

Statistical and Mathematical Modeling in HIV: Estimation and Control

H. T. Banks

Center for Research in Scientific Computation

NC STATE University



Research Team

B.M. Adams (Sandia)

H.T. Banks

D. Bortz (U. Michigan)

M. Davidian (Statistics-NCSU)

S. Grove

S. Hu

H-D Kwon (Inha U, S. Korea)

Y. Ma (Statistics-Texas A&M)

H.K. Nguyen

E. S. Rosenberg (Mass General/Harvard Med)

J.A. Toivanen

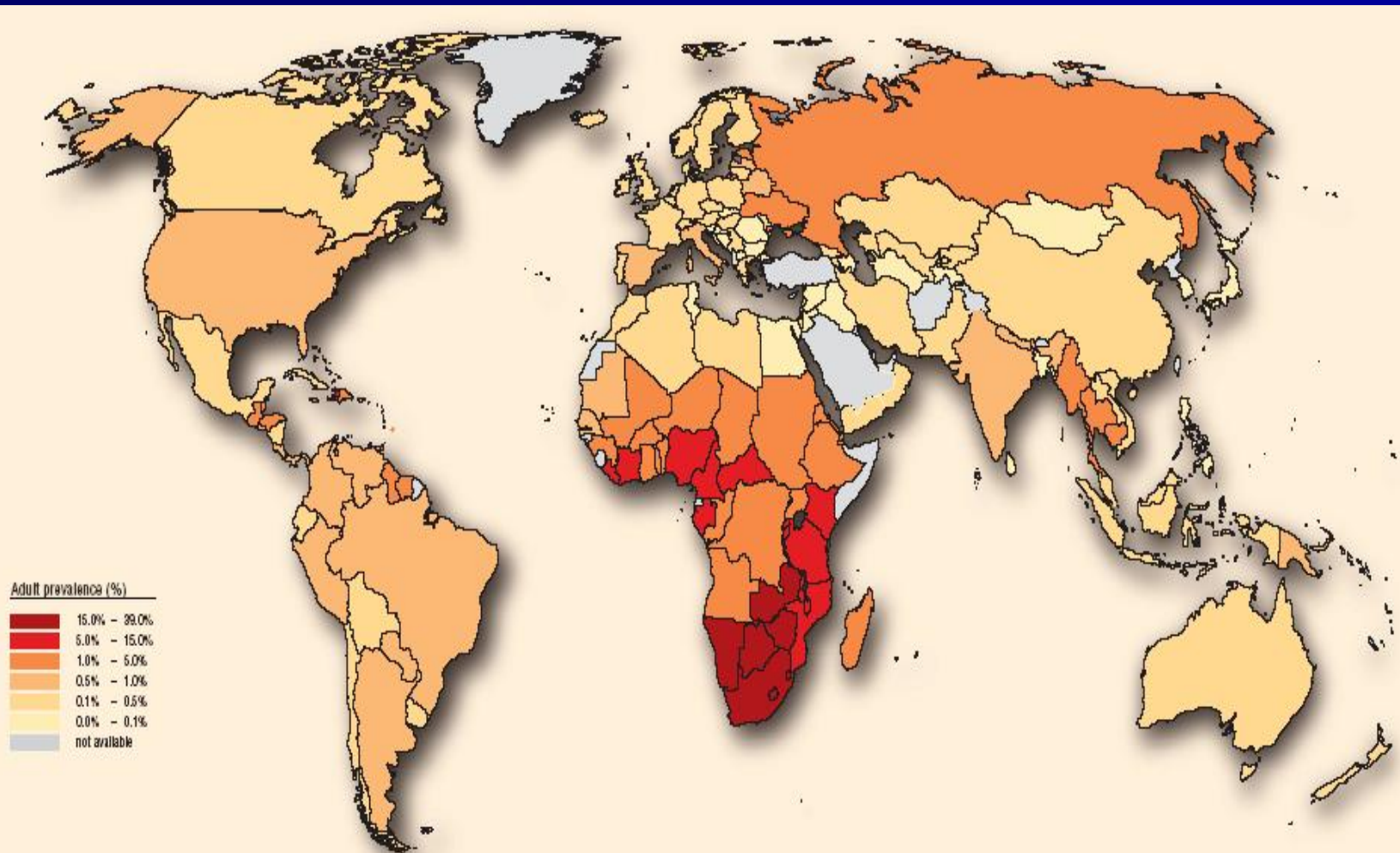
H.T. Tran

S.N. Wynne

HIV – An Overview

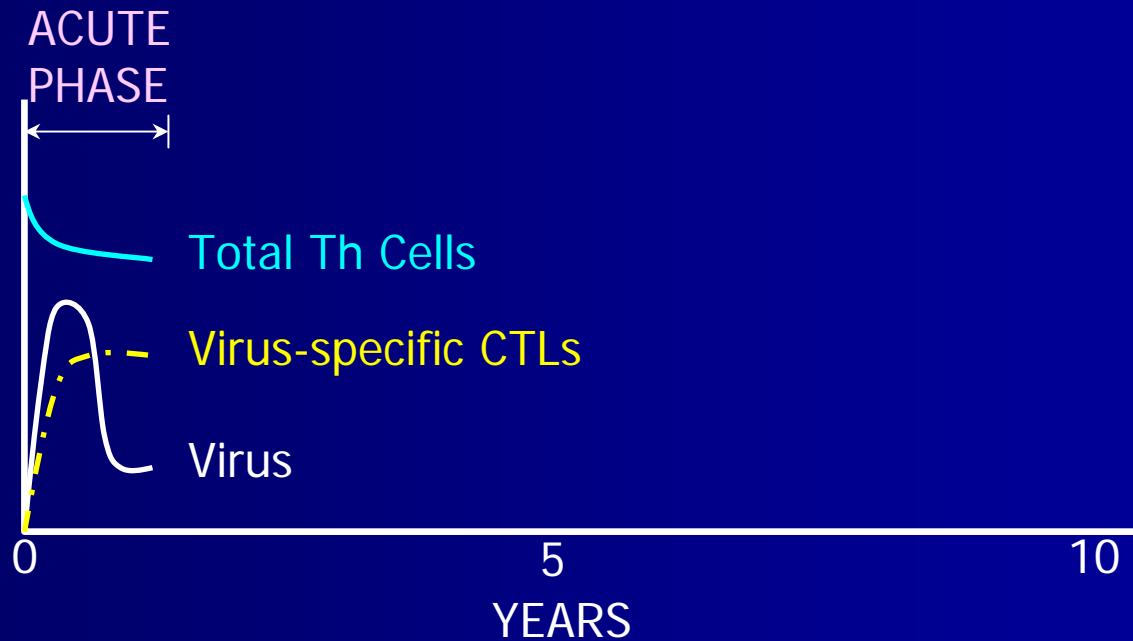
Human immunodeficiency virus (HIV)

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



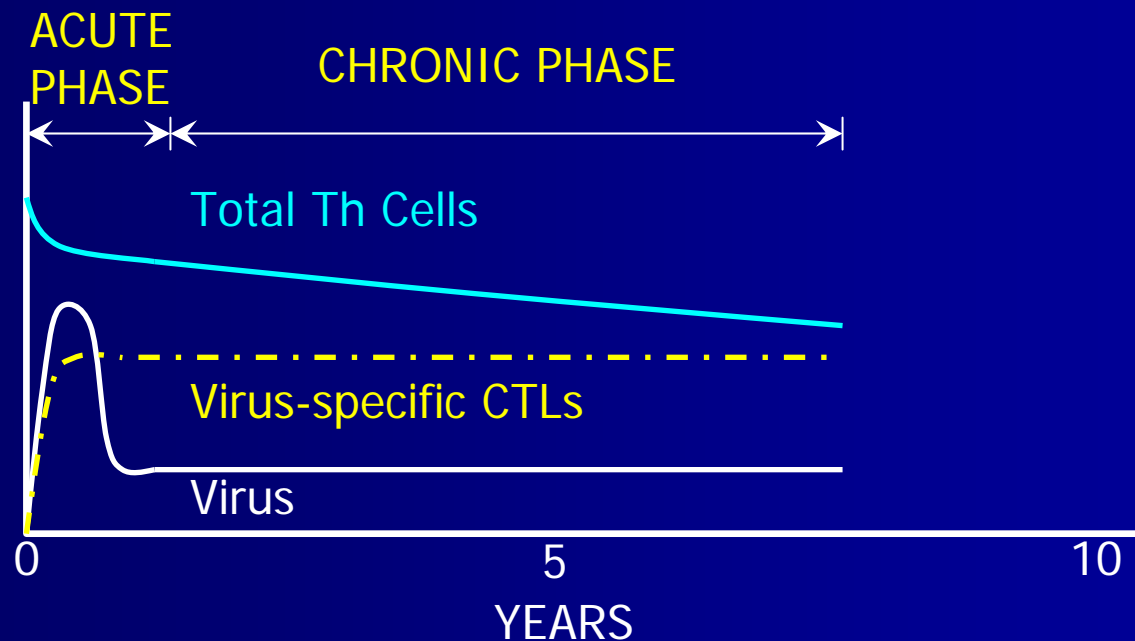
Dynamics of HIV Infection

- *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*



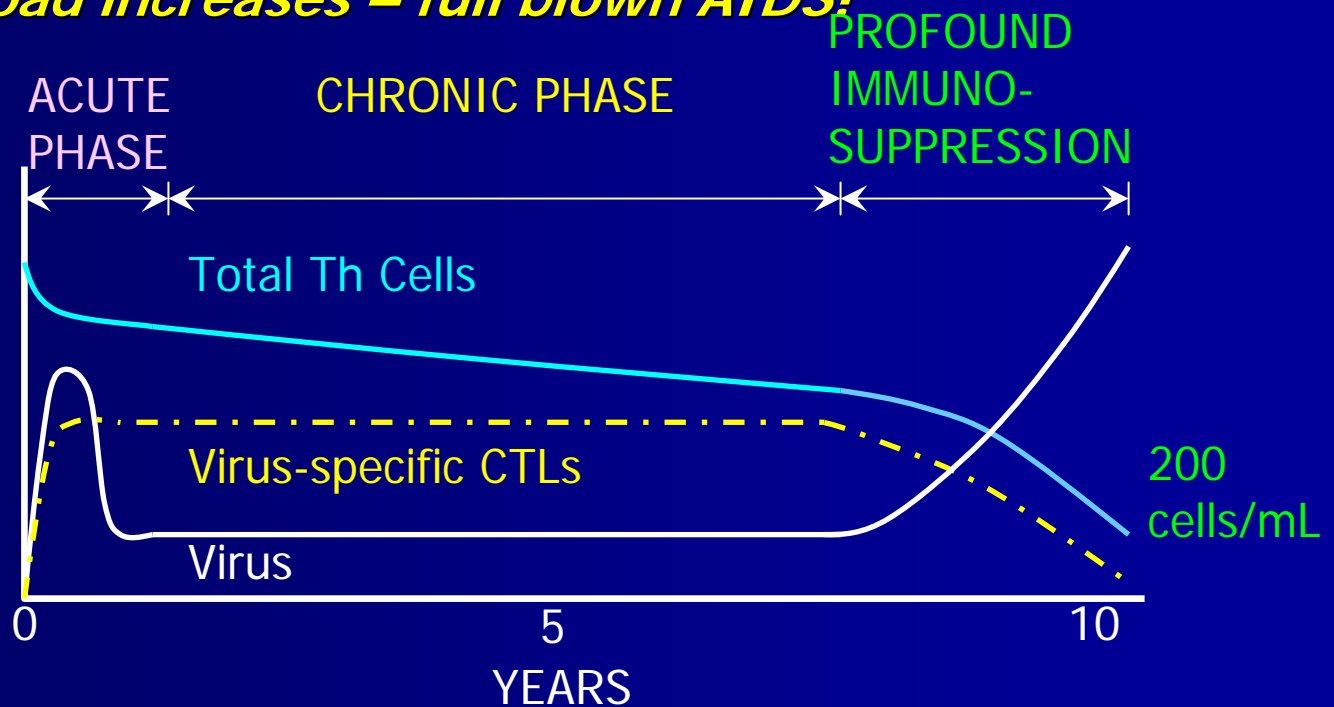
Dynamics of HIV Infection (cont'd)

- *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)

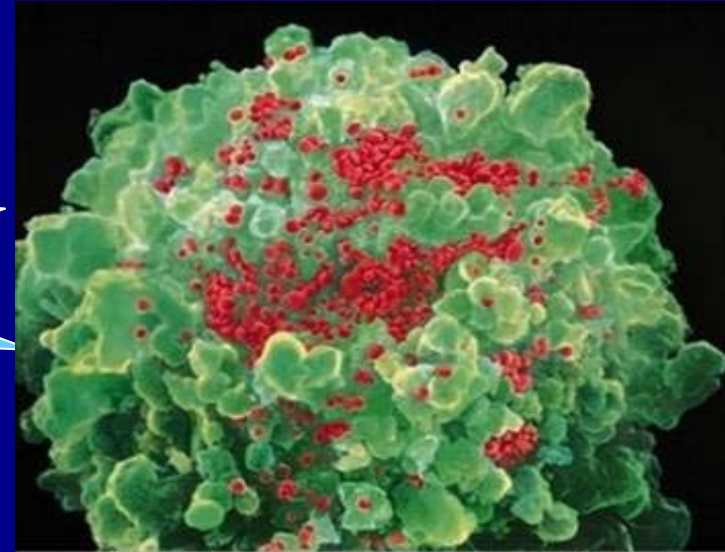
- *As the chronic phase progresses, the Th cells slowly decreases (because these cells are killed by the viral infection)*
- *Eventually, there are not enough Th cells left to provide the help needed by CTLs*
- *When this happens, CTLs also begins to decline*
- *Viral load increases – full blown AIDS!*



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**




What's Happening during the Chronic Phase? (cont'd)

- *The reverse transcriptase enzyme used to copy the viral RNA is error-prone*
 - *It makes about one error (mutation) each time it copies a piece of viral RNA*
 - *The mutation might kill the virus*
 - *Worse ! – the mutations may help the virus adapt to its environment, so that it can become more damaging*
 - *The virus can mutate so that CTLs can no longer recognize it*
 - *New CTL will have to be activated*
 - *At the same time, the virus continues to replicate*

The mutation rate of the AIDS virus is so high that it can effectively stay one step ahead of CTLs or antibodies directed against it

