Simple models of the immune response

# What kind of immunology to improve epidemiology?

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# Extending epidemiology with immunology

- For most pathogens immune response is complex and poorly understood, at least quantitatively:
  - is infection controlled by humoral or cellular immunity?
  - what is the role of target cell limitation?
  - how important is the innate immune response?
- Unbalanced to extend simple (SIR) models with large and complicated immune system models:
  - Challenge is to develop appropriate caricature models
- **Most important**: Variability between individuals:
  - differences in pathogen load and infectivity
  - differences in type of immune response (Th1, Th2)
  - MHC and KIR polymorphism; SNPs in cytokine genes

CD8$^+$ Cytotoxic T cells
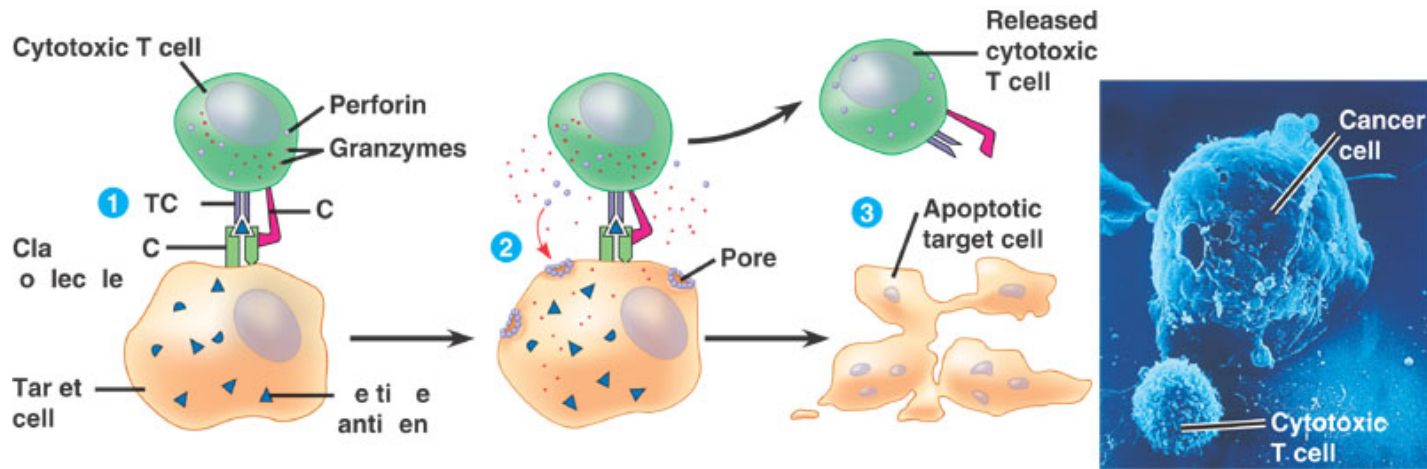
From: Campbell & Reece, Biology 7th Ed, 2005: Fig. 43.16

Two caricatures of the immune response
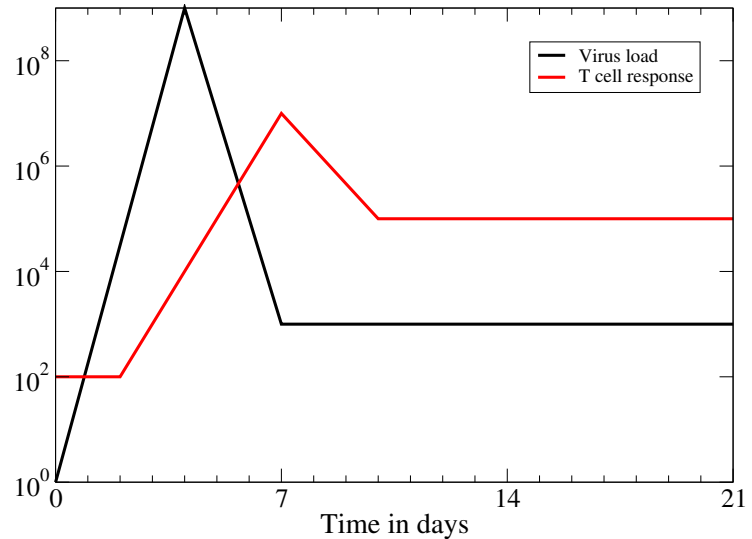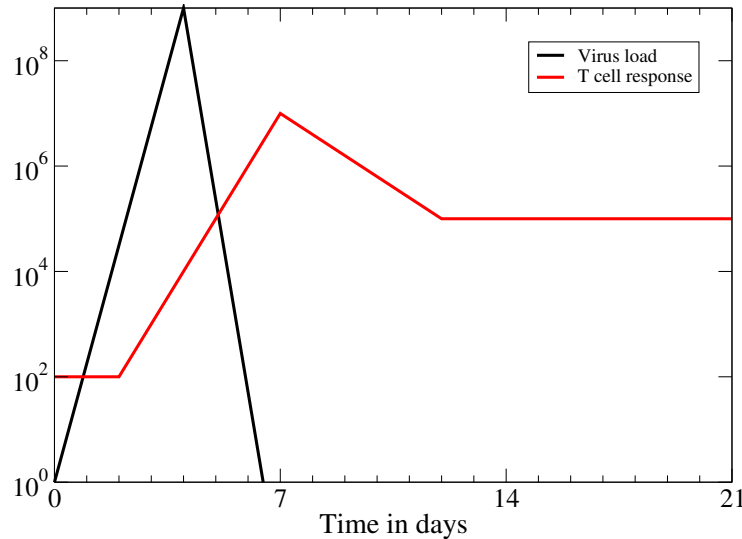
- if pathogen is rejected: life long systemic memory
- → local T cell memory in tissue may be short lived
- T cell response seems programmed
- → expansion, contraction, and memory phase
- Chronic response looks similar, but is poorly understood
- → Human CMV and HIV-1: 10% of response specific

Large variability between hosts

- MHC (Björn Peters): polymorphism of > 1000 alleles

$\rightarrow$ HIV-1: long term non progressors (Keşmir)

- KIR (NK cell receptor): many haplotypes with variant number of loci, inhibitory or stimulatory (Carrington: HIV-1).

