Modeling the Impacts of HIV from the Cellular to Full Systemic Response

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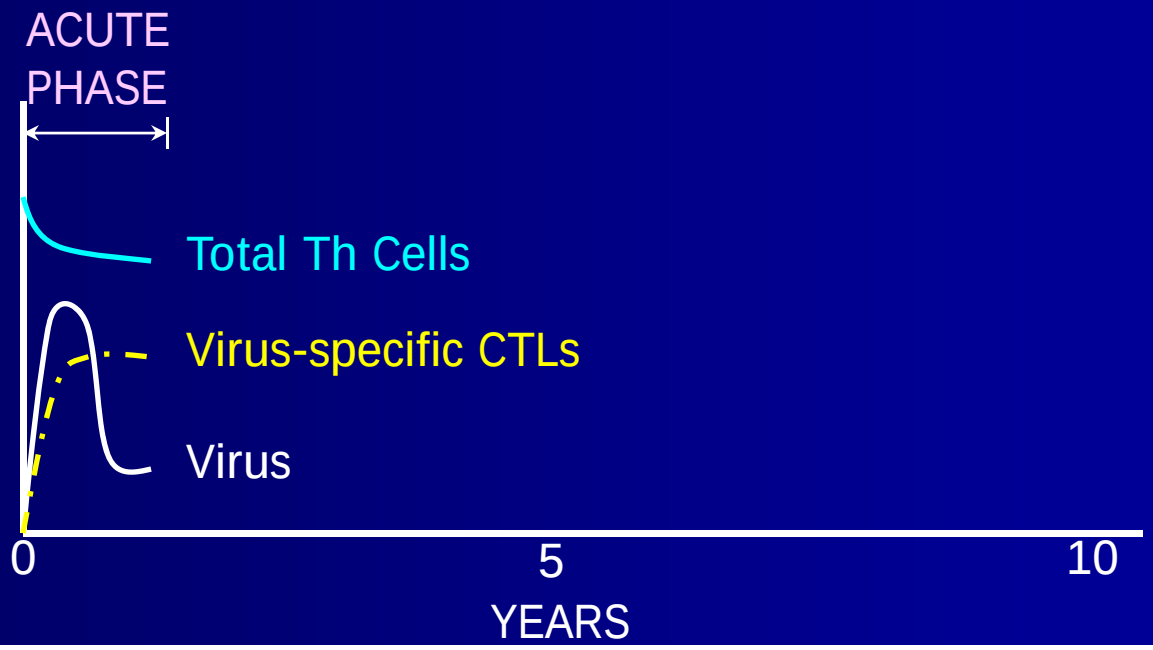
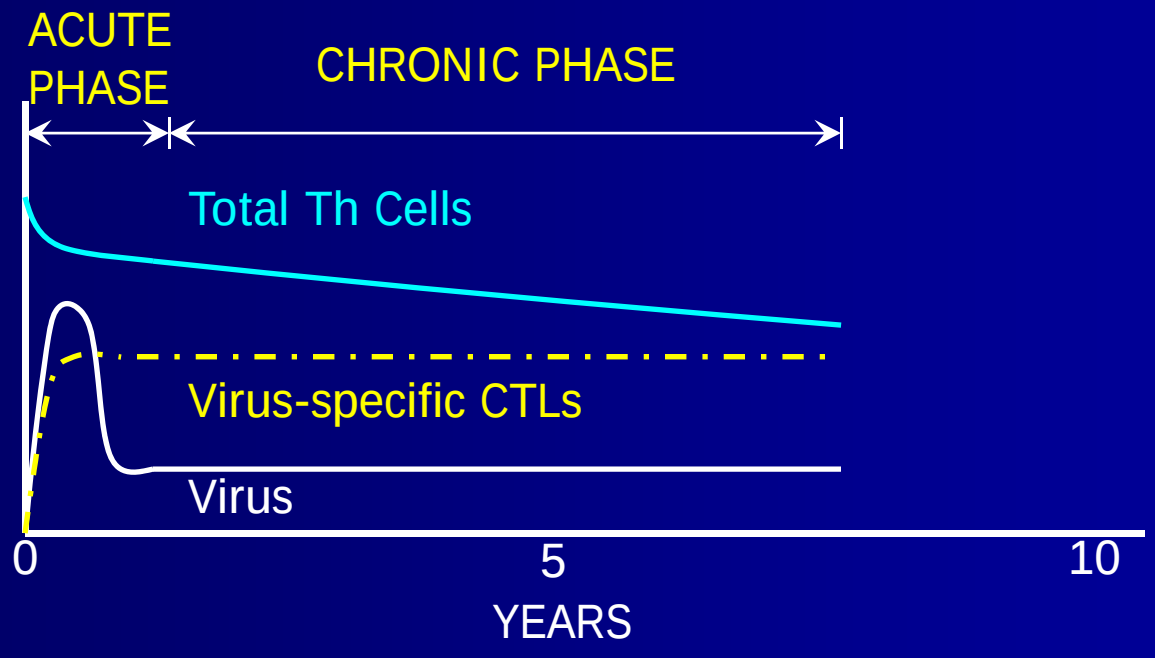
Dynamics of HIV Infection

- *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*



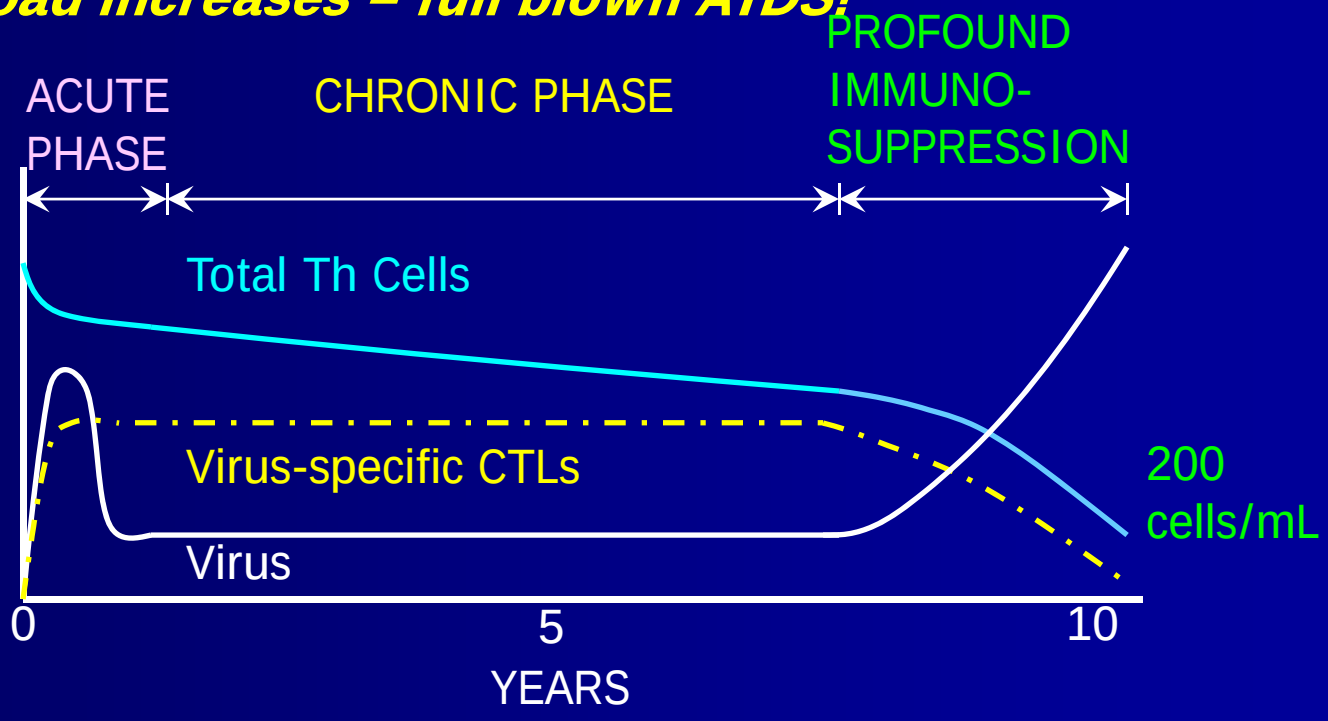
Dynamics of HIV Infection *(cont'd)*

- ***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 at the Cellular Level 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 intracellular copies of virus to be encapsulated and exported for extracellular infections

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

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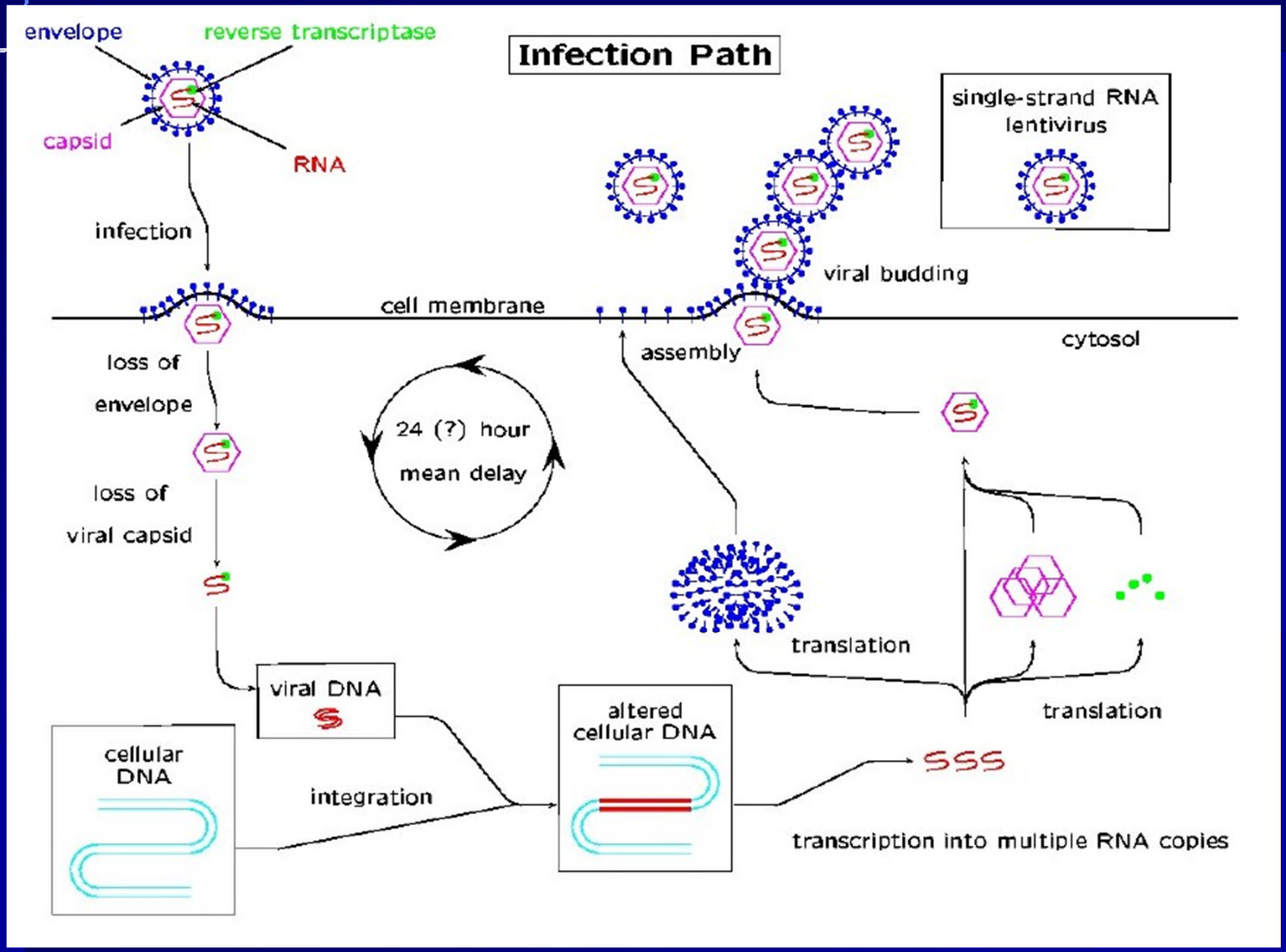
Cellular Level