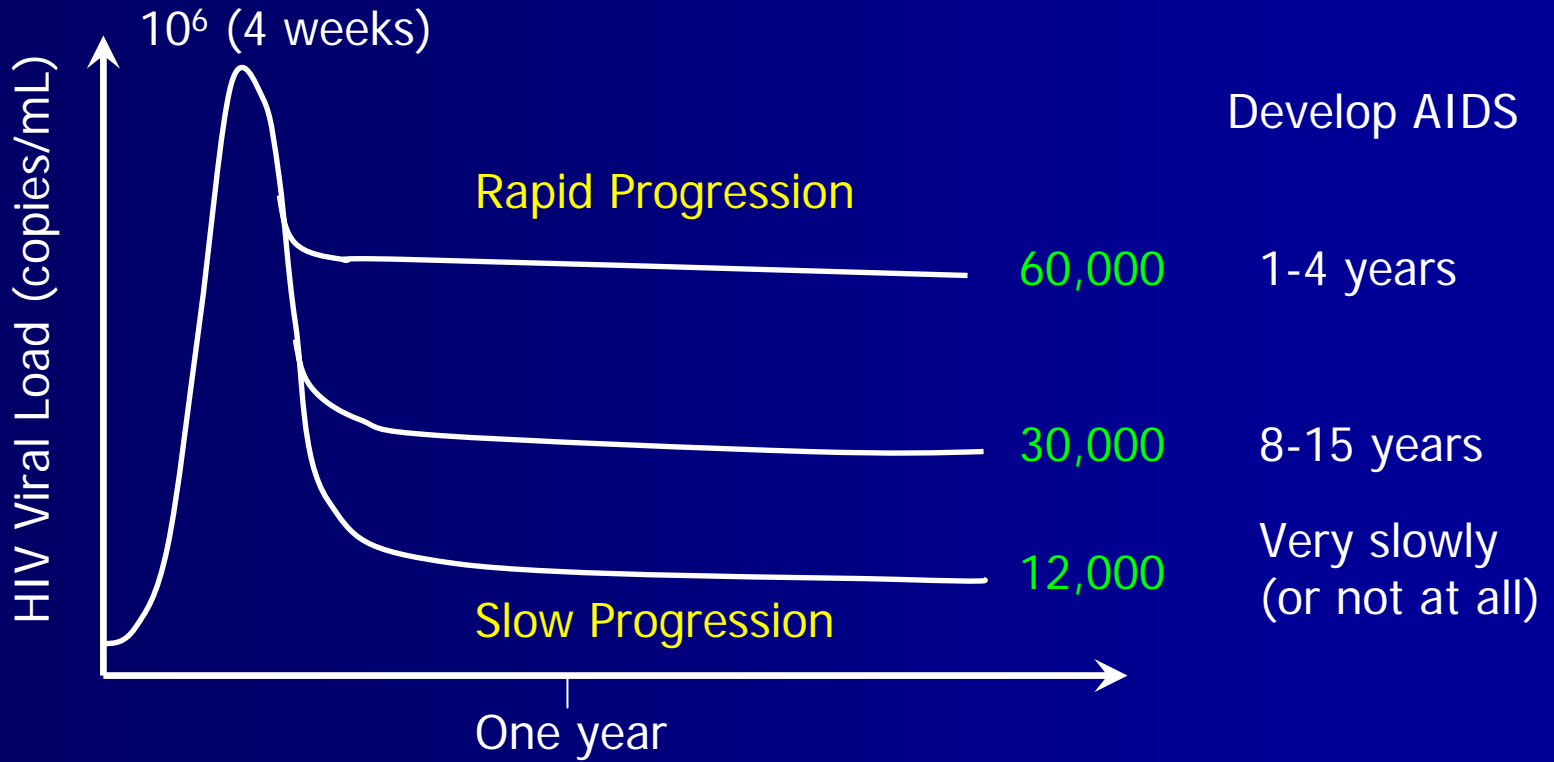
What's Happening during the Chronic Phase? (cont'd)

- *HIV virus specifically targets cells of the immune system: helper T cells and macrophages*
 - *The docking protein that HIV binds to is the CD4 (found on surfaces of helper T cells)*
 - *Disrupt the immune system response*
 - ***Worse !** – makes them targets for killing by CTLs*



The killing of helper T cells that leads to the immunosuppression eventually results in the death of the patient

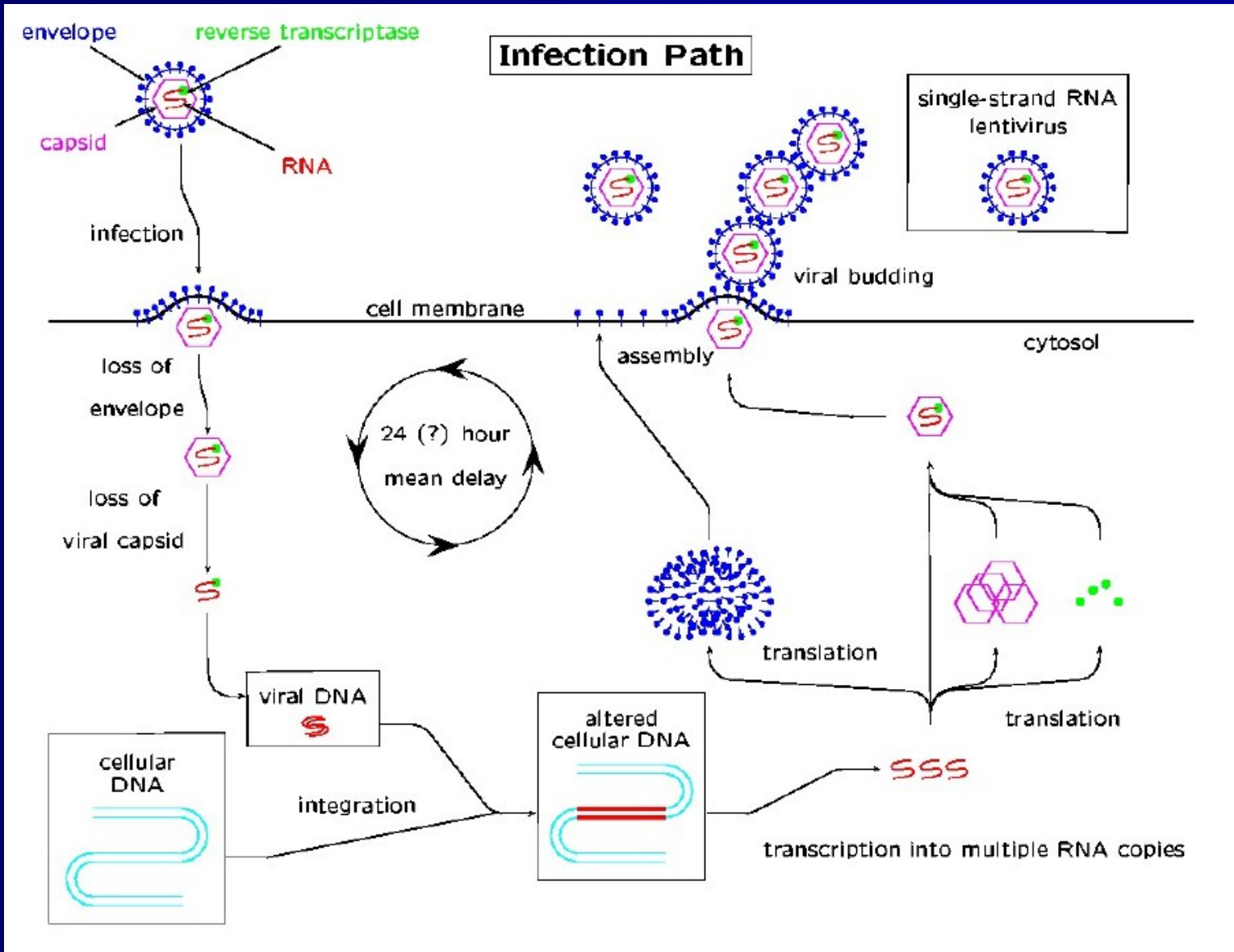
HIV Viral Load - Untreated



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:



Involves systems of equations of the form (generally nonlinear)

$$\frac{dV}{dt} = -cV(t) + n_a A(t - \tau) + n_c C(t) - n_{vt} V(t)T(t)$$

where τ is a production delay (distributed across the population of cells). That is, one should write

$$\frac{dV}{dt} = -cV(t) + n_a \int_0^{\infty} A(t - \tau)k(\tau)d\tau + n_c C(t) - n_{vt} V(t)T(t)$$

where k is a probability density to be estimated from aggregate data.

Even if k is given, these systems are nontrivial to simulate—require development of fundamental techniques.

HIV Model:

$$\dot{V}(t) = -cV(t) + n_A \int_0^r A(t-\tau) d\pi_1(\tau) + n_C C(t) - p(V, T)$$

$$\dot{A}(t) = (r_v - \delta_A - \delta X(t))A(t) - \gamma \int_0^r A(t-\tau) d\pi_2(\tau) + p(V, T)$$

$$\dot{C}(t) = (r_v - \delta_C - \delta X(t))C(t) + \gamma \int_0^r A(t-\tau) d\pi_2(\tau)$$

$$\dot{T}(t) = (r_u - \delta_u - \delta X(t))T(t) - p(V, T) + S$$

where $C(t) = \mathcal{E}_2 \{C(t; \tau)\} = \int_0^r C(t; \tau) d\pi_2(\tau)$, $A =$ acute cells

$$V(t) = V_A(t) + V_C(t), \quad V_A(t) = \mathcal{E}_1 \{V_A(t; \tau)\} = \int_0^r V_A(t; \tau) d\pi_1(\tau)$$

$\pi_1 \sim$ delay from acute infection to viral production

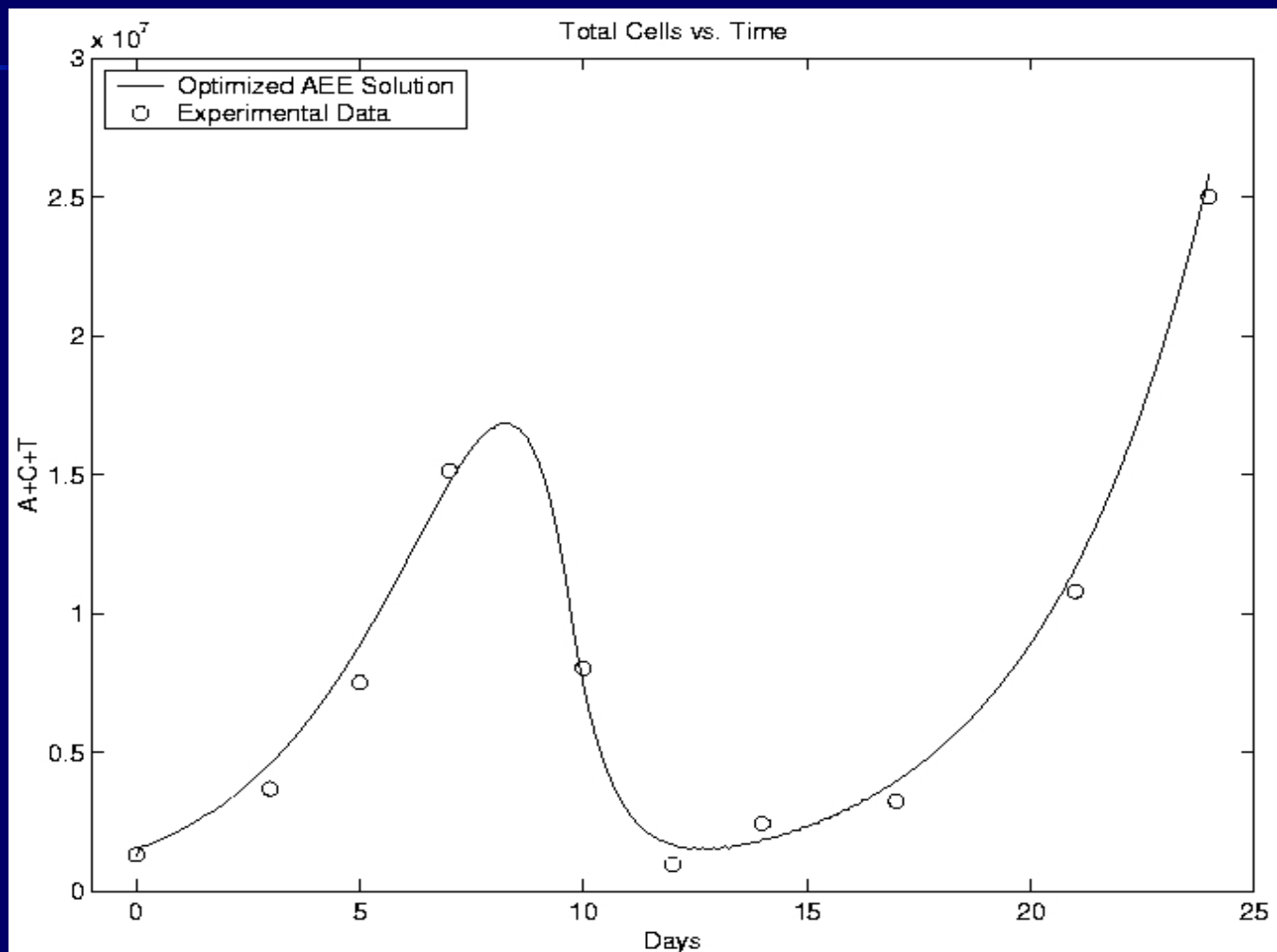
$\pi_2 \sim$ delay from acute infection to chronic infection

$T =$ target cells, $X =$ total (infected+uninfected) cells

In the inverse problem calculations, we used **numerical approximation methods** for the FDE's (both discrete delays and continuous probability density functions were used). The approximation methods were **spline-based** as developed in [**Banks-Kappel**, J. Diff. Eqn.,34(1979),pp.496-522] and [**Banks**, in *Nonlinear Phenomena in the Mathematical Sciences*(V.Lakshmikantham, ed.),Academic Press,N.Y.(1982),pp.47-55].

In the results reported below and in [2], we estimated **p** of nonlinear term **p(V,T)**, and measures $\pi_1 = \delta_{\tau_1}$ and $\pi_2 = \delta_{\tau_1+\tau_2}$ associated with the delays from acute infection to viral production and from acute infection to chronic infection.

- [2] **H. T. Banks, D. M. Bortz, and S. E. Holte**, Incorporation of variability into the modeling of viral delays in HIV infection dynamics, CRSC-TR01-25, Sept, 2001; Math Biosciences **183**(2003), 63-91.



Results from inverse problem calculations ($\tau_1^* = 24.33$, $\tau_2^* = 2.88$) using experimental data from [Rogel, Wu, and Emerman, J. Virology 69(1995),882-888].

COMPUTATIONAL RESULTS

Estimated	p^*	τ_1^*	τ_2^*	$J^{32}(q^*)$
$q_{00} = (p, 0, 0)$	4.28×10^{-8}	----	----	8.53×10^5
$q_0 = (p, \tau_1, 0)$	1.28×10^{-6}	23.4	----	2.57×10^5
$q = (p, \tau_1, \tau_2)$	1.33×10^{-6}	22.8	3.2	2.37×10^5

Carried out statistical analysis of significance of adding delays using methodology of

H.T.Banks and B.G.Fitzpatrick, *Statistical methods for model comparison in parameter estimation for distributed systems*, J. Math. Biology 28(1990),p. 501-527. See also Chapter 5 of H.T. Banks and K. Kunisch, *Estimation Techniques for Distributed Parameter Systems*, Birkhauser Boston, 1989.