- SNPs in various cytokine genes

$\rightarrow$ host genotype influences type of immune response

- SNPs in Toll like receptor molecules

$\rightarrow$ Adrian Hill, Ann Rev Gen 2006 (MAL/TLR4): malaria

$\rightarrow$ Mark Feinberg: Sooty Mangabeys no INF-α

- polymorphism in APOBEC3G (Sawyer, Plos Biol, 2004)
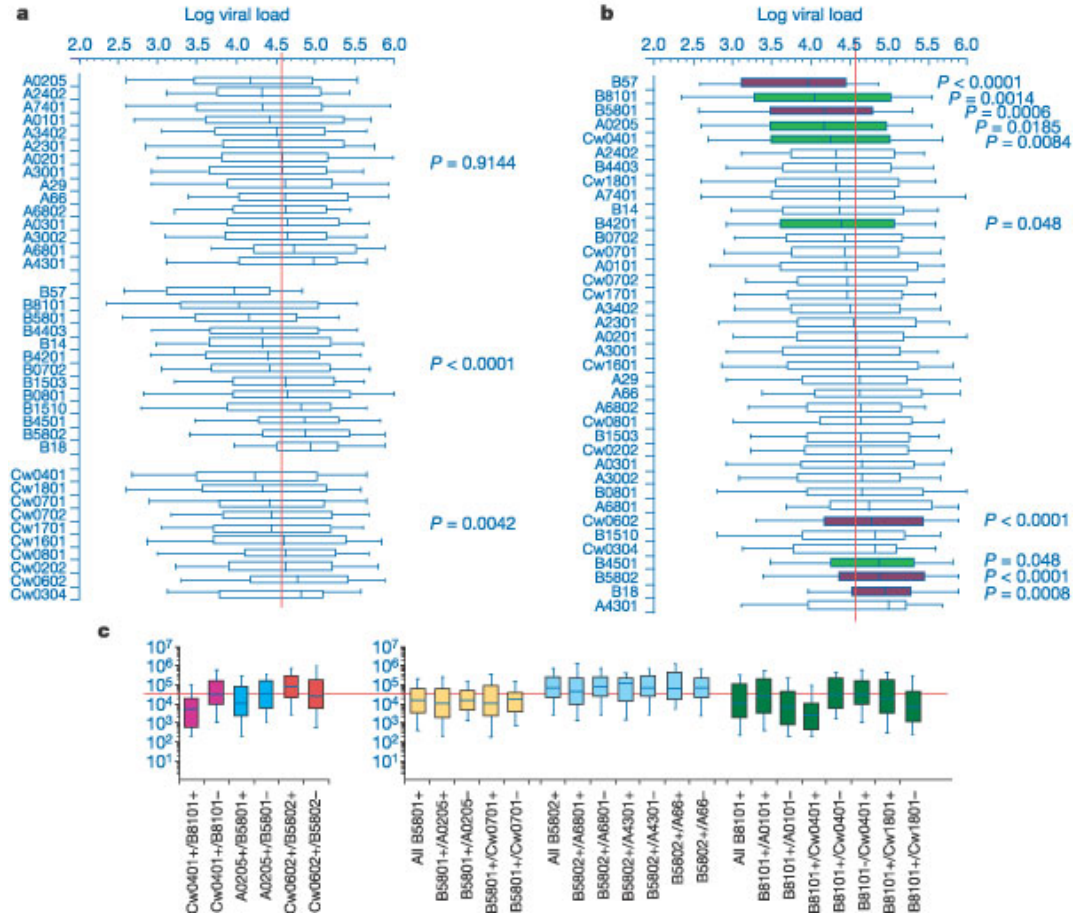
From: Kiepiela, Nature, 2004

MHC diversity due to frequency dependent selection?
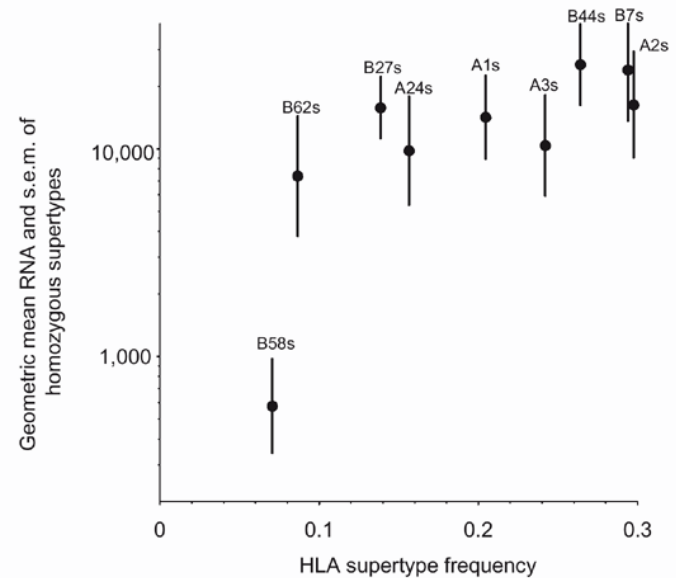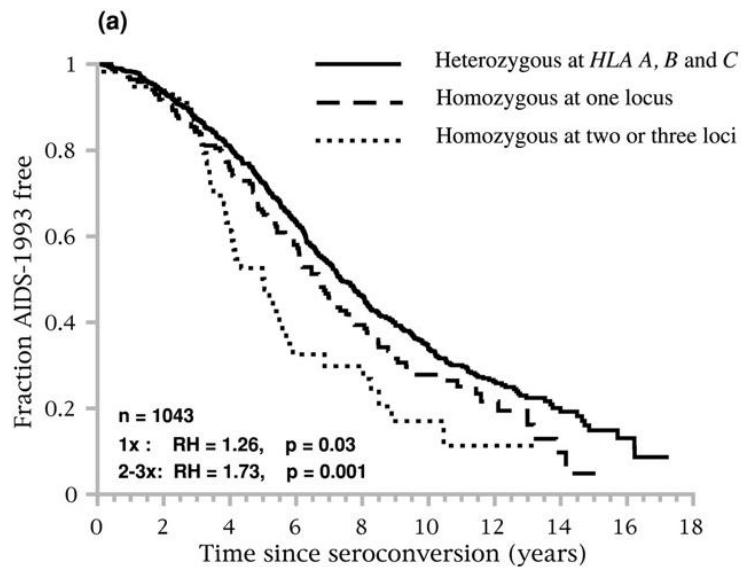
From: Carrington.arm03 (left) and Trachtenberg.nm03 (right)

Can Keşmir: B58 is not only rare but very special

MHC diversity due to frequency dependent selection?

Model (DeBoer.ig04, Borghans.ig04):

• host-pathogen co-evolution model

→ bit strings for MHC and peptides

• diploid hosts and many (fast) pathogen species

→ heterozygote advantage by itself not sufficient

→ pathogen co-evolution: frequency dependent selection

• Can Keşmir and Boris Schmid: host gene frequencies are shifting towards protective HLAs, but HIV-1 is not.

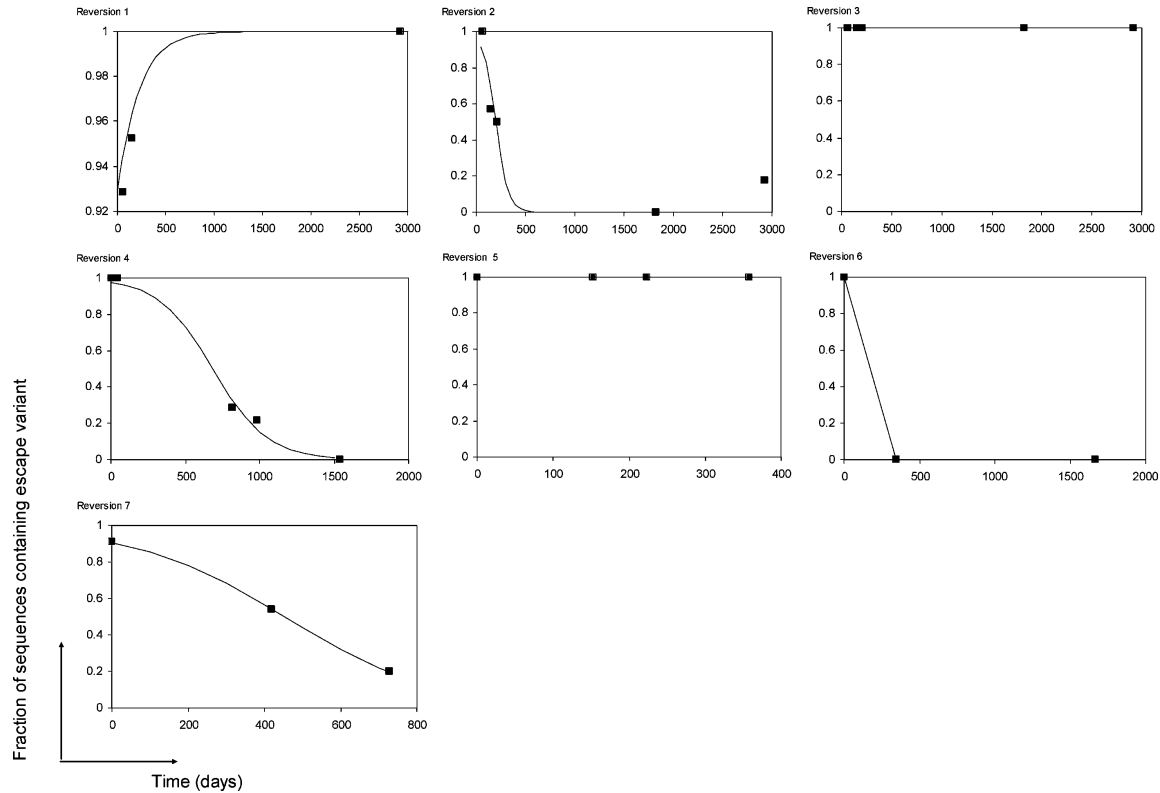• HIV-1 reverses crippling immune escape mutations in new hosts