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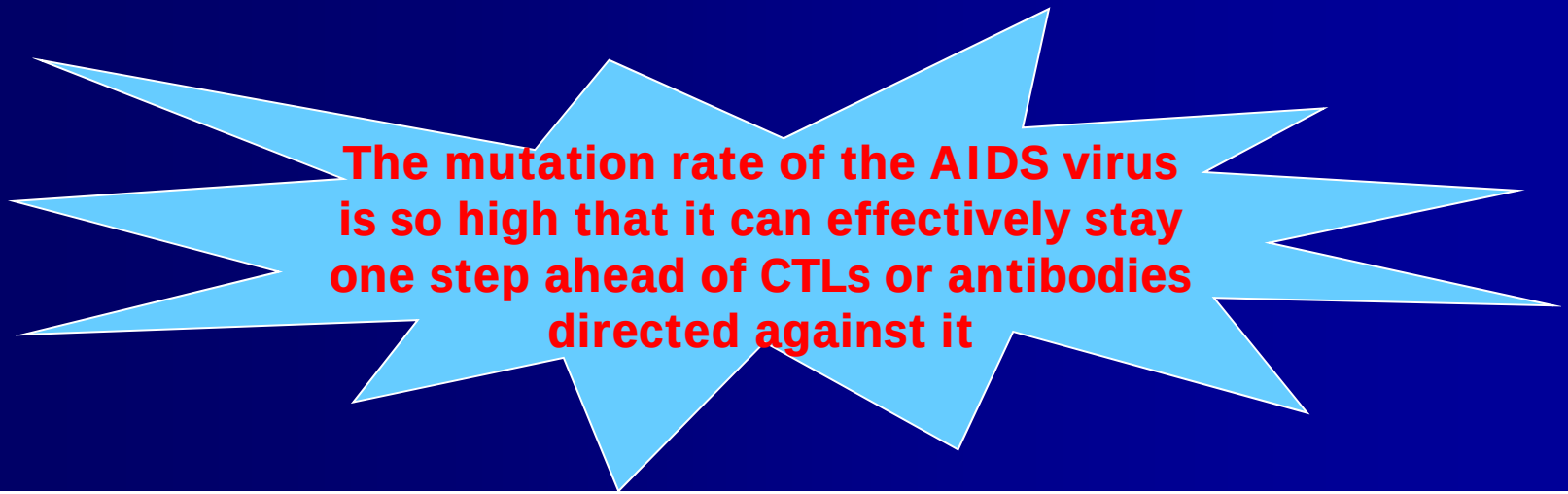
What's Happening during the Chronic Phase? (cont'd)

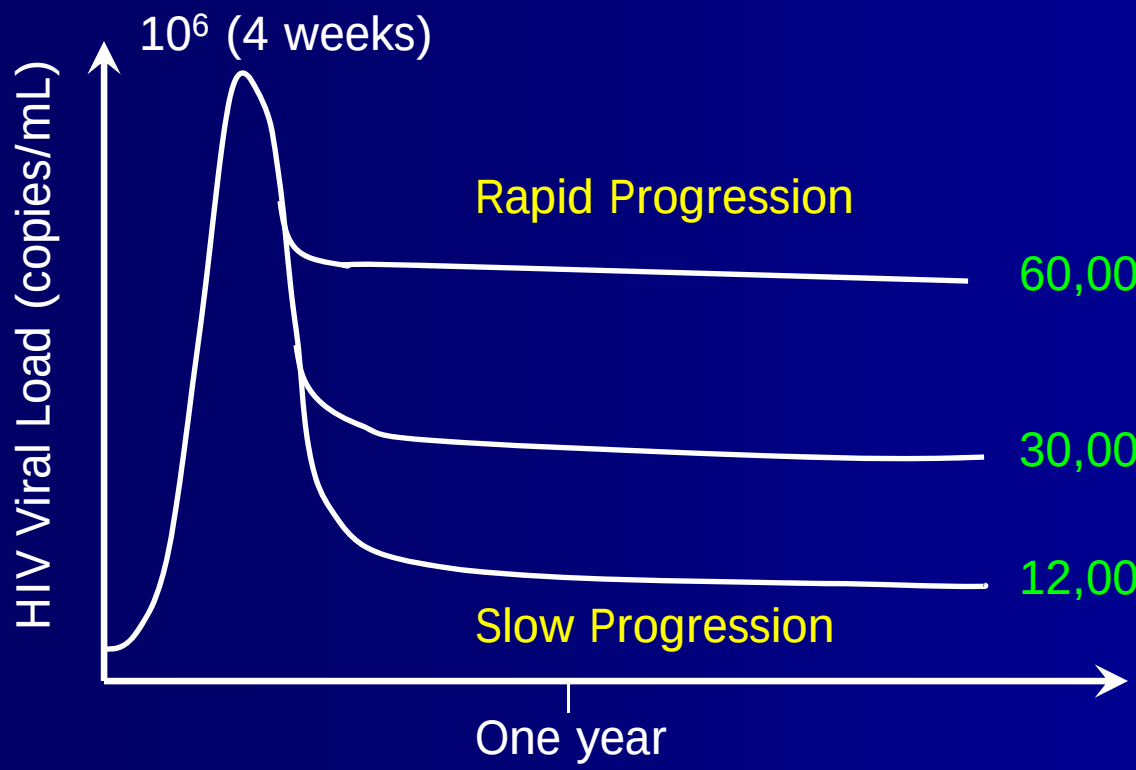
- The reverse transcriptase enzyme used to copy the viral RNA is error-prone
  - It makes about one error (mutation) each time it copies a piece of viral RNA
    - The mutation might kill the virus
    - Worse ! – the mutations may help the virus adapt to its environment, so that it can become more damaging
  - 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



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***

HIV Viral Load - Untreated



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

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Scientific Goals:

Develop models of sufficient fidelity

- ***to aid in understanding cellular level mechanisms (in vitro cellular level data)***
- ***with predictive capabilities -specifically, use early acute infection patient data to predict longitudinal set points! (in vivo system level data)***
- ***for use in control in structured treatment interruptions (STI) and clinical design***
- ***to help provide plausibility scenarios for remission of progression to aids***

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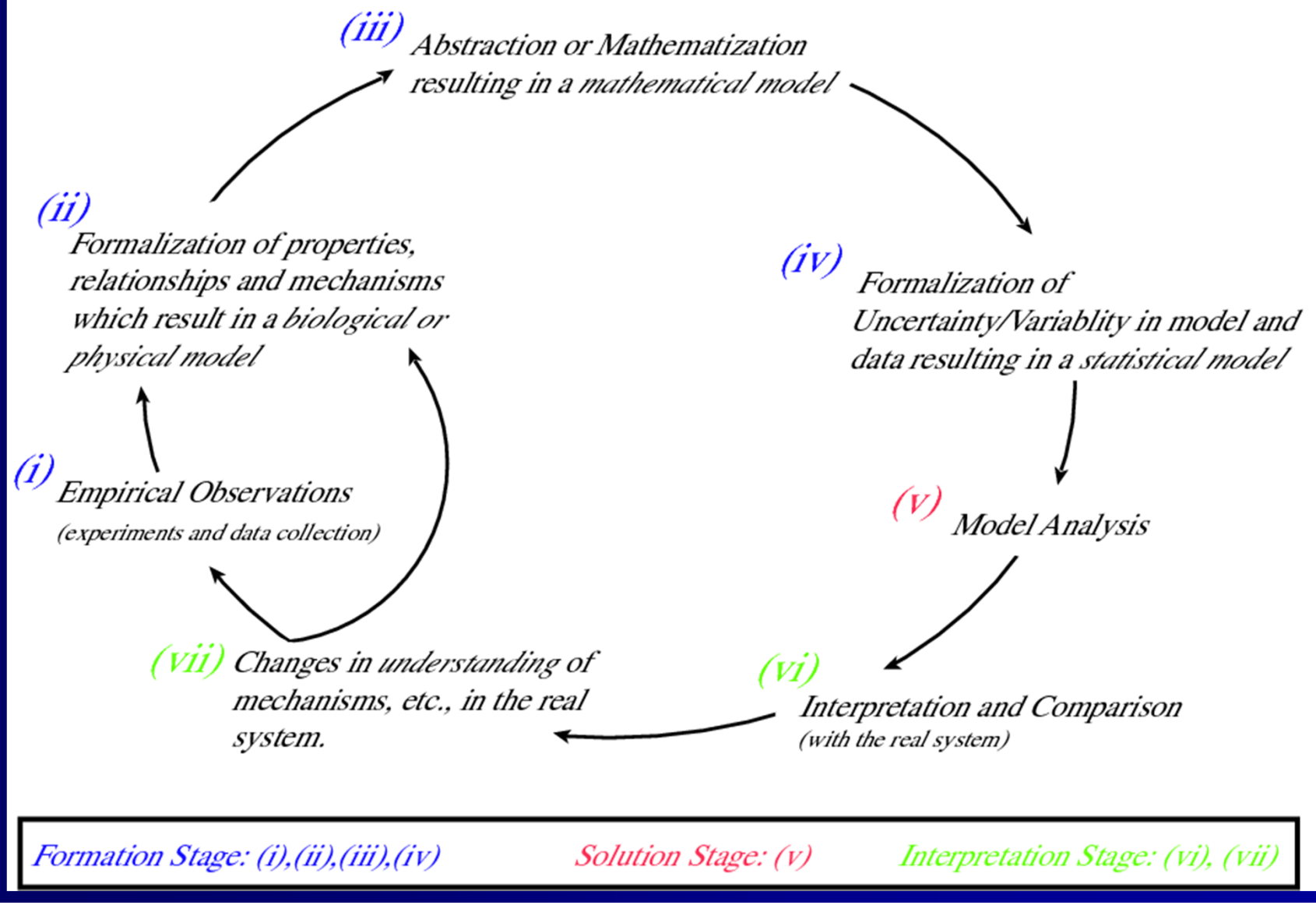
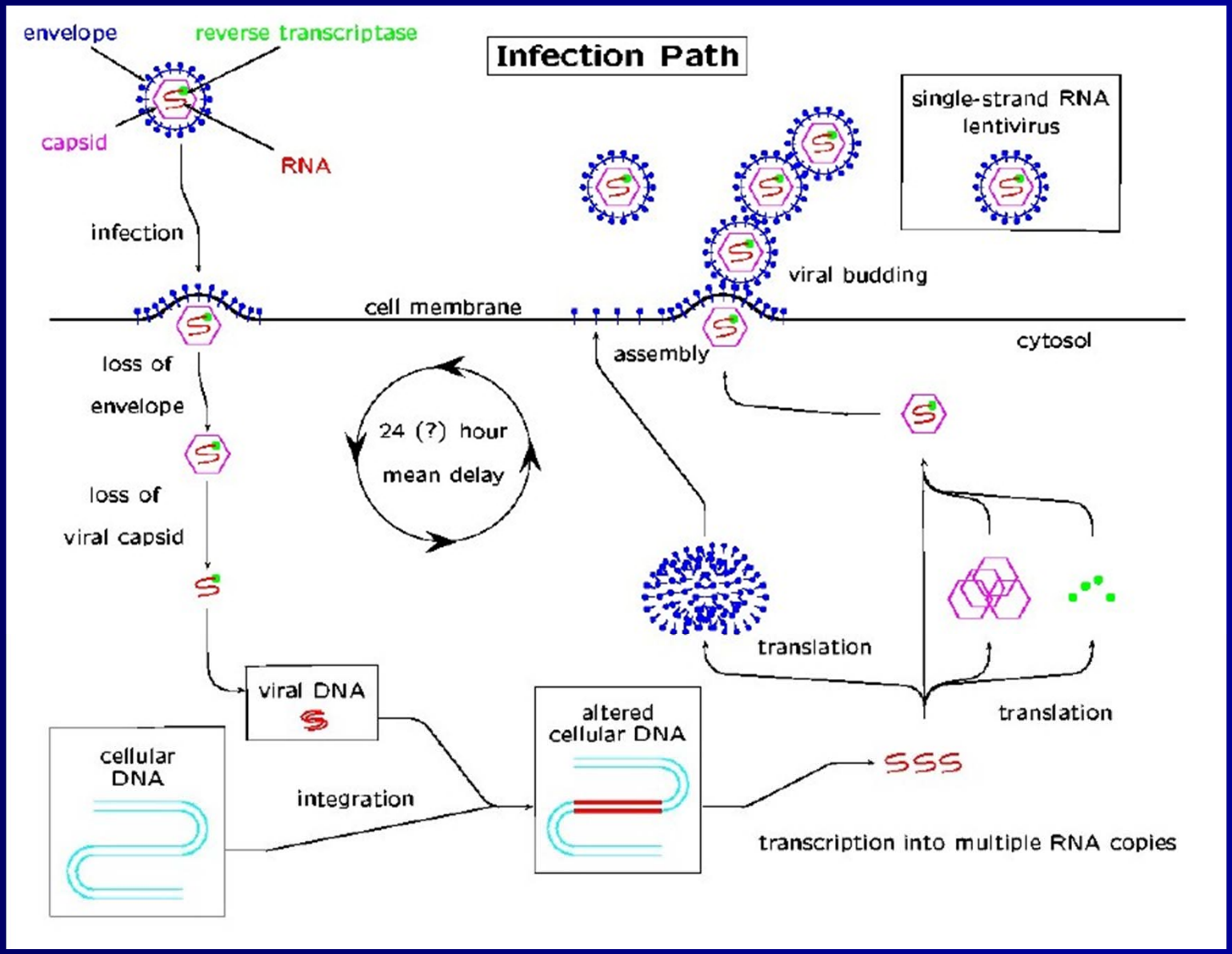
The Iterative Modeling Process



