Immune System Modelling Examples

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- Case studies

Goal of Modelling

- Predict *quantitative* behaviour of a complex system
  - (« What if ») Analyze hypotheses in silico
  - Interprete conclusions from experiment

« *Mean proliferation and death rates of CD4 + T cells are elevated threefold or more with HIV-infection, but subsequently reduce to nearly normal levels after 1 year of antiretroviral therapy 93. These quantitative results strongly indicate that the CD4 + lymphocyte depletion observed in AIDS is primarily a consequence of increased cellular destruction, and not decreased production* » [Alan Perelson 02]

- Understand role of microscopic components in *emergent* behaviour

"A means of asking questions about the behaviour of a biological system that may not be answerable by conventional experimental approach"
[Robin Callard 02]

« Modelling indicated that the [HIV] virus could quickly become resistant to any single drug, particularly those that required one mutation to generate resistance. » [Alan Perelson 02]

- Assist in the *formulation* of the complete behaviour

"*The process of building the model highlights gaps and inconsistencies in our understanding of the immune response*" [Chao03].

Ex: TCR affinity to MHC/peptide complex is the sum of binding to MHC and to peptide

Modeling Methods

- Deterministic
  - ODE, PDE
  - Low numerical complexity
  - Provides answers to: kinetics, stability
- Stochastic
  - model complexity and emerging behaviour more truly
  - May have very large numerical complexity
  - techniques:
    - Simulator
      - Cellular Automaton
      - Markov Process
    - Stage structured population

Immune System Modelling at EPFL

- An emerging interest in I&C school of EPFL
  - exploratory phase (feasibility)
- Prof Le Boudec + Martinoli + others
  - Successful experience in modeling engineered systems
- Scientific interest
  - stochastic models, rare events
  - contribute to understanding of Immune System
- What we would like to do
  - contribute to the understanding of biology by quantitative modelling and simulation

Case Studies

- Some examples of the kind of research we can pursue
- List of case studies planned for student seminar
  - Chao: Modelling the Cytotoxic T Cell Response
  - Van Den Berg, Rand and Burroughs: A Reliable and Safe T Cell Repertoire based on Low-affinity T Cell Receptors
  - Van den Berg and Rand: Foreignness as a matter of degree: the relative immunogenicity of peptide/MHC ligands
  - Robin Callard ODE models
  - Rob de Boer 1 general model
  - Rob de Boer 2 HIV
  - Castiglione's application of simulator
  - Alan Perelson's overview 2002
- Today: a glimpse of one of them

Chao: « Modelling The Cytotoxic T-Cell Response »

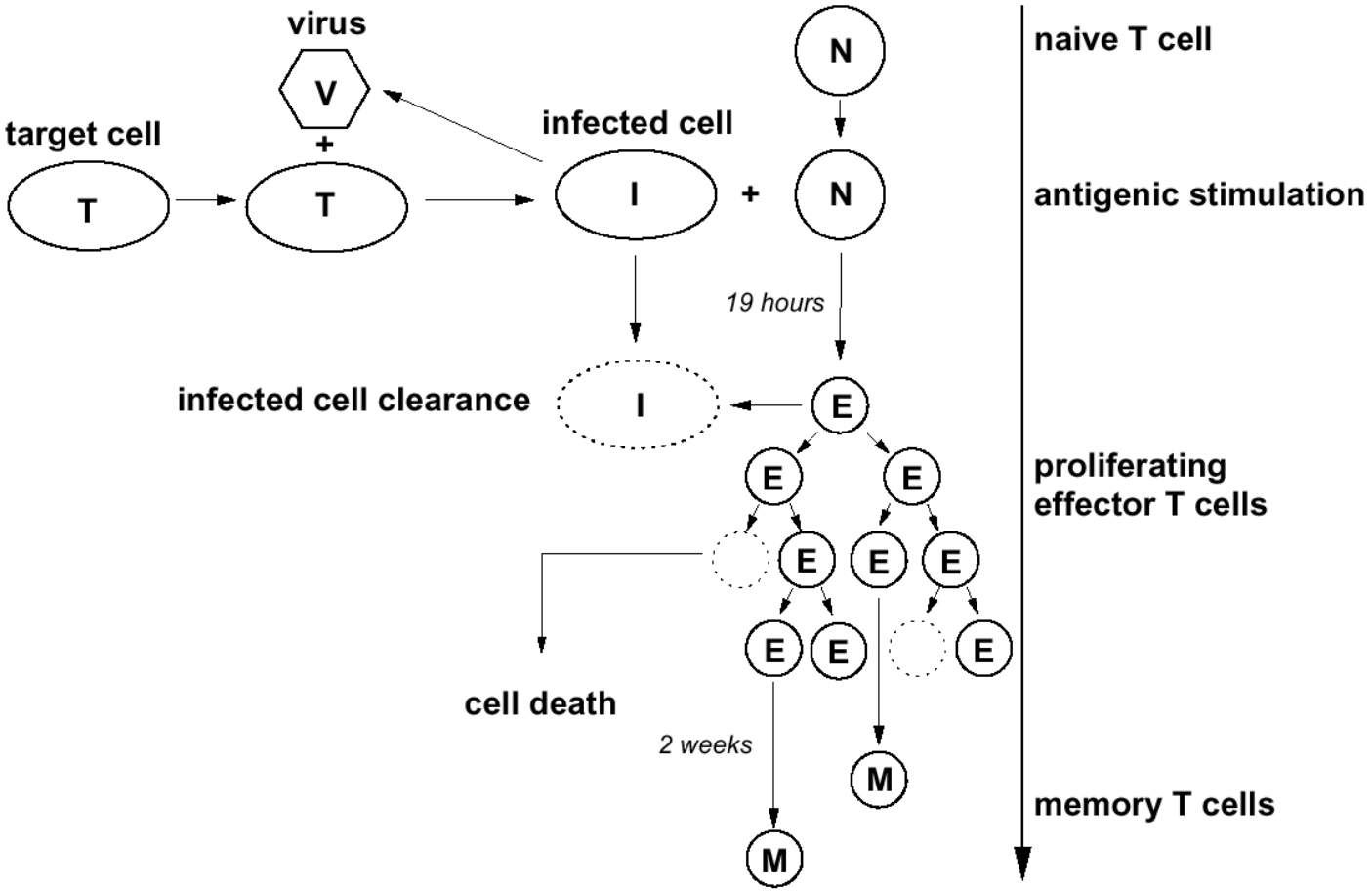
- PhD Thesis by Dennis Chao, U. New Mexico, Prof. Stephanie Forrest. Joint work with Alan Perelson (Santa Fe) and Miles Daveport (Sidney, AUS)
- Further studied by Eric Winnington, EPFL Master Thesis, due March 2005