HIV-1 reverses immune escape mutations in new hosts

Table 2 Fate of TW10 variants after transmission

| Subject	HLA type	Time point	Genetic material	TSTLQEQIGW	Number of clones
SMH-05-Mother	B57/7	5 months	DNA	--N-----A-	16/16
		7 months	RNA	--N-----A-	17/17
		8 years	DNA	--N-----A-	13/13
			RNA	--N-----A-	Population sequencing
SMH-05-Child	B7/–	2 months	DNA	--N-----A-	14/14
		5 months	DNA	--N-----A-	12/21
				--------A-	9/21
		7 months	RNA	--N-----A-	6/12
				--------A-	6/12
		5 years	RNA	--------A-	16/16
		8 years	DNA	--N-----A-	3/17
				--------A-	14/17
				TSTLQEQIAW	

From: Leslie, Nature Medicine, 2004

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From: Asquith Plos Biol 2006

Pathogens and immune responses

- LCMV non cytolytic mouse virus: vigorous response
$\rightarrow$ acute (Armstrong) and chronic (clone 13)
- Listeria infection: similar programmed response
- HIV-1, HBV, HCV: begin to be characterized
- Human influenza: innate, antibodies, CD8$^+$ T cells
- Coccidios (Don Klinkenberg): detailed case study

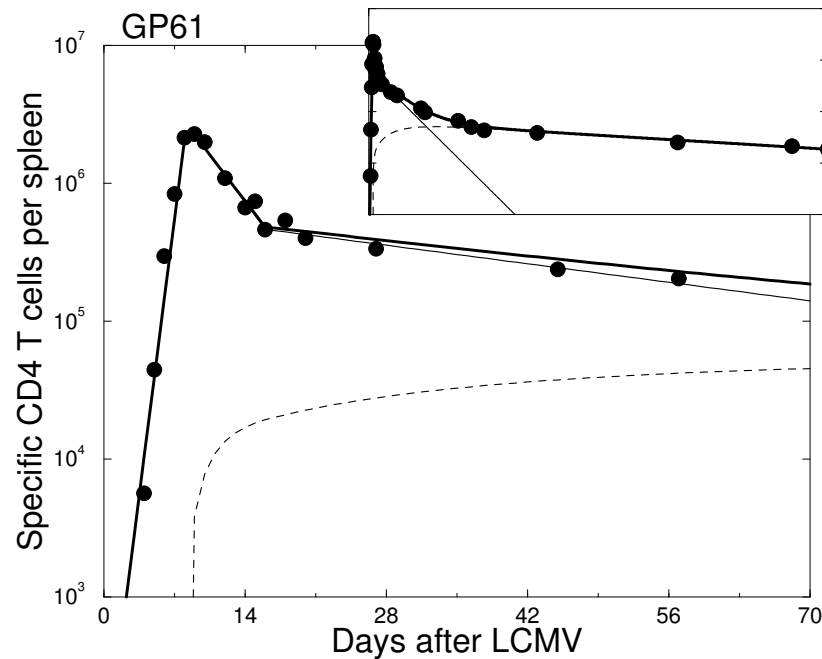**Elaborate two examples: LCMV & HIV-1**

LCMV: CD8 acute dynamics
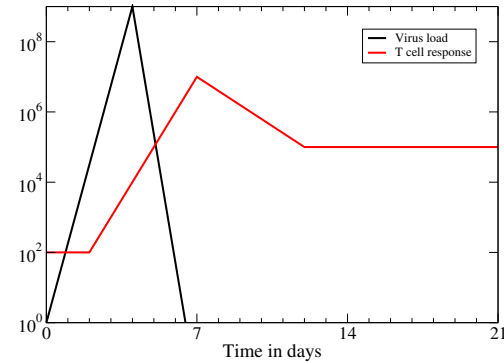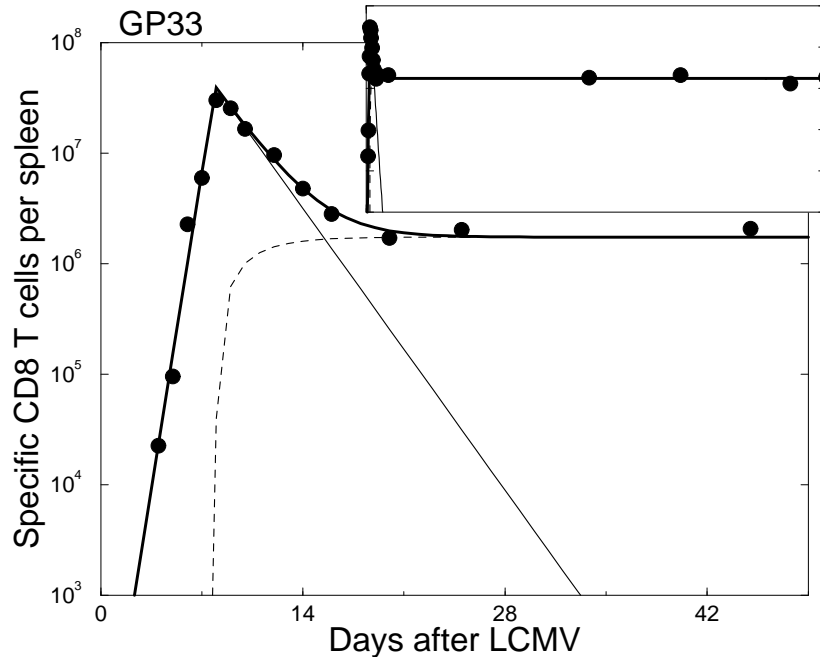
C57BL/6 CD8$^+$ T cell response to GP33 from LCMV Armstrong (data: Dirk Homann, model: DeBoer.ji03)

Expansion phase, contraction phase, and memory phase
The inset depicts 912 days: memory is stable