Drug Therapy

- *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)*
  - *Usually given in "cocktails" that can be adaptively modified as efficacy decreases or serious side effects develop*

Cellular level models - with short term (days) in vitro data



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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

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

π_1 ⇒ delay from acute infection to viral production

π_2 ⇒ delay from acute infection to chronic infection

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

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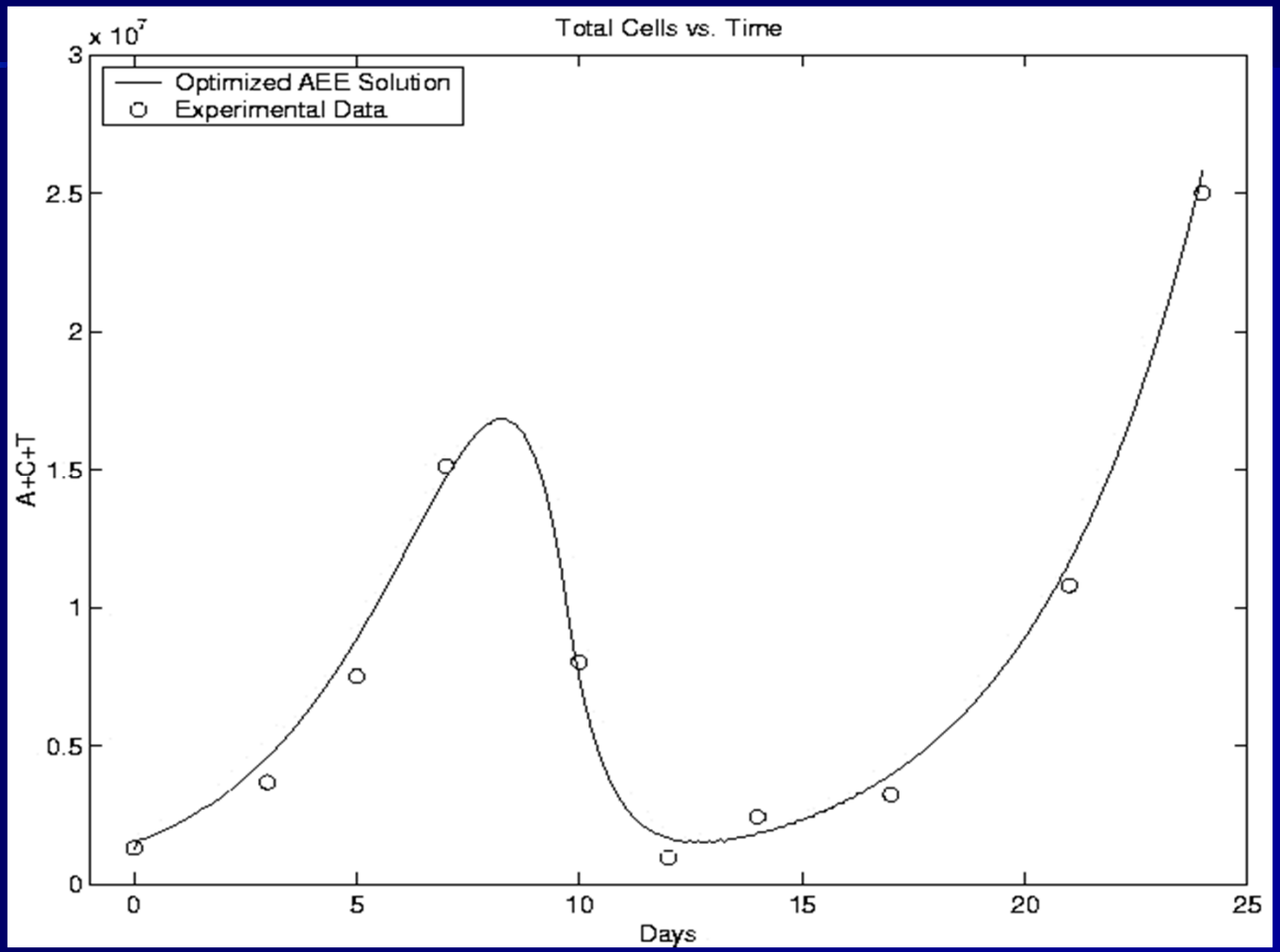
In the inverse problem calculations, we used **numerical approximation methods** for the FDE's (both discrete delays and continuous probability density functions were used). The approximation methods were **spline-based** as developed in [Banks-Kappel, J. Diff. Eqn.,34(1979),pp.496-522] and [Banks, in *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 *in vitro* experimental data from [Rogel, Wu, and Emerman, J. Virology 69(1995),882-888].

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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), 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.,

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

as $n \to \infty$, 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

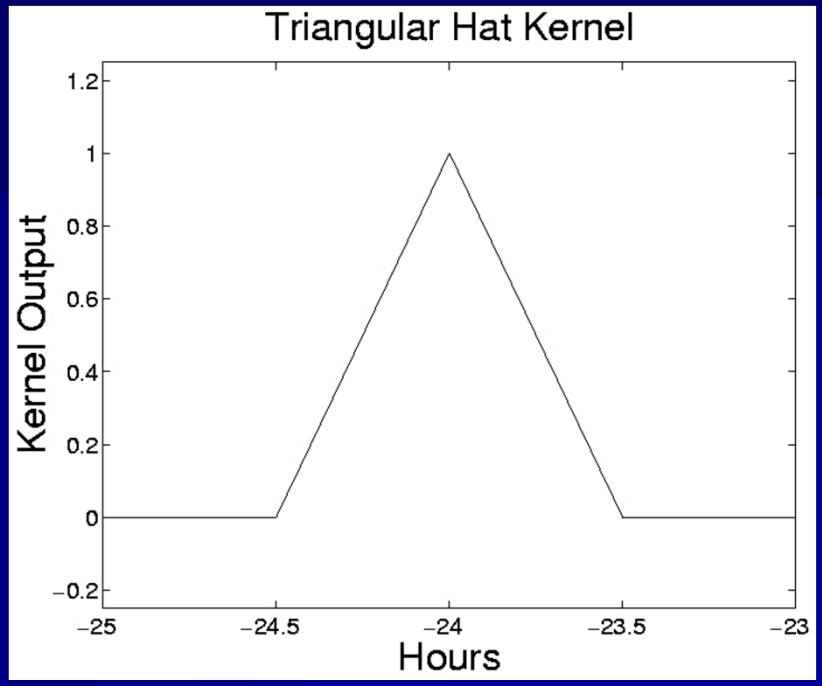
$$U_{10}^{32}((p^*,\tau_1^*,0),(p^*,\tau_1^*,\tau_2^*)) = 0.84,$$

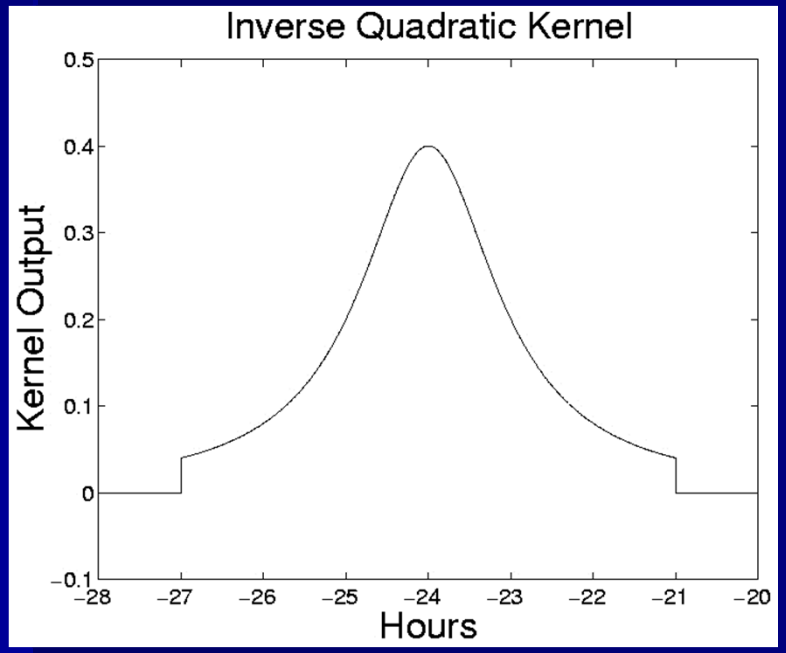
suggesting improvement is significant only at confidence levels at 94% or lower!!

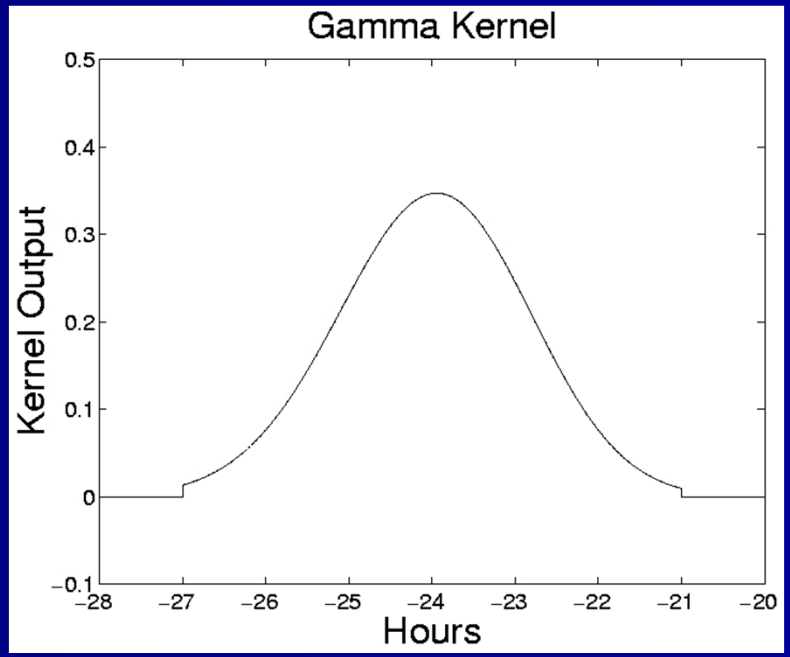
Probability density kernels

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

with mean $\mu = 24$.







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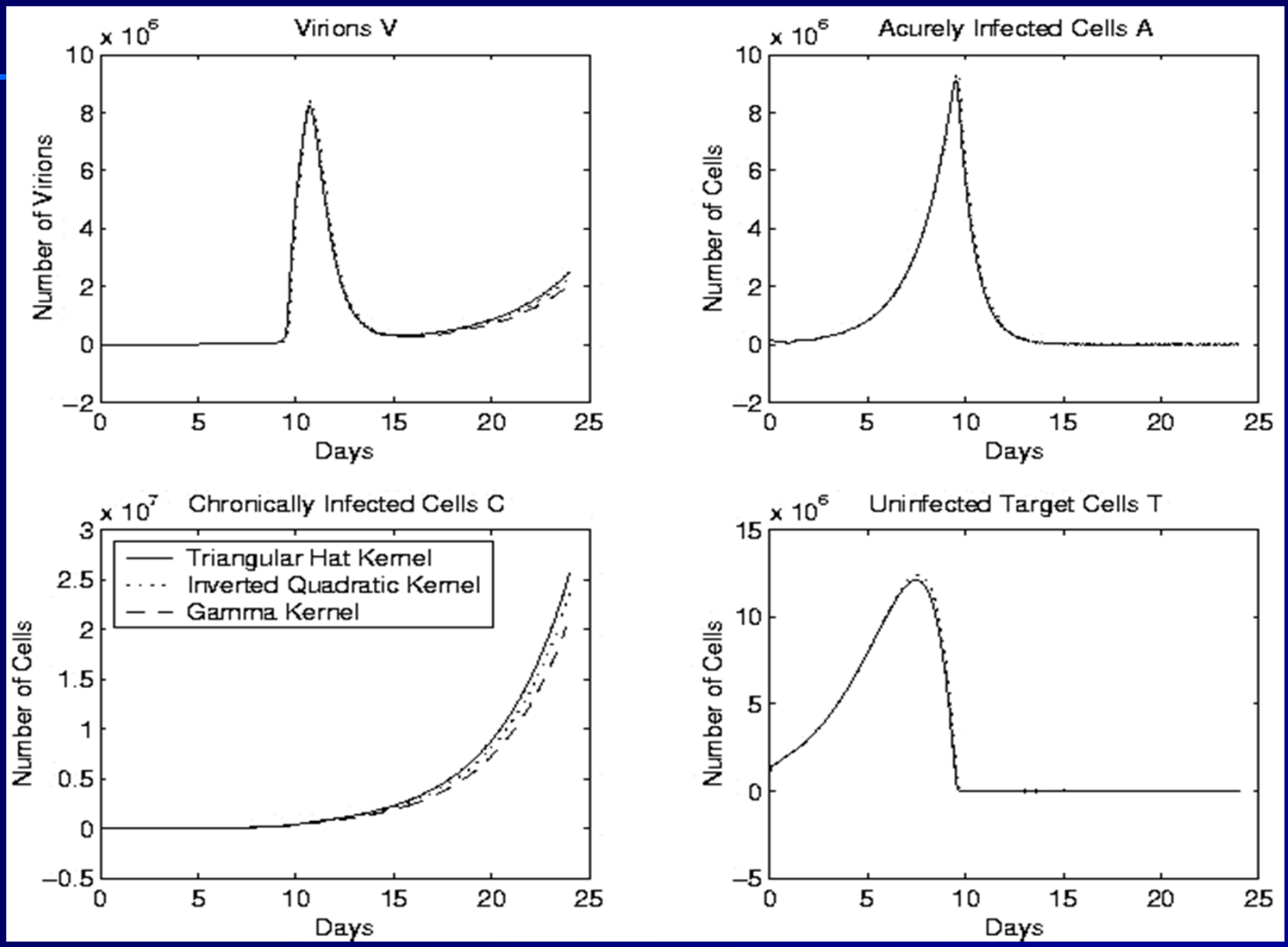

Comparison of forward solutions using triangular hat, inverted quadratic and gamma probability density kernels.