- Contents
  1. Chao's model
  2. Results in Chao's dissertation
  3. Results by Eric Winnington

1. Chao's Model Focuses on CTL response

- Goal: model CTL response
  - dynamics
  - role of affinity
  - role of distribution of naive/memory CTLs
- Macroscopic model
  - no detail on tissue, lymphocyte trafficking, immune system elements other than CTLs
  - model is: number of cells of each type (tissue, infected, various CTLs) + virus load as a function of time
  - stochastic model; randomness is in T-cell repertoire, binding and lifetime and reproduction
    - stage structured approach == numerical approximation of Markov process

Elements present in Model

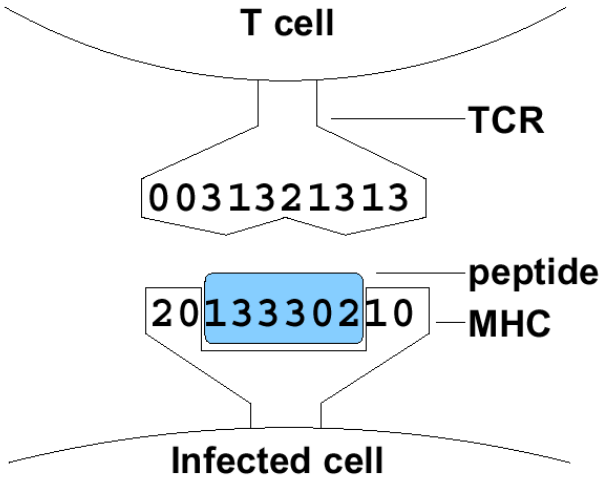


source: Dennis Chao's dissertation

TCR Matching

- Affinity is measured by 1 out of 3 hypothetical bit matching rule
  1. Hamming distance (alphabet size =3, string length=32+48)
  2. Xor distance (an ad-hoc distance ??? : d(3,1)=2 d(3,0)=3 d(2,1)=3 d(5,10)=15) alphabet size = 128, string length=4+6
  3. Modified L^1 (Manhattan) distance: sum of distances modulo n ; n = 16 d(1,5)=4, d(0,15)=1; alphabet size = 32, string length=4+6
- Distance between pMHC and TCR is sum of distances between digits

- Calibrated by fitting mouse data
  - T-cell repertoire
  - number of responding clones per epitope



source: Dennis Chao's dissertation

Avidity and Affinity

- avidity (== recruitment rate) of a naïve T-cell into Activated T-cell is saturating function of affinity and epitope density e:

recruitment rate = γ Stimulation

with γ = maximum recruitment rate (1 per day)

$$\text{Stimulation} = \frac{\sum \frac{e_i I_i}{K_i}}{1 + \sum \frac{e_i I_i}{K_i}}$$

