A control engineering perspective of structured treatment interruption in HIV treatment

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Why would an Electrical Engineer be interested in biology?

- Feedback Control studies in Electrical Engineering
  - Sense
  - Think
  - Act
- To do this well, needs:
  - Mathematical modelling (mechanistic?)
  - Dynamic Systems ('differential' equations – how does behaviour evolve in time – causality...)
  - Inference (I can almost never sense everything I need)
  - Prediction (to regulate 'behaviour' usually requires some degree of predictability)
- Could these concepts be helpful in biology as well?

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Why would an Electrical Engineer be interested in HIV?

- High profile disease
- History of Mathematical Modelling (e.g. Perelson et al)
- Some studies in Control Engineering
- An example question studied ‘in silico’ by control engineers:
  - Is it possible, by cleverly manipulating treatment, to get a patient to a state of being a long term non-progressor?
  - Answer: For some simple mathematical models, computer simulation studies say yes?
  - Caveat: Limitations of the mathematical models.

Simplified biochemical description of HIV infection

Some Important Species:

- T: Healthy CD4+ cells 'T Lymphocytes'
- T^*: Infected T cells
- V: Virus

#	Reaction	Rate	Comments
1.	$T+V \rightarrow T^*$	βTV	Viral Infection of Healthy T Cells
2.	$T^* \rightarrow T^{*}+V$	pT^*	Viral replication in infected T Cells
3.	$\rightarrow T$	s_T	Thalmic production of T-Cells
4.	$T \rightarrow$	$d_T T$	Natural death of T Cells
5.	$T^* \rightarrow$	$d_{T^*} T^*$	Clearance of infected T Cells
6.	$V \rightarrow$	$d_V V$	Viral clearance

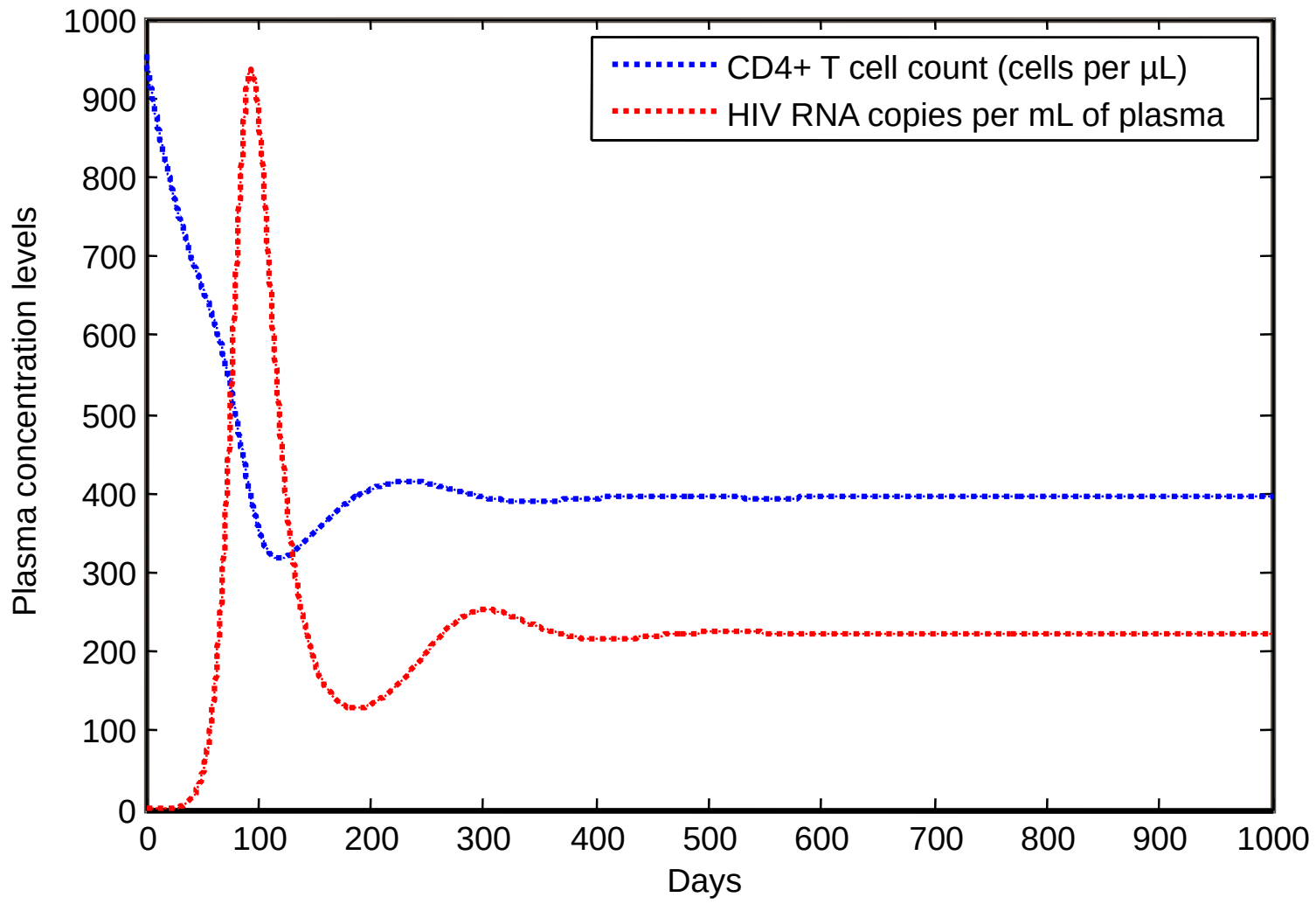
Simplified mathematical description of HIV infection