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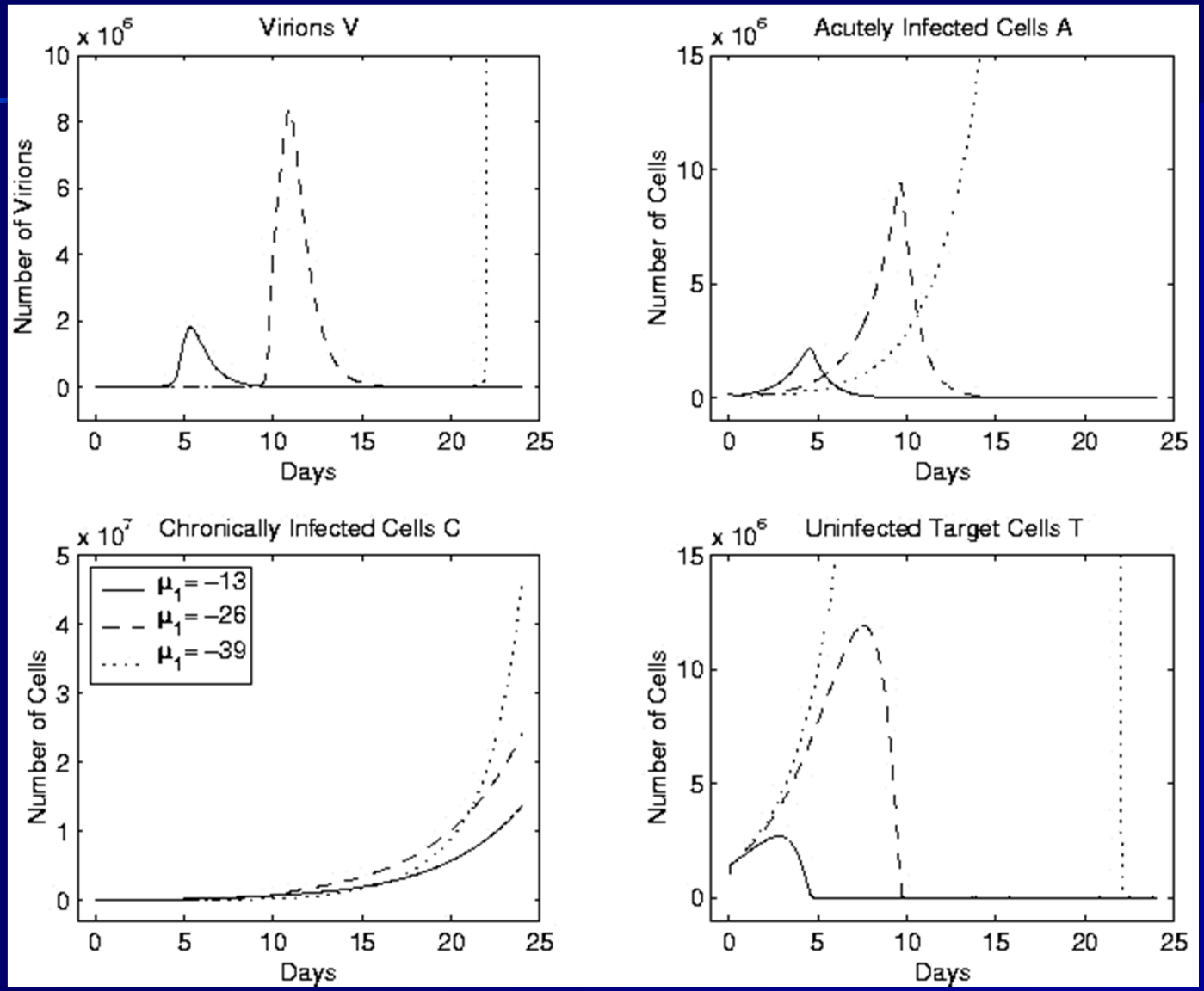

Sensitivity of solutions wrt mean μ in triangular hat kernel.

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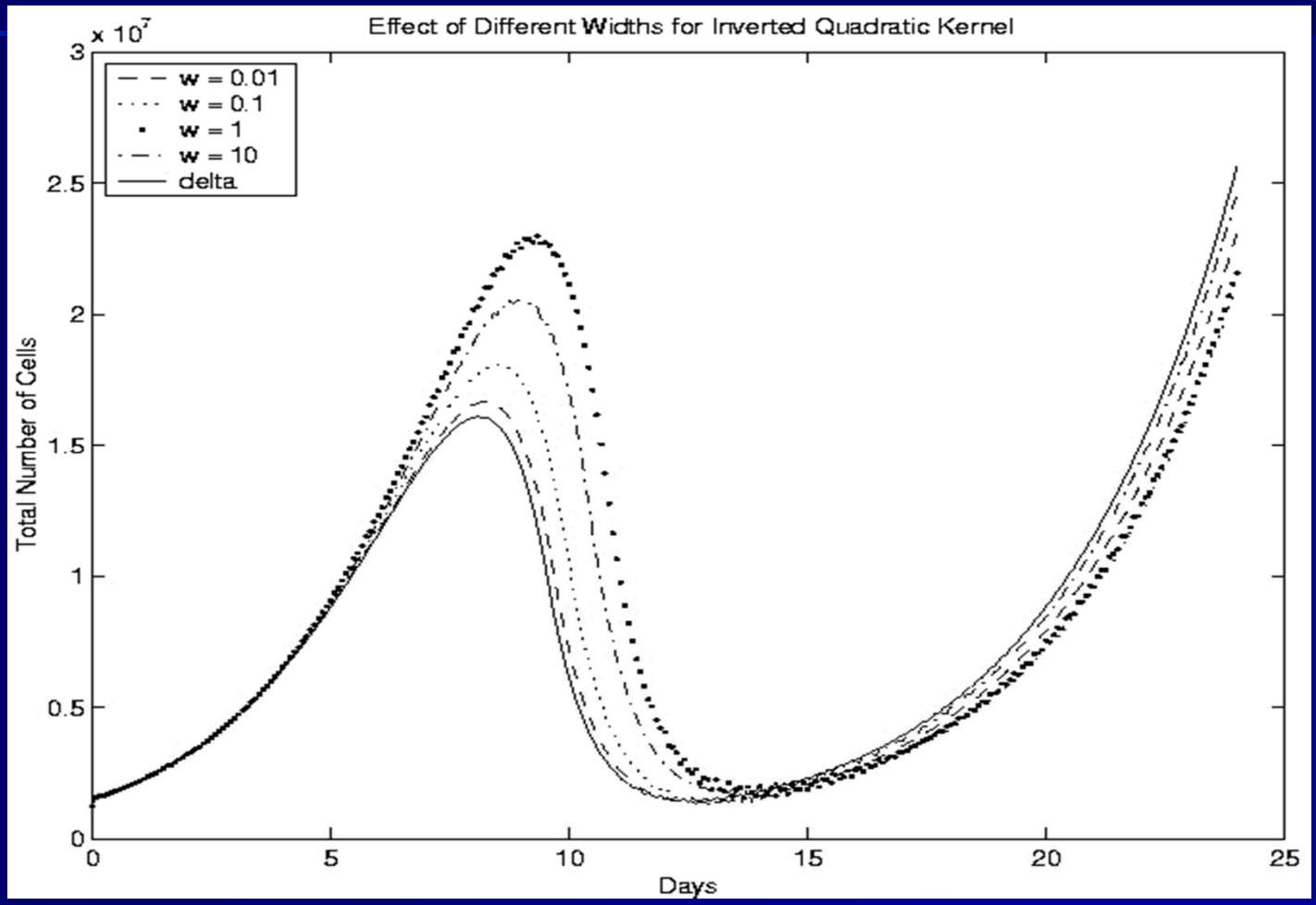

Response A+C+T=total no. of cells as a function of width w in inverted quadratic density kernel.

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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., 323 (2005), 146-161.

v) HTB, S.Dediu and H K Nguyen, Math Biosci and Engr., 4 (2007), 403-430.

vi) HTB, S.Dediu, and H K Nguyen, IFAC Annual Reviews in Control, 31 (2007), 17-26.

- *new mathematics on sensitivity wrt probability distributions of solutions of dynamical systems depending on probability measures-directional derivatives wrt parameters in a convex subset of TVS*

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Brief summary of theory: Prohorov Metric Framework

Needs:(to carry out a careful mathematical analysis)

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

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

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

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

RANDOM VARIABLES and ASSOCIATED METRIC SPACES

- $\mathcal{P} = \mathcal{P}(\mathrm{Q}) = \{ P : P \text{ are probability measures on } \mathrm{Q} \}$.

$(\mathcal{P}(\mathrm{Q}), \rho)$ *is a metric space with the Prohorov metric* ρ.

- *It is a complete metric space and is compact if* Q *is compact.*

PROHOROV METRIC

$$\rho(P^k, P) \to 0 \;\Leftrightarrow\; \int_{\mathrm{Q}} g\,dP^k \to \int_{\mathrm{Q}} g\,dP \quad \text{for all } g \in C(\mathrm{Q})$$

$$\Leftrightarrow \text{ convergence in expectation}$$

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

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.

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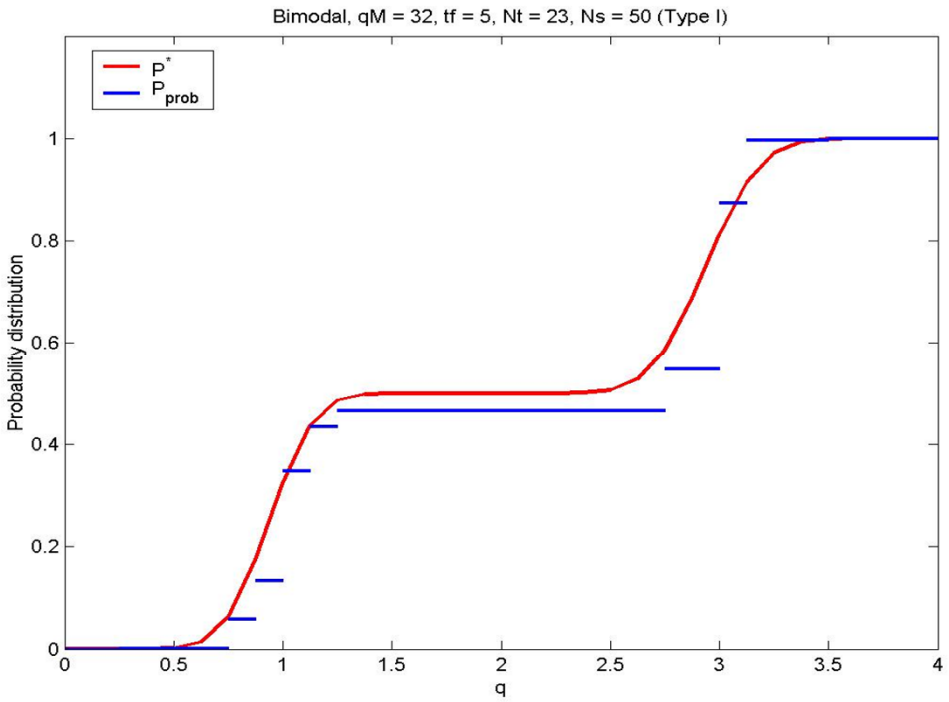
APPROXIMATION RESULTS

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

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

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

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



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

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2. Finite combinations of piecewise linear splines