Can argue that ratio of reduction in residual to residual is asymptotic to chi square, i.e.,

$$U_n^N(q_{00}, q_0) = n \frac{J^N(p^*, 0, 0) - J^N(p^*, \tau_1^*, 0)}{J^N(p^*, \tau_1^*, 0)} \rightarrow \chi^2(1)$$

as $n \rightarrow \infty$, where n is the number of observations (data points)

For the HIV data (*in vitro*), $n=10$, we found

$$U_{10}^{32}((p^*, 0, 0), (p^*, \tau_1^*, 0)) = 23.2,$$

$$U_{10}^{32}((p^*, 0, 0), (p^*, \tau_1^*, \tau_2^*)) = 26,$$

(both suggesting improvement is statistically significant at all confidence levels), where as

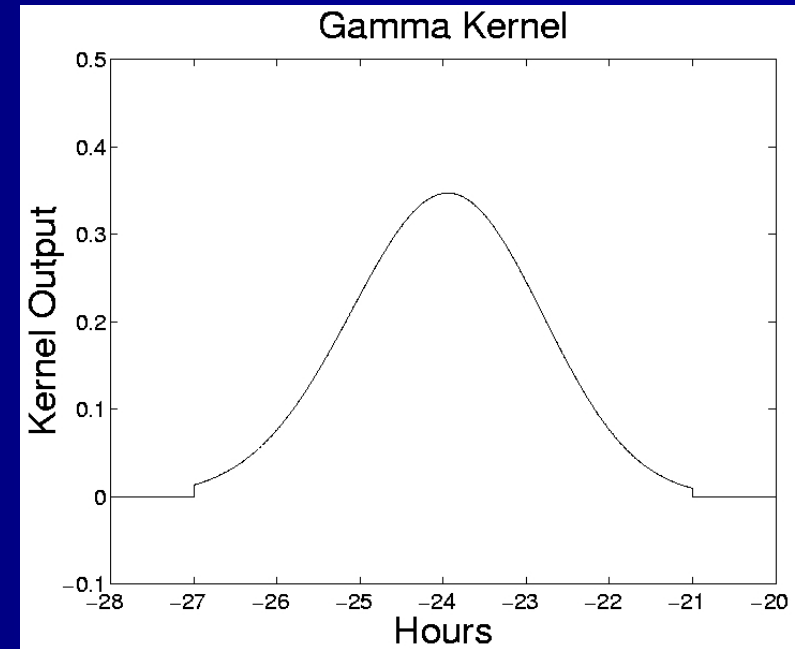
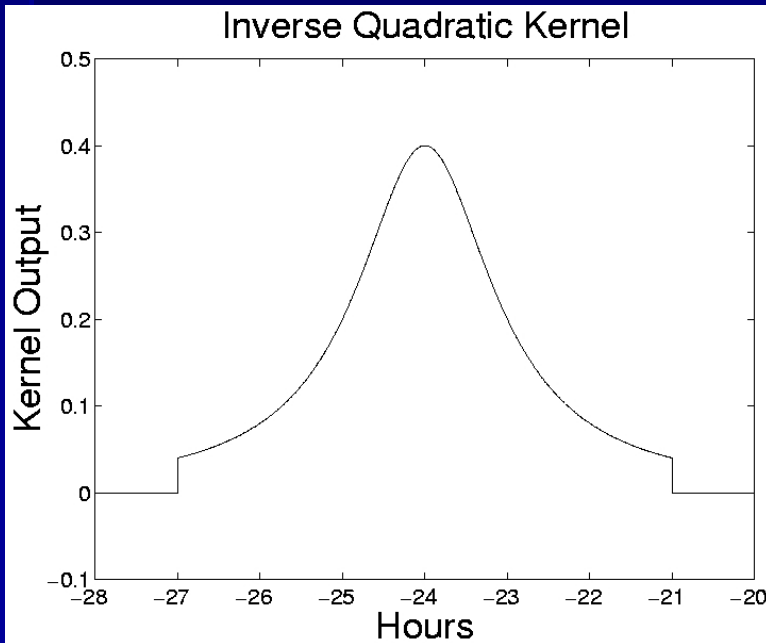
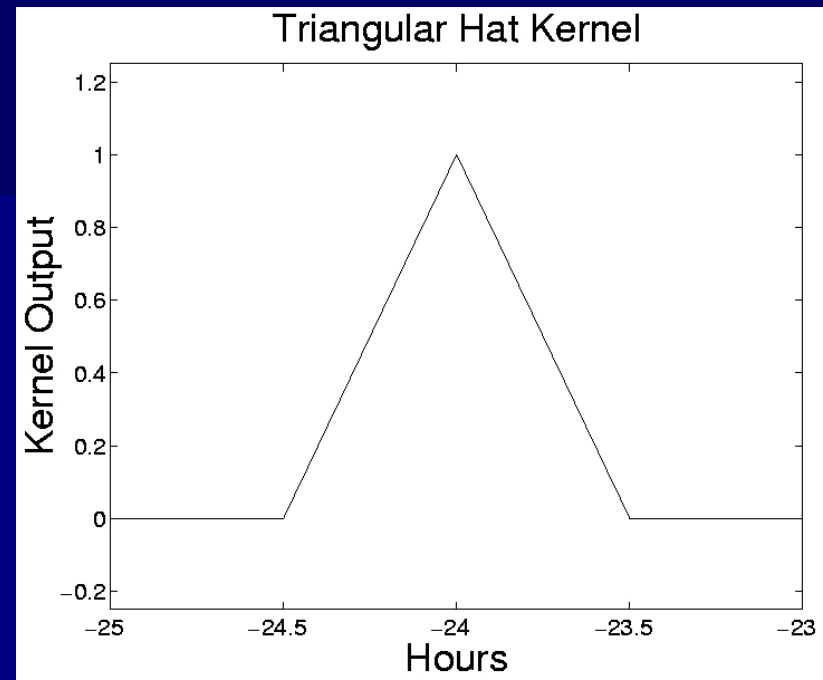
$$U_{10}^{32}((p^*, \tau_1^*, 0), (p^*, \tau_1^*, \tau_2^*)) = 0.84,$$

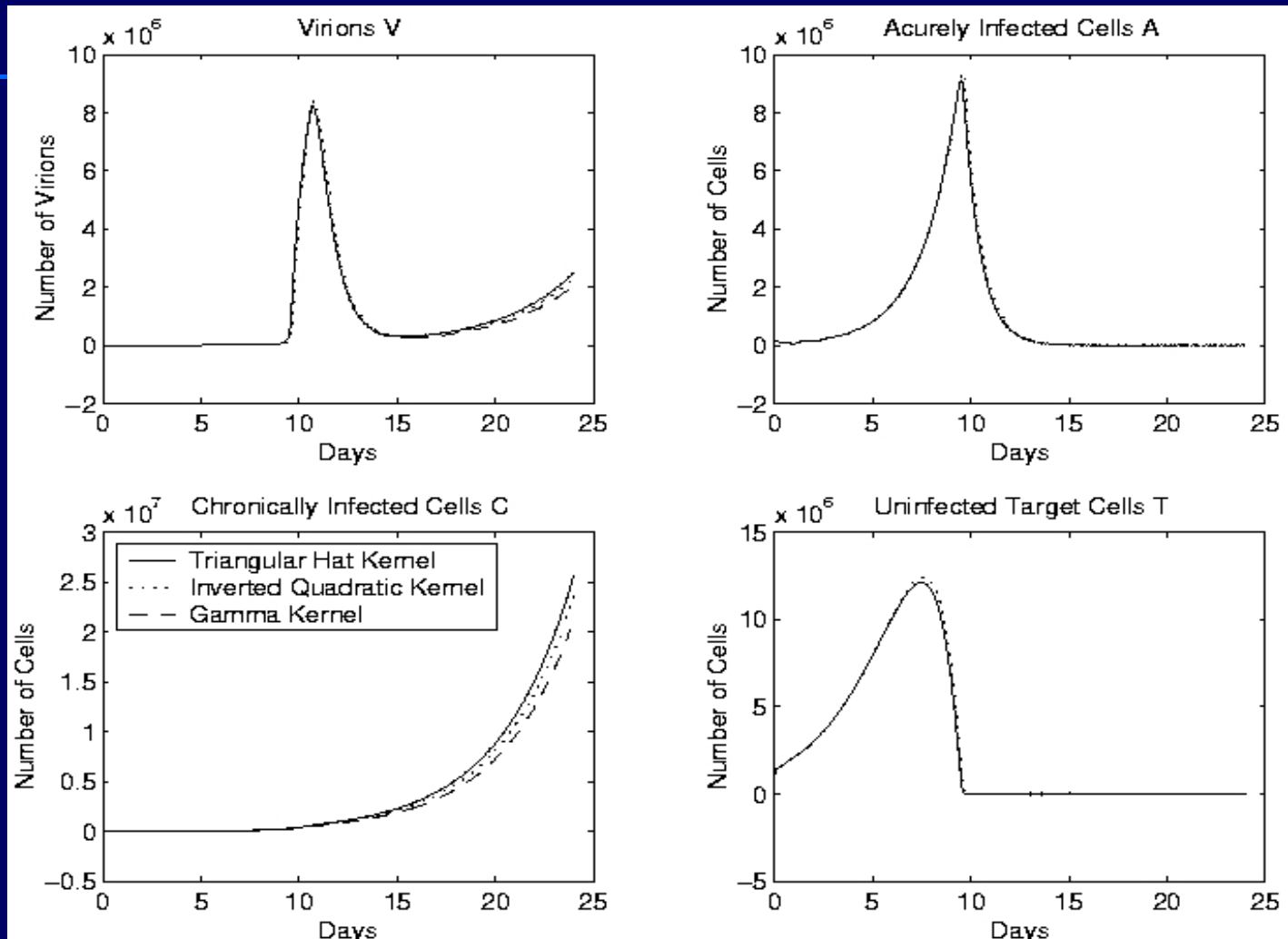
suggesting improvement is significant only at confidence levels at 94% or lower!!

Probability density kernels

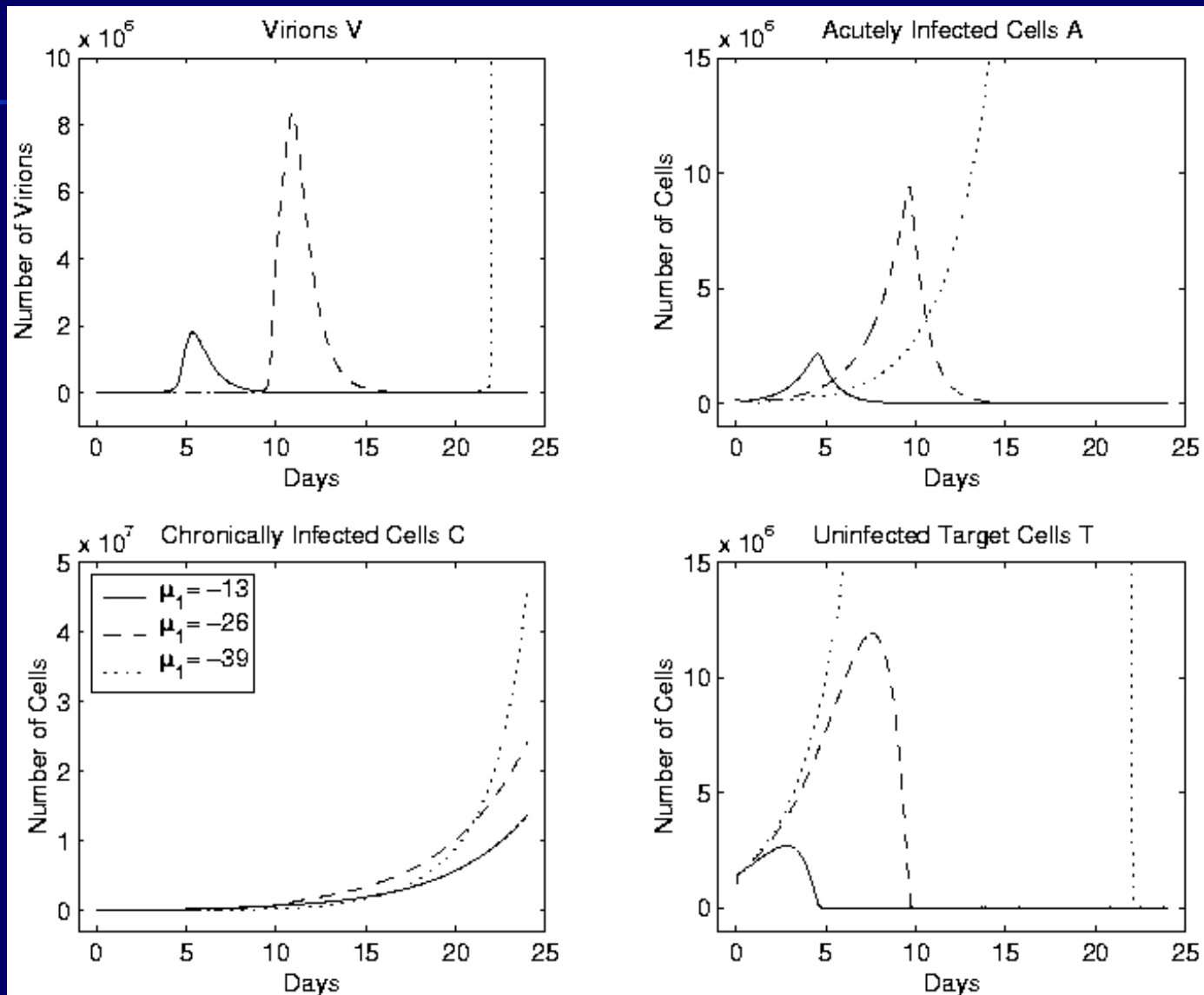
k in $d\pi(\tau) = k(\tau)d\tau$

with mean $\mu = 24$.





Comparison of forward solutions using triangular hat, inverted quadratic and gamma probability density kernels.



Sensitivity of solutions wrt mean μ in triangular hat kernel.

Gamma Distribution

$$k(\tau; b, n) = \frac{\tau^{n-1}}{(n-1)!b^n} \quad (\text{with } \mu = nb, \sigma^2 = nb^2)$$

Introducing internal variables y (n dimensional), equations become
e.g.,

“method
of
stages”

$$\dot{V}(t) = -cV(t) + n_c C(t) + n_a y_n(t) - pV(t)T(t)$$

$$\dot{y}_1(t) = (A(t) - y_1(t)) / b$$

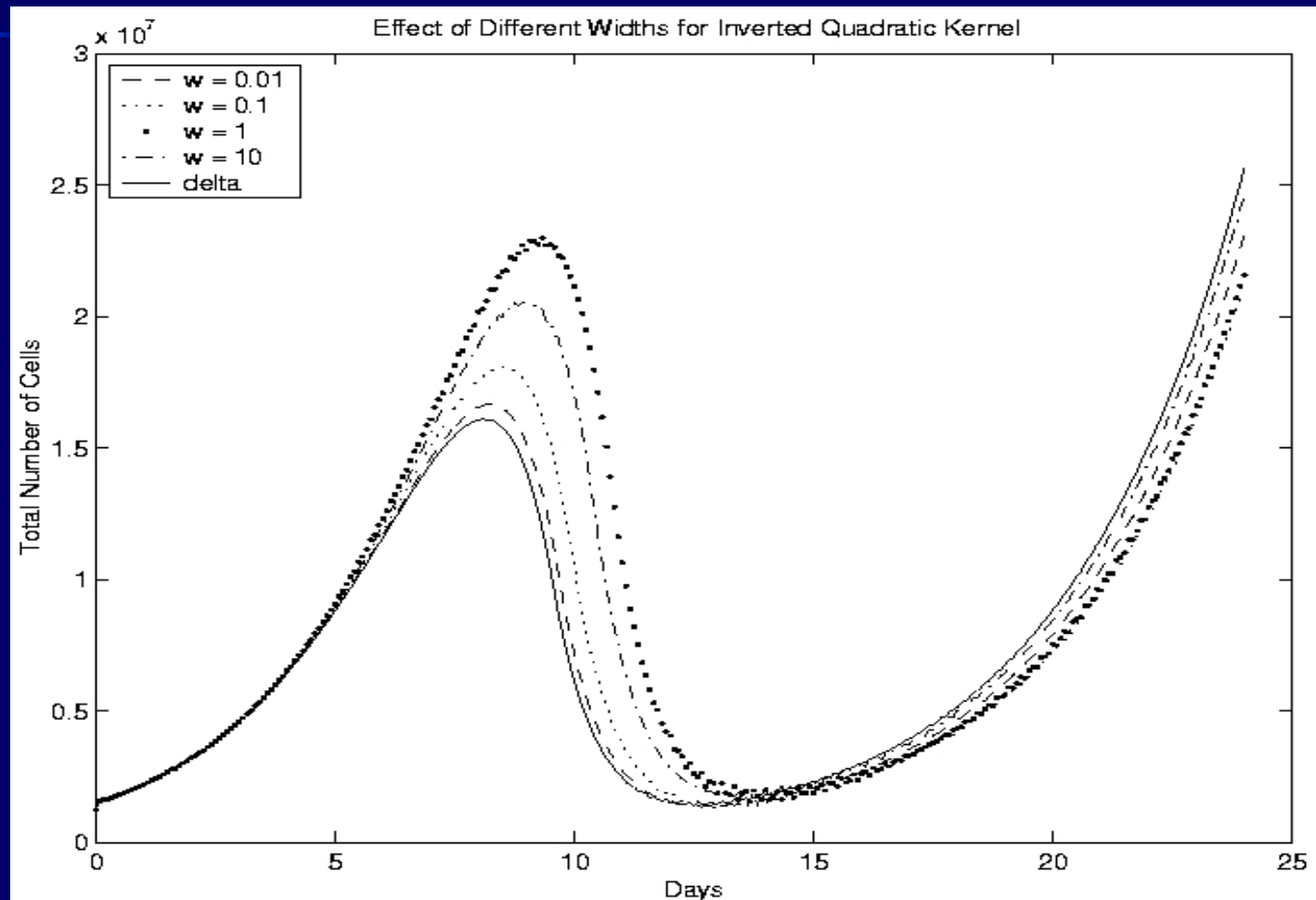
$$\dot{y}_2(t) = (y_1(t) - y_2(t)) / b$$

$$\vdots \quad \quad \quad \vdots$$

$$\dot{y}_n(t) = (y_{n-1}(t) - y_n(t)) / b$$

in place of

$$\frac{dV}{dt} = -cV(t) + n_c C(t) + n_a \int_0^{\infty} A(t-\tau)k(\tau)d\tau - pV(t)T(t)$$



Response $A + C + T =$ total no. of cells as a function of width w in inverted quadratic density kernel.

