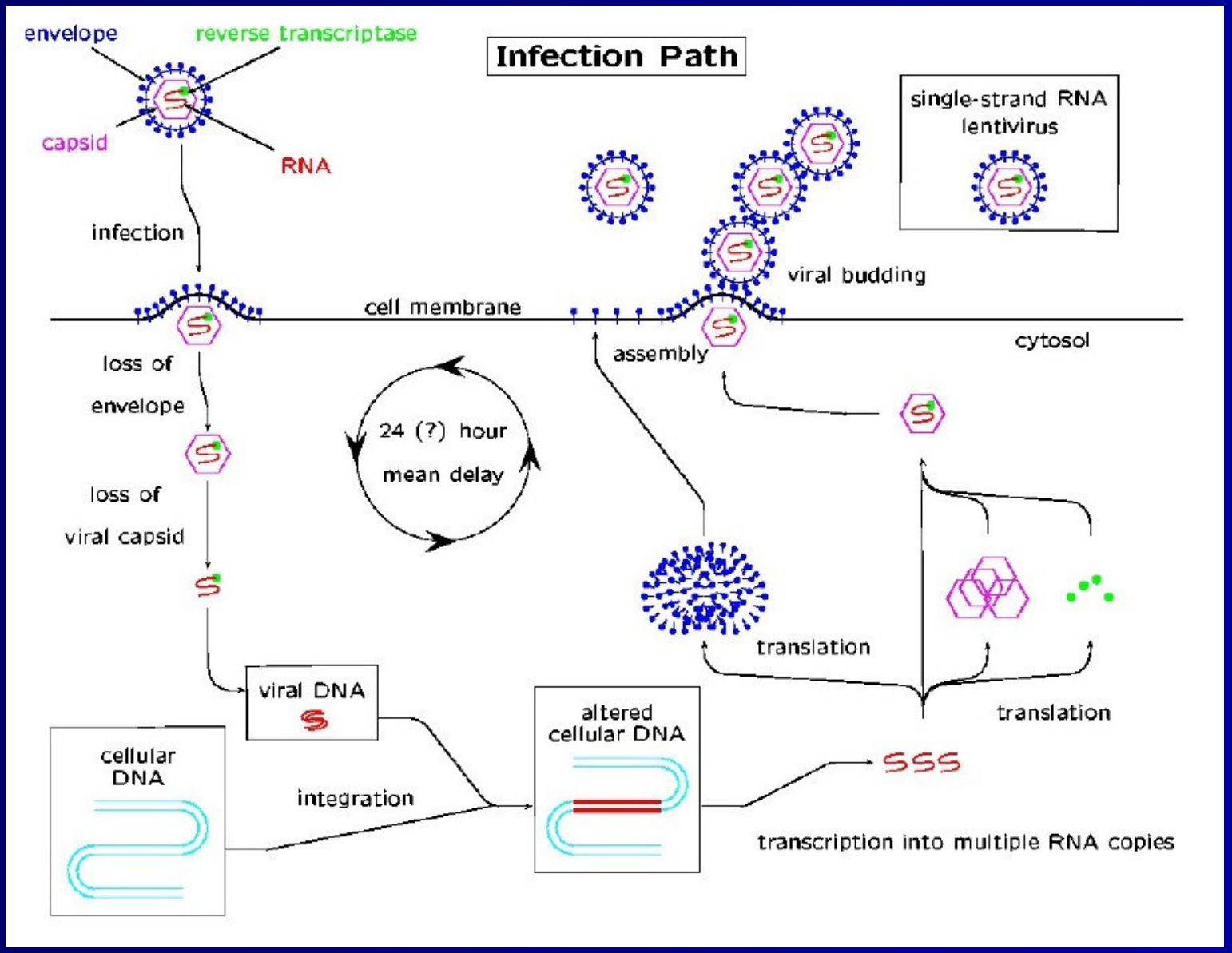
Drug Therapy

- HIV virus is RNA with a protective capsid
  - After it enters a cell, the RNA is copied by an enzyme called reverse transcriptase to make a piece of "copy" DNA (cDNA)
  - Next, the DNA of the cell is cut by an enzyme (integrase) carried by the virus, and the viral cDNA is inserted into the gap in the cellular DNA
  - Once the viral DNA is integrated into the cellular DNA, it can just sit there
  - Transcribed to produce intracellular copies of virus to be encapsulated and exported for extracellular infections
- Most anti-HIV drugs (> 20) fall into one of the two categories:
  - Reverse transcriptase (RT) inhibitors (prevent HIV RNA from being converted into DNA)
  - Protease inhibitors (PIs) (affect the final stage of the viral life cycle – prevent viral particles from being packaged for export as infectious agents)

Cellular Level Models:



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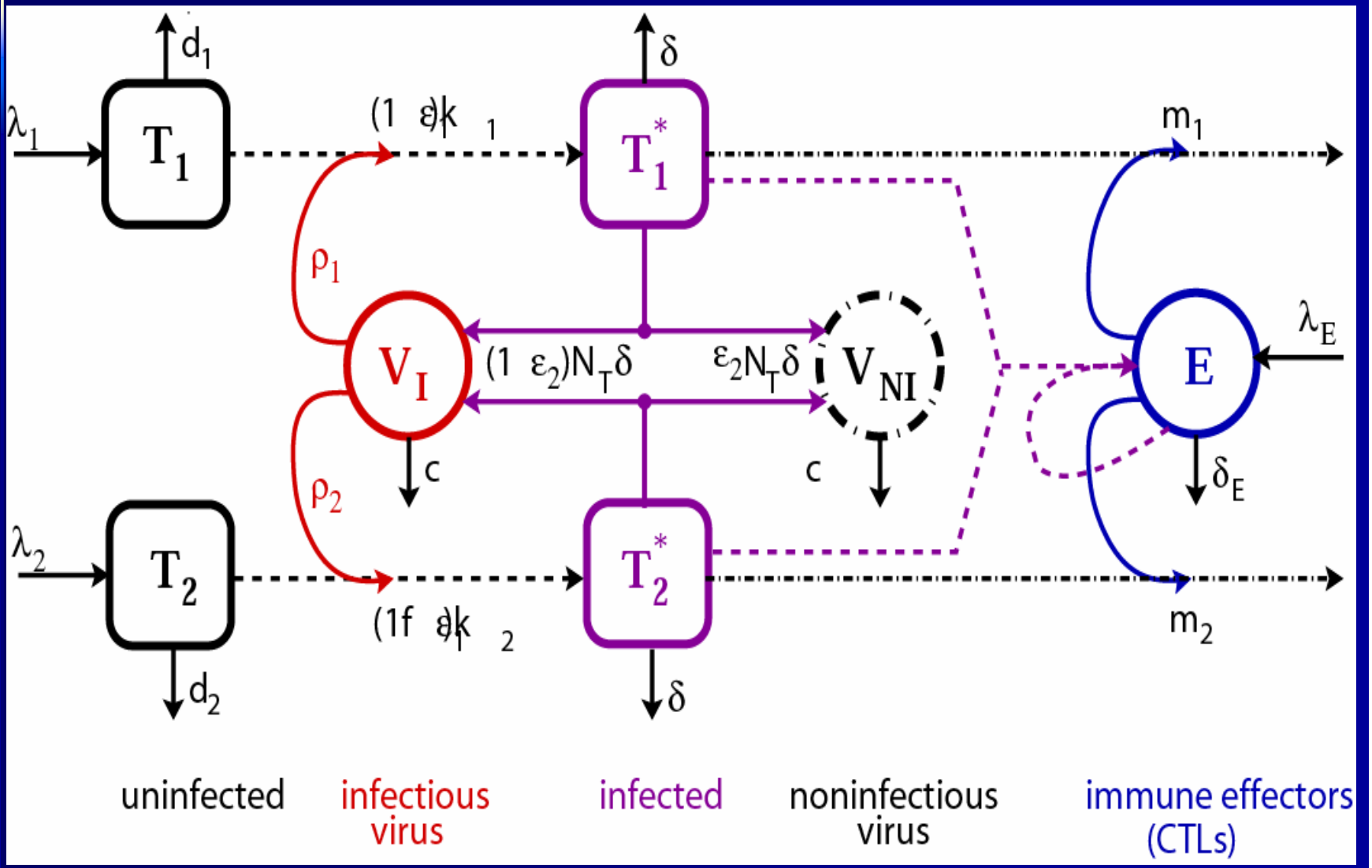
System Level Models:



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SYSTEM LEVEL MODEL

$$\frac{dT_1}{dt} = \lambda_1 - d_1 T_1 - (1-\varepsilon_1) k_1 V T_1$$

$$\frac{dT_2}{dt} = \lambda_2 - d_2 T_2 - (1- f\varepsilon_1) k_2 V T_2$$

$$\frac{dT_1^*}{dt} = (1-\varepsilon_1) k_1 V T_1 - \delta T_1^* - m_1 E T_1^*$$

$$\frac{dT_2^*}{dt} = (1- f\varepsilon_1) k_2 V T_2 - \delta T_2^* - m_2 E T_2^*$$

$$\frac{dV}{dt} = (1-\varepsilon_2) N_T \delta (T_1^* + T_2^*) - cV - [(1-\varepsilon_1)\rho_1 k_1 T_1 + (1- f\varepsilon_1)\rho_2 k_2 T_2]V$$

$$\frac{dV_{NI}}{dt} = \varepsilon_2 N_T \delta (T_1^* + T_2^*) - cV_{NI}$$

$$\frac{dE}{dt} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E$$

Observables:

$$z = \begin{pmatrix} T_1 + T_1^* \\ V_I + V_{NI} \end{pmatrix}$$

Therapy:

$$\varepsilon_1 = RTI$$

$$\varepsilon_2 = PI$$

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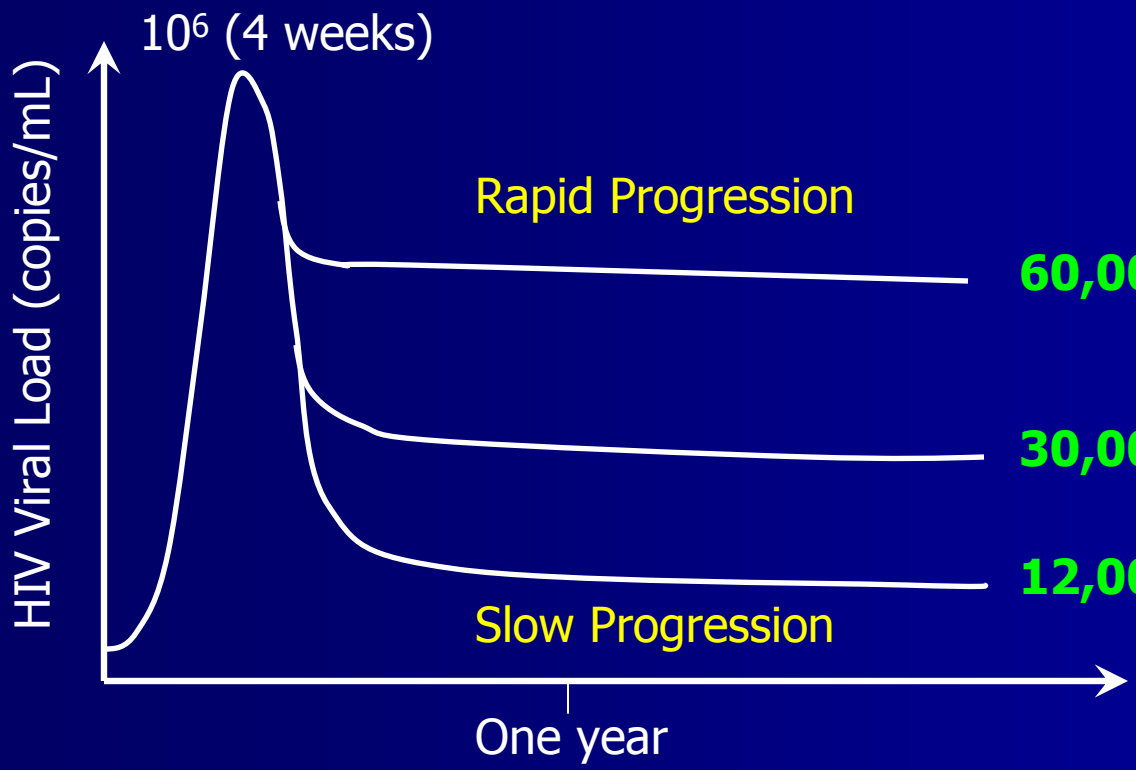
HIV Viral Load - Untreated



	Develop AIDS
60,000	1-4 years
30,000	8-15 years
12,000	Very slowly (or not at all)

Questions:

1) Can we predict this from early observations of patient?