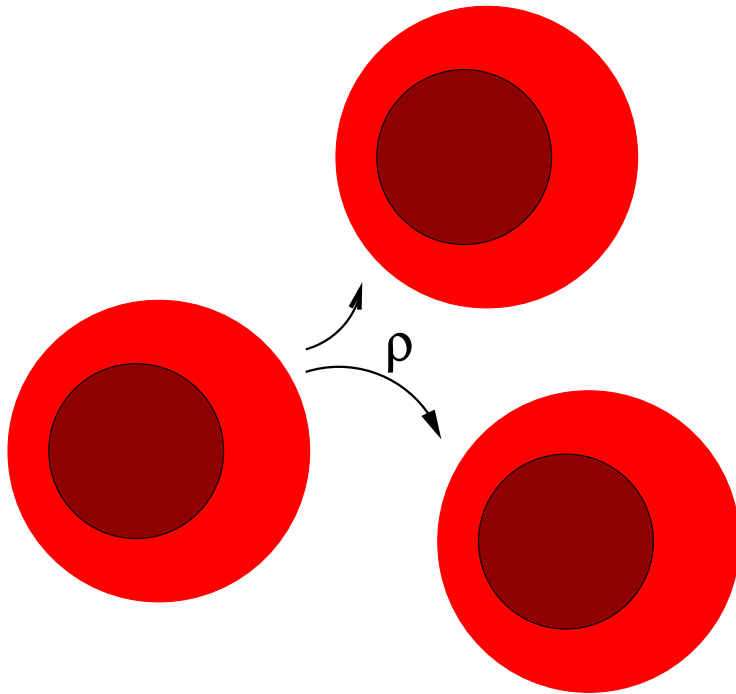# CD4$^+$ T cells obey a very similar program

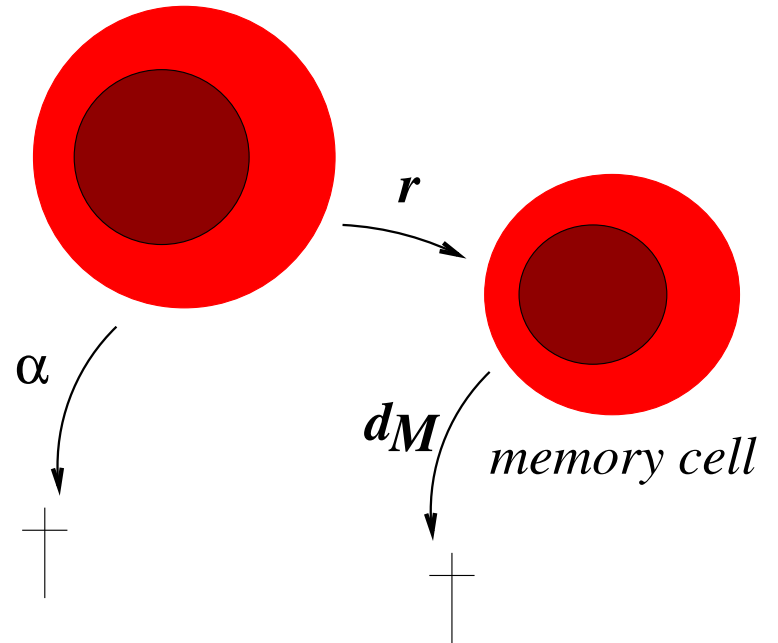C57BL/6 CD4$^+$ T cell response to GP61 from LCMV Armstrong (data: Dirk Homann, model: DeBoer.ji03)

Biphasic contraction phase, memory phase not stable

expansion of activated cells   *contraction*

ρ

r

α

d_M

memory cell

$t < T$

$t > T$

Simple mathematical model

During the expansion phase, i.e., when $t < T$, activated T cells, A, proliferate according to

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \rho A,$$
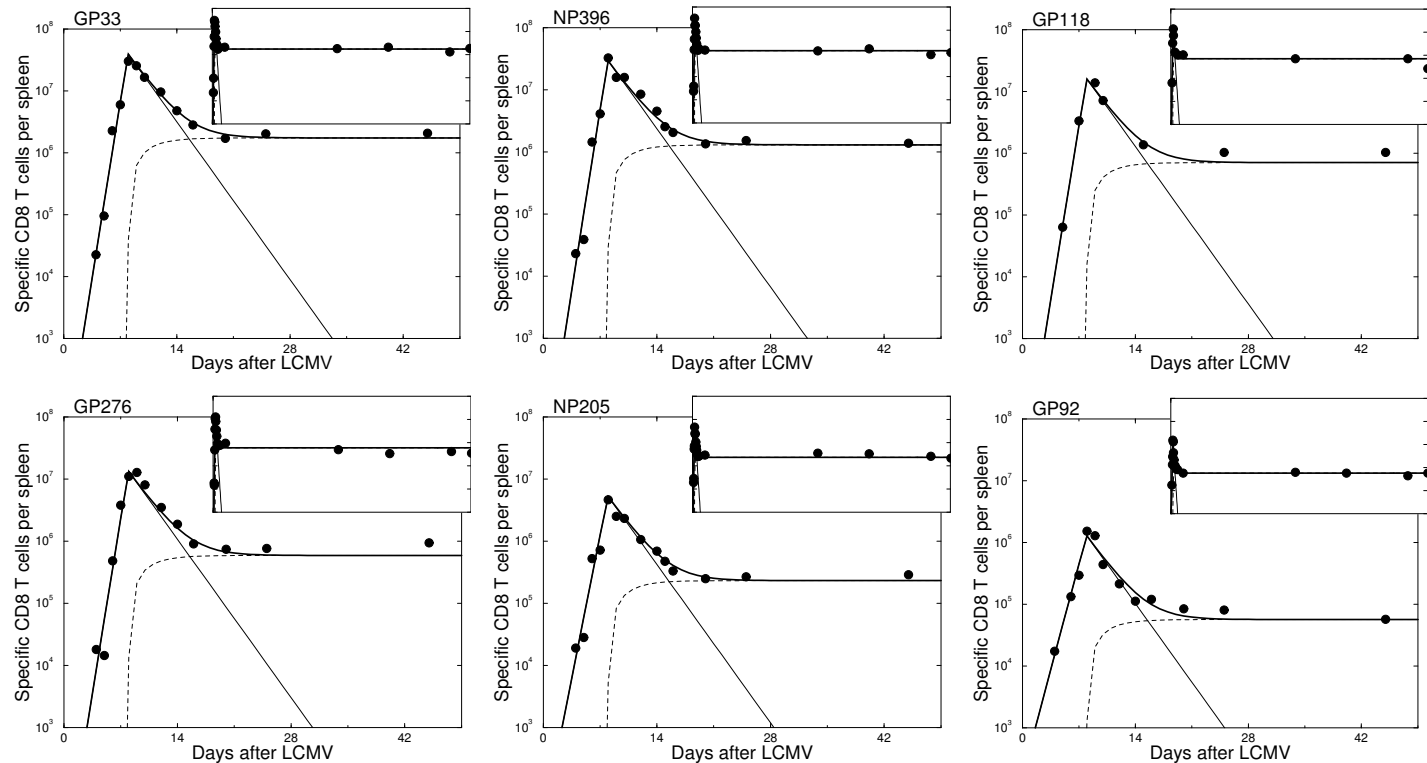
where ρ is the net expansion rate.