- constant K implemented in model as a function of distance MHC/peptide <-> TCR so as to match experimental data on mouse

$$\begin{aligned} K_{xor} &= 5,000 + 15,000 \times e^{(D_{xor} - 115)/3} \\ K_H &= 5,000 + 5,000 \times e^{2\times(D_H - 31)} \\ K_{L1'} &= 5,000 + 10,000 \times e^{2\times(D_{L1'} - 15)} \end{aligned}$$

source: Dennis Chao's dissertation

The Complete Model

- One separate sub-model for each CTL clone
  - multiple T-cell populations are modelled as distinct populations
  - all CTLs in one clone have identical TCRs
- Complete model (for one clone) is

$$S = (T, I, V, N_T, M_T, A_T^j, A_{MT}^k, E_{T_A}^i, E_{MT_A}^i, E_{T_B}^{il}, E_{MT_B}^{il}, W_{MT}^m)$$

with $i = 0 \cdots 17$ number of times a T-Cell can divide
$j = 0 \ldots (19 \cdot tsph) - 1$ delay from the activation of a T-cell to effectiveness
$k = 0 \ldots tsph - 1$ delay from activation of a memory T-cell to effectiveness
$l = 0 \ldots (5 \cdot tsph) - 1$ delay before cell division finishes
$m = 0 \ldots (14 \cdot tspd) - 1$ delay before cells converting to memory become inactivated memory T-cells

source: Eric Winnington, EPFL

Evolution of Model State is Random

- composition of T-cell clone (number of T-cells in each category) evolves randomly, based on presence of antigen and affinity
  - eg: naïve T-cell
- same for viral load and number of infected tissue cells
- laws of evolution are based on the increment functions given next

- Example
  - Recruitment rate of naïve T-cells is given by avidity formula seen earlier; call it μ ; (is a function of I, number of infected cells)
    - proba that a given cell becomes recruited between t and t+dt is
      $\mu\, dt + o(dt)$
  - N_T: number of naive T-cells in one clone is thus random
    - we have a markov process with state S = $(T, I, V, N_T, \ldots)$

The Simulator Approximates the Markov Process using the Stage Structured Approach

- The simulator advances time by increments δ =10 mn
- For example, the value of N_T is updated according to

$$N_T(t+1) = N_T(t) - B\left(N_T(t), 1 - e^{-\mu\delta}\right)$$

where B is the binomial distribution

- See next for the complete list of evolution equations

- This is an approximation valid for small δ
  - the approx is that μ depends on state S, assumed constant during 10 mn

$$I_{t+1} = I_t + B(T_t, 1.0 - e^{(-2\cdot 10^{-7}/TSPD)\cdot V_t}) - B(T_t, 1.0 - e^{-0.7/TSPD}) - P(\frac{(Tclear/TSPD)\cdot \sum E_* \cdot I_t \cdot Pl}{Affinity + I + \sum E_*})$$

$$V_{t+1} = V_t + P(I_t \cdot 100/TSPD) - B(T_t, 1.0 - e^{-2.3/TSPD})$$

$$N_{T_{t+1}} = N_{T_t} - B(N_{T_t}, 1.0 - e^{\frac{\frac{I_t \cdot Pl}{Affinity}}{1+\frac{I_t \cdot Pl}{Affinity}} \cdot NtE/TSPD})$$

$$A^0_{T_{t+1}} = B(N_{T_t}, 1.0 - e^{\frac{\frac{I_t \cdot Pl}{Affinity}}{1+\frac{I_t \cdot Pl}{Affinity}} \cdot NtE/TSPD}) - B(A^0_{T_t}, 1.0 - e^{-0.6/TSPD})$$

$$A^j_{T_{t+1}} = A^{j-1}_{T_t} - B(A^{j-1}_{T_t}, 1.0 - e^{-0.6/TSPD})$$

$$A^E_{T_{t+1}} = A^{E-1}_{T_t} - B(A^{E-1}_{T_t}, 1.0 - e^{-0.6/TSPD})$$

$$E^0_{T_{A_{t+1}}} = A^E_{T_t} + E^0_{T_{A_t}} - B(E^0_{T_{A_t}}, 1.0 - e^{-0.6/TSPD}) - B(E^0_{T_{A_t}}, 1.0 - e^{\frac{-1.0}{((Ct-Bd)\cdot TSPH)}}) - B(E^0_{T_{A_t}}, 0.02)$$

$$E^i_{T_{A_{t+1}}} = E^i_{T_{A_t}} + 2\cdot E^{i-1E}_{T_{B_t}} - B(E^i_{T_{A_t}}, 1.0 - e^{-0.6/TSPD}) - B(E^i_{T_{A_t}}, 1.0 - e^{\frac{-1.0}{((Ct-Bd)\cdot TSPH)}}) - B(E^i_{T_{A_t}}, 0.02)$$