2) Can we affect viral load set points thru therapy?

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INVERSE PROBLEMS WITH CLINICAL DATA

Clinical data from E. Rosenberg-Mass General Hospital-Early on used POD to organize and reduce data sets

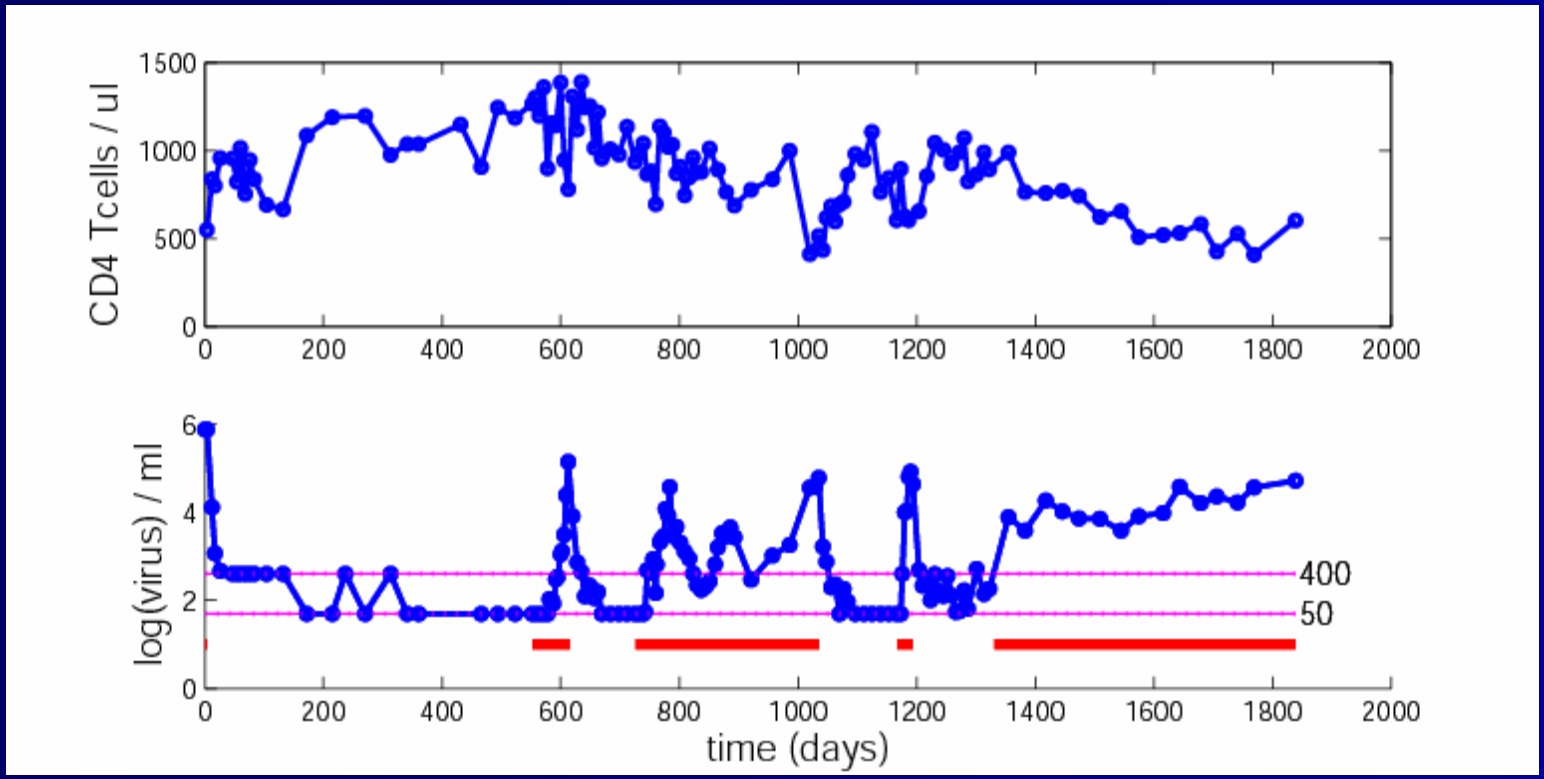
Censored Data: 400 or 50 copies/ml

Carry out inverse problems to estimate parameters
-both at ***individual*** and ***population*** level

Verify that model has predictive capabilities

Use to design control strategies (STI's)