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

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

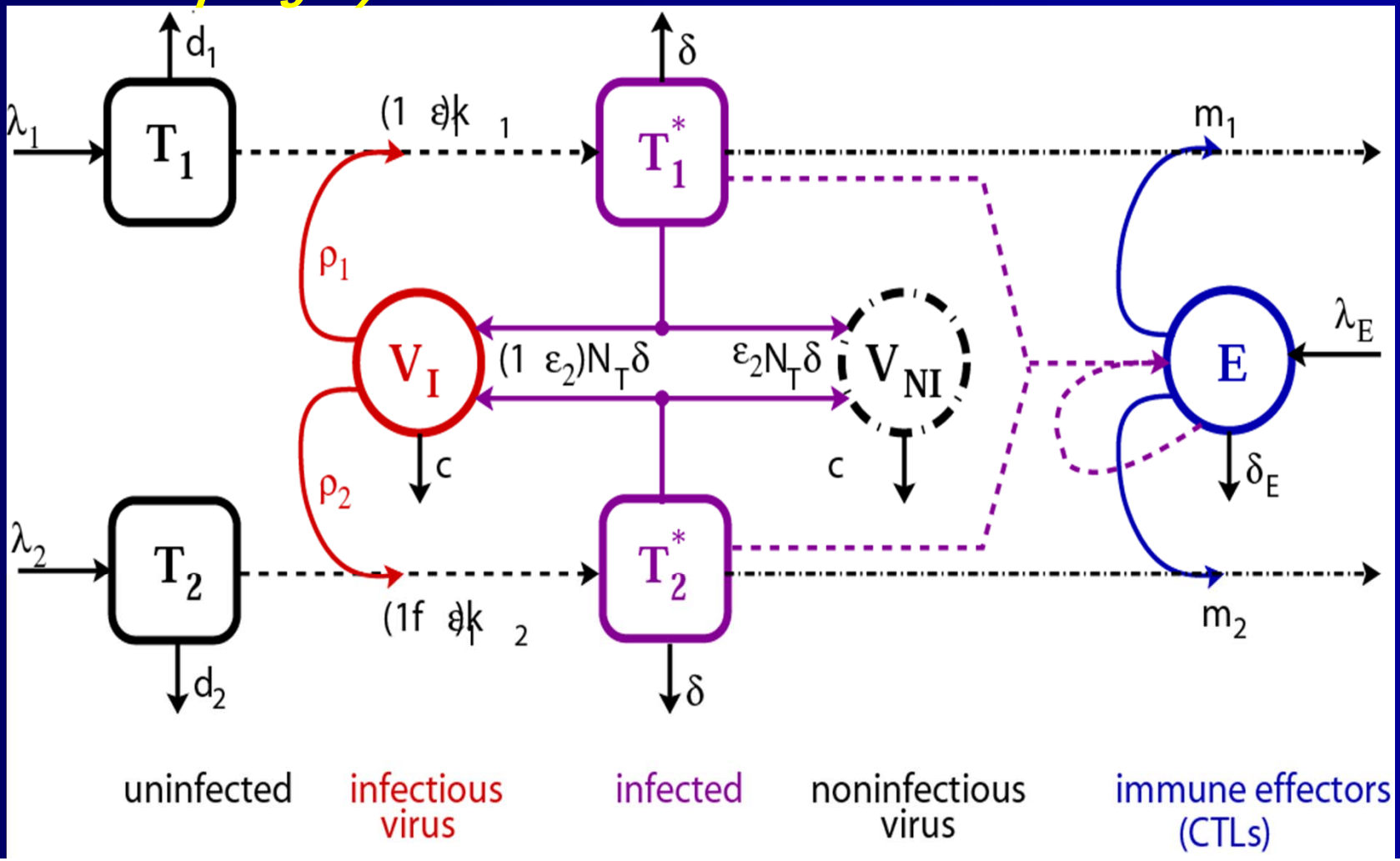
if $$\mathcal{P}_{\mathcal{F}^\mathrm{M}} \equiv \{F_\mathrm{M} \in \mathcal{P}(\mathrm{Q}) : F_\mathrm{M} = \int f^\mathrm{M},\ f^\mathrm{M} \in \mathcal{F}^\mathrm{M}\},$$

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

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.

System level models-with long term (years) in vivo data

- *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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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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INVERSE PROBLEMS WITH CLINICAL DATA

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

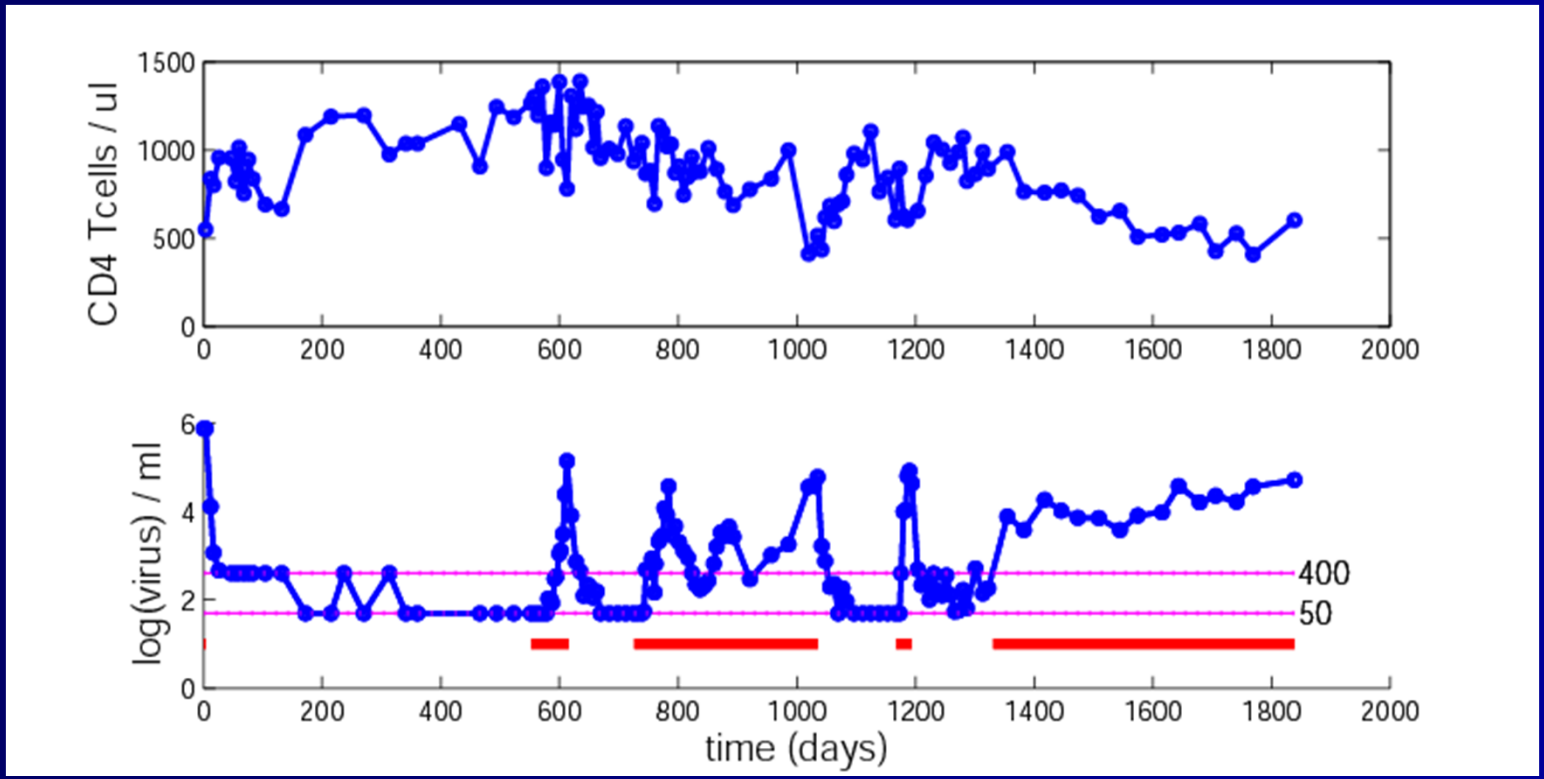
Censored Data: 400 or 50 copies/ml

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

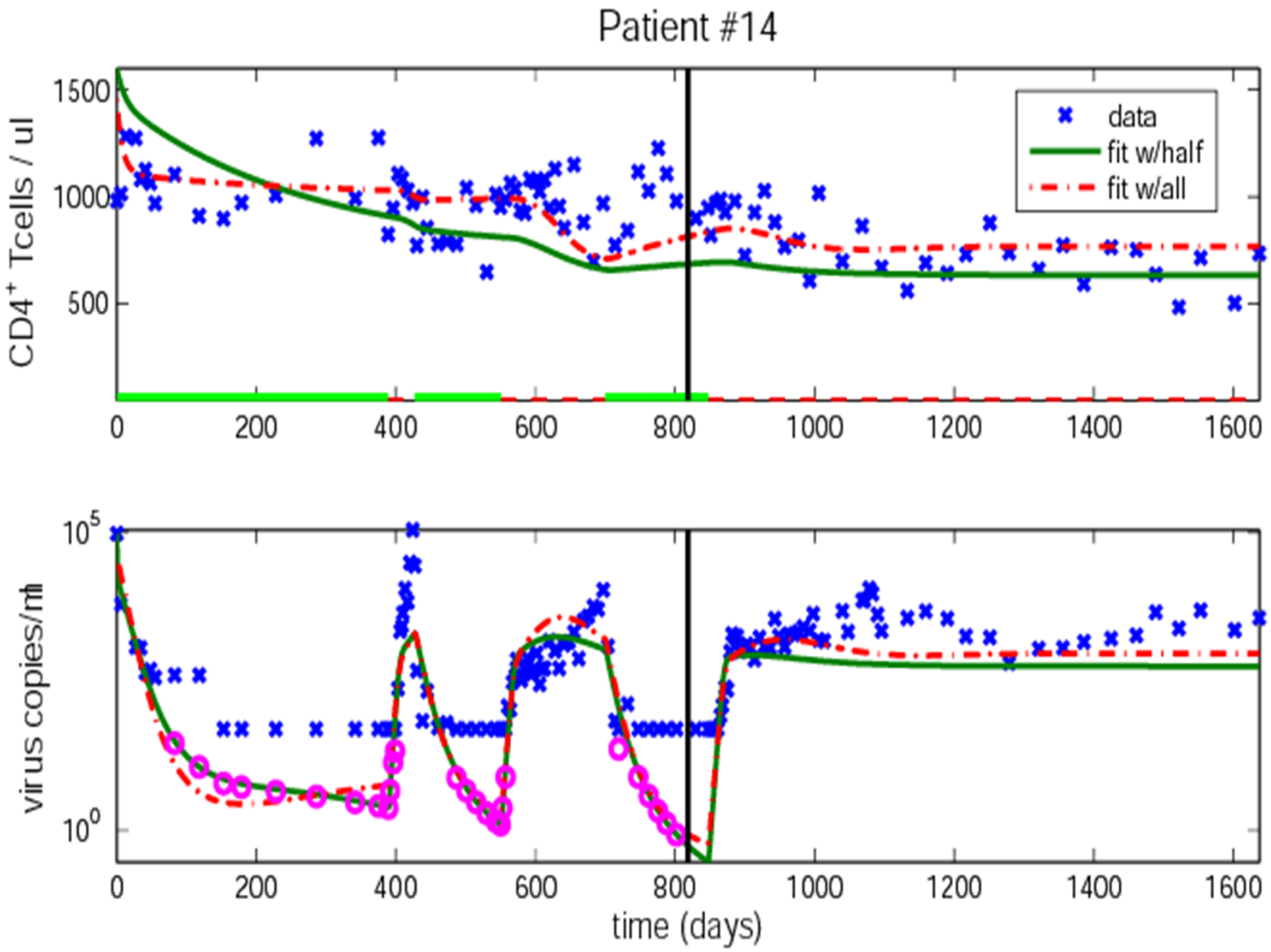
- 2 step optimization: i) hypercube sampling-based DIRECT (direct search) on all 27 parameters ii) gradient based optimization in ***censored data EM*** algorithm

- ***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

Details in: B. M. Adams, H. T. Banks, M. Davidian, and E. S. Rosenberg ,*Model fitting and prediction with HIV treatment interruption data,* Bull. Math Biology, 69 (2007), 563-584