$$E^E_{T_{A_{t+1}}} = E^E_{T_{A_t}} + 2 \cdot E^{E-1E}_{T_{B_t}} - B(E^{E-1E}_{T_{B_t}}, 1.0 - e^{-0.6/TSPD}) - B(E^E_{T_{A_t}}, 0.02)$$

$$E^{i0}_{T_{B_{t+1}}} = B(E^i_{T_{A_t}}, 1.0 - e^{\frac{-1.0}{((Ct-Bd)\cdot TSPH)}})$$

$$E^{il}_{T_{B_{t+1}}} = E^{il-1}_{T_{B_t}} - B(E^{il-1}_{T_{B_t}}, 1.0 - e^{-0.6/TSPD}) - B(E^{il}_{T_{B_t}}, 0.02)$$

$$E^{iE}_{T_{B_{t+1}}} = E^{iE-1}_{T_{B_t}} - B(E^{iE-1}_{T_{B_t}}, 1.0 - e^{-0.6/TSPD}) - B(E^{iE}_{T_{B_t}}, 0.02)$$

source: Eric Winnington, EPFL

$$W^0_{MT_{t+1}} = \sum B(E_*, 0.02)$$
$$W^m_{MT_{t+1}} = W^{m-1}_{MT_t}$$
$$W^E_{MT_{t+1}} = W^{E-1}_{MT_t}$$

$$M_{T_{t+1}} = W^E_{MT_t} + M_{T_t} - B(M_{T_t}, 1.0 - e^{\frac{\frac{I_t \cdot Pl}{Affinity}}{1+\frac{I_t \cdot Pl}{Affinity}} \cdot NtE/TSPD})$$

$$A^0_{MT_{t+1}} = B(M_{T_t}, 1.0 - e^{\frac{\frac{I_t \cdot Pl}{Affinity}}{1+\frac{I_t \cdot Pl}{Affinity}} \cdot NtE/TSPD}) - B(A^0_{MT_t}, 1.0 - e^{-0.4/TSPD})$$
$$A^k_{MT_{t+1}} = A^{k-1}_{MT_t} - B(A^{k-1}_{MT_t}, 1.0 - e^{-0.4/TSPD})$$
$$A^E_{MT_{t+1}} = A^{E-1}_{MT_t} - B(A^{E-1}_{MT_t}, 1.0 - e^{-0.4/TSPD})$$
$$E^0_{MT_{A_{t+1}}} = A^E_{MT_t} + E^0_{MT_{A_t}} - B(E^0_{MT_{A_t}}, 1.0 - e^{\frac{-1.0}{((Ct-Bd)\cdot TSPH)}}) - B(E^0_{MT_{A_t}}, 1.0 - e^{-0.4/TSPD}) - B(E^0_{MT_{A_t}}, 0.02)$$
$$E^i_{MT_{A_{t+1}}} = E^i_{MT_{A_t}} + 2 \cdot E^{i-1E}_{MT_{B_t}} - B(E^i_{MT_{A_t}}, 1.0 - e^{-0.4/TSPD}) - B(E^i_{MT_{A_t}}, 1.0 - e^{\frac{-1.0}{((Ct-Bd)\cdot TSPH)}}) - B(E^i_{MT_{A_t}}, 0.02)$$
$$E^E_{MT_{A_{t+1}}} = E^E_{MT_{A_t}} + 2 \cdot E^{E-1E}_{MT_{B_t}} - B(E^E_{MT_{A_t}}, 1.0 - e^{-0.4/TSPD}) - B(E^E_{MT_{A_t}}, 0.02)$$
$$E^{i0}_{MT_{B_{t+1}}} = B(E^i_{MT_{A_t}}, 1.0 - e^{\frac{-1.0}{((Ct-Bd)\cdot TSPH)}})$$
$$E^{il}_{MT_{B_{t+1}}} = E^{il-1}_{MT_{B_t}} - B(E^{il-1}_{MT_{B_t}}, 1.0 - e^{-0.4/TSPD}) - B(E^{il}_{MT_{B_t}}, 0.02)$$
$$E^{iE}_{MT_{B_{t+1}}} = E^{iE-1}_{MT_{B_t}} - B(E^{iE-1}_{MT_{B_t}}, 1.0 - e^{-0.4/TSPD}) - B(E^{iE}_{MT_{B_t}}, 0.02)$$

source: Eric Winnington, EPFL

How the model is run

- generate one or several pMHC complexes
- generate the T-cell clones that cross-react to them
  - only those CTLs that can react to pathogen are explicitly created in the simulator (this is called « Lazy Evaluation »)
- submit clones to positive and negative selection (thymus)
- start one stage-structured instance per T-cell clone and run the model step by step