TYPICAL PATIENT DATA



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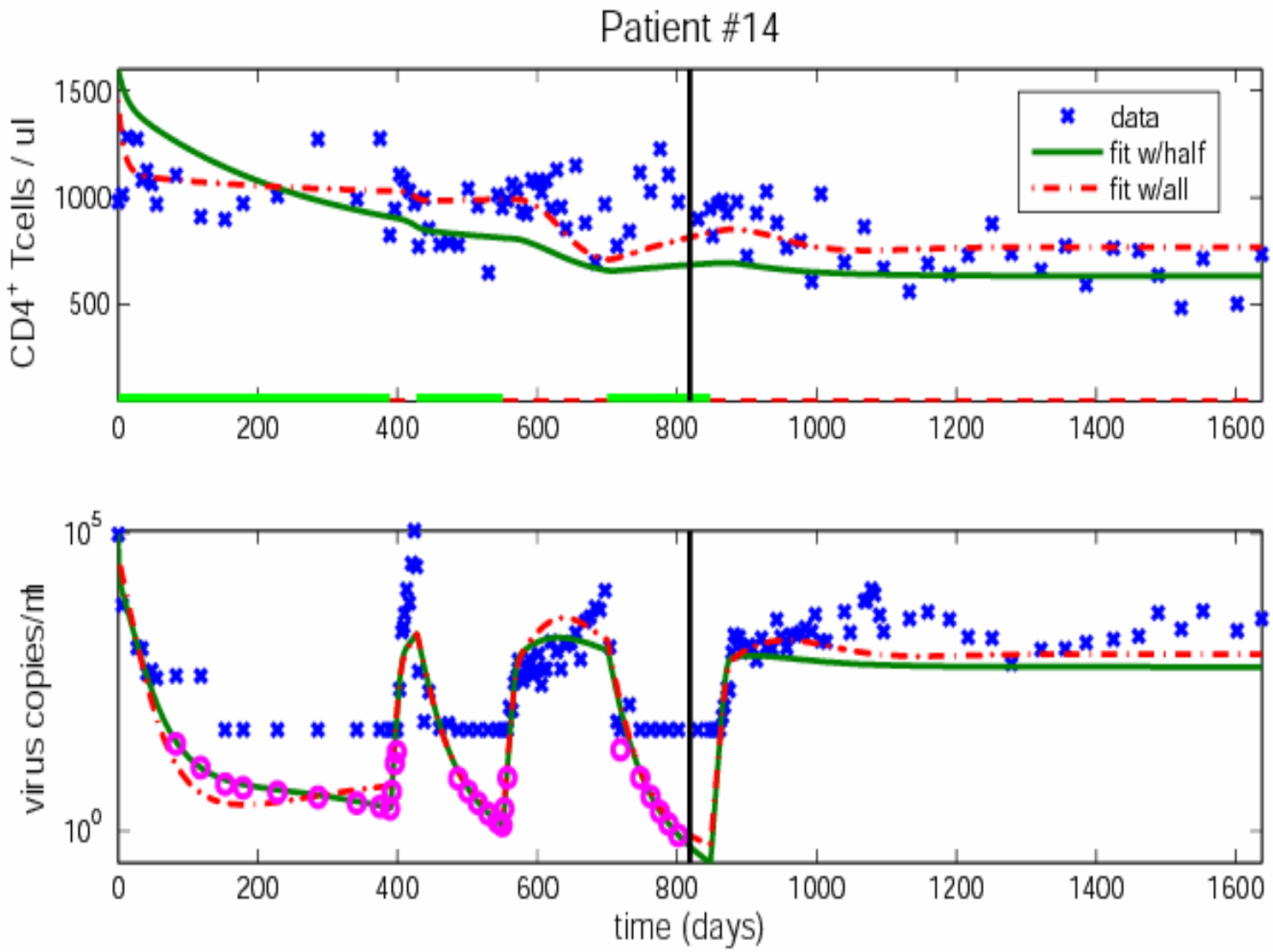
ESTIMATION OF PARAMETERS (individuals)

- Data: CD4 counts + censored viral loads for 45 MGH patients (4 to 5 years with varied interruption protocols)
- 20 model parameters + 7 initial conditions = 27 parameter values to be estimated with data for each patient
- Use ½ (~ 2 years) of rich data set for each individual in EM censored data algorithm
- 2 step optimization: i) hypercube sampling-based DIRECT (direct search) on all 27 parameters ii) gradient based optimization in censored data EM algorithm

- Expected Maximization (EM) algorithm: MLE with censored data points replaced by expected values using distribution based on truncated log normal with mean, variance determined by censoring levels, data and model predictions

- Use 45 individuals, obtain population averages, then fix 16 (12 model, 4 IC), then re-estimate 11 (8 model, 3 IC) to simulate clinical setting for predictive use of early patient data

SIMULATION WITH ESTIMATED PARAMETERS (individuals)-predictive!!!



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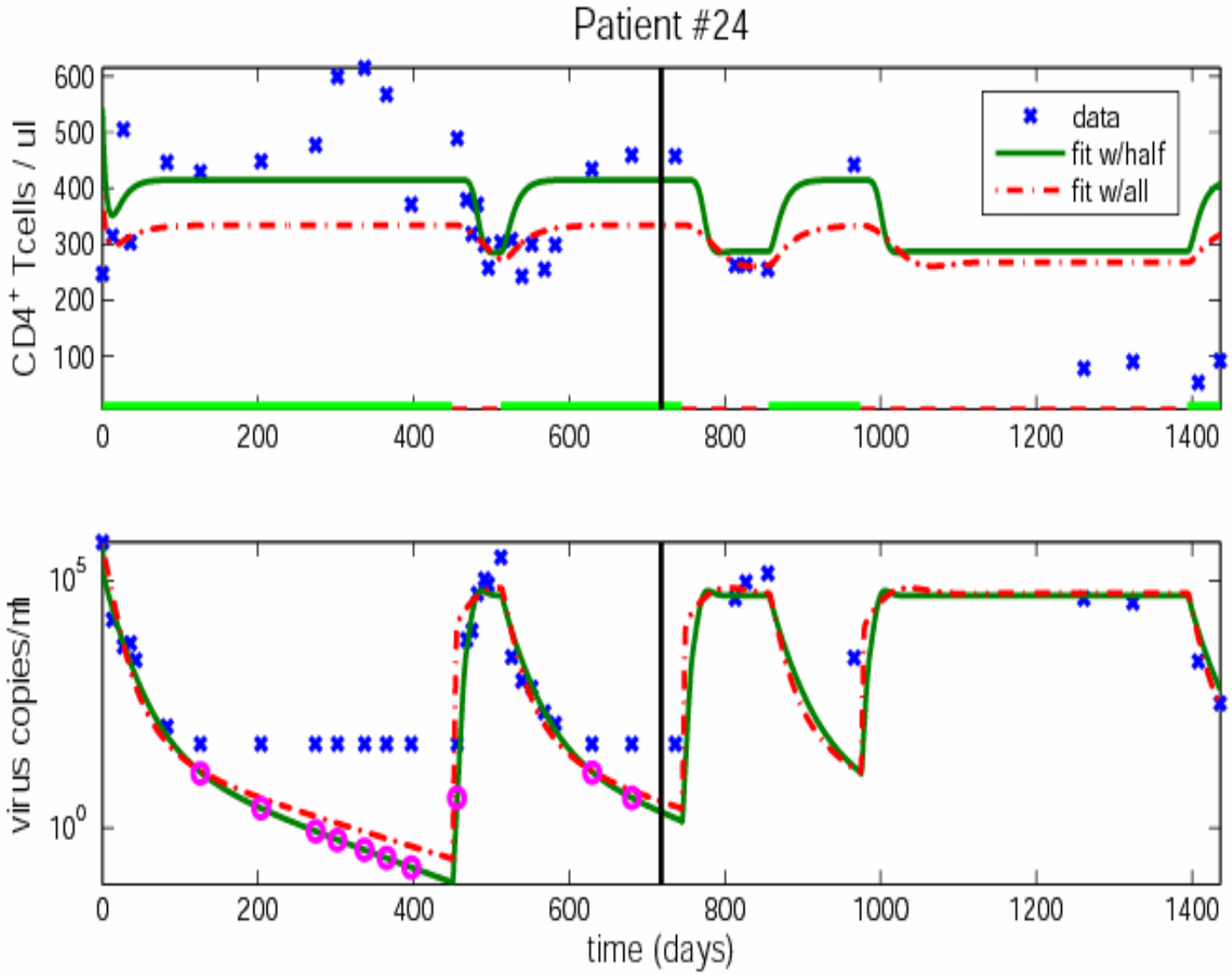
SIMULATION WITH ESTIMATED PARAMETERS