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



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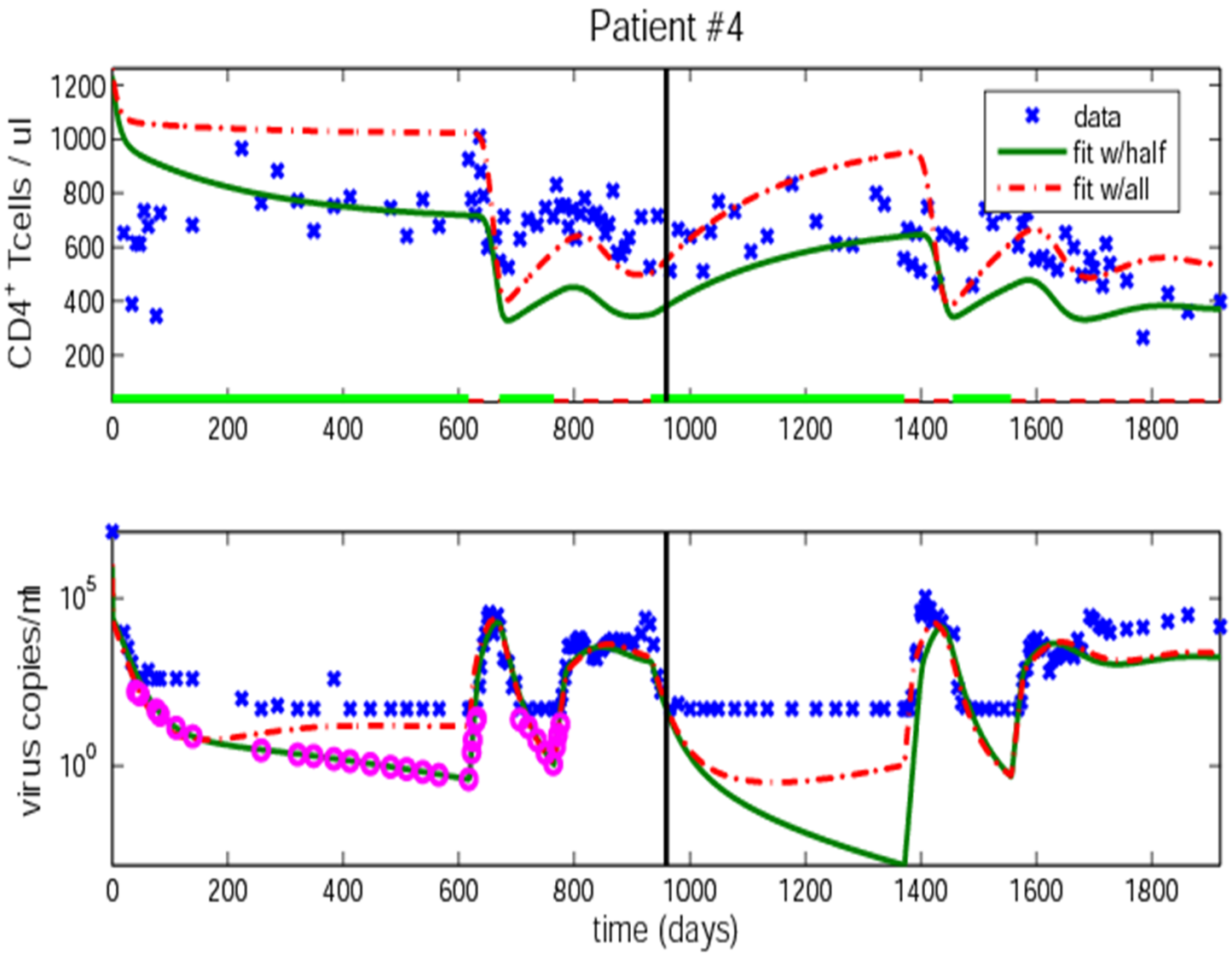

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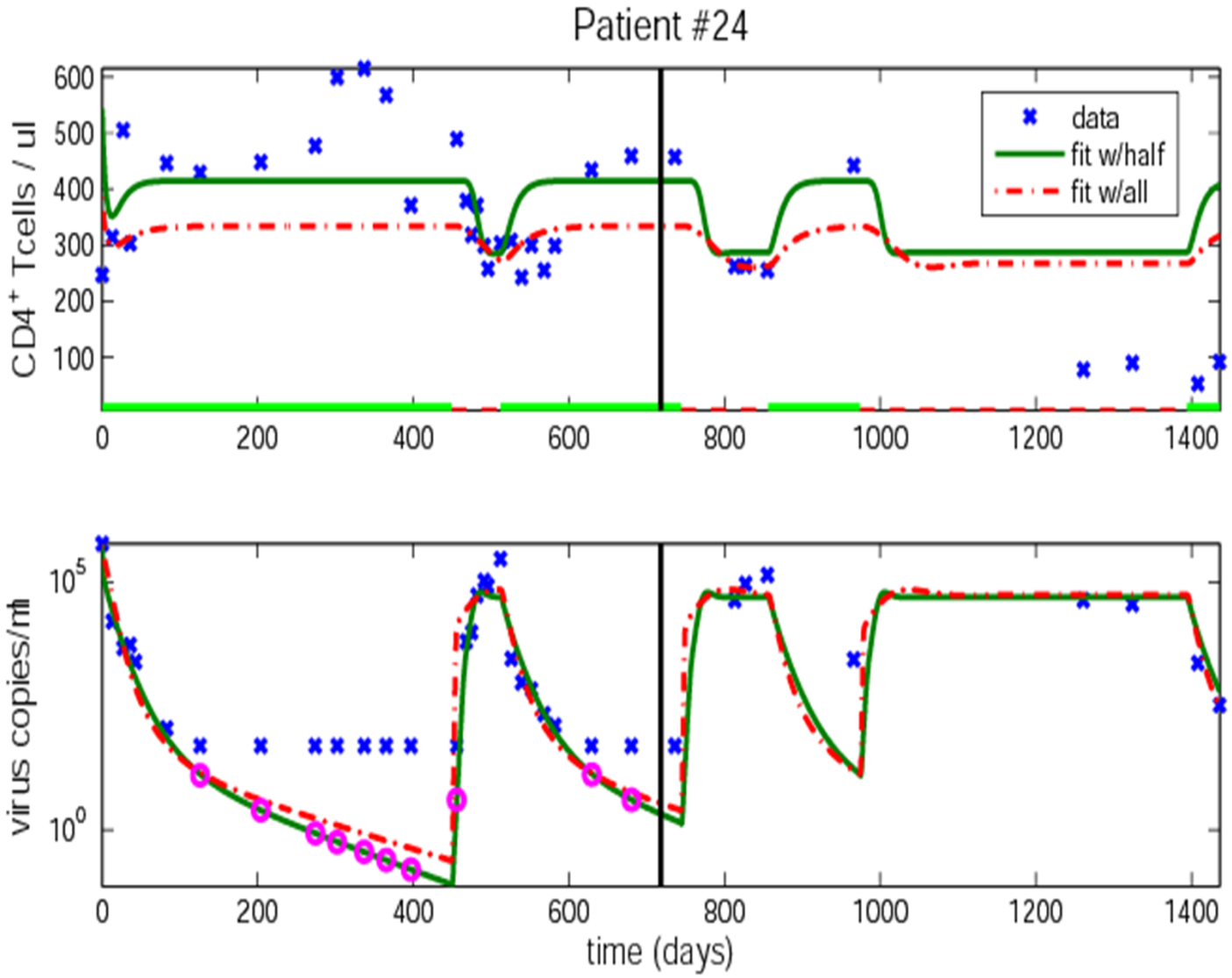
SIMULATION WITH ESTIMATED PARAMETERS

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



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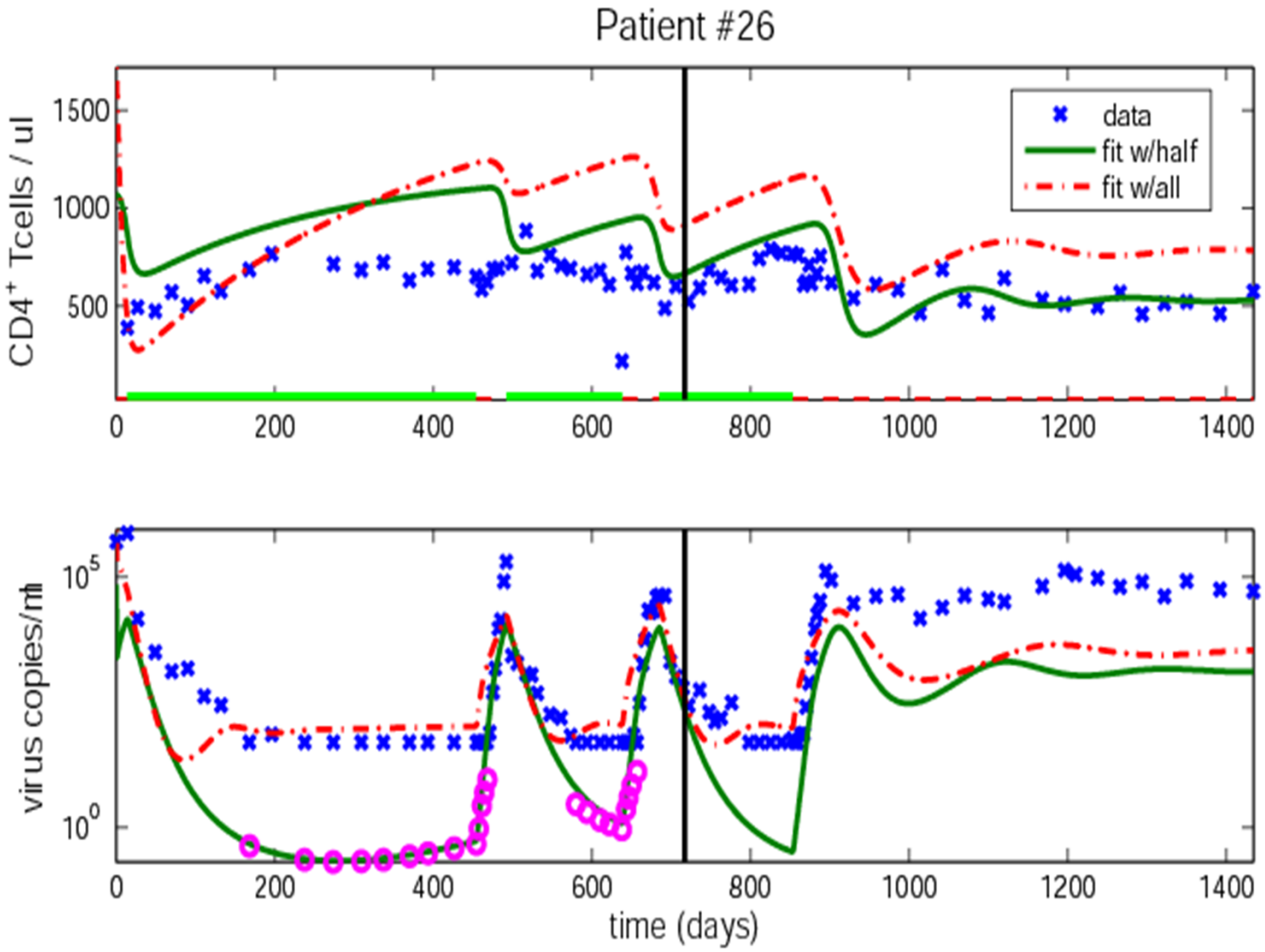
SIMULATION WITH ESTIMATED PARAMETERS

But not perfect even with observation of 2 interruptions!