Parameters of Model

attribute	*value*
time step (Δt)	10 minutes
naïve cell clone size	10 cells*
maximum T cell recruitment rate (γ)	1 day^{-1}
delay before a stimulated naïve cell becomes an effector (τ_n)	19 hours†
delay before a stimulated memory cell becomes an effector (τ_m)	1 hour‡
naïve-derived active CTL death rate (δ_E)	0.6 day^{-1}§
memory-derived active CTL death rate (δ_{E_m})	0.4 day^{-1}§
time in B phase for CTL	5 hours‖
average CTL cell cycle time	6 hours‖
infected cell clearance rate (k^c)	12 day^{-1}¶

* Casrouge et al. (2000)

† Oehen and Brduscha-Riem (1998); Gett and Hodgkin (2000); Veiga-Fernandes et al. (2000); van Stipdonk et al. (2001)

‡ Bachmann et al. (1999); Barber et al. (2003)

§ Veiga-Fernandes et al. (2000)

‖ van Stipdonk et al. (2001)

¶ Barchet et al. (2000)

Table 3.1: A summary of model parameters.

source: Dennis Chao's dissertation

Model is fitted to the mouse

	Mouse	Human	Hamming	xor	L_1'
# of self peptides	$10^4 - 10^5$*		30,000	30,000	30,000
# of MHC types	3	4	3	3	3
universe of TCRs (or # of possible TCR strings)		10^{15}†	1.47×10^{38}	1.18×10^{21}	1.13×10^{15}
# of pre-selection clones	$< 10^9$	10^{13}	8×10^7	2.5×10^8	2.5×10^8
# of naïve clones	$10^6 - 10^7$‡	10^7§	3.17×10^6	2.02×10^6	1.95×10^6
foreign peptide response frequency	$10^{-5} - 10^{-6}$		8.39×10^{-6}	1.27×10^{-5}	1.43×10^{-5}
thymic selection window size	1-3%		3.96%	0.807%	0.778%
% killed in negative selection	50-66%		46%	61%	70%
# of clones per epitope	10-20‖		26.6	25.7	27.9

* Bevan (1997); Müller and Bonhoeffer (2003); Bandeira and Faro (2003)
† Davis and Bjorkman (1988)
‡ Pannetier et al. (1993); Casrouge et al. (2000)
§ Arstila et al. (1999)
‖ Blattman et al. (2002)

source: Dennis Chao's dissertation

Other Modelling Assumptions

- CTLs do not interact with non infected self cells
- Virus can mutate
  - implemented as change in one digit of the peptide in MHC/peptide complex
  - implemented by probability *p* that a virus in newly infected cell undergoes one mutation
- T-cell exhaustion

2. Chao's Result Example
Impact of CTL clone size

- smaller initial clone size induces a larger virus load peak and then a faster decay