M. Emerman *in vitro* data

- i) HTB, D. Bortz and S. Holte, Math. Biosci., 183 (2003), 63-91***
- i) HTB and D. Bortz, J. Math. Bio., 50 (2005), 607-625.***
- ii) HTB and D. Bortz, J. Inverse and Ill-Posed Problems, 13 (2005), 103-121***
- iv) HTB and H.K. Nguyen, J. Math. Anal. Appl., 2005, to appear.***

OTHER APPROACHES:

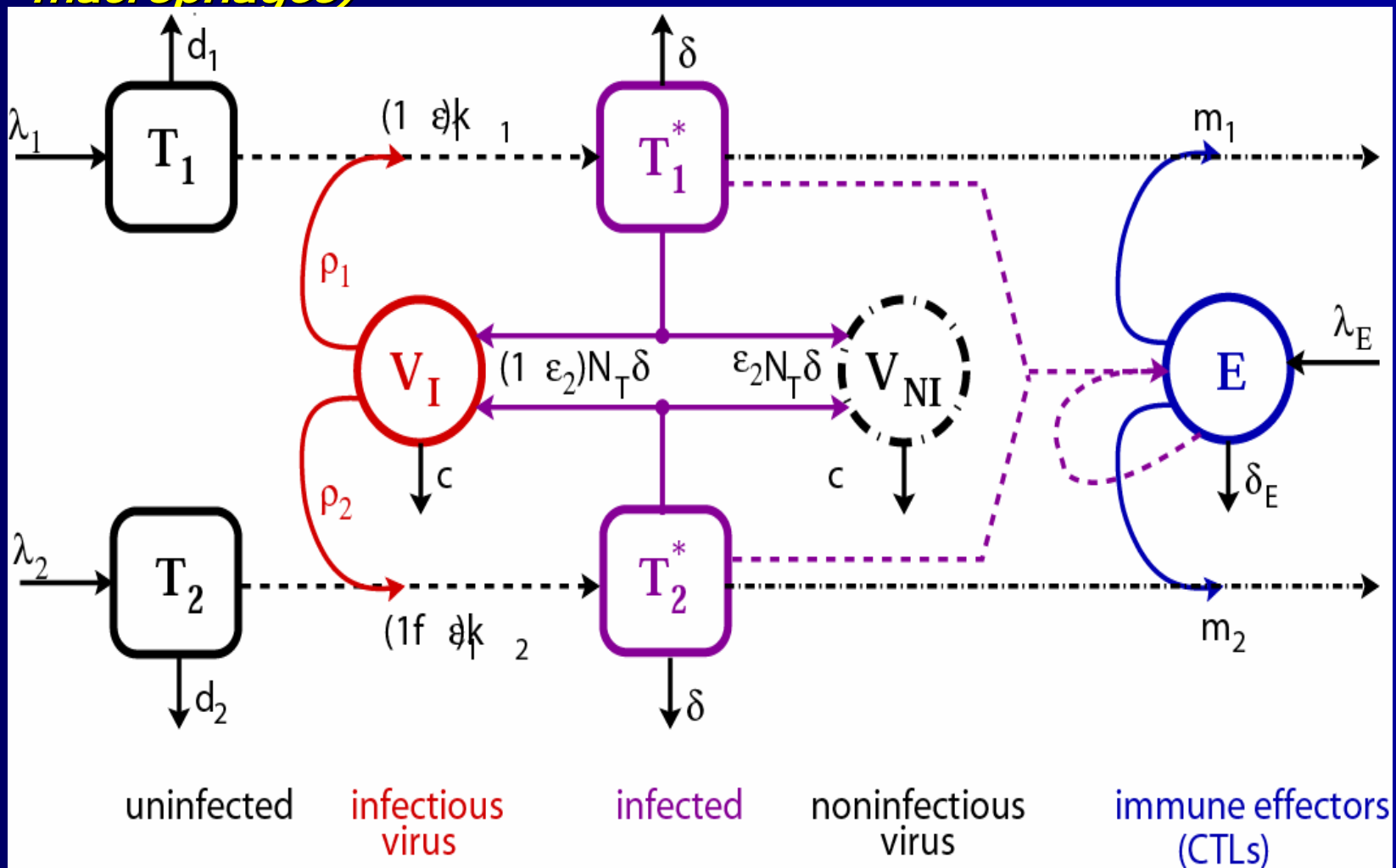
1) Bayesian/MCMC approach

J. Kaipio, V. Kolehmainen, E. Somersalo, and M. Vauhkonen, Statistical inversion and Monte Carlo sampling methods in electrical impedance tomography, *Inverse Problems* **16**(2000),1487-1522.

2) Homogenization

System Level Models:

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



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:

$$\varepsilon_1 = RTI$$

$$\varepsilon_2 = PI$$

INVERSE PROBLEMS WITH CLINICAL DATA

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

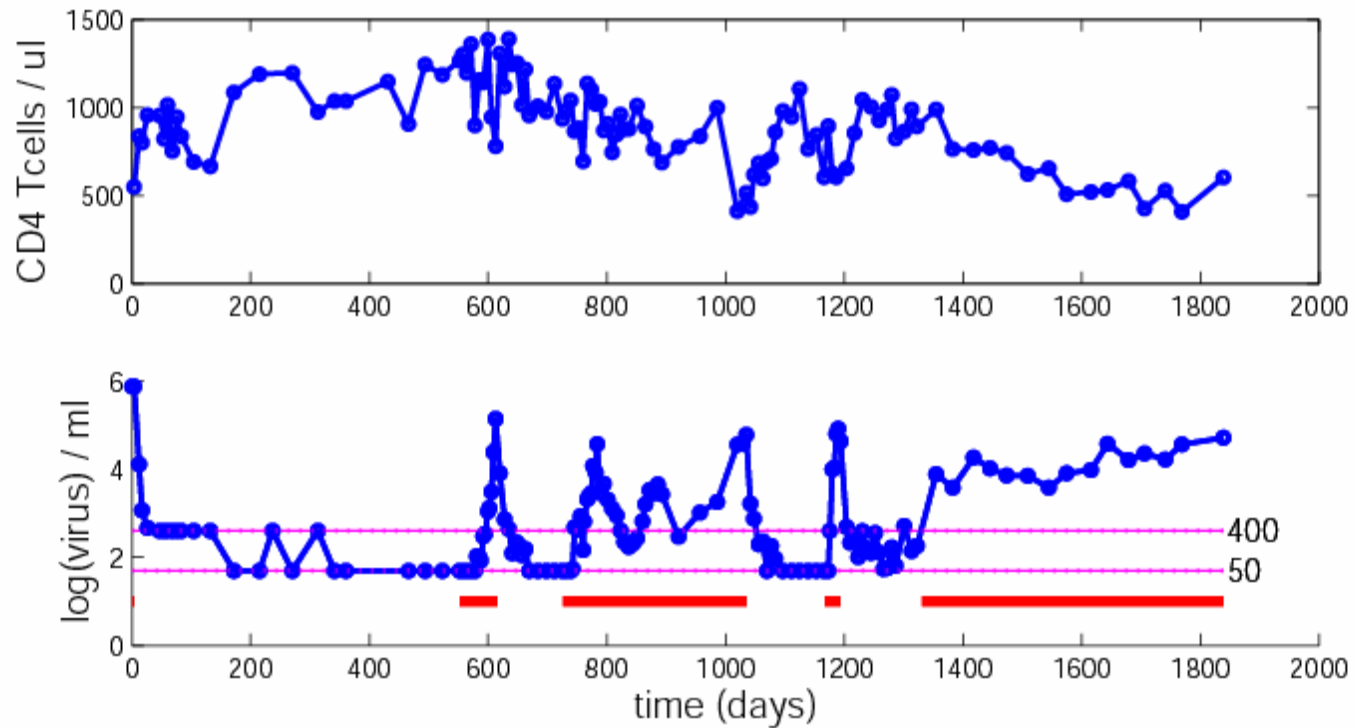
Censored Data: 400 or 50 copies/ml

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



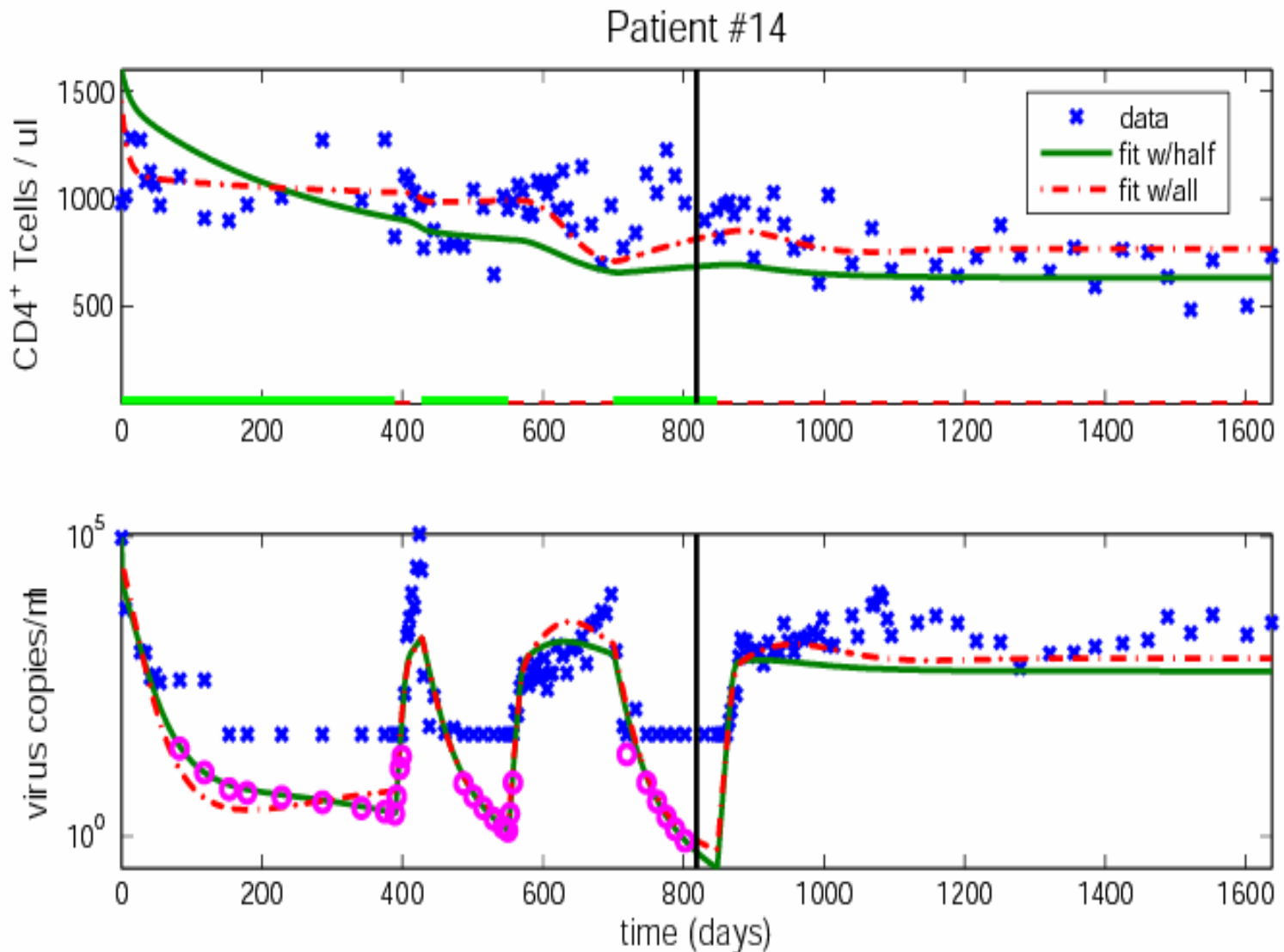
ESTIMATION OF PARAMETERS (individuals)

- 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 $\frac{1}{2}$ (~ 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

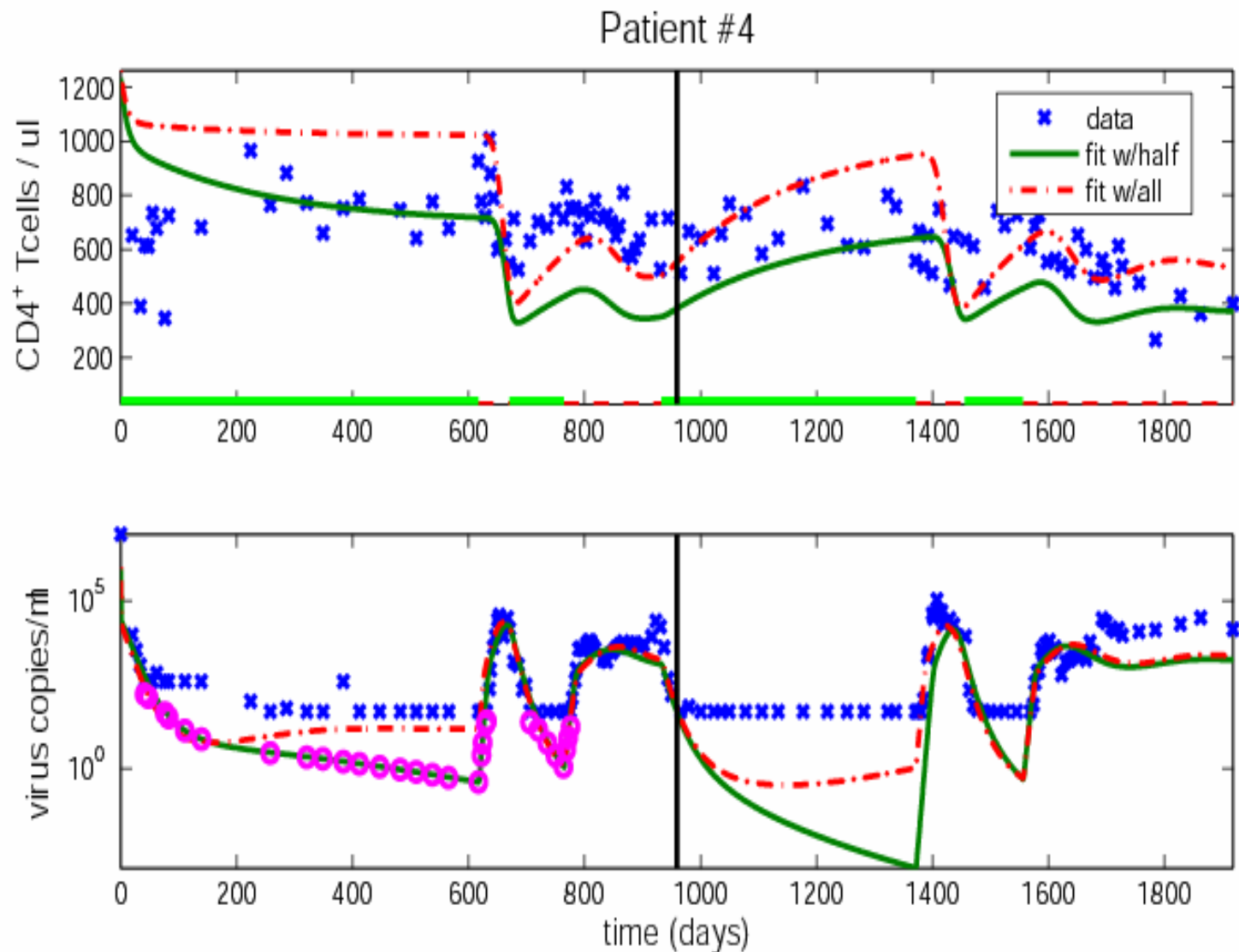
➤ Expected Maximization (EM) algorithm: MLE with censored data points replaced by expected values using distribution based on truncated log normal with mean, variance determined by censoring levels, data and model predictions

➤ 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!!!