During the contraction phase, i.e., when $t < T$, activated T cells, A, die and form memory cells:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = -(r + \alpha)A$$

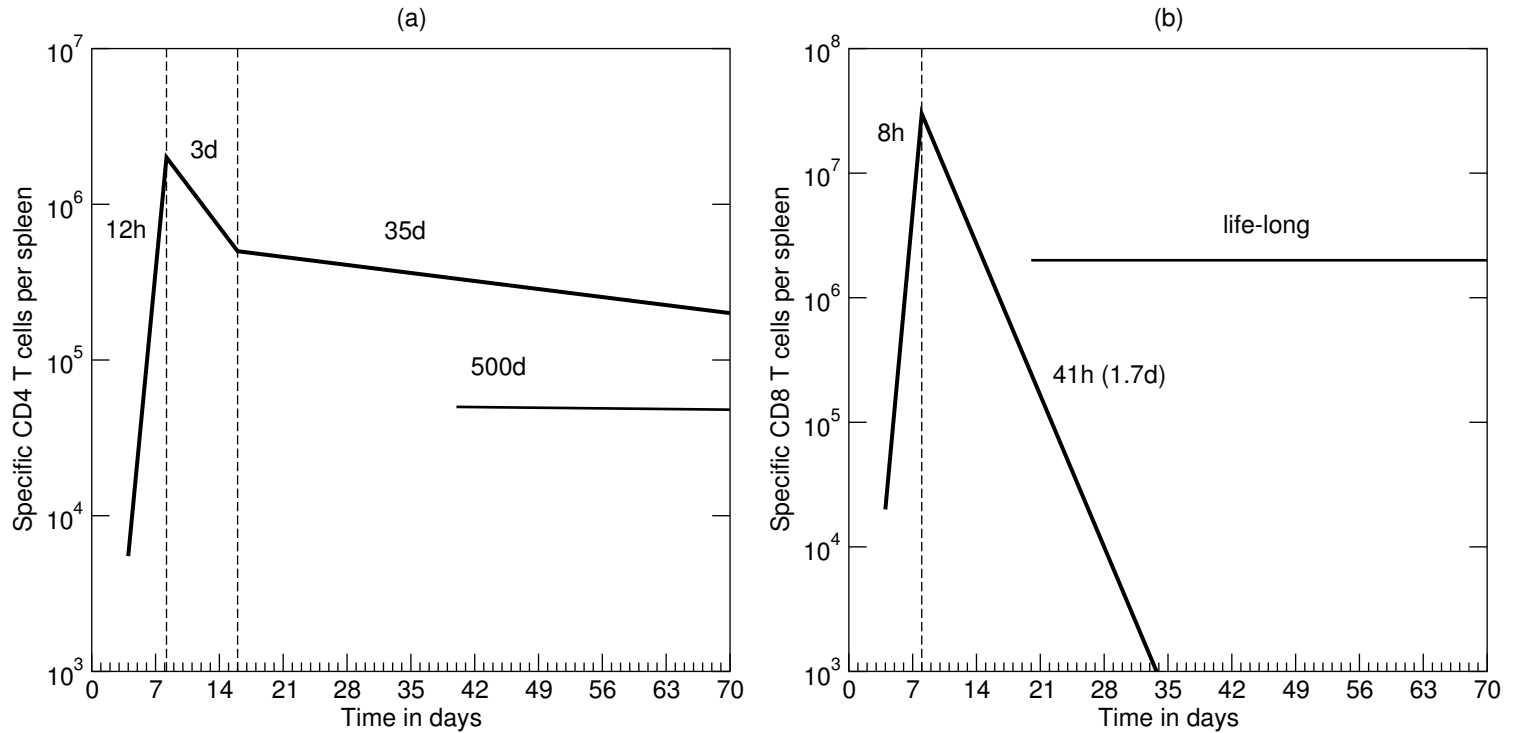$$\frac{\mathrm{d}M}{\mathrm{d}t} = rA - \delta_M M$$

where α is a parameter representing rapid apoptosis.
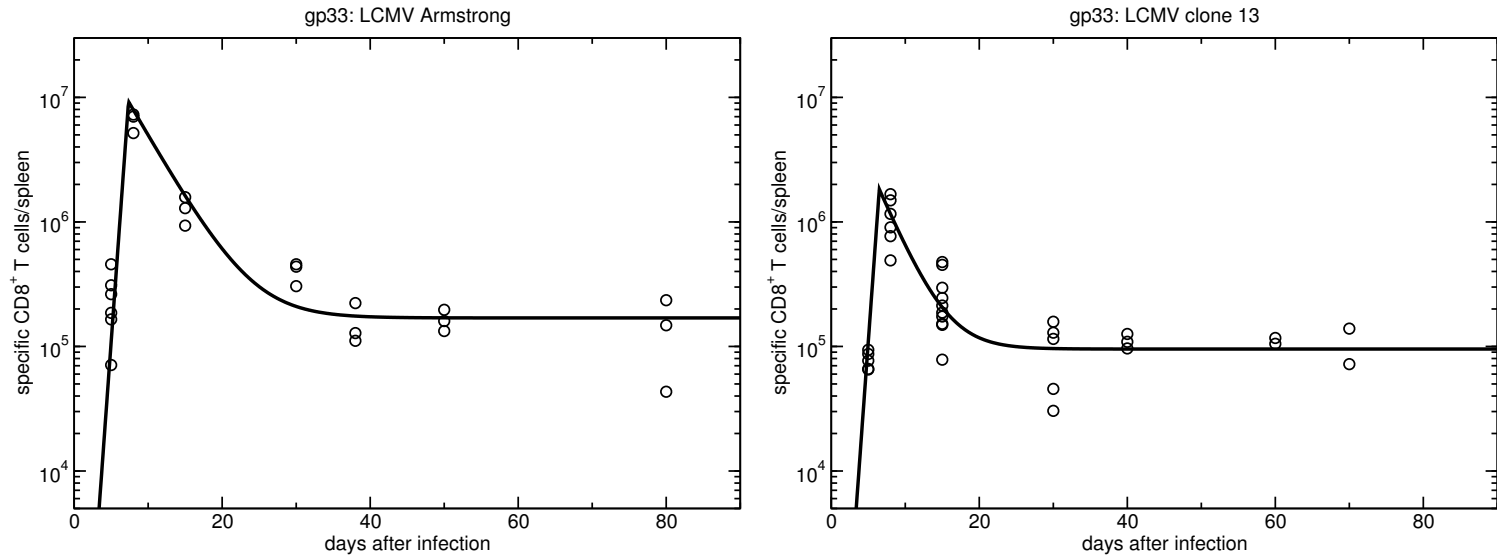
Six CD8 epitopes: immunodominance of responses

Immunodominance "explained" by small differences in recruitment (and division rates for the last two).