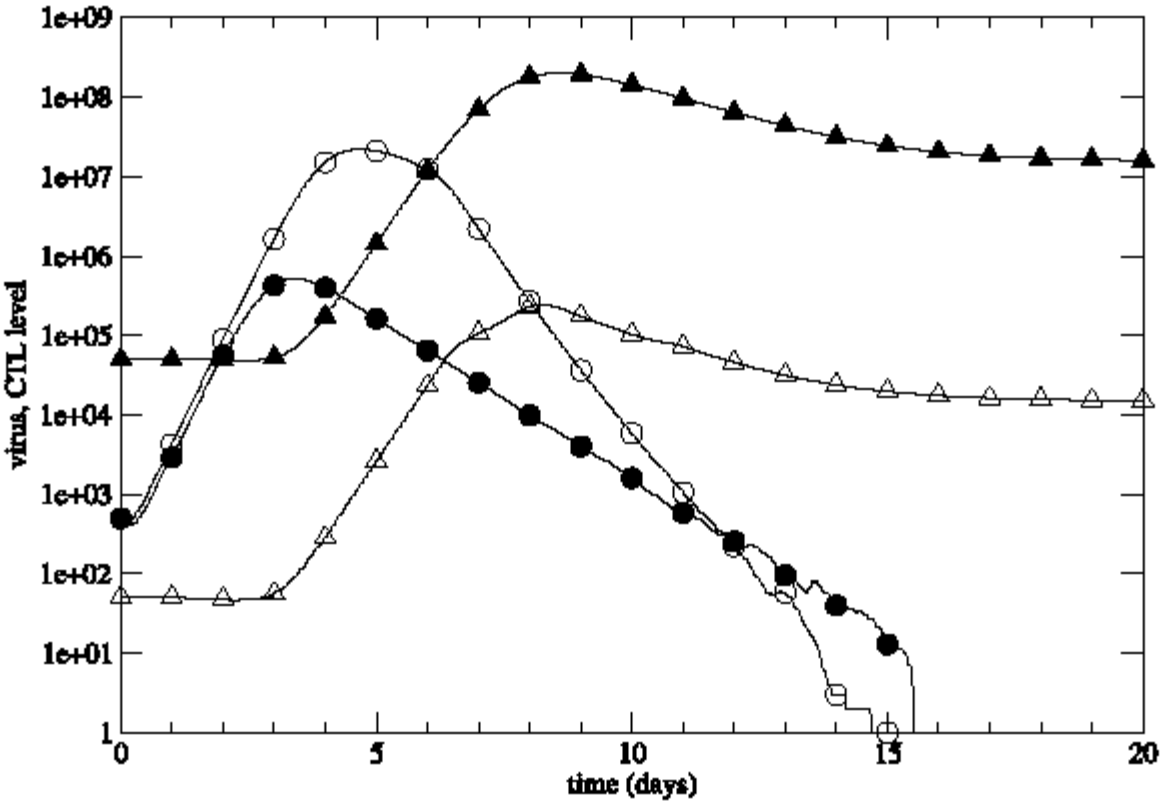


Figure 5.9: The effect of increasing the number of naïve cells. One model run was initialized with 50 naïve cells (△) and a viral load of 500 (○). The other model run started with 50,000 naïve cells (▲) and the same initial virus load (●).