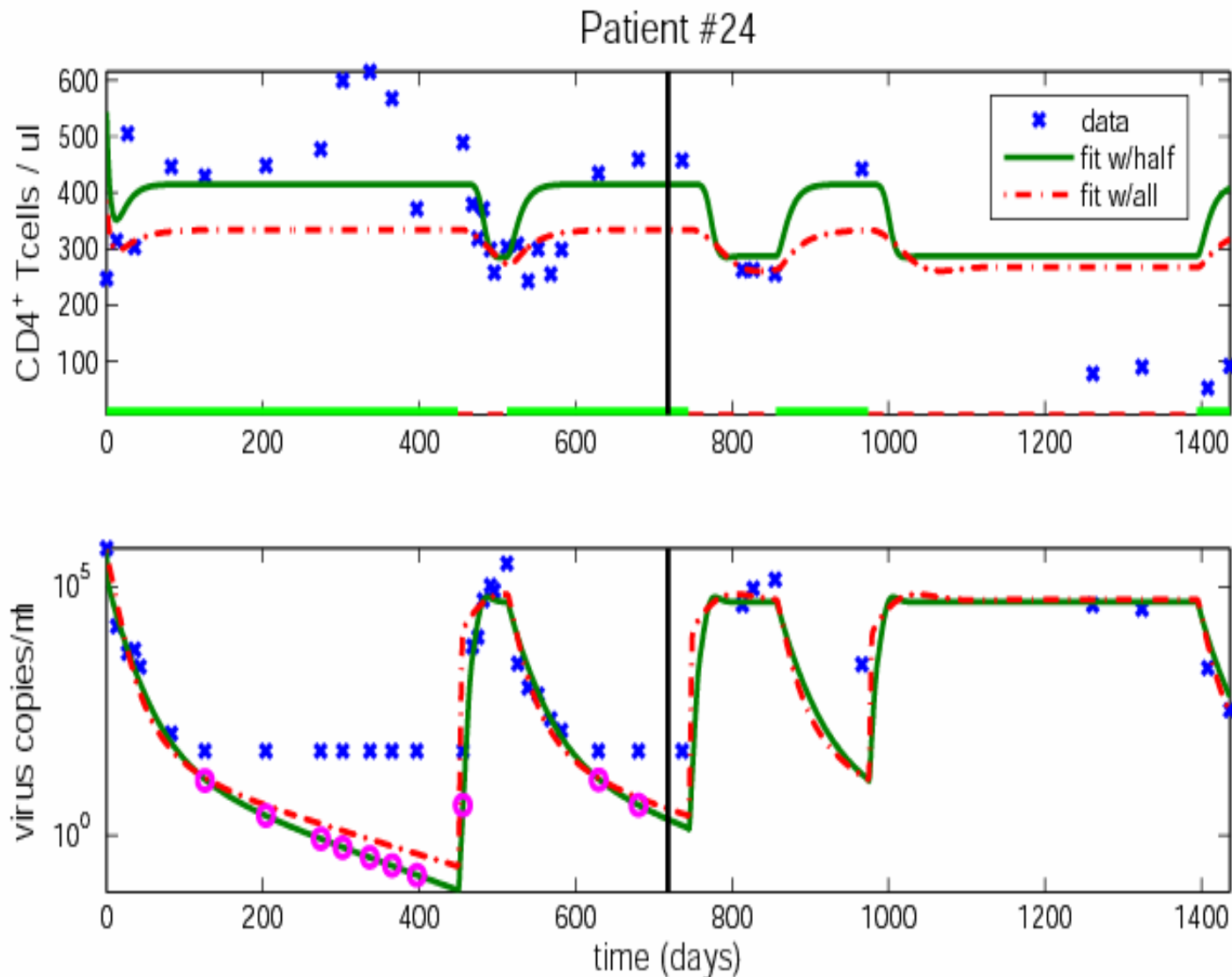


SIMULATION WITH ESTIMATED PARAMETERS (individuals)-predictive!!!



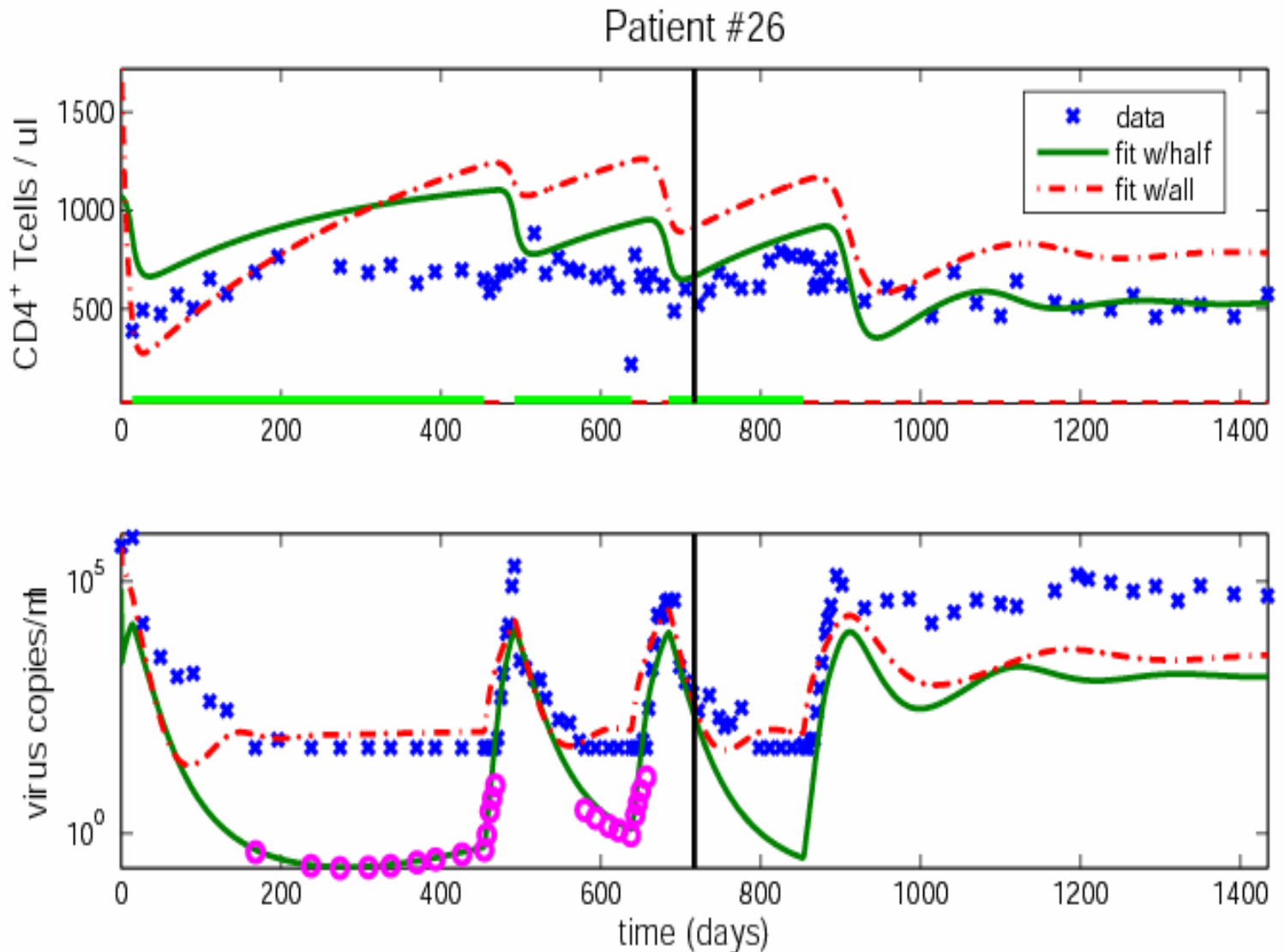
SIMULATION WITH ESTIMATED PARAMETERS

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



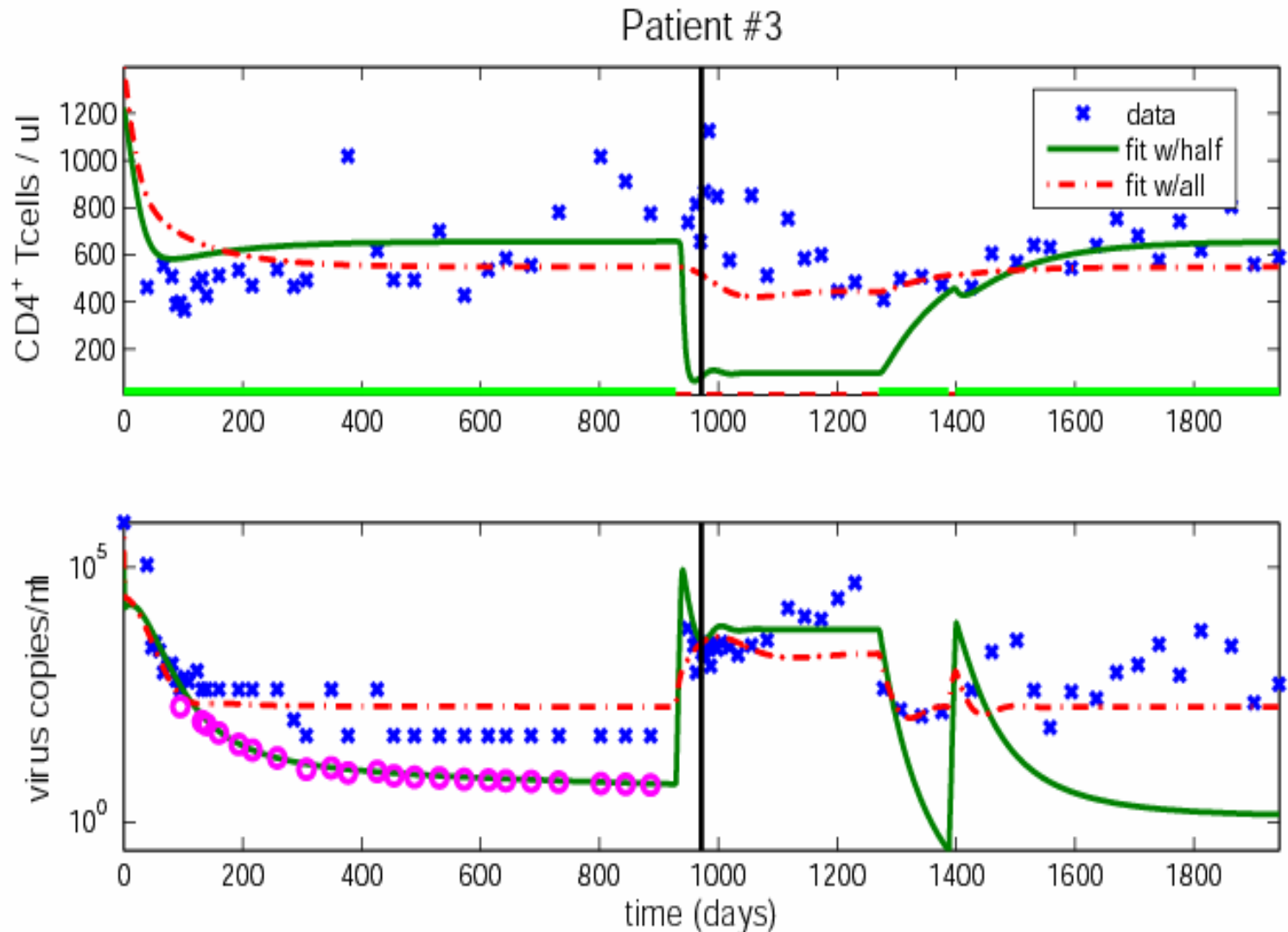
SIMULATION WITH ESTIMATED PARAMETERS

But not perfect even with observation of 2 interruptions!

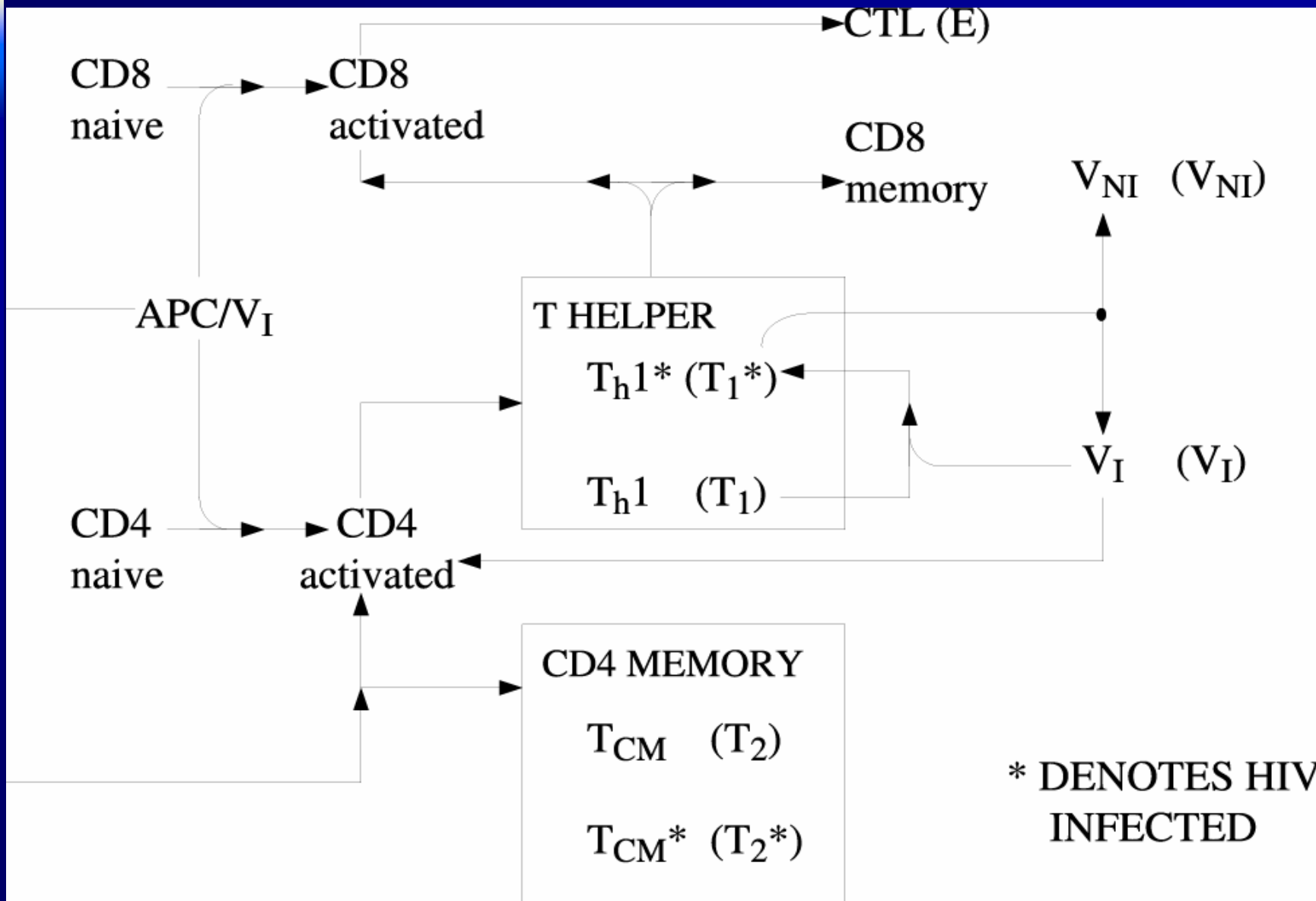


SIMULATION WITH ESTIMATED PARAMETERS

Model not predictive for individuals w/o interruption!!!