Model is predictive even when data has only one interruption!!



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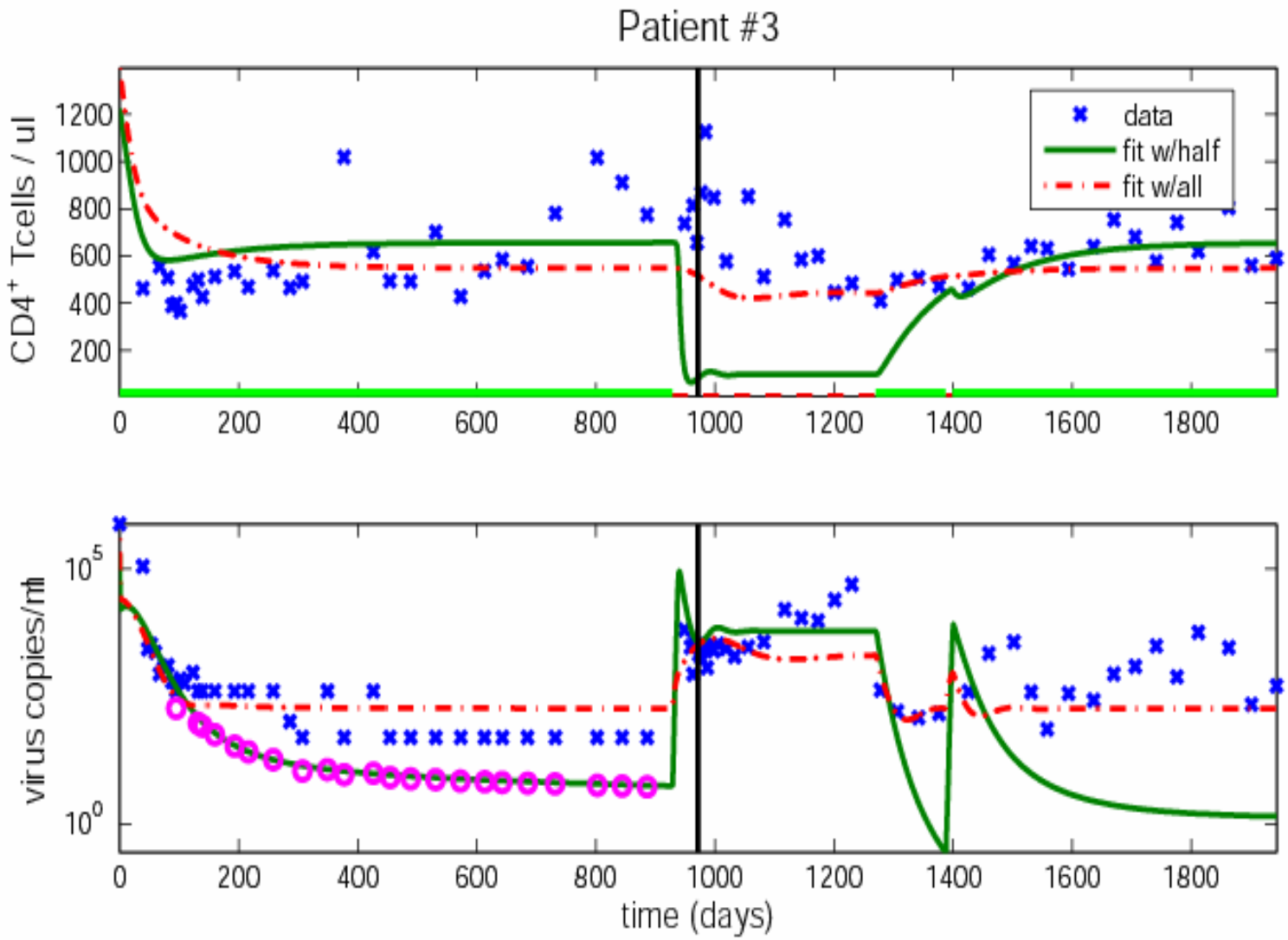
SIMULATION WITH ESTIMATED PARAMETERS
Model not predictive for individuals w/o interruption!!!