source: Dennis Chao's dissertation

Example: Clonal Composition of CTL Response

- secondary response has a higher affinity

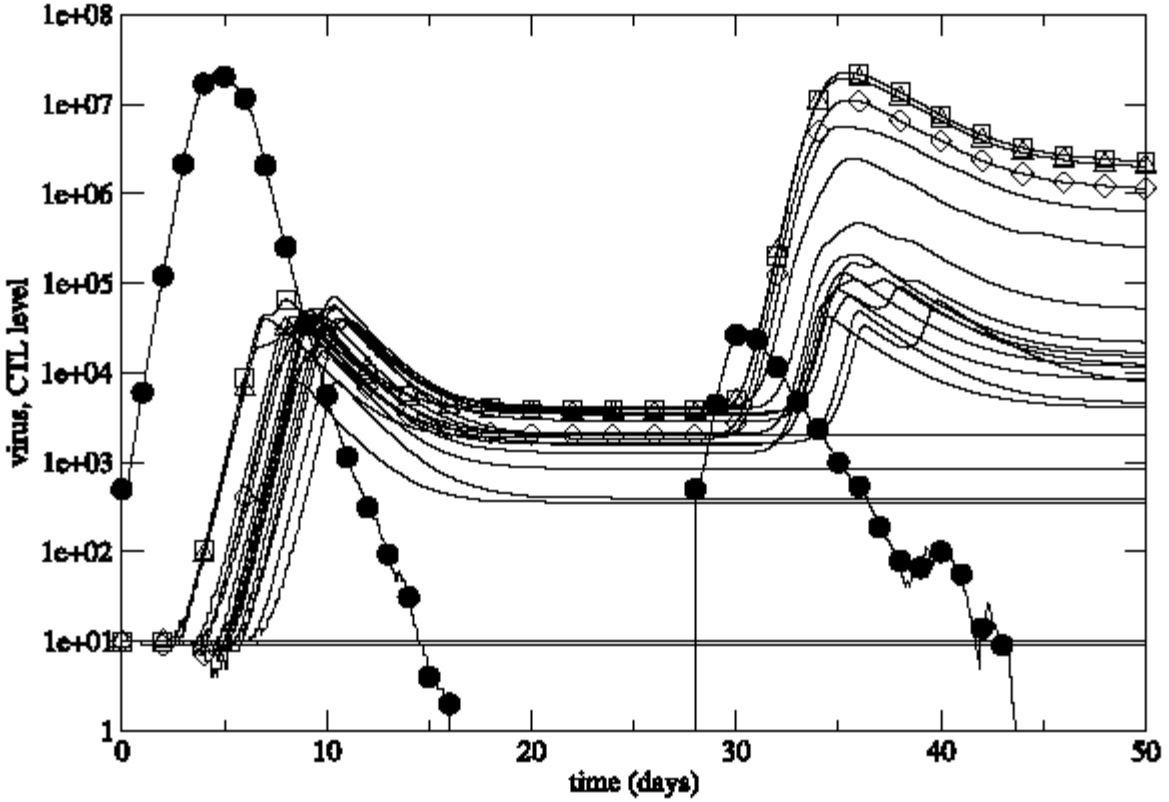
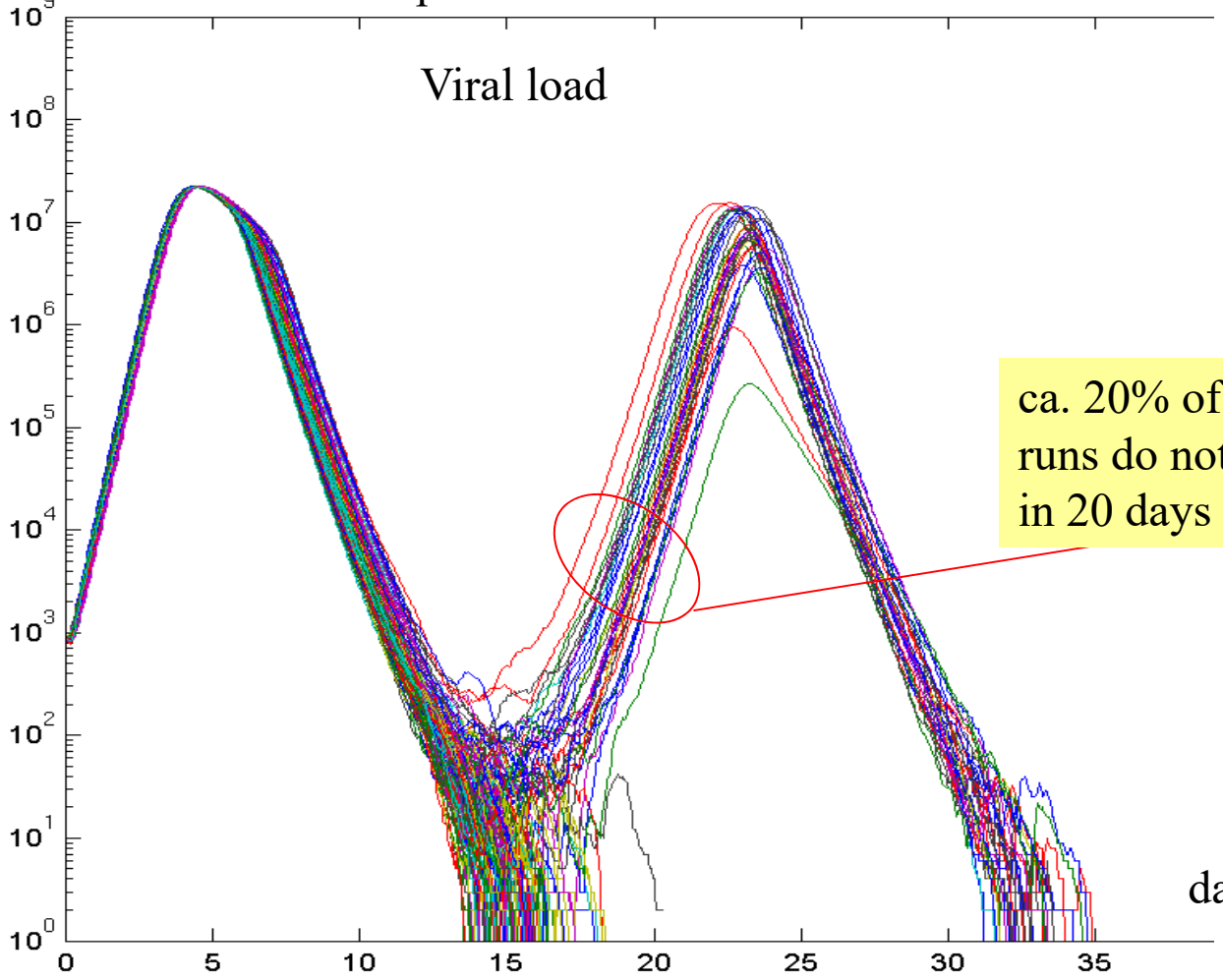


Figure 5.11: Primary and secondary CTL responses to a viral infection. 500 viral units were injected on days 0 and 28. The virus levels are indicated by • and the number of CTLs in the three highest-affinity clones as □, △, and ◊ (in decreasing order of affinity). Lower-affinity clones are represented by lines with no markers. Each CTL clone initially has 10 unstimulated naïve cells.