CTL (E)/immune response model not adequate description of biology:



GENERIC INVERSE PROBLEM : "Individual" Dynamics

Data: $d_i \sim Cx(t_i; q)$

Dynamics: $\frac{dx}{dt} = f(t, x(t), q) \quad q \in Q$

where f can represent ordinary, functional, or partial differential equation

Minimize $J(P) = \sum_i |CE[x(t_i; q) : P] - d_i|^2$

over $P \in \mathcal{P}(Q) = \{\text{probability measures over } Q\}$

Includes as special cases usual problems with constant R.V.'s (i.e., usual vector or function space parameters)

Here

$$\bar{x}(t; P) = \mathcal{E}[x(t; q) : P] \equiv \int_{\mathcal{Q}} x(t; q) dP(q)$$

In this case, one has individual dynamics for each realization q of a random variable with distribution P . One solves the system many times for these realizations and then computes the expected value of x with respect to P . This is then used with the data in the estimation- i.e., optimization of

$$J(P) = \sum_i |C\mathcal{E}[x(t_i; q) : P] - d_i|^2$$

over $P \in \mathcal{P}(\mathcal{Q})$ in Ordinary Least Squares (OLS)

Brief summary of theory:

Prohorov Metric Framework

Needs: (to carry out a careful mathematical analysis)

i) Topology on $\mathcal{P} = \mathcal{P}(Q)$

ii) Continuity of $P \rightarrow J(P)$

iii) Compactness of $\mathcal{P}(Q)$

*iv) Approximation of $\mathcal{P}(Q)$ by finite
dimensional $\mathcal{P}^M(Q)$*

RANDOM VARIABLES and ASSOCIATED METRIC SPACES

- $\mathcal{P} = \mathcal{P}(Q) = \{ P : P \text{ are probability measures on } Q \}$.
- $(\mathcal{P}(Q), \rho)$ is a metric space with the Prohorov metric ρ .
- It is a complete metric space and is compact if Q is compact.

PROHOROV METRIC

$$\rho(P^k, P) \rightarrow 0 \Leftrightarrow \int_Q g dP^k \rightarrow \int_Q g dP \text{ for all } g \in C(Q)$$

\Leftrightarrow convergence in expectation

$$\Leftrightarrow P^k[A] \rightarrow P[A] \text{ for all Borel } A \subset Q \text{ with } P(\partial A) = 0$$

For details on Prohorov metric and an initial approximation theory, see

H.T.Banks and K.L.Bihari, Modeling and estimating uncertainty in parameter estimation, CRSC-TR99-40, NCSU, Dec.,1999; Inverse Problems 17(2001),1-17.

GENERAL THEORETICAL FRAMEWORK

Application here to ODE systems that include population models, molecular reptation models, etc.

$$\text{System : } \begin{aligned} \frac{dx}{dt} &= f(t, x(t), q) & q \in Q \\ x(0) &= x_0 \end{aligned}$$

- *argue that $(t, x, q) \rightarrow f(t, x, q)$ is continuous from $[0, T] \times R^n \times Q$ to R^n , locally Lipschitz in x*
- *then by continuous dependence on parameters results for ODE, can obtain that $q \rightarrow x(t; q)$ is continuous from Q to R^n for each t .*

- yields continuity of $P \rightarrow J(P) = \sum_i |C\bar{x}(t_i; P) - d_i|^2$ from $\mathcal{P}(Q)$ to R^1 , with respect to ρ , the Prohorov metric
- $(\mathcal{P}(Q), \rho)$ is compact for compact Q
- then general theory of Banks - Bihari (Inverse Problems, 2001) can be followed to obtain *existence and stability* for inverse problems (continuous dependence wrt to observations of solutions of the inverse problem)
- moreover, an *approximation theory* as a basis for computational methods is obtained

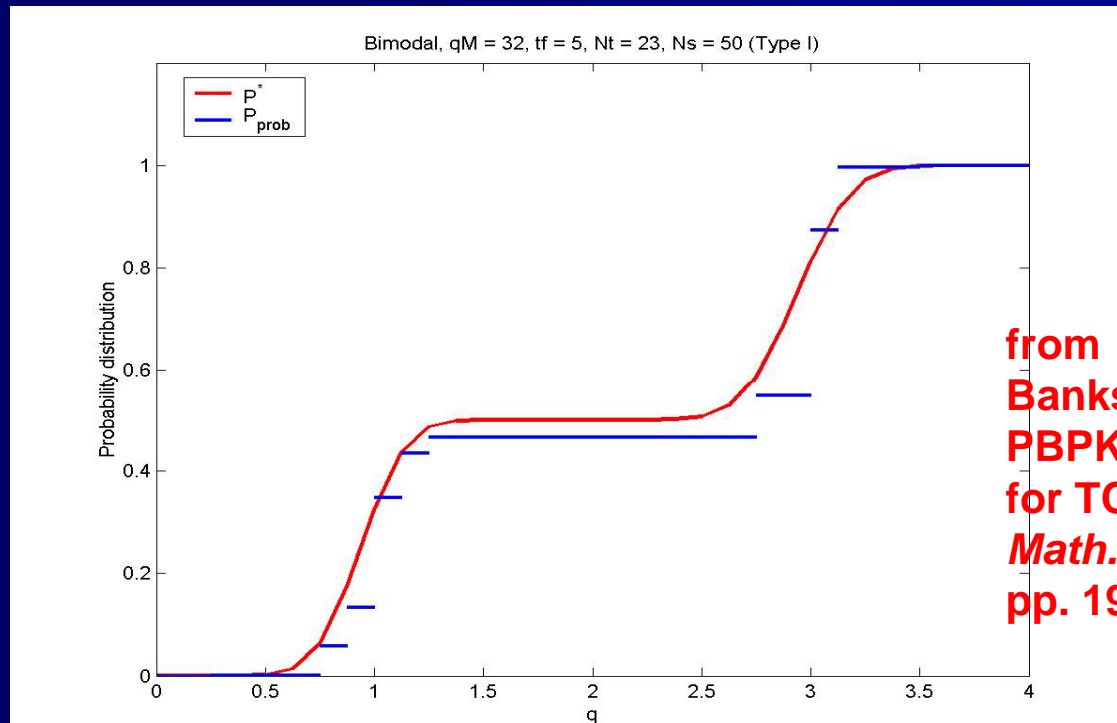
APPROXIMATION RESULTS

1. Finite no. of Dirac delta measures (B&Bihari)

Let $Q_M = \{q_j^M\} \subset Q$ be such that $\bigcup_M Q_M$ is dense in Q , $\delta_q = \Delta'_q$,

$$P^M(Q) \equiv \left\{ P_M \in \mathcal{P}(Q) : P_M = \sum_{j=1}^M p_j \Delta_{q_j^M}, q_j^M \in Q_M, p_j \text{ rat}, p_j \geq 0 \right\}.$$

Then $\bigcup_M P^M(Q)$ is dense in $\mathcal{P}(Q)$ in the ρ metric



from
Banks-Potter:
PBPK models
for TCE,
Math. Biosci.,192(2004),
pp. 193-225

2. Finite combinations of piecewise linear splines

Let \mathcal{F} be a weakly compact subset of $L^2(Q)$, Q compact and let $\mathcal{P}_{\mathcal{F}}(Q) \equiv \{F \in \mathcal{P}(Q) : F' = f, f \in \mathcal{F}\}$. Then $\mathcal{P}_{\mathcal{F}}(Q)$ is compact in $(\mathcal{P}(Q), \rho)$. Moreover, if we define $\{l_j^M\}$ to be the linear splines on Q corresponding to the partition Q_M , where $\bigcup_M Q_M$ is dense Q , and define

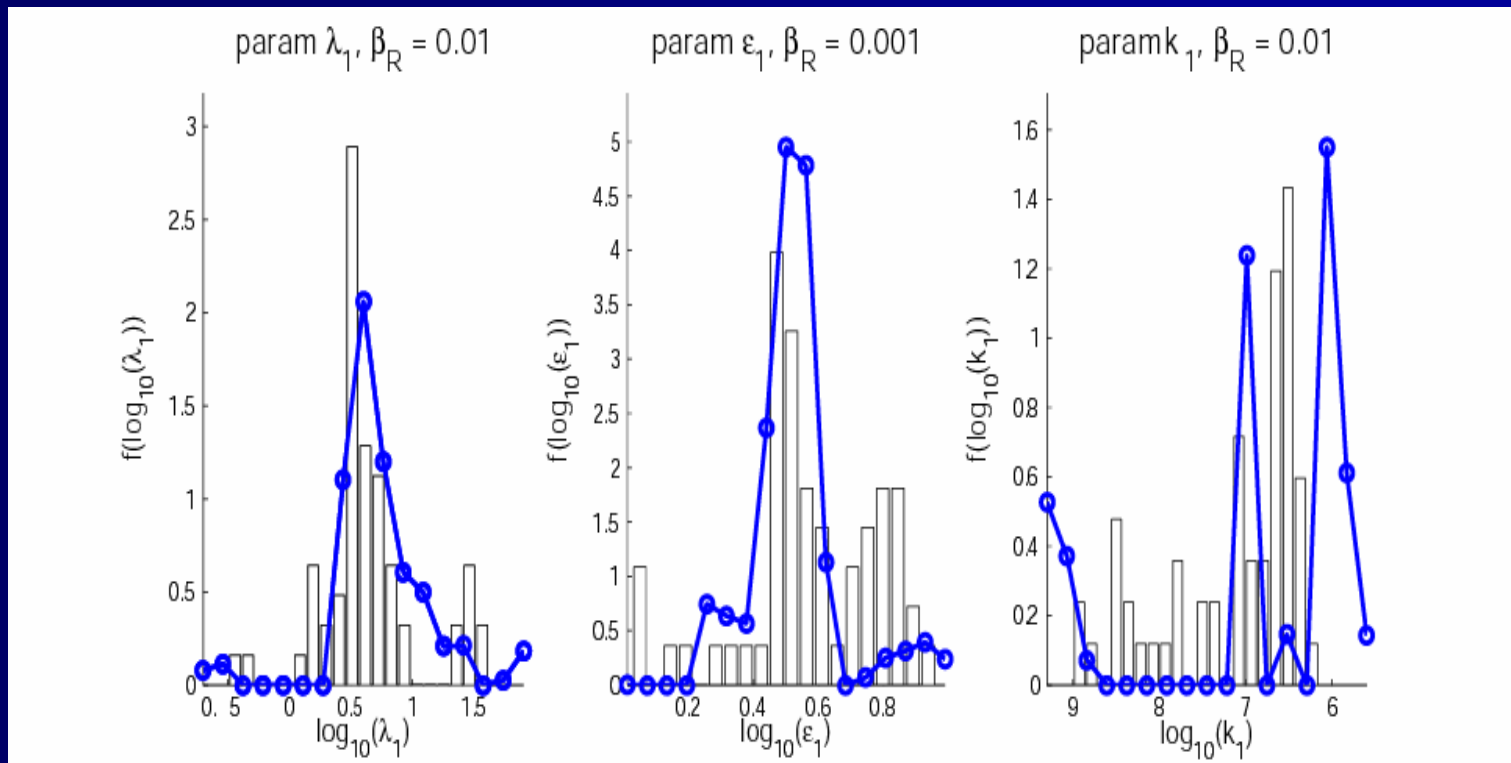
$\mathcal{F}^M \equiv \{f^M : f^M = \sum_j b_j^M l_j^M, b_j^M \text{ rational}\}$. Then

if $\mathcal{P}_{\mathcal{F}^M} \equiv \{F_M \in \mathcal{P}(Q) : F_M = \int f^M, f^M \in \mathcal{F}^M\}$,

we have $\bigcup_M \mathcal{P}_{\mathcal{F}^M}$ is dense in $(\mathcal{P}_{\mathcal{F}}(Q), \rho)$.

H.T. Banks and G.A. Pinter, A probabilistic multiscale approach to hysteresis in shear wave propagation in biotissue, *SIAM J. Multiscale Model. Simul.*, 3(2005), pp. 395- 412.