CD8 kinetics much faster than that of CD4s

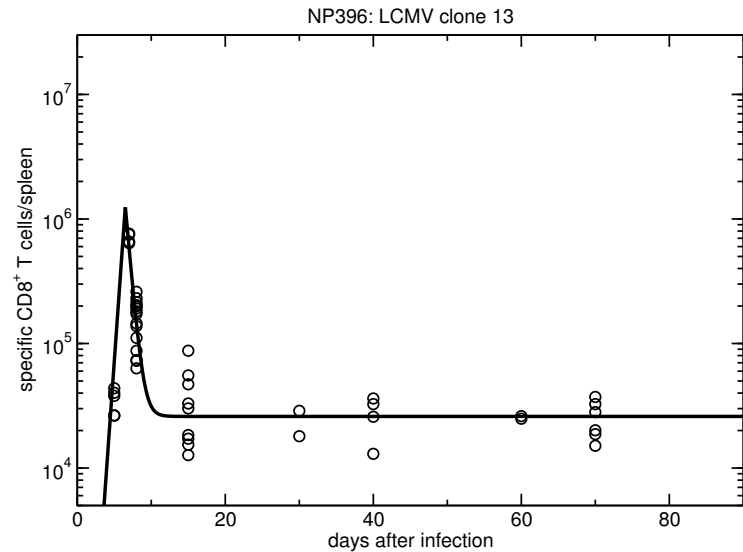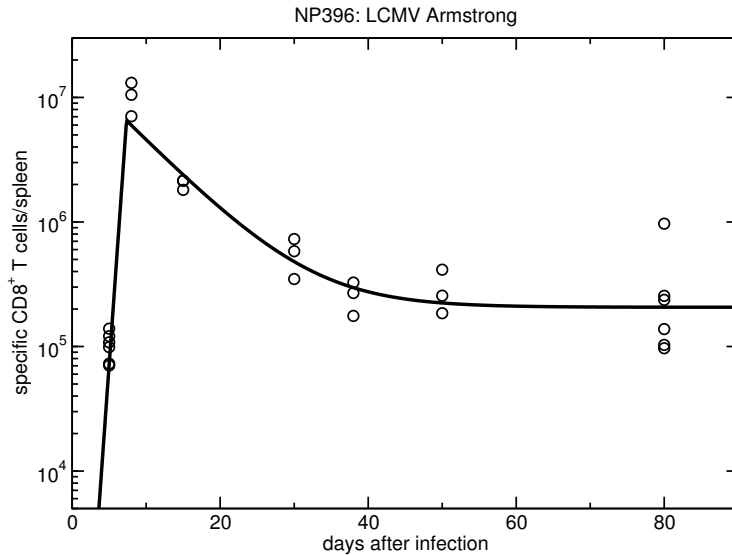Immunodominant CD4$^+$ (a) and CD8$^+$ (b) immune responses.

Acute and chronic LCMV: same GP33 epitope

Data: John Wherry (J.Virol. 2003); modeling Christian Althaus

In chronic infection we find an earlier peak and a faster contraction.

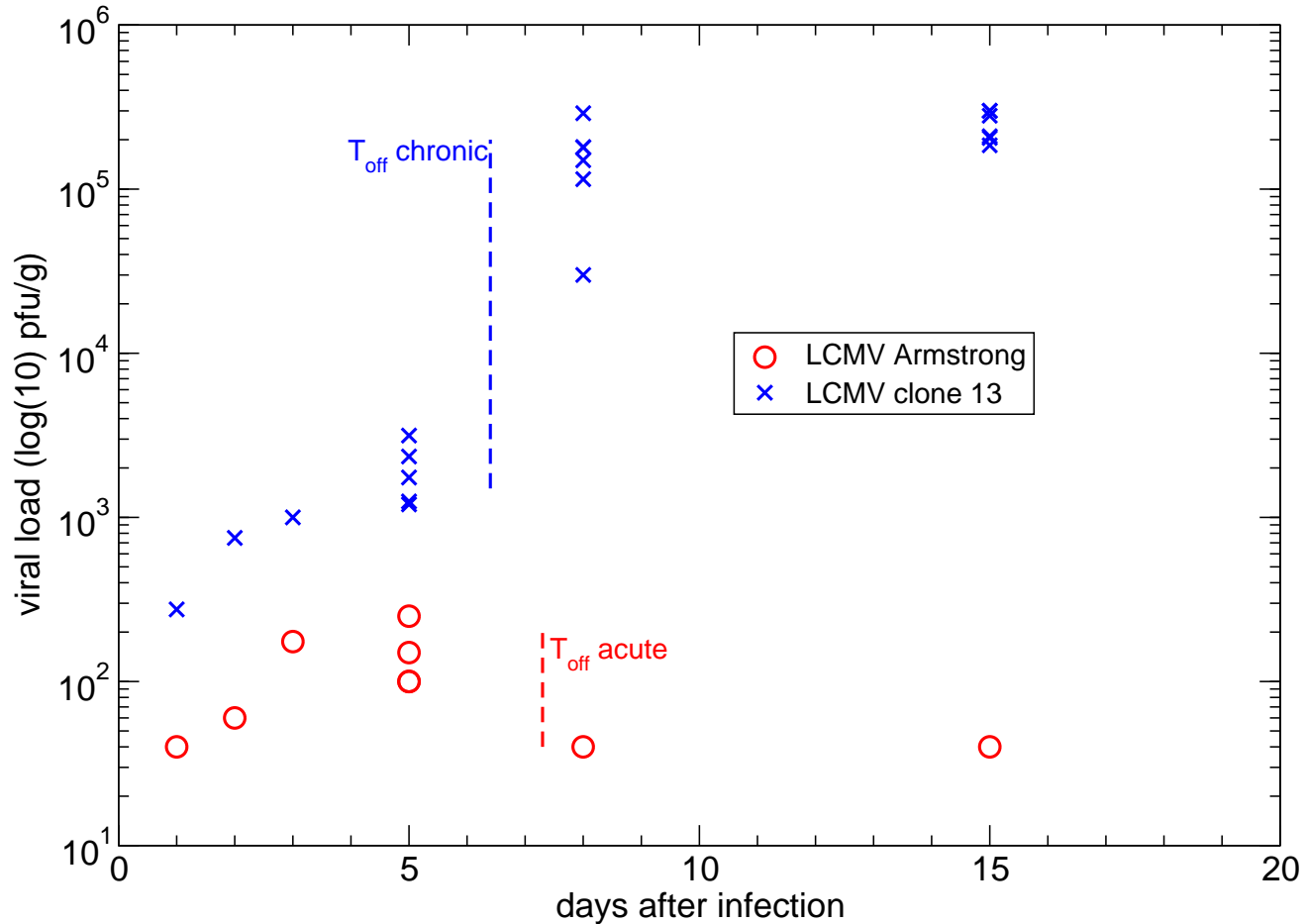# Acute and chronic LCMV: co-dominant NP396 epitope

A lot more contraction: shift of immunodominance

Mechanism very different
- are the effector/memory cells fully functional?
- what are the rules at the end of the contraction phase