Simplified 'Ordinary Differential Equations'

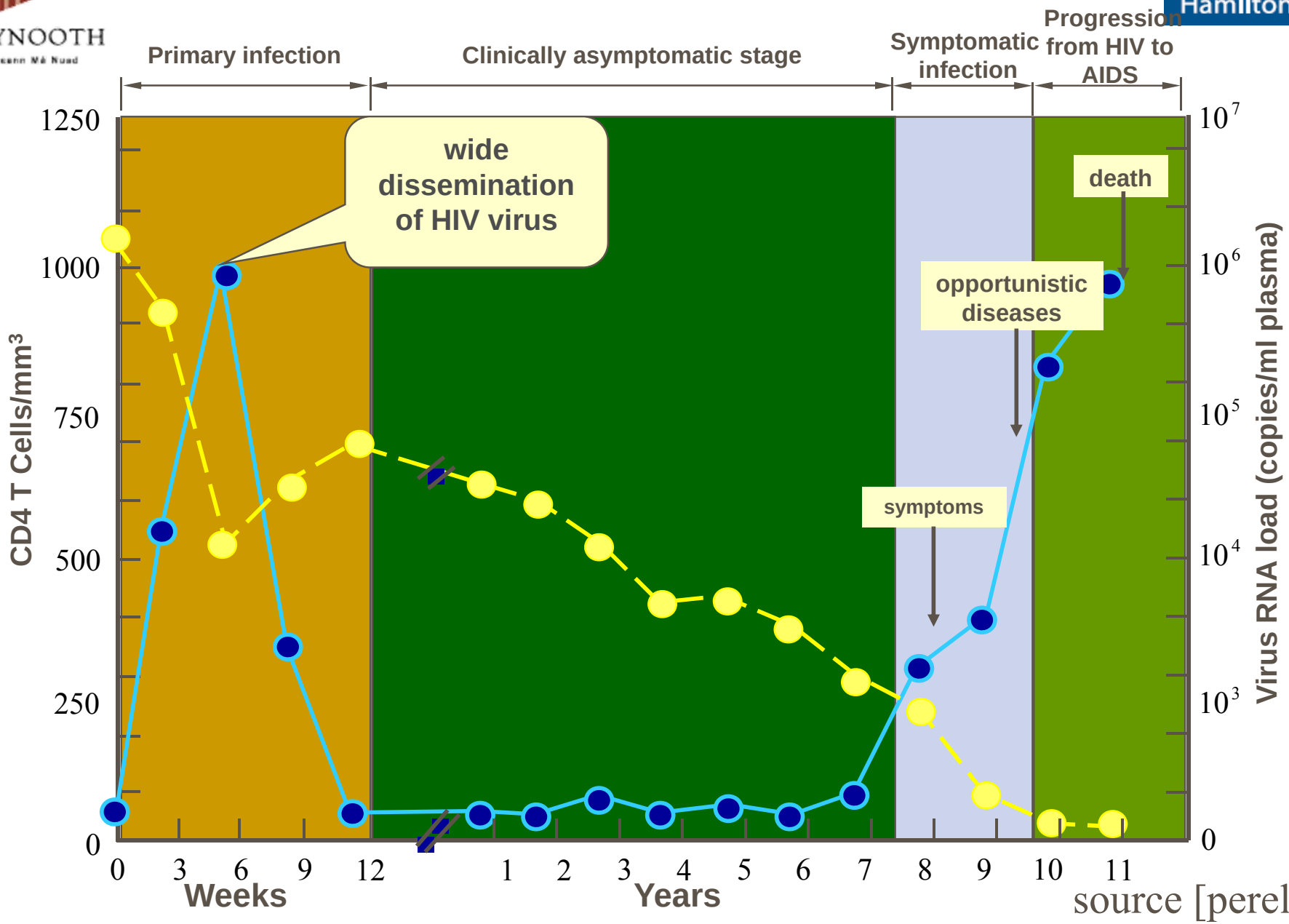
$$\frac{d}{dt}T = s_T - d_T T - \beta V T$$