**ESTIMATION OF POPULATION PROBABILITY DENSITIES
VS.
HISTOGRAMS OF INDIVIDUAL PARAMETER ESTIMATES
(59 PATIENTS)**



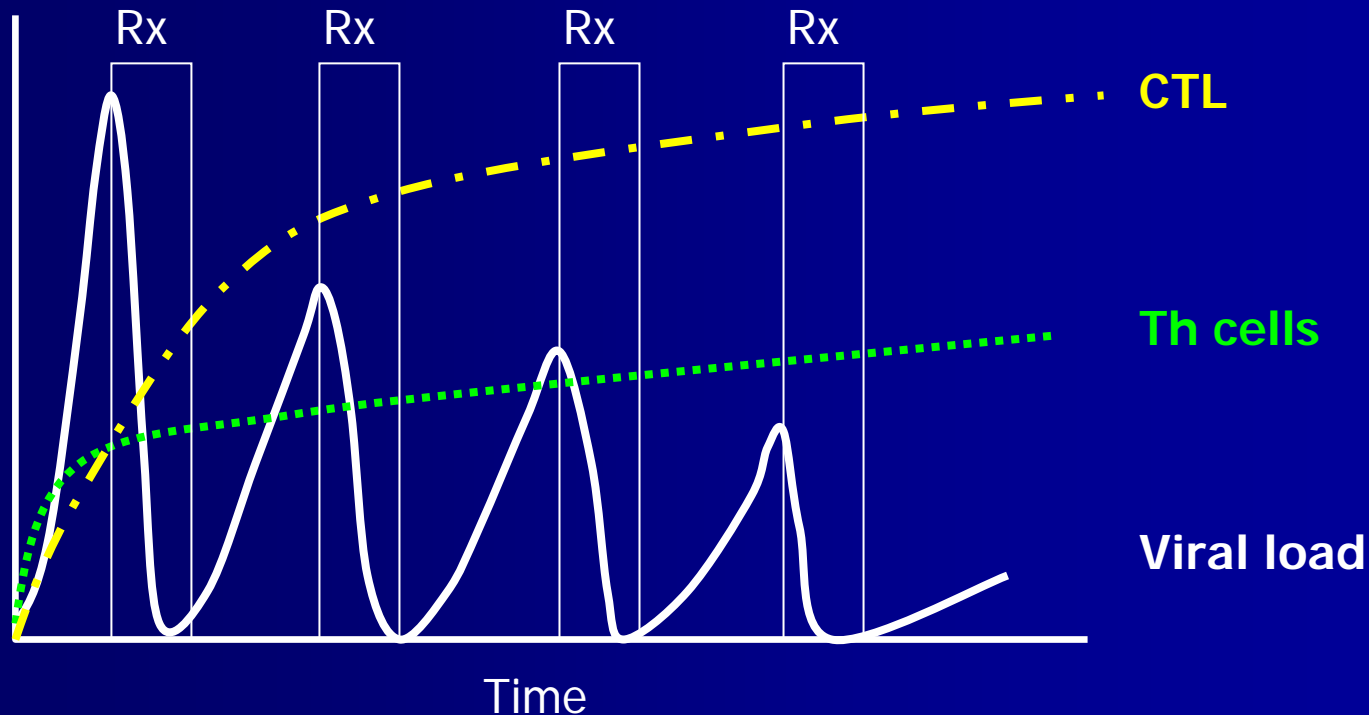
Problems with Continuous Therapy

- *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?*

Modeling Goals

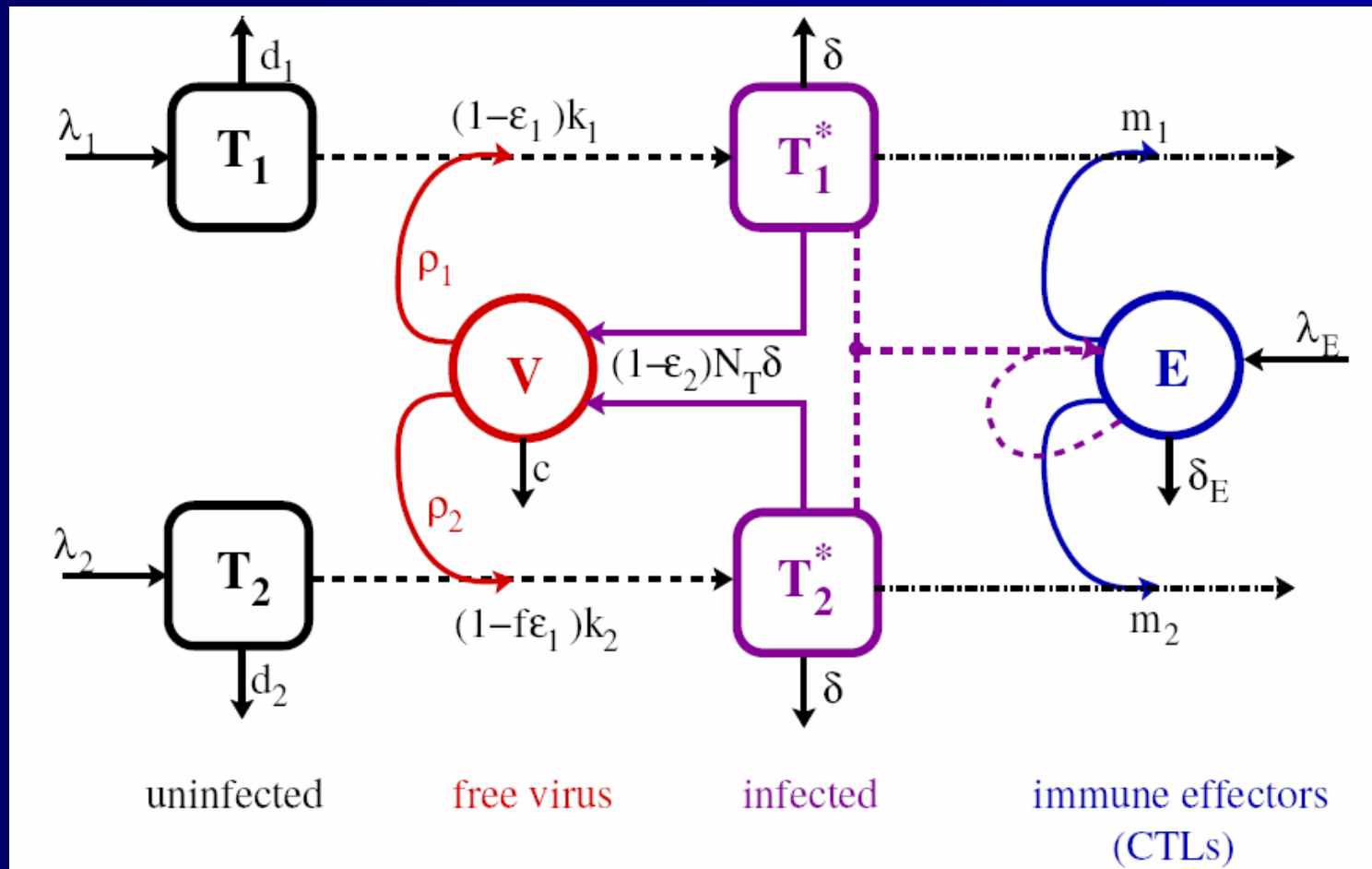
- *To obtain insights into the relationship between drug therapy and long-term immunological control of HIV*
- *To determine optimal treatment protocols*

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)



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

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

ε_1 - RT inhibitors

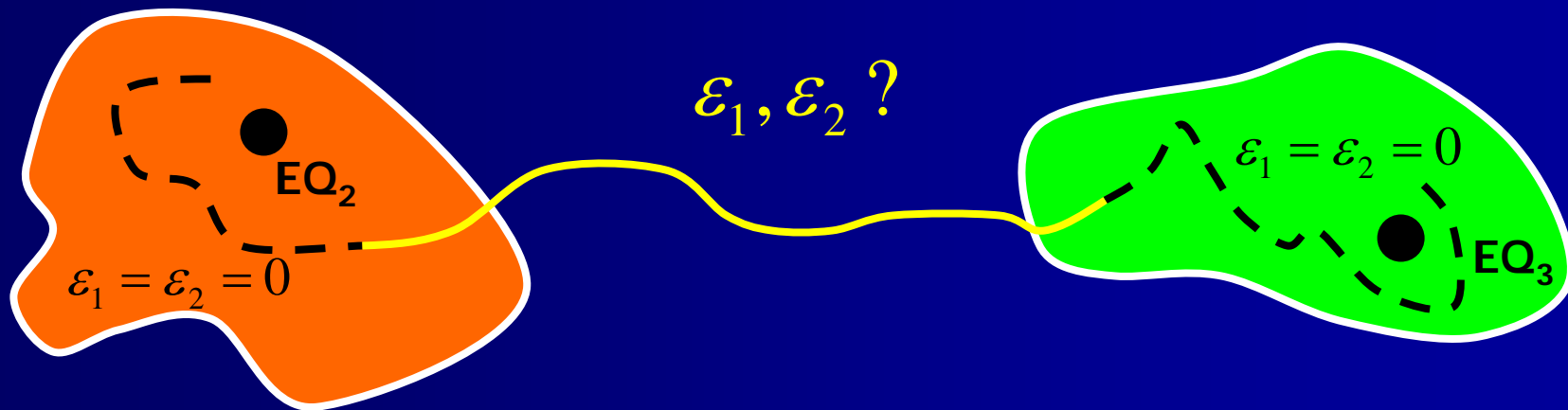
ε_2 - PI

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 ?*

Control Objective



Stable "unhealthy"
(viral dominant)
state

Stable "healthy"
(immune dominant)
state

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

$$0 \leq a_1 \leq \varepsilon_1 \leq b_1 \leq 1$$

$$0 \leq a_2 \leq \varepsilon_2 \leq b_2 \leq 1$$

Optimality System

- Define the Lagrangian

$$\begin{aligned} L = & QV + R_1 \varepsilon_1^2(t) + R_2 \varepsilon_2^2(t) - SE(t) \\ & + \xi_1[\lambda_1 - d_1 T_1 - (1 - \varepsilon_1)k_1 V T_1] \\ & + \xi_2[\lambda_2 - d_2 T_2 - (1 - f \varepsilon_1)k_2 V T_2] \\ & + \xi_3[(1 - \varepsilon_1)k_1 V T_1 - \delta T_1^* - m_1 E T_1^*] \\ & + \xi_4[(1 - f \varepsilon_1)k_2 V T_2 - \delta T_2^* - m_2 E T_2^*] \\ & + \xi_5[(1 - \varepsilon_2)N_T \delta(T_1^* + T_2^*) - cV - \\ & \quad - [(1 - \varepsilon_1)\rho_1 k_1 T_1 + (1 - f \varepsilon_1)\rho_2 k_2 T_2]V] \\ & + \xi_6\left[\lambda_E + \frac{b_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E\right] \\ & - w_{11}(\varepsilon_1 - a_1) - w_{12}(b_1 - \varepsilon_1) \\ & - w_{21}(\varepsilon_2 - a_2) - w_{22}(b_2 - \varepsilon_2) \end{aligned}$$

Necessary Conditions

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

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

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

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

$$\frac{dV}{dt} = (1 - \varepsilon_2) N_T \delta (T_1^* + T_2^*) - cV$$

$$-[(1 - \varepsilon_1) \rho_1 k_1 T_1 + (1 - f \varepsilon_1) \rho_2 k_2 T_2] V$$

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

State Equations

$$\frac{d\xi_1}{dt} = -\frac{\partial L}{\partial T_1}$$

$$\frac{d\xi_2}{dt} = -\frac{\partial L}{\partial T_2}$$

$$\frac{d\xi_3}{dt} = -\frac{\partial L}{\partial T_1^*}$$

$$\frac{d\xi_4}{dt} = -\frac{\partial L}{\partial T_2^*}$$

$$\frac{d\xi_5}{dt} = -\frac{\partial L}{\partial V}$$

$$\frac{d\xi_6}{dt} = -\frac{\partial L}{\partial E}$$

Co-state Equations

Optimal Control

$$\begin{aligned}\frac{\partial L}{\partial \varepsilon_1} &= 2R_1\varepsilon_1 + (\xi_1 - \xi_3 + \rho_1\xi_5)k_1VT_1 \\ &\quad + (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VT_2 \\ &\quad - w_{11} + w_{12} \\ &= 0\end{aligned}$$

$w_{ij} \geq 0$ satisfying

$$w_{11}(\varepsilon_1^*(t) - a_1) = 0$$

$$w_{12}(b_1 - \varepsilon_1^*(t)) = 0$$



$$\varepsilon_1^* = \max\left(a_1, \min\left(b_1, -\frac{(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VT_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VT_2}{2R_1}\right)\right)$$

Similarly,

$$\varepsilon_2^* = \max\left(a_2, \min\left(b_2, \frac{\xi_5 N_T \delta(T_1^* + T_2^*)}{2R_2}\right)\right)$$

Continuous Optimal Therapy (Open-loop)

- Early infection (perturbing the “uninfected” unstable steady state)

$$T_1(0) = 10^6$$

$$T_2(0) = 3198$$

$$T_1^*(0) = 10^{-4}$$

$$0 \leq \varepsilon_1 \leq 0.7$$

$$T_2^*(0) = 10^{-4}$$

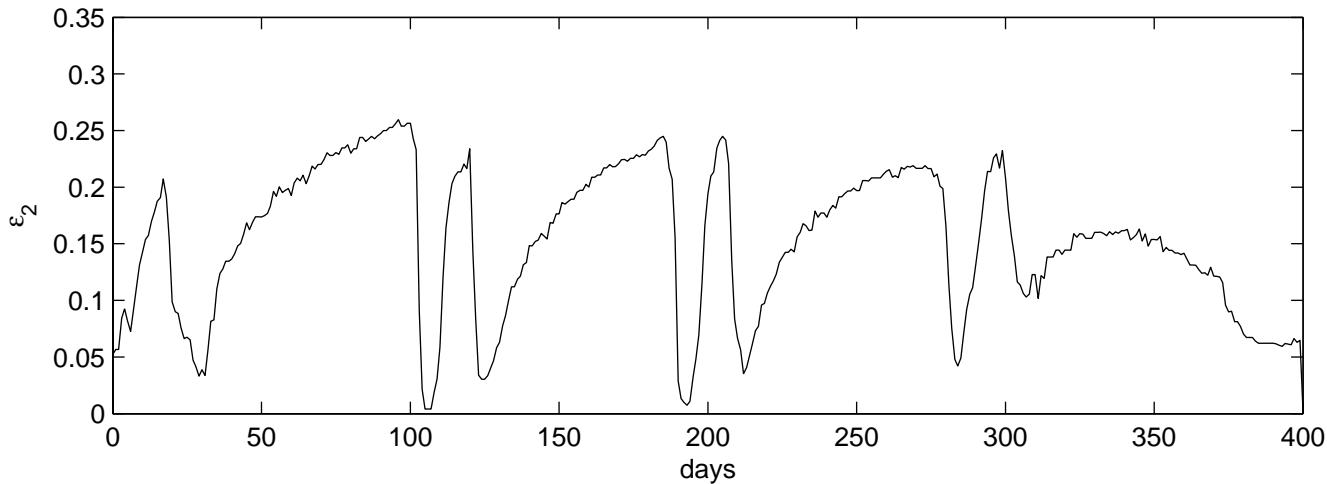
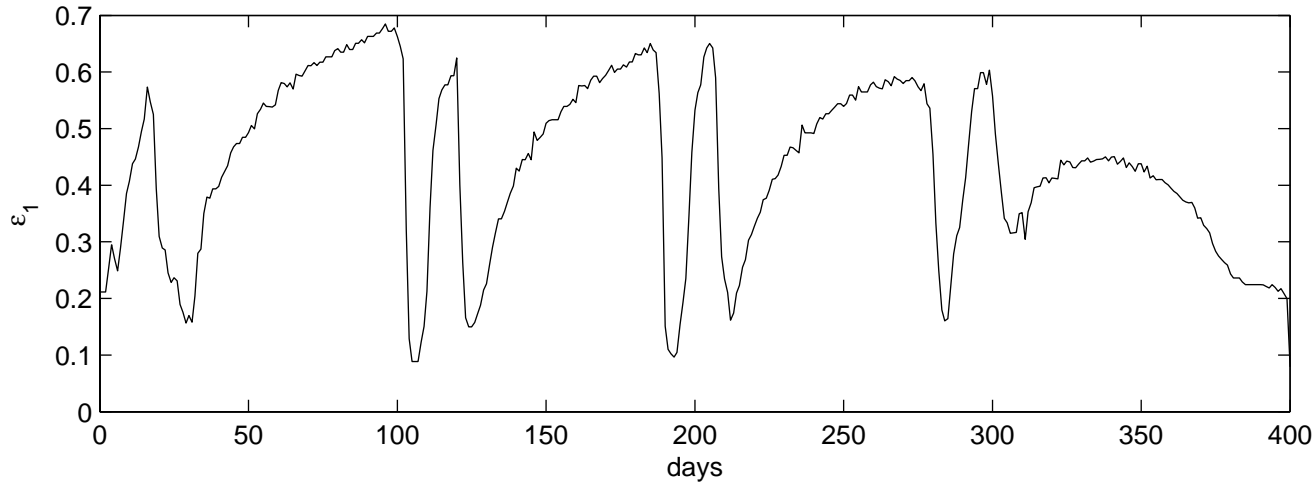
$$0 \leq \varepsilon_2 \leq 0.3$$

$$V(0) = 1$$

$$E(0) = 10$$

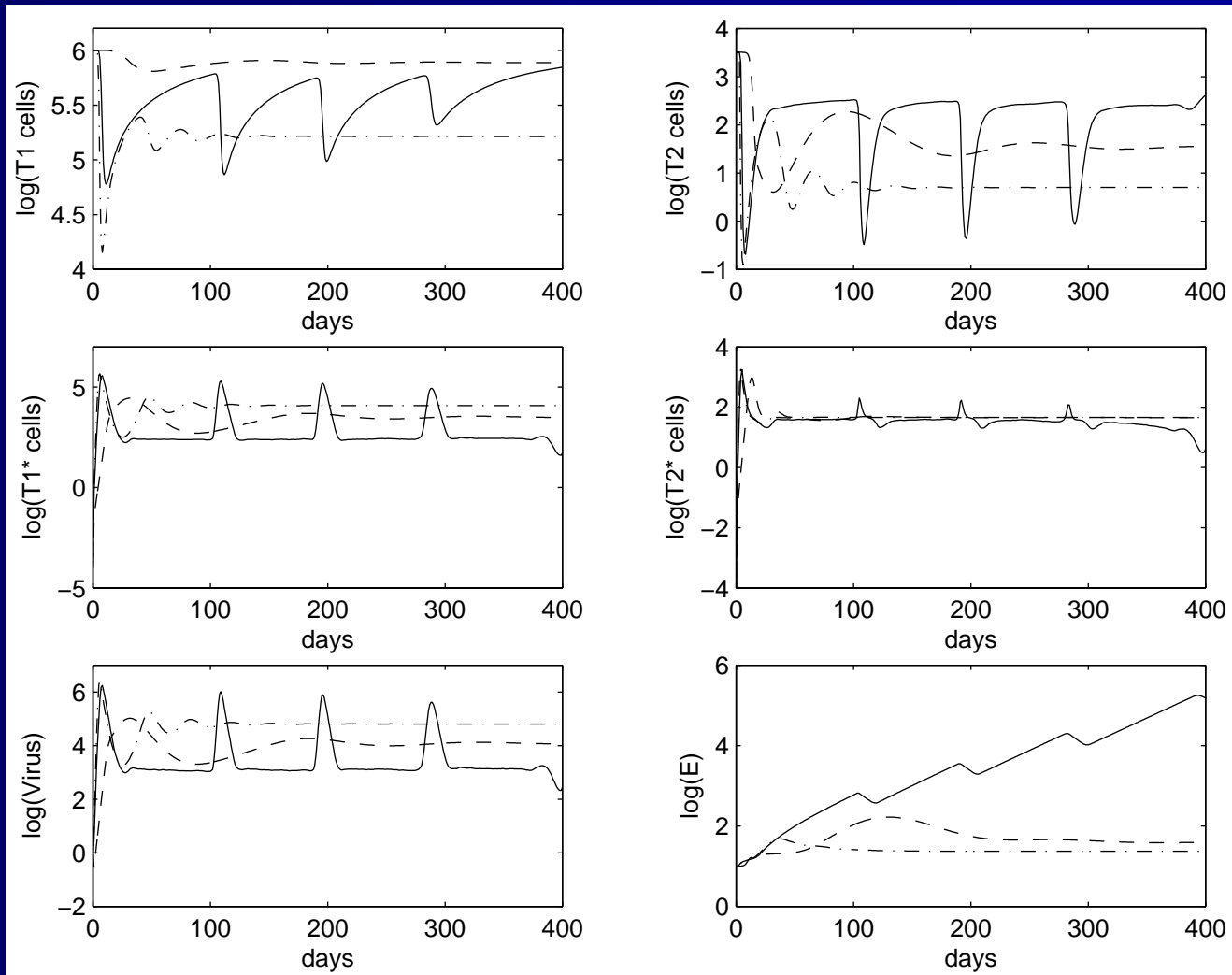
Weighting coefficients: $Q = 0.1, R_1 = R_2 = 20000, S = 1000$