Viral load: LCMV Armstrong and clone 13

Data: John Wherry (J.Virol. 2003); Picture: Christian Althaus

2nd example: Vaccination to HIV/AIDS

- vaccines successfully boost CD8$^+$ T cell responses
- we know that CD8 response is very important
$\rightarrow$ depletion expts, HLA, immune escape
- vaccinated monkeys nevertheless have no sterilizing immunity and very similar acute phase of infection.
- specific CD8$^+$ T cells do respond: failure not due to immune escape
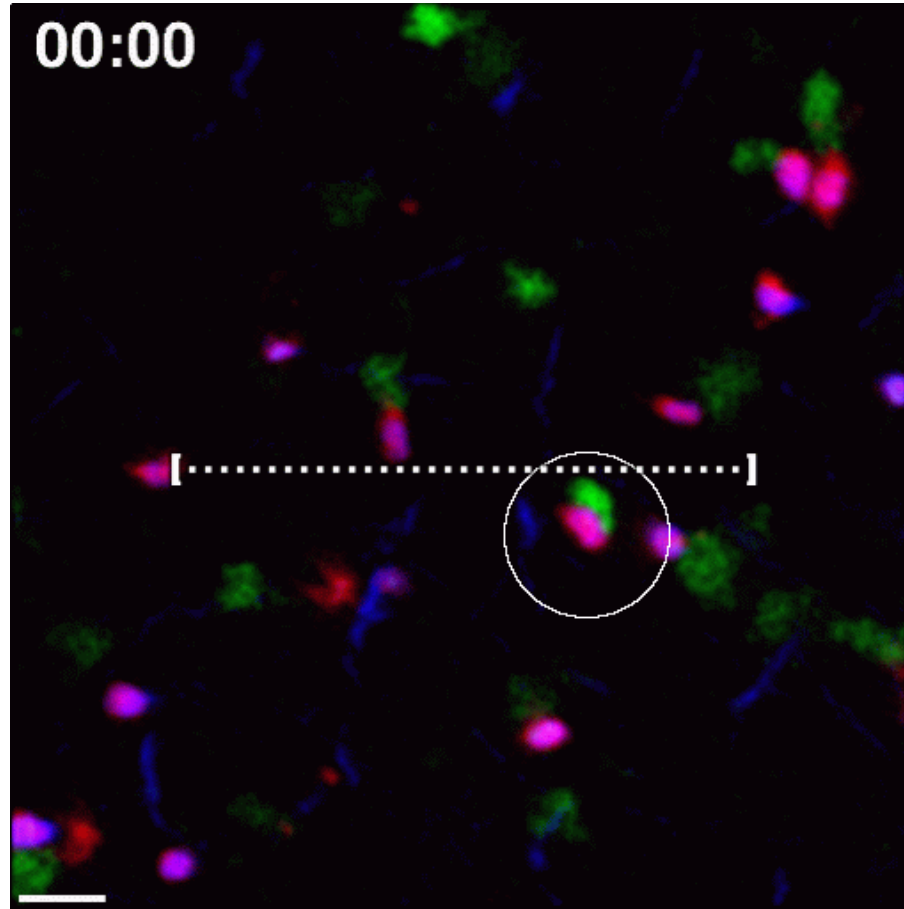
We know little about CTL killing rates
- *in vitro* high E:T ratios required
- HTLV-1: one CTL kills about 5 target cells/d (Asquith.jgv05)
- 2PM movies: killing takes more than 30 minutes

Two photon microscopy
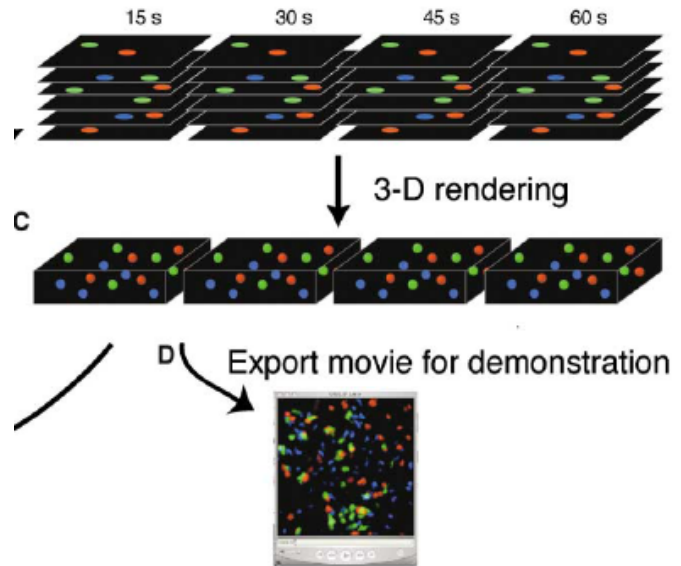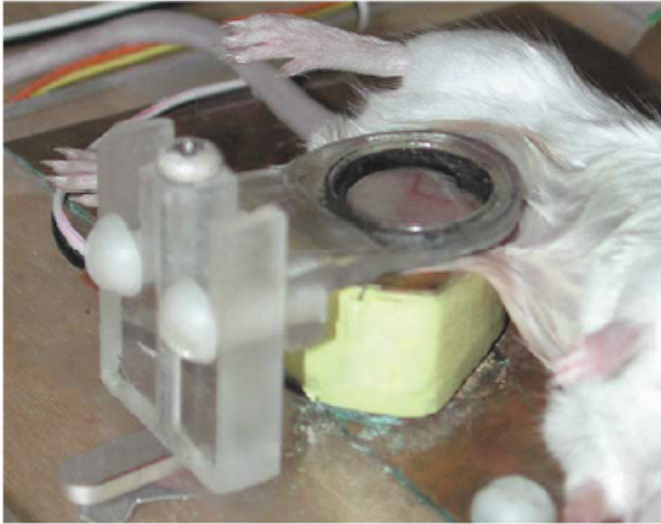
Trace cells *in vivo*!

CTL: green, B cell purple, B cell death: white (52 min).

Movies: Cellular Potts Model (advertisement)