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Problems with Continuous Therapy

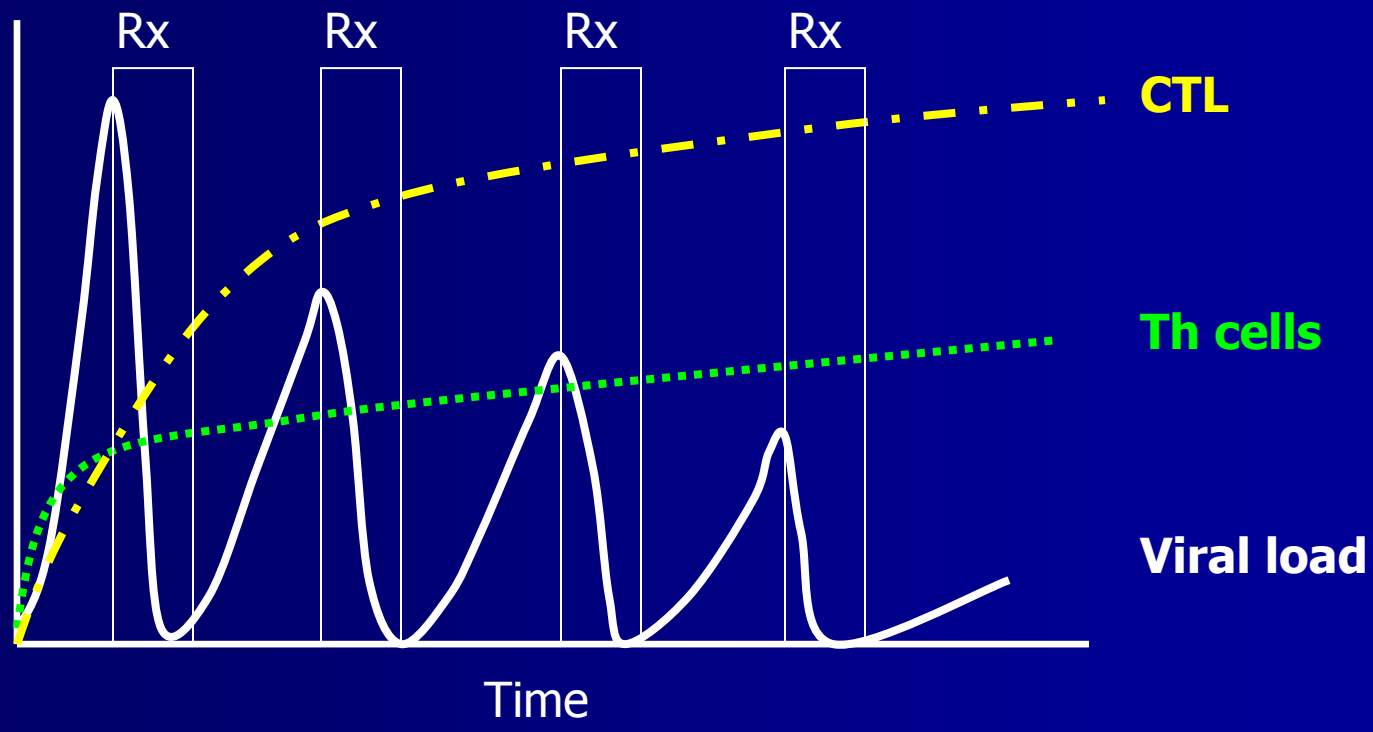
- Serious side effects of long-term treatment
- Variable patient adherence; lack of availability / high cost of drugs
- Drug efficacy fades as virus mutates, becomes resistant
- Eradicating virus decimates immune system

Why Interrupt Treatment?

- Lessons from "Berlin" patient
  - Treated during acute HIV infection phase
  - Interruption in therapy 4 weeks later – resulting in viral rebound to 5,000 copies (within a week)
  - Restarted therapy …
  - Second interruption 6 months later prompted by acute Hepatitis A infection
  - 3 years later, maintains a viral load consistently < 1,000 copies (usually < 50)

- Reduce side effects and drug treatment cost
- Boost the immune system

Augment HIV-specific Immunity - Hypothesis



- *Will HIV-specific immune response generated and maintained during acute infection be enough to control the virus?*
- *If virus returns once therapy is discontinued, will this further boost the immune response?*

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Modeling Goals

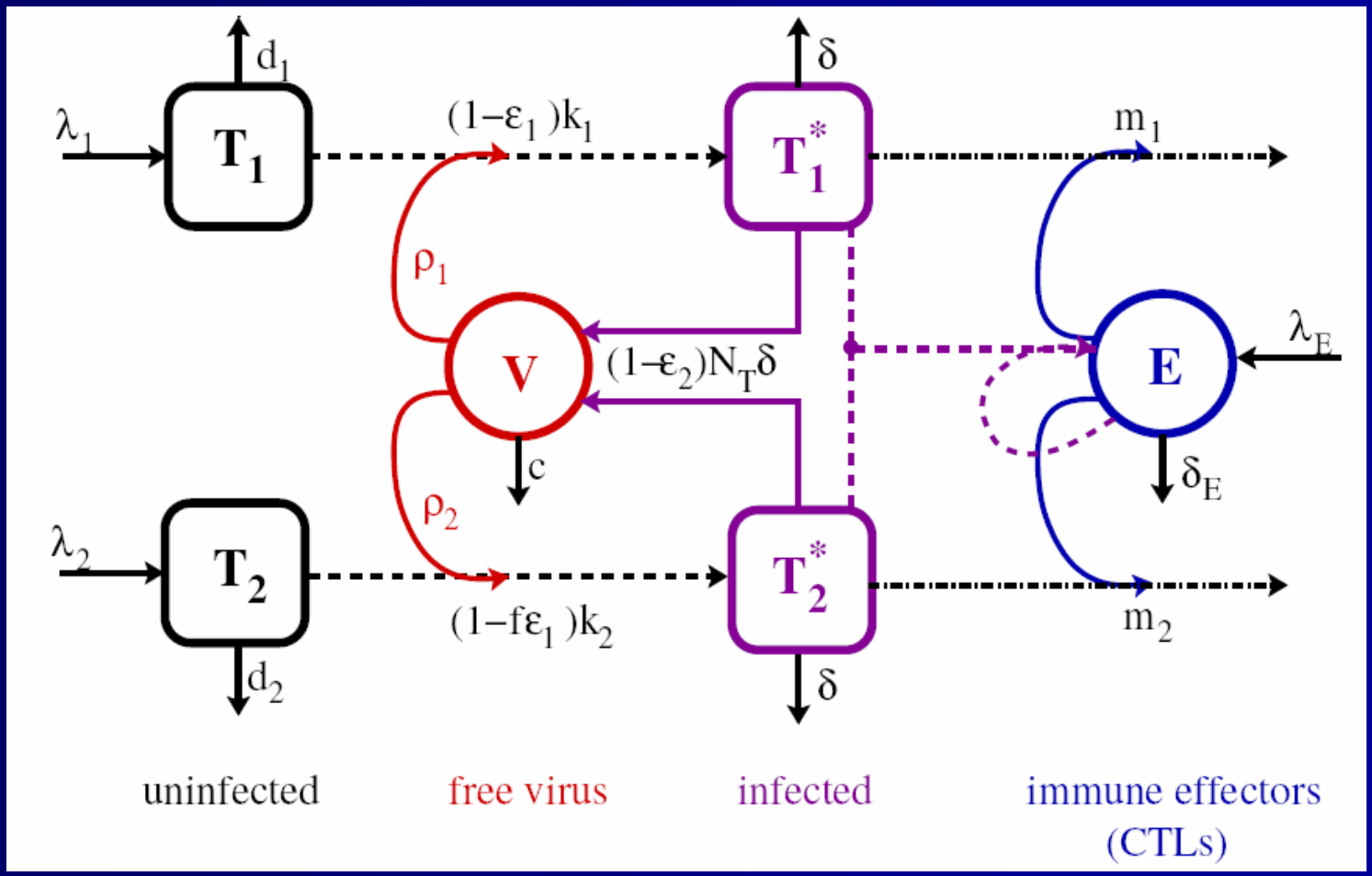
- To obtain insights into the relationship between drug therapy and long-term immunological control of HIV
- To determine optimal treatment protocols