source: Dennis Chao's dissertation

3. Eric Winington's Result Example
The Immune Response is Random

- The same model can be run more extensively and one finds random results
  - randomness due to naïve T-cell repertoire



ca. 20% of simulation runs do not clear virus in 20 days

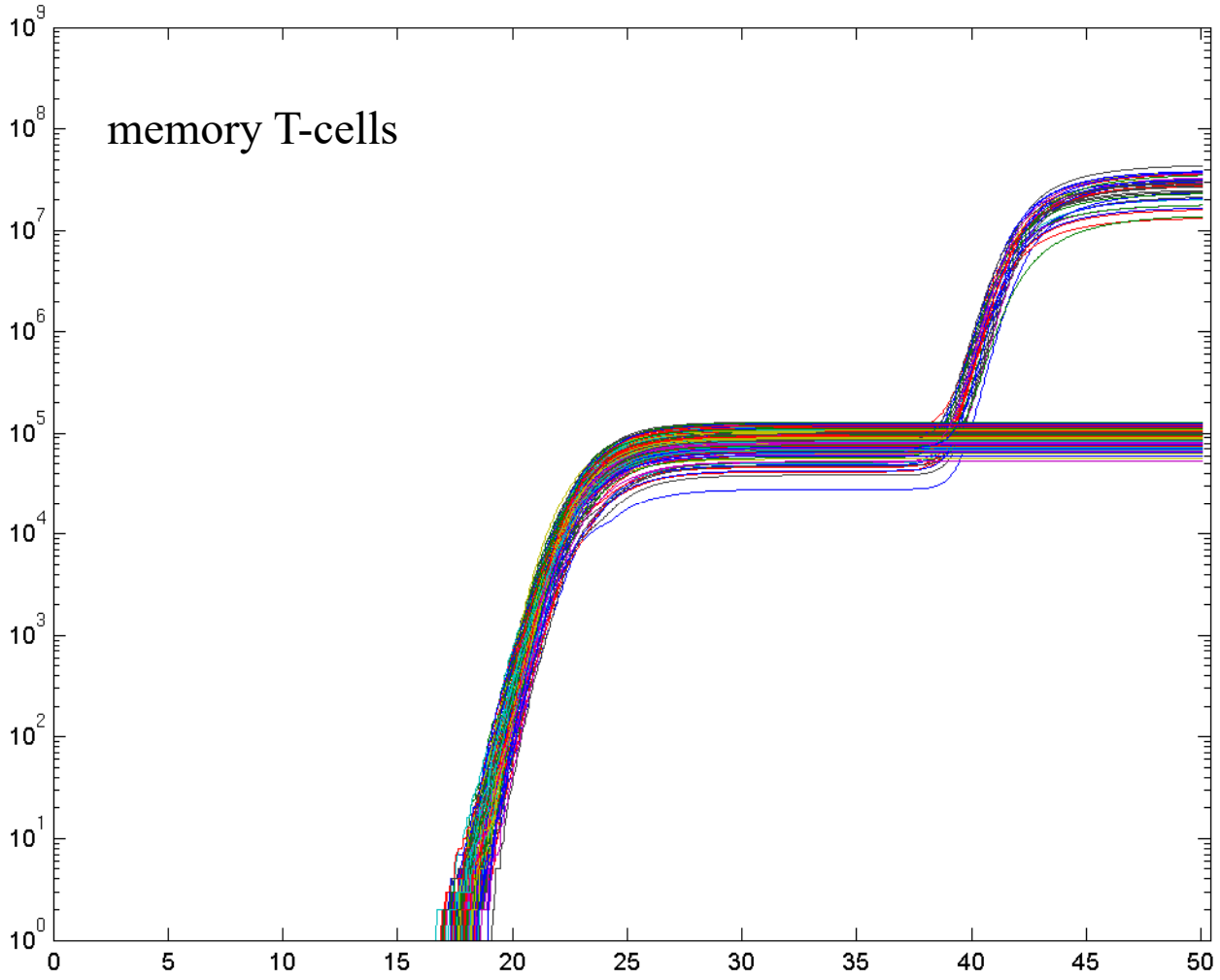
source: Eric Winnington, EPFL

1kHN

Secondary reaction without re-infection may occur with small probability

- Not cleared by primary reaction (after 20 days)

5h	Hamming	15.0%
	Manhattan	31.7%
	Xor	31.0%
1k	Hamming	22.5%
	Manhattan	31.5%
	Xor	37.0%



source: Eric Winnington, EPFL

1kHN

Conclusion

- The examples show what we can do and what a stochastic model can tell us
- We would like now to apply this and other types of modelling to specific cases of interest

Checklist

- how many TCRs per CTL?
- How is avidity computed in the model ?
- How is epitope mapped to MHC/peptide complex ?
- Multiple epitopes / antigen specificity: how does the model reflect this ?
  - how are the original T-cells created from the model ?
  - H: all T cells are same, I different pathogen types
  - what does « T-cell specific to a particular antigen » mean ?
  - is there more than one antigen specificity anywhere in the applications of the model ?
- Replace : in effector mediated clearance Poisson by Binomial
- Compare to ODE method (mean values)
- Can auto-immunity occur in this model ? (a peptide—MHC complex close to many self complexes)