$$\frac{d}{dt}T^* = \beta V T - d_{T^*} T^*$$

$$\frac{d}{dt}V = pT^* - d_V V$$



The different stages of HIV infection



source [perelson99]

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Model Extensions

- Effect of Drugs:

  Alters reaction rate constants: e.g. β or p

- Immune response to virus:
  - Helper Independent Cytotoxic T Lymphocytes (CTL), ***Z***

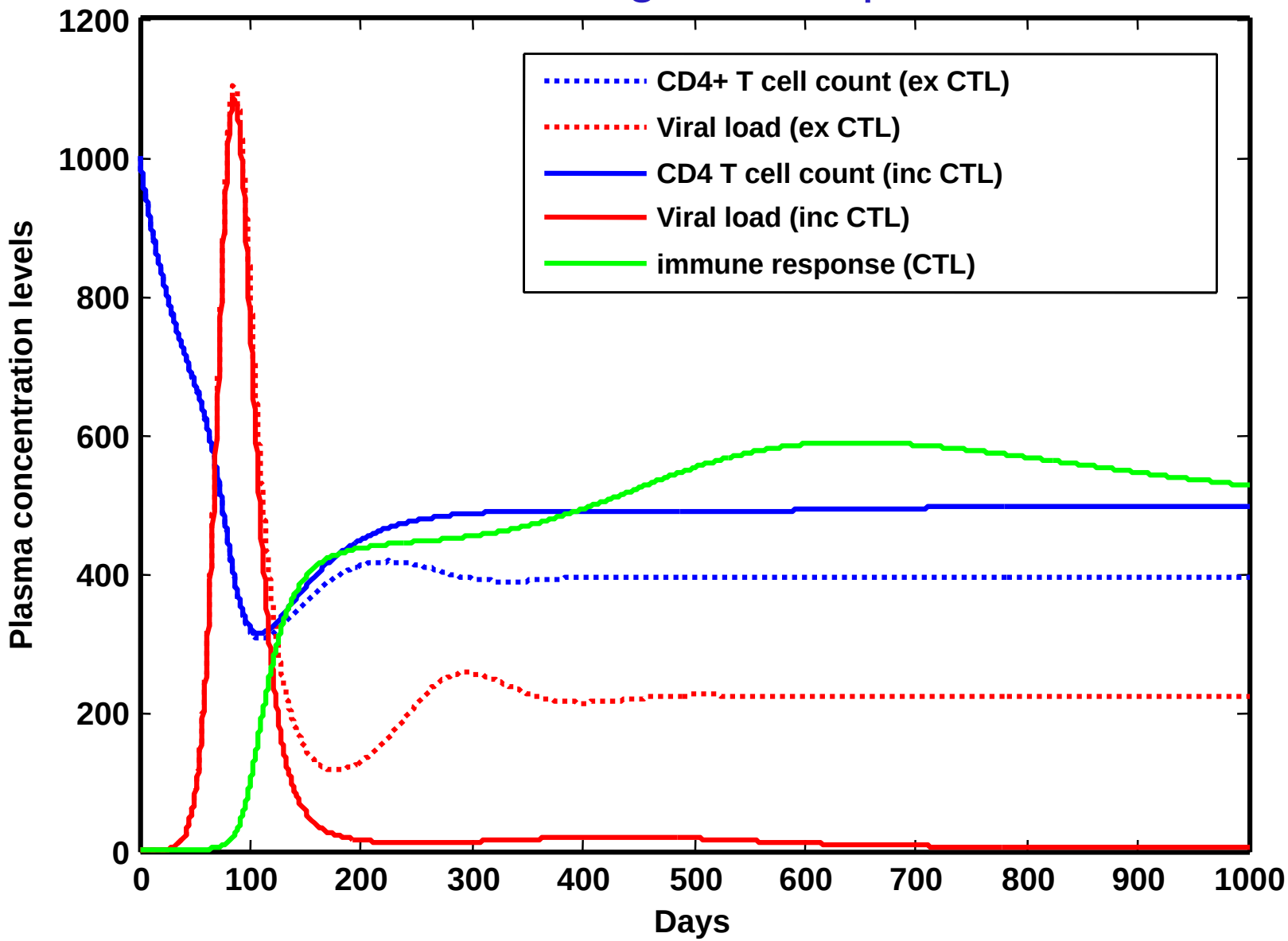
$Z+T^* \rightarrow Z$	CTL induced destruction of infected cells
$(T^*+Z) \rightarrow (T^*+Z)+Z$	Pathogen induced CTL replication
$Z \rightarrow$	Clearance rate of CTL Effector cells

  - Also, Macrophages, helper dependent CTLs, memory T cells, ...

Model Deficiencies & Possible Extensions

- Heterogeneous (multi-compartment) models
- Viral Mutation
- Resting T Cells, homing?, long term ‘exhaustion’ of the immune system
- Other viral targets...