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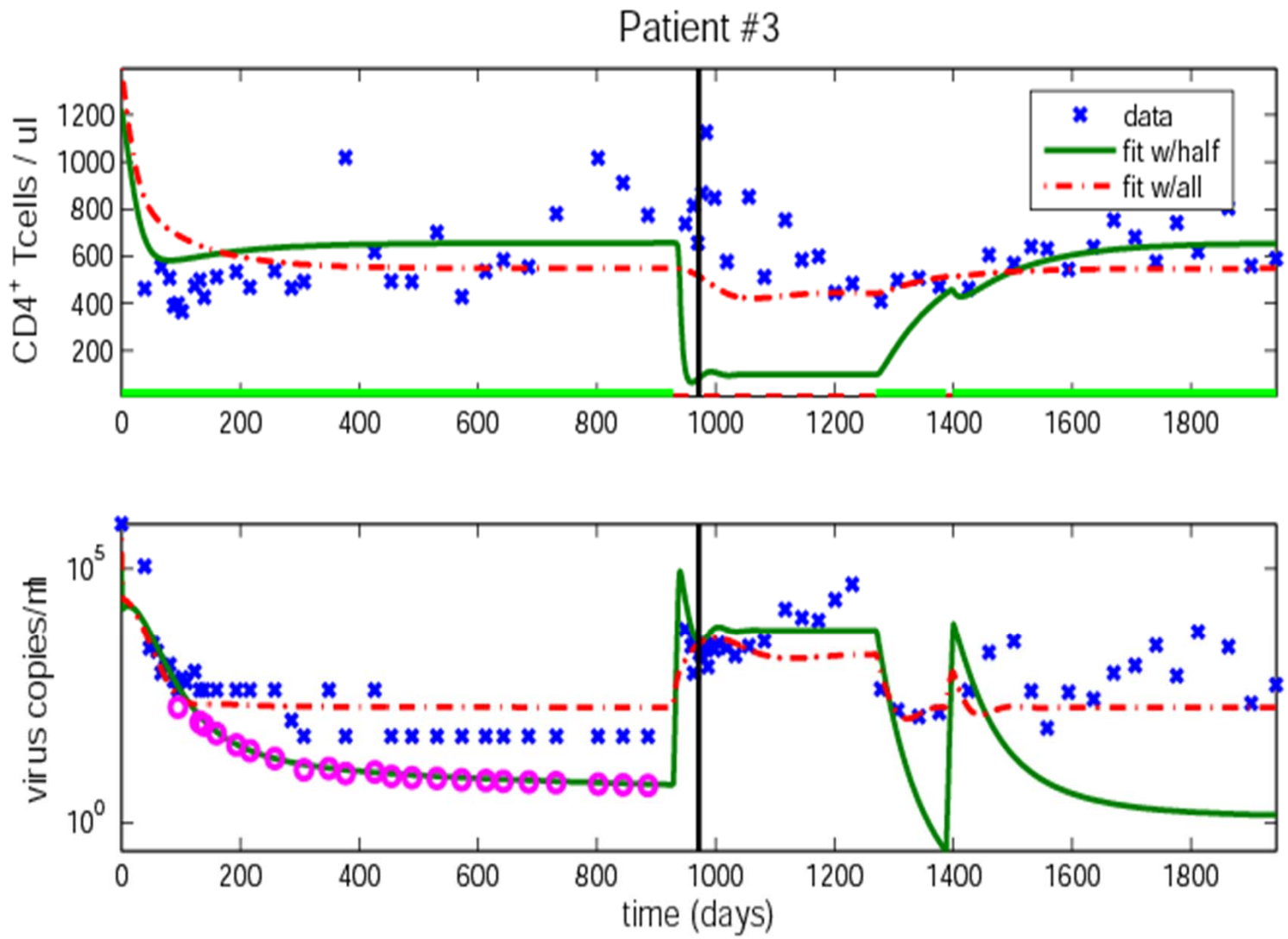
SIMULATION WITH ESTIMATED PARAMETERS
Model not predictive for individuals w/o interruption!!!



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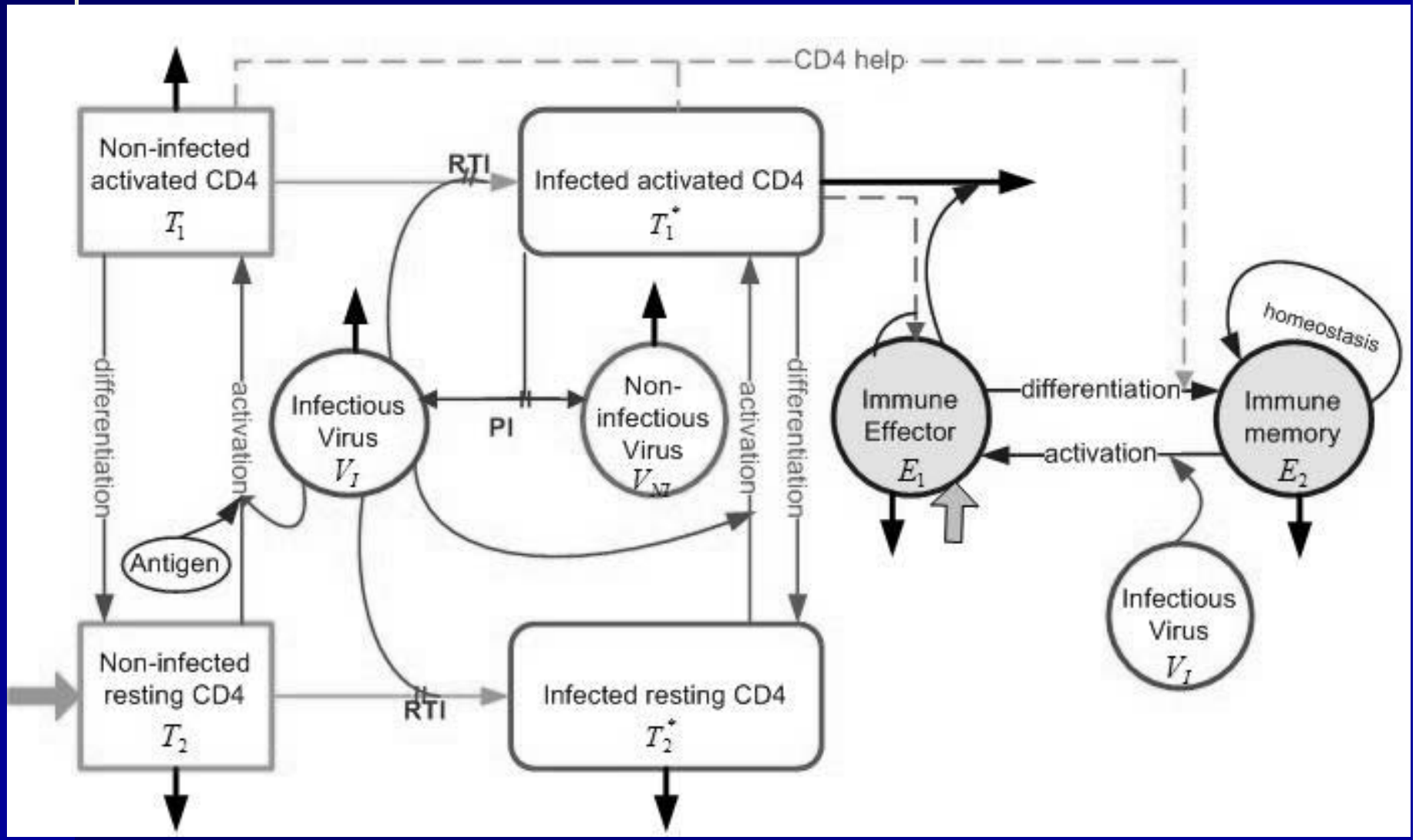
CTL (E) / immune response model *not* adequate description of biology-next generation model:



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The corresponding compartmental ordinary differential equation (ODE) model for in-host HIV infection dynamics is based on balance laws and is given by

$$
\begin{aligned}
\dot{T}_1 &= -d_1 T_1 - (1-\xi_1(t))k_1 V_I T_1 - \gamma_T T_1 + p_T\left(\frac{a_T V_I}{V_I+K_V} + a_A\right) T_2,\\
\dot{T}_1^* &= (1-\xi_1(t))k_1 V_I T_1 - \delta T_1^* - mE_1 T_1^* - \gamma_T T_1^* + p_T\left(\frac{a_T V_I}{V_I+K_V} + a_A\right) T_2^*,\\
\dot{T}_2 &= \lambda_T \frac{K_s}{V_I+K_s} + \gamma_T T_1 - d_2 T_2 - (1-f\xi_1(t))k_2 V_I T_2 - \left(\frac{a_T V_I}{V_I+K_V} + a_A\right) T_2,\\
\dot{T}_2^* &= \gamma_T T_1^* + (1-f\xi_1(t))k_2 V_I T_2 - d_2 T_2^* - \left(\frac{a_T V_I}{V_I+K_V} + a_A\right) T_2^*,\\
\dot{V}_I &= (1-\xi_2(t))10^3 N_T \delta T_1^* - cV_I - 10^3[(1-\xi_1(t))\rho_1 k_1 T_1 + (1-f\xi_1(t))\rho_2 k_2 T_2]V_I,\\
\dot{V}_{NI} &= \xi_2(t)10^3 N_T \delta T_1^* - cV_{NI},\\
\dot{E}_1 &= \lambda_E + \frac{b_{E1}T_1^*}{T_1^*+K_{b1}}E_1 - \frac{d_E T_1^*}{T_1^*+K_d}E_1 - \delta_{E1}E_1 - \gamma_E\frac{T_1+T_1^*}{T_1+T_1^*+K_\gamma}E_1 + \frac{p_E a_E V_I}{V_I+K_V}E_2,\\
\dot{E}_2 &= \gamma_E\frac{T_1+T_1^*}{T_1+T_1^*+K_\gamma}E_1 + \frac{b_{E2}K_{b2}}{E_2+K_{b2}}E_2 - \delta_{E2}E_2 - \frac{a_E V_I}{V_I+K_V}E_2,
\end{aligned}
\tag{1}
$$

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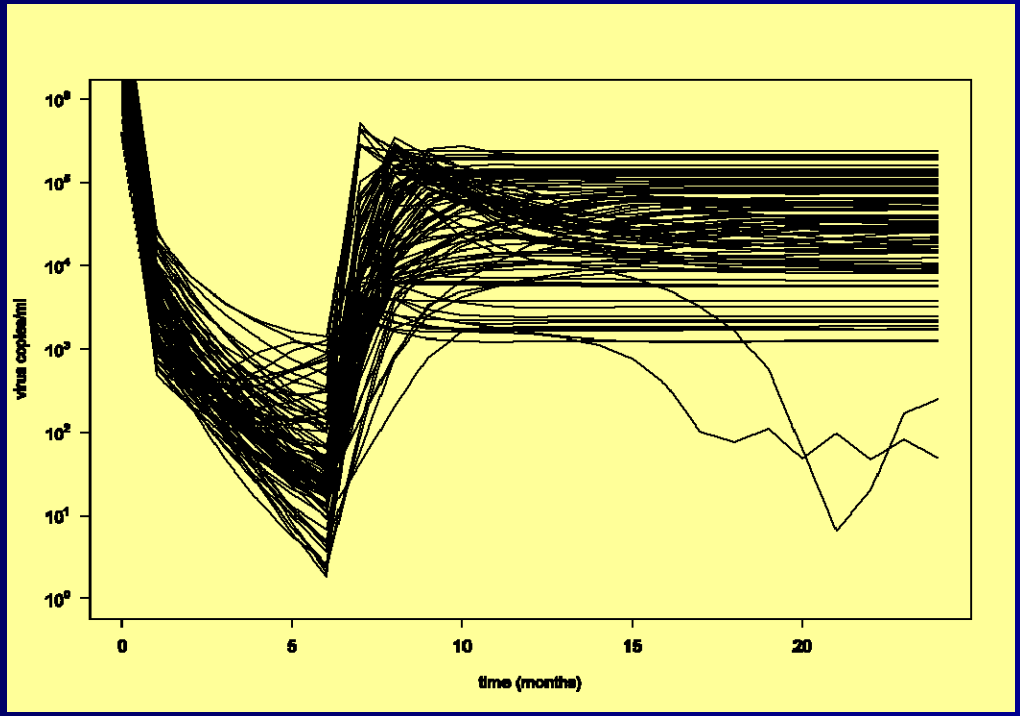
New model developed and analyzed in

HTB, M Davidian, S Hu, GM Kepler, and E. Rosenberg, CRSC-TR07-09, March, 2007; J. Biological Dynamics, 2 (2008), 357-385.

- *Again excellent fits to MGH clinical data with great predictive capabilities*
- *Mechanisms for secondary infections—prediction of viral blimps while undergoing therapy*
- *But some questions about existence of and control between multiple equilibria (high viral load to low viral load)*

USE OF MODELS FOR CLINICAL TRIAL DESIGN

- Construct "population" distributions for parameters
- Draw from these to predict population outcomes to different treatment scenarios via simulation



E.S. Rosenberg, M. Davidian, and HTB, Drug and Alcohol Dependence, 88S (2007), S41-S51.