Modeling Features

- Multiple stable steady states: viral dominant; immune dominant
- Ability to incorporate single or multi-drug therapy, appropriate sensitivity to drug treatment
- At minimum, model state variables (compartments) to reflect HIV biology
  - Uninfected and infected Th-cells
  - Free plasma virus
  - Immune response

HIV Infection Dynamics Model

- Based on Callaway-Perelson (2001), Bonhoeffer, et. al. (2000) models
- Two target cell populations T_1 (CD4 Th-cells) and T_2 macrophages)



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HIV Infection Dynamics Model (cont'd)

CD4 Th-cells

$$\frac{dT_1}{dt} = \lambda_1 - d_1 T_1 - (1-\varepsilon_1) k_1 V T_1$$

macrophages

$$\frac{dT_2}{dt} = \lambda_2 - d_2 T_2 - (1- f\varepsilon_1) k_2 V T_2$$

ε_1 – RT inhibitors

ε_2 – PI

Infected CD4 Th-cells

$$\frac{dT_1^*}{dt} = (1-\varepsilon_1) k_1 V T_1 - \delta T_1^* - m_1 E T_1^*$$

Infected macrophages

$$\frac{dT_2^*}{dt} = (1- f\varepsilon_1) k_2 V T_2 - \delta T_2^* - m_2 E T_2^*$$

Virus

$$\frac{dV}{dt} = (1-\varepsilon_2) N_T \delta (T_1^* + T_2^*) - cV - [(1-\varepsilon_1)\rho_1 k_1 T_1 + (1- f\varepsilon_1)\rho_2 k_2 T_2] V$$

CTL

$$\frac{dE}{dt} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E$$

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Steady State Analysis

	EQ_1	EQ_2	EQ_3
T_1 (cells/mL)	1,000,000	163,573	967,839
T_2 (cells/mL)	3,198	5	621
T_1^* (cells/mL)	0	11,945	76
T_2^* (cells/mL)	0	46	6
V (copies/mL)	0	63,919	415
E (cells/mL)	10	24	353,108
Local Stability	Unstable	Stable	Stable
	Uninfected	Viral Dominant	Immune Dominant

QUESTION: ***Does there exist a treatment protocol that would take the system from a viral dominant equilibrium state to an immune dominant equilibrium state ?***

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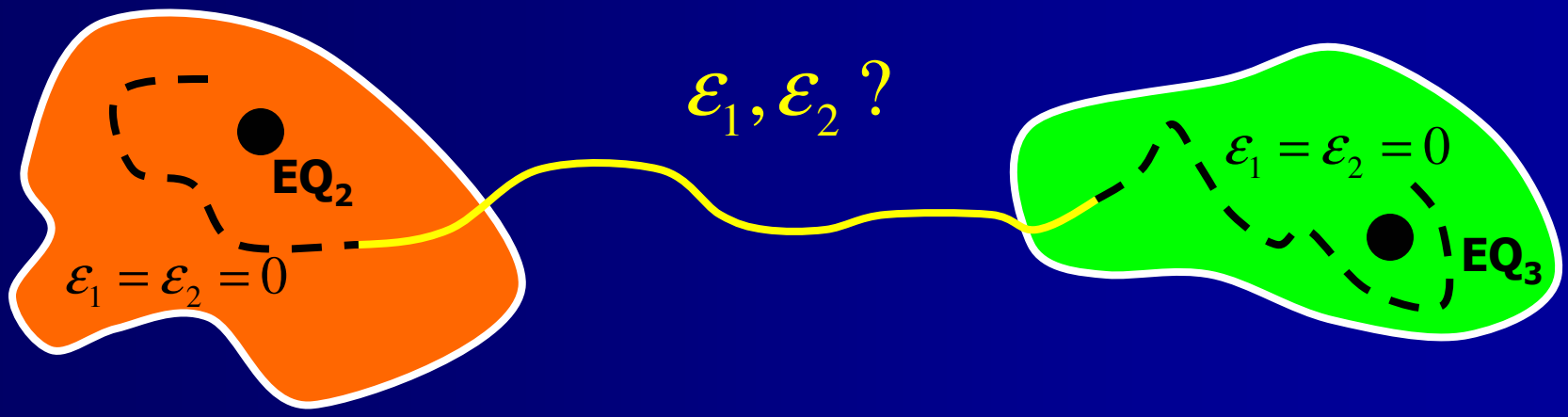
Control Objective



Stable "unhealthy" (viral dominant) state

Stable "healthy" (immune dominant) state

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Optimal Drug Treatment: Problem Formulation