Model Including CTL response



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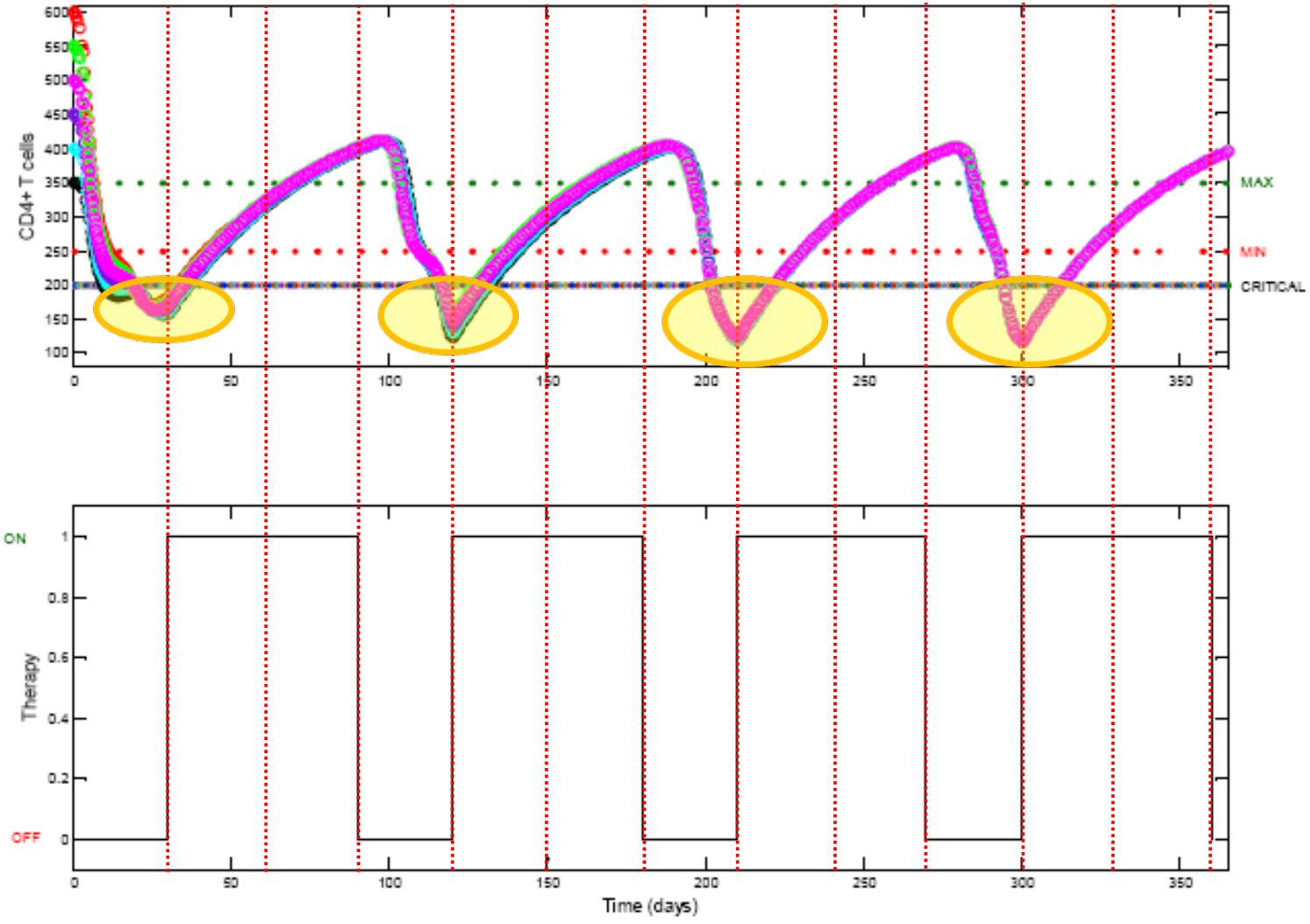
Some control engineering questions?

- Was the SMART (Strategy for Management of Anti Retroviral Therapy) study well designed?
- Large study, control group (HAART) & study group (form of structured treatment interruption)
  - Healthy T cell count > 350, remove from therapy
  - Healthy T cell count < 250, recommence therapy

In Silico study of SMART



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In Silico study conclusions

- The regime proposed in SMART will result in large transients in CD4+
- Transients may go as low as 100, and may remain below 200 for over a week.
- Transients are caused by:
  - Too infrequent sampling
  - Lack of prediction (even if currently above 350, where will CD4+ level be in two months time?)
- Transients could be reduced substantially by regime designed on both CD4+ and viral load

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More control engineering questions?

- What is the best way to use the available therapies to treat infection?
- Can we cleverly schedule treatment, to get a patient to a state of being a LTNP?
  - Answer: Simple model + CTL, computer simulation studies say yes?
  - Caveats: Models maybe too simple, and not well connected to biomedical literature on LTNPs.
  - However: HAART seems to have the undesirable effect of suppressing CTL response to HIV infection without ever completely eliminating the virus.

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More control engineering questions?

- With the ‘normal’ clinical measurements available, is it possible to build a computer system for inferring and predicting short term infection dynamics?
  - Caveat: Maybe, but number and types of measurements required may be impractical
- Can we guess at possible outcomes of clinical trials of new therapies (avoid mistakes like SMART):
  - (e.g) recent clinical studies of removing healthy CD4+, genetically mutating for CCR5, clone mutant CD4+, reinject