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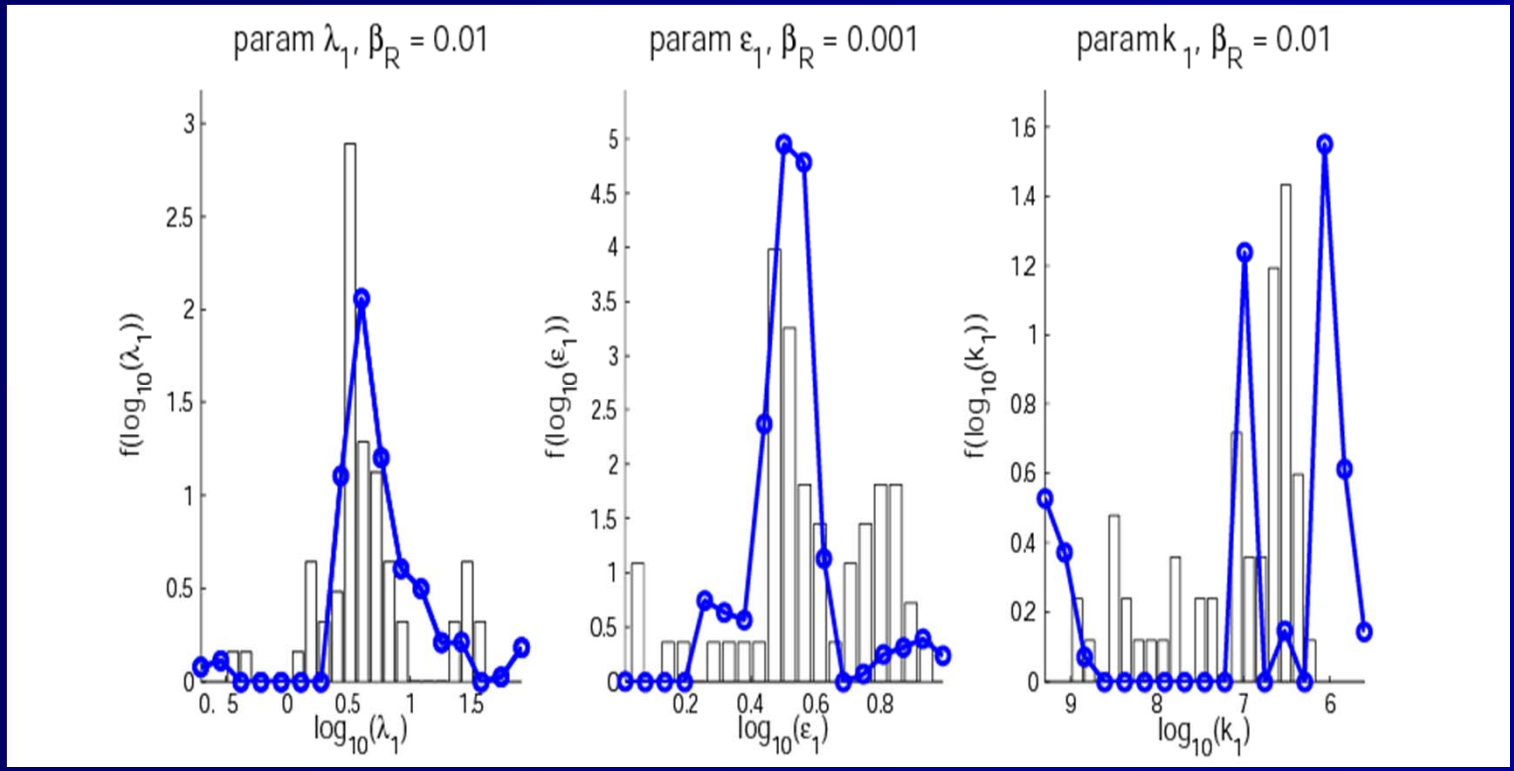
ESTIMATION OF POPULATION PROBABILITY DENSITIES
vs.
HISTOGRAMS OF INDIVIDUAL PARAMETER ESTIMATES
(59 PATIENTS)



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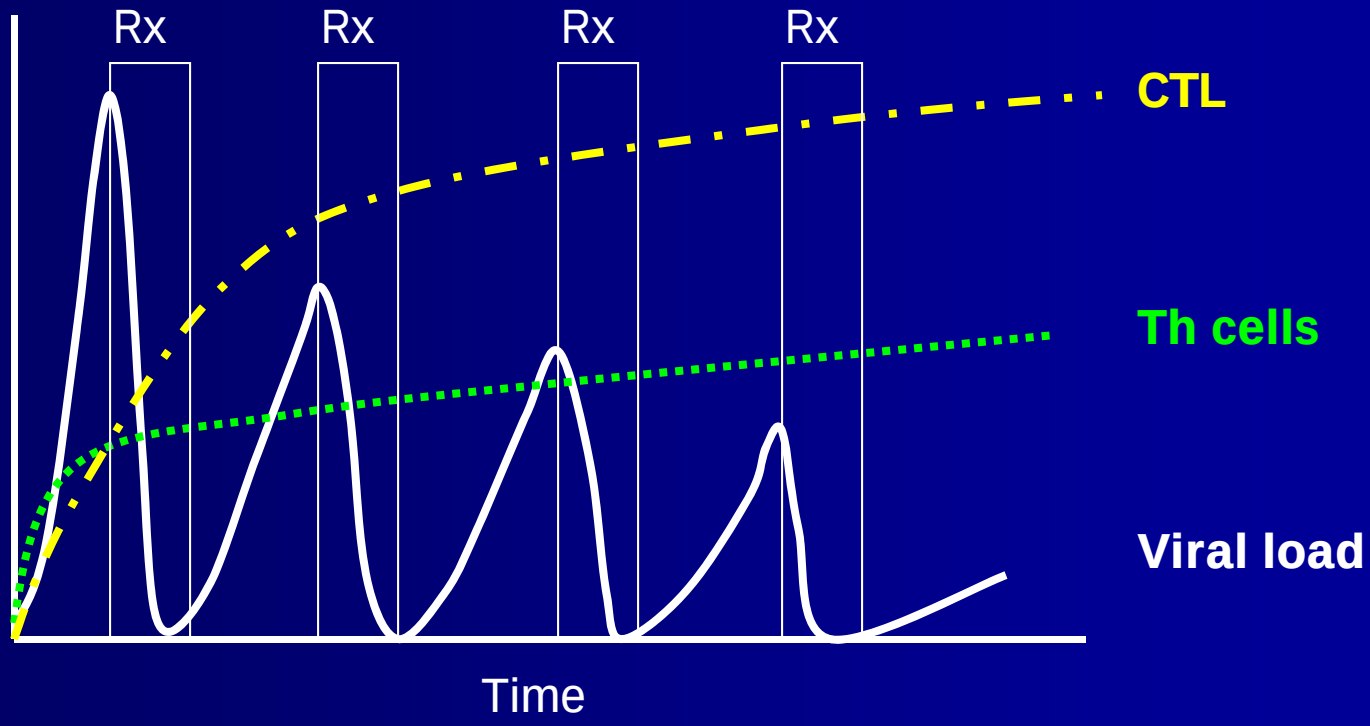
Problems with Continuous Therapy

- *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?*

Modeling Goals

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

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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 *(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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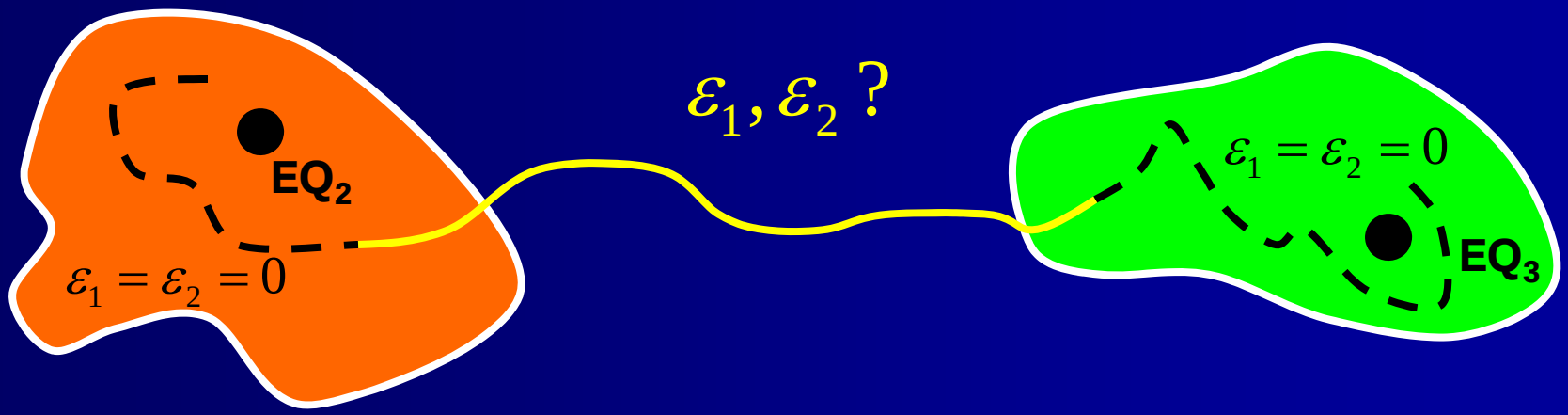
Control Objective



Stable “unhealthy” (viral dominant) state

Stable “healthy” (immune dominant) state

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Optimal Drug Treatment: Problem Formulation (Open Loop Control)

- 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

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

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

- ***Formulate optimality systems with state/costate (ξ_i) systems***
- ***Maximum Principle***
- ***Computation of approximate optimal controls***

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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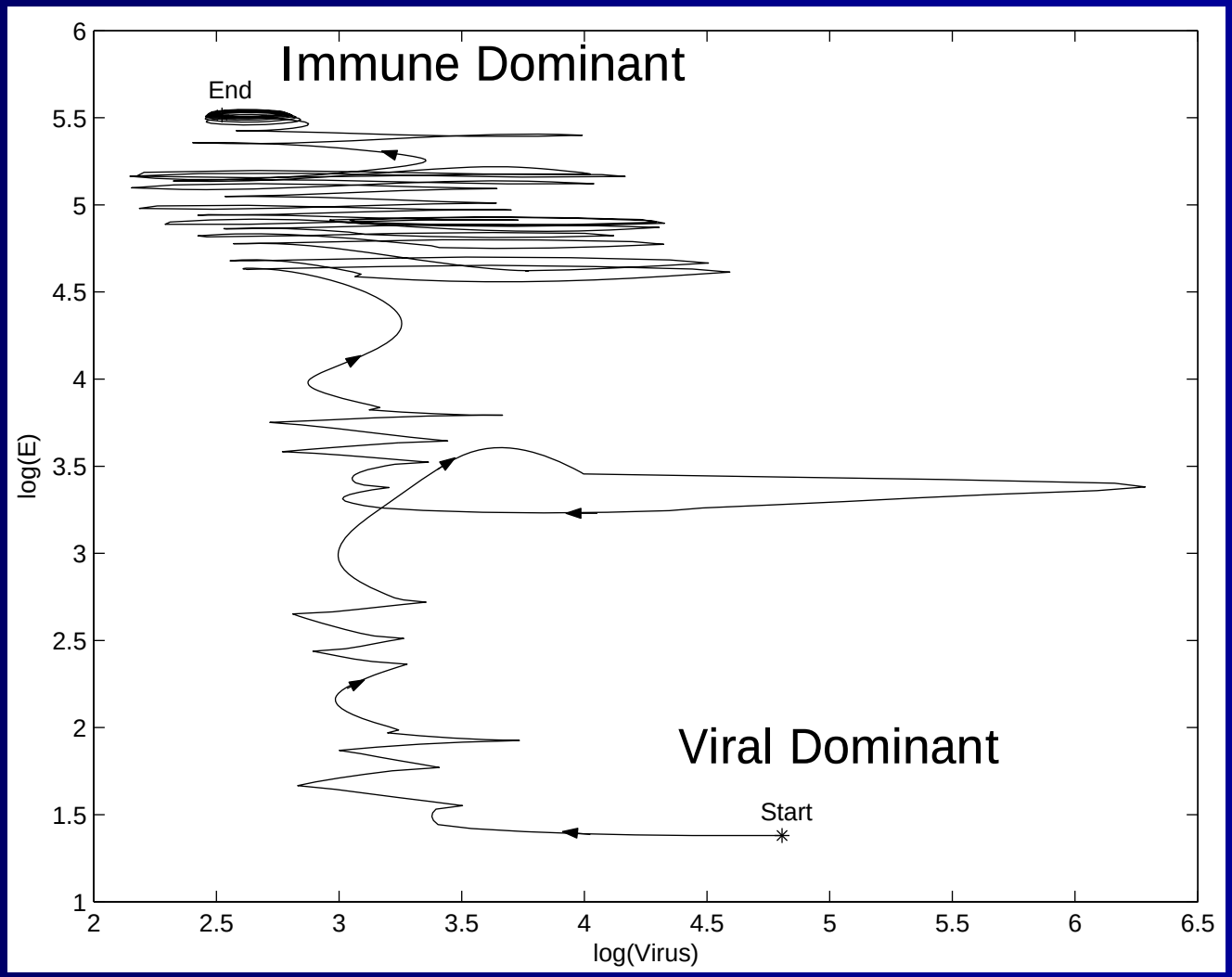
Phase Plane – Virus versus CTL



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In recent efforts, similar results with feedback control!!

- ***State Dependent Riccati Equation (SDRE) estimator approach***
- ***Receding Horizon Control***
- ***Extended Kalman Filter (state estimation as well as parameter estimation)***
- ***Application to extended model with drug-resistant viral strains***

Summary

Using control theory paradigm in an HIV-therapeutic setting, some of 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 (2005). 10-49,***
- ***Dynamic Multidrug Therapies for HIV: Optimal and STI Control Approaches, Math. Biosci. Engr., 1 (2004), 223-241.***
- ***An SDRE Based Estimator Approach for HIV Feedback Control, Optimal Control Appl. And Methods, 27 (2006), 93-121.***

Current efforts:

- ***Model designed clinical trials for treatment strategies in acute phase begin in Fall/Winter 2007 at MGH***
- ***Continuing efforts on drug resistant viral strains***
- ***Efforts on HCV, CMV and other transplant related viruses (in this case immune response is voluntarily compromised) MGH***

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