Optimal Controls



Structured
Treatment
Interruption
type
controls

Optimal Solutions



Structured Treatment Interruption (STI)

- Controls ε_1 and ε_2 are **discrete** take on values of 0 (drug is off) or b_i (full treatment)
- *Direct Search Algorithm:*
 1. Select any pair of ε_1 and ε_2 from the control set
 2. Solve the state equations using the pair as controls
 3. Select another pair of controls and again solve the state equations
 4. Evaluate the objective functions and select the control pair that gives a smaller cost
 5. Go back to step 3 until all possible pairs from the control set are used

For a 900 days simulation, it requires $(2^{900})^2$ objective function evaluations

Computationally
infeasible

Sub-optimal STI (cont'd)

- Daily treatment for drug therapies is not clinically feasible
- Consider a five-day segment treatment: the number of objective function evaluation is reduced to $(2^{(900/5)})^2$ (still expensive)
- **Subperiod Procedure:** (similar to dynamic programming)
 1. Consider subperiods $[0,30]$, $[0,60]$, $[0,90]$, $[0,120]$, ... , $[0,900]$.
 2. Begin with period $[0,30]$, find an optimal STI control pair $(\varepsilon_{1,1}^*, \varepsilon_{2,1}^*)$ using the reduced iteration technique (five-day segment)
 3. Using this control pair for the first 30 days of the next segment $[0,60]$ to find the last six elements in

$$\varepsilon_{1,2} = [\varepsilon_{1,1}^*, *, *, *, *, *, *] \text{ and } \varepsilon_{2,2} = [\varepsilon_{2,1}^*, *, *, *, *, *, *]$$

that make an optimal STI control pair over $[0,60]$

4. Repeat this process

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?

$$T_1(0) = 163573$$

$$T_2(0) = 5$$

$$T_1^*(0) = 11945$$

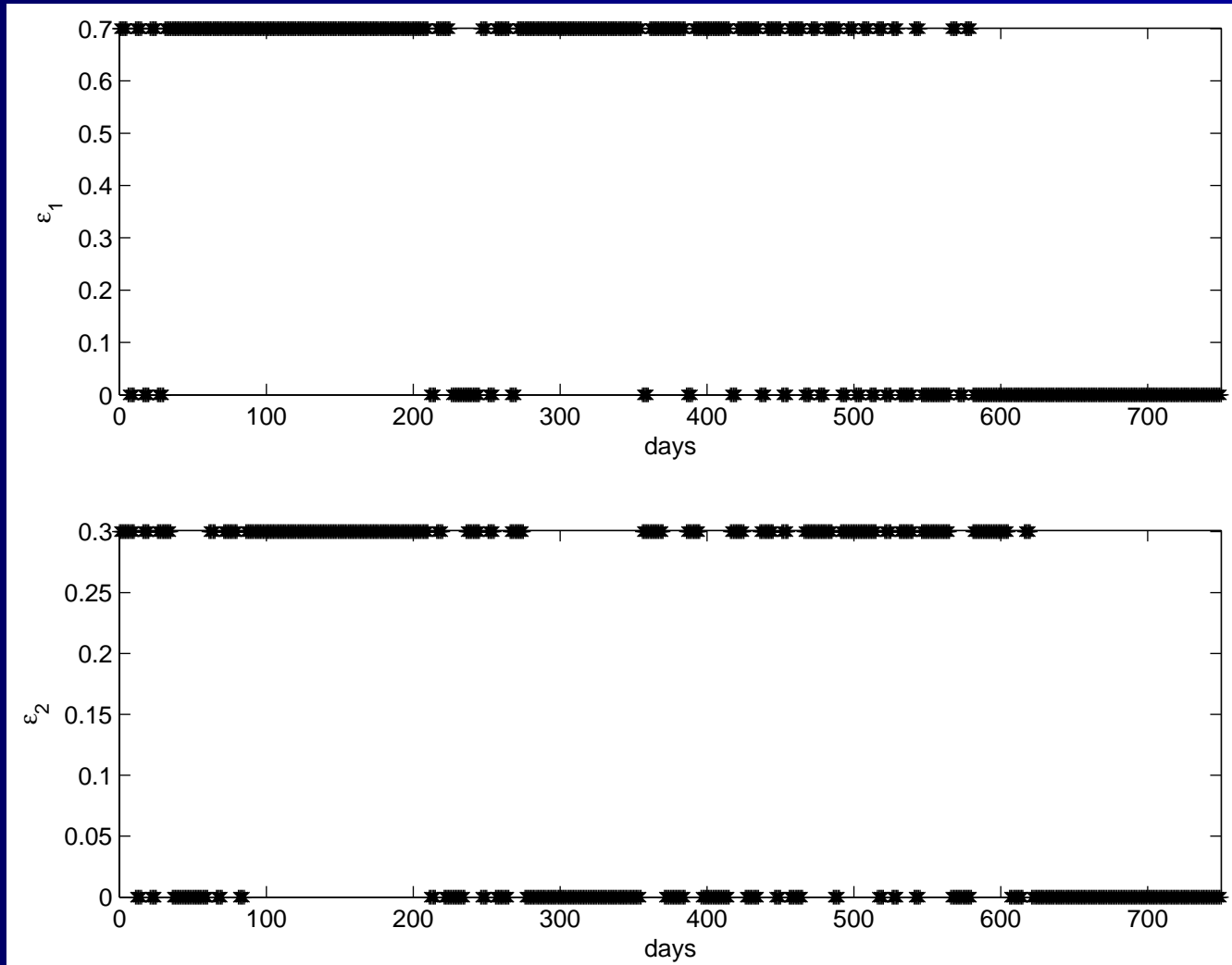
$$T_2^*(0) = 46$$

$$V(0) = 63919$$

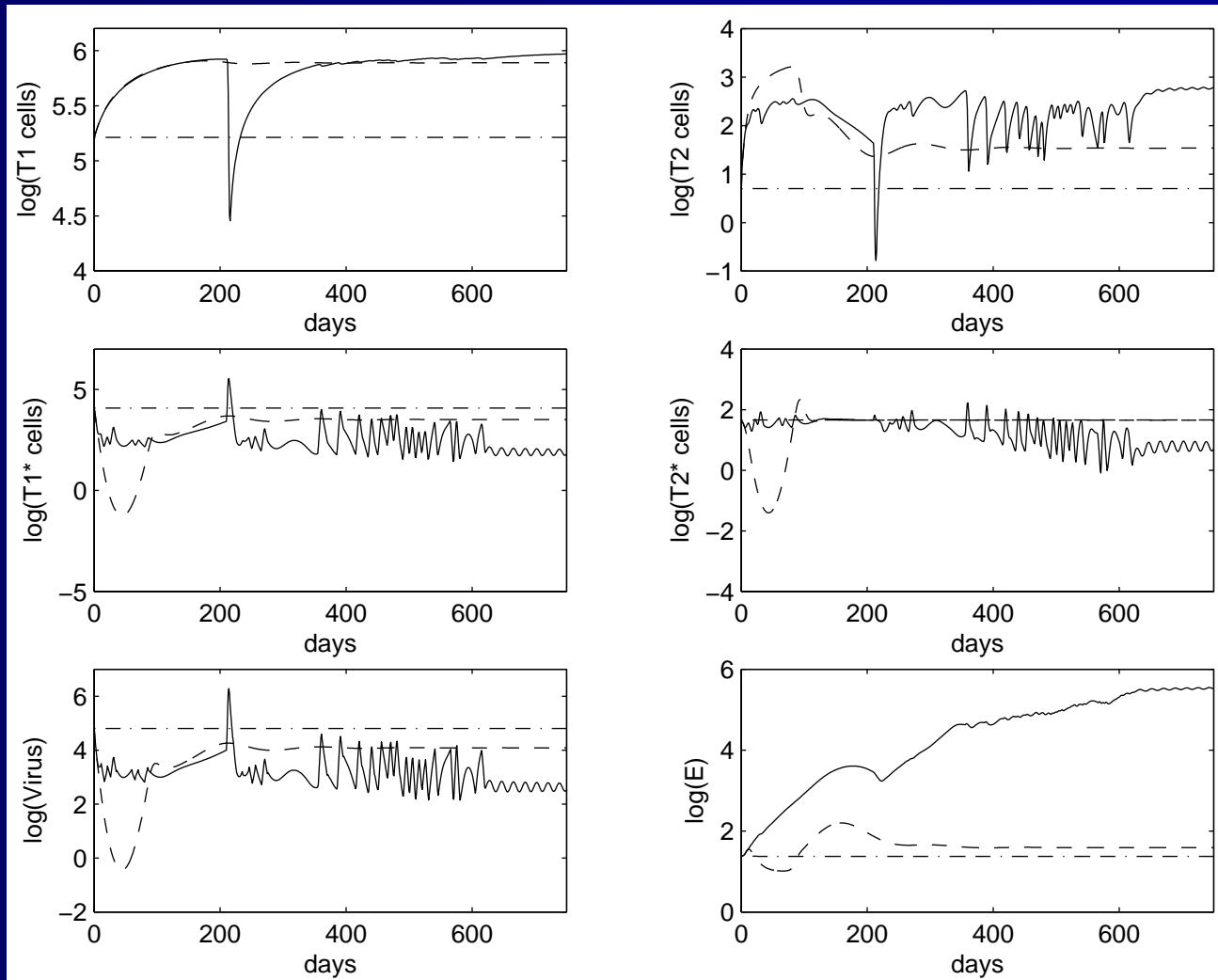
$$E(0) = 24$$

Viral
Dominant
(stable)

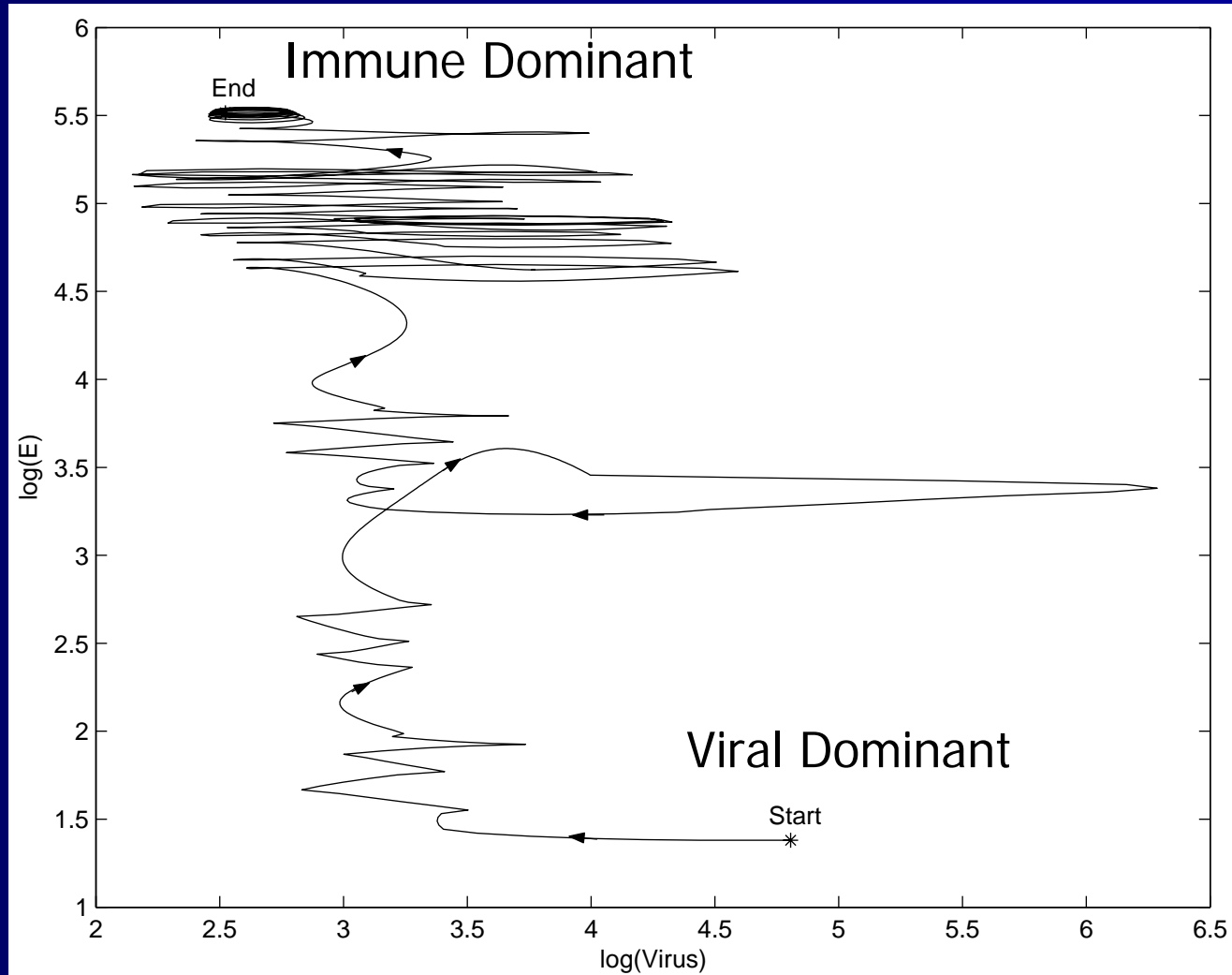
Sub-optimal STI Controls



Sub-optimal Solutions



Phase Plane – Virus versus CTL



***In recent efforts, similar results
with feedback control!!***

***--State Dependent Riccati Equation
(SDRE) estimator approach***

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, J. Comp. Appl. Math, special issue on Mathematics Applied to Immunology, 184:10-49,2005.*
- *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.*