- Find an optimal drug efficacy pair $(\varepsilon_1^*, \varepsilon_2^*)$ such that

$$J(\varepsilon_1^*, \varepsilon_2^*) = \min \int_{t_0}^{t_1} [QV(t) + R_1\varepsilon_1^2(t) + R_2\varepsilon_2^2(t) - SE(t)]dt$$

subject to

ODE system

$$0 \le a_1 \le \varepsilon_1 \le b_1 \le 1$$

$$0 \le a_2 \le \varepsilon_2 \le b_2 \le 1$$

Continuous Optimal Therapy (Open-loop)

- Early infection (perturbing the "uninfected" unstable steady state)

$$T_1(0) = 10^6$$
$$T_2(0) = 3198$$
$$T_1^*(0) = 10^{-4}$$
$$T_2^*(0) = 10^{-4}$$
$$V(0) = 1$$
$$E(0) = 10$$

$$0 \le \varepsilon_1 \le 0.7$$
$$0 \le \varepsilon_2 \le 0.3$$

Weighting coefficients: $Q = 0.1, R_1 = R_2 = 20000, S = 1000$

Sub-optimal STI – A Case Study

- **Question:** Is there an STI therapy that would transfer an HIV patient from a viral dominant state to an immune dominant state?

$$T_1(0) = 163573$$
$$T_2(0) = 5$$
$$T_1^*(0) = 11945$$
$$T_2^*(0) = 46$$
$$V(0) = 63919$$
$$E(0) = 24$$

Viral Dominant (stable)

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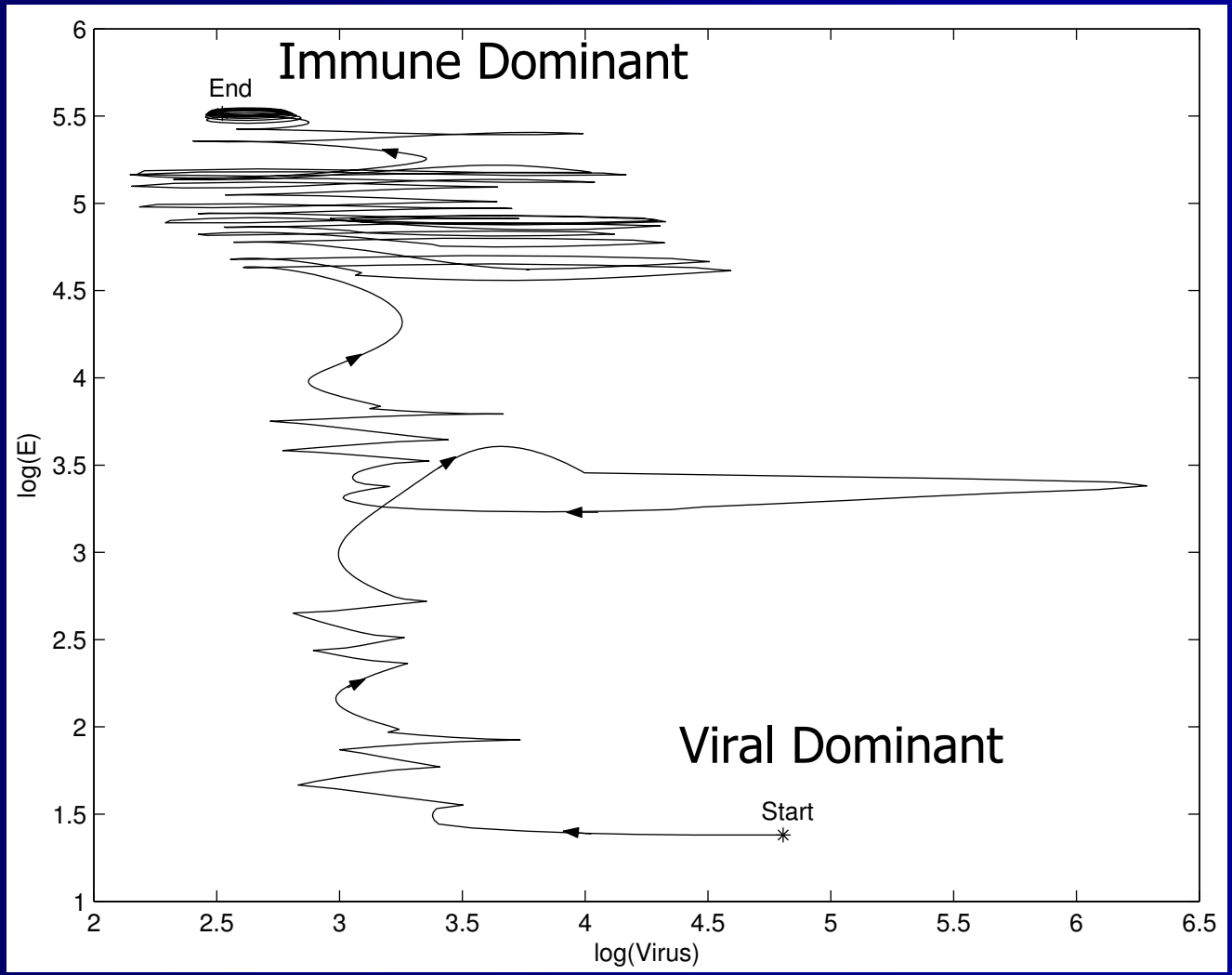
Phase Plane – Virus versus CTL



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Summary

Using control theory paradigm in an HIV-therapeutic setting, our modeling results clearly suggest the possibility that STI used in an optimal way will lead to immune boosting and subsequent control of viral load without the lifetime need for drugs

Some publications:

- ***HIV Dynamics: Modeling, Data Analysis, and Optimal Treatment Protocols, JCAM, special issue on Mathematics Applied to Immunology, 2005 (in press).***
- ***Dynamic Multidrug Therapies for HIV: Optimal and STI Control Approaches, Math. Biosci. Engr., 1(2): 223-241, 2004.***
- ***An SDRE Based Estimator Approach for HIV Feedback Control, Optimal Control & Appl., to appear.***