00:00
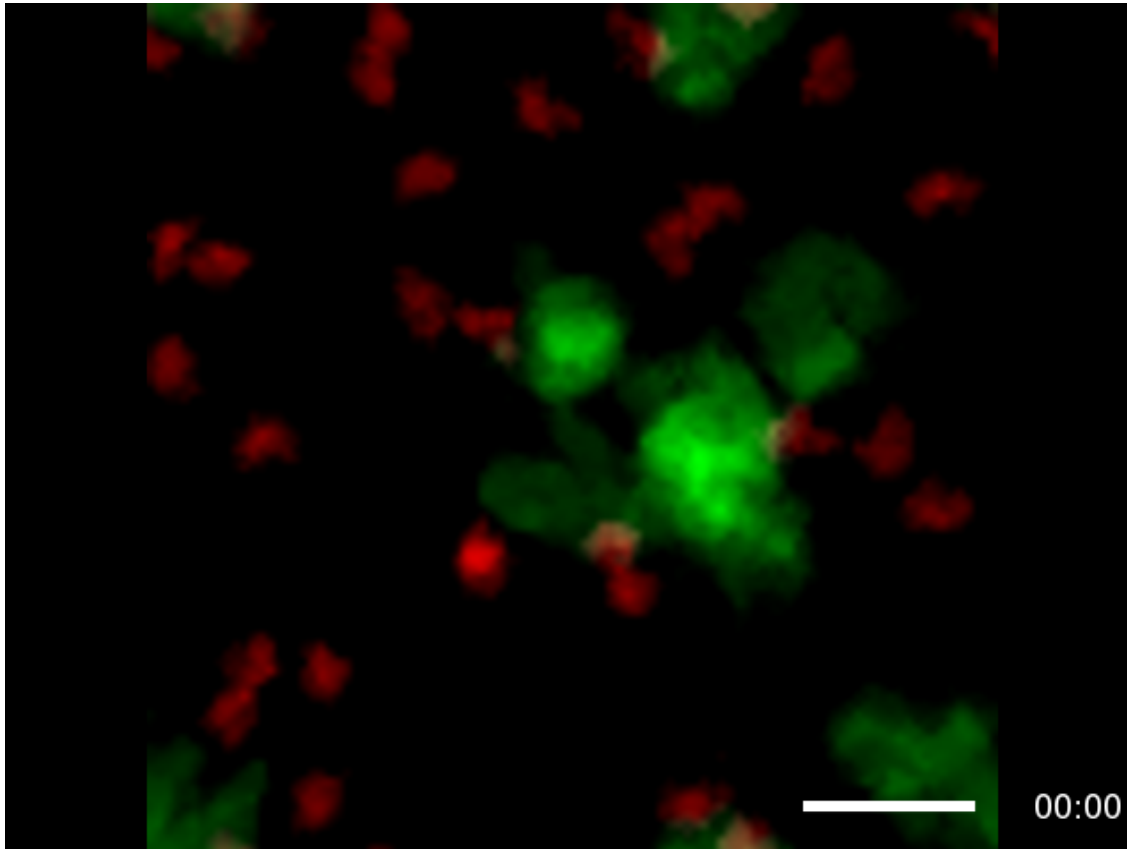
With Joost Beltman and Stan Marée

Data: SIV vaccination fails to affect acute dynamics
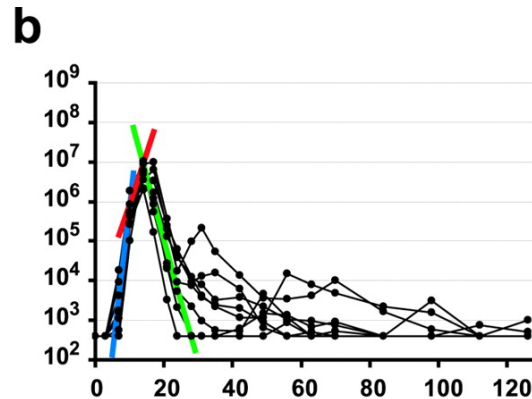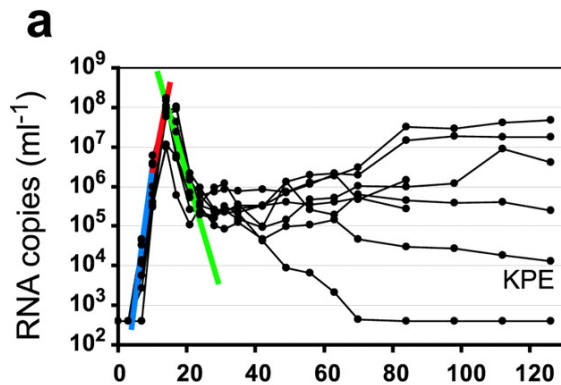
Virus rates:
replication: $1.7\ \mathrm{d^{-1}}$
contraction: $0.7\ \mathrm{d^{-1}}$
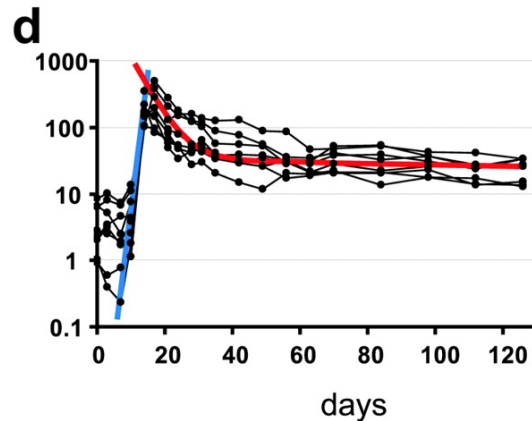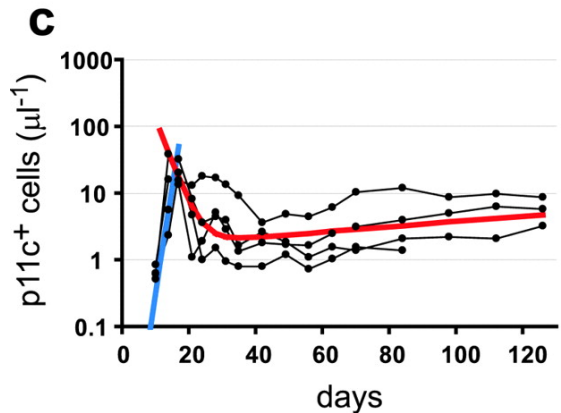
CD8$^+$ T cells:
expansion: $0.9\ \mathrm{d^{-1}}$

Acute SHIV-89.6P response in naive (left) or vaccinated (right) Rhesus monkeys (Data: Barouch.s00, Figure: Davenport.jv04).

Simple model with pathogen growing faster than immune response

$$\frac{\mathrm{d}P}{\mathrm{d}t} = rP - \frac{kPE}{h+P} \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ ,$$

where $r > \rho$, can typically not control the pathogen:
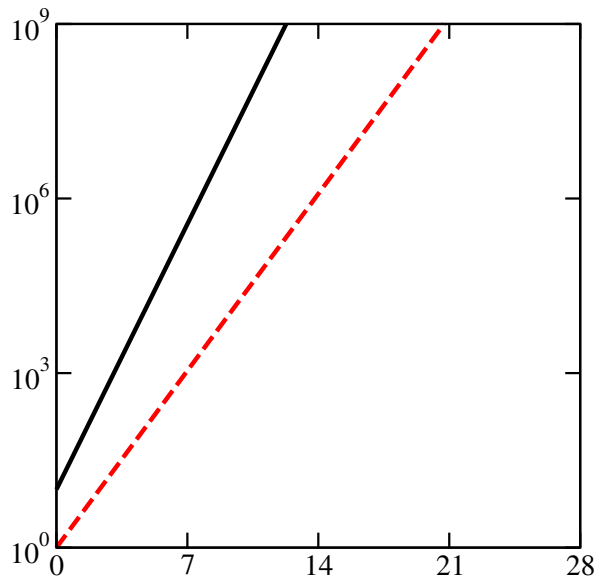
P: pathogen, **E**: response

Time in days

Mathematical explanation

At high pathogen densities the model

$$\frac{\mathrm{d}P}{\mathrm{d}t} = rP - \frac{kPE}{h+P} \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ ,$$

approaches

$$\frac{\mathrm{d}P}{\mathrm{d}t} = rP - kE \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \ .$$

When P grows faster than E:

$$\frac{\mathrm{d}P}{\mathrm{d}t} > 0$$

See: Pilyugin.bmb00

Per pathogen, per infected cell, the killing rate approaches the Effector:Target ratio: $-kE/P$.

Control when pathogen growth limited at high density

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \frac{rP}{1+\epsilon P} - \frac{kPE}{h+P} \quad \text{and} \quad \frac{\mathrm{d}E}{\mathrm{d}t} = \rho E \;,$$
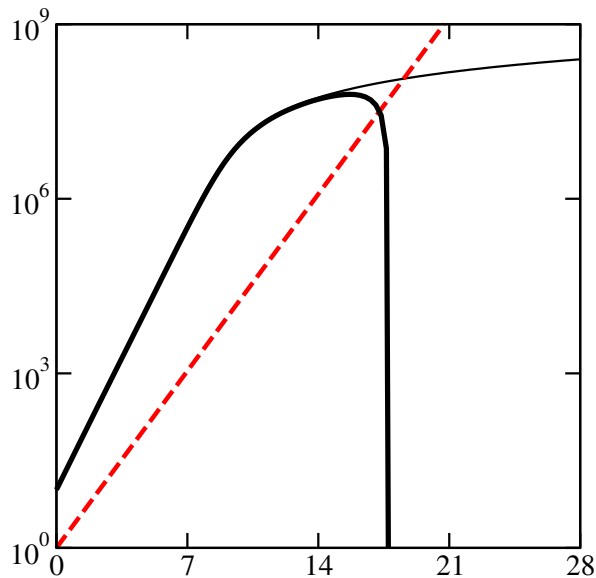
Time in days

P: pathogen, E: response

P: pathogen in absence of response

SIV parameters: $r = 1.5$ d^{-1}, $\rho = 1$ d^{-1}, $k = 5$ d^{-1}.

Interpretation

- Immune control only when E:T ratio is sufficiently large
- When pathogen grows faster than immune response this is never achieved.
- Early innate control, or target cell limitation, is required for cellular immune control
- antibody response *can* catch up with fast pathogen

CTL only control infections that are already controlled

Mechanistic statement:

cell-to-cell contacts → high E:T ratio → failure.

Recruitment takes longer after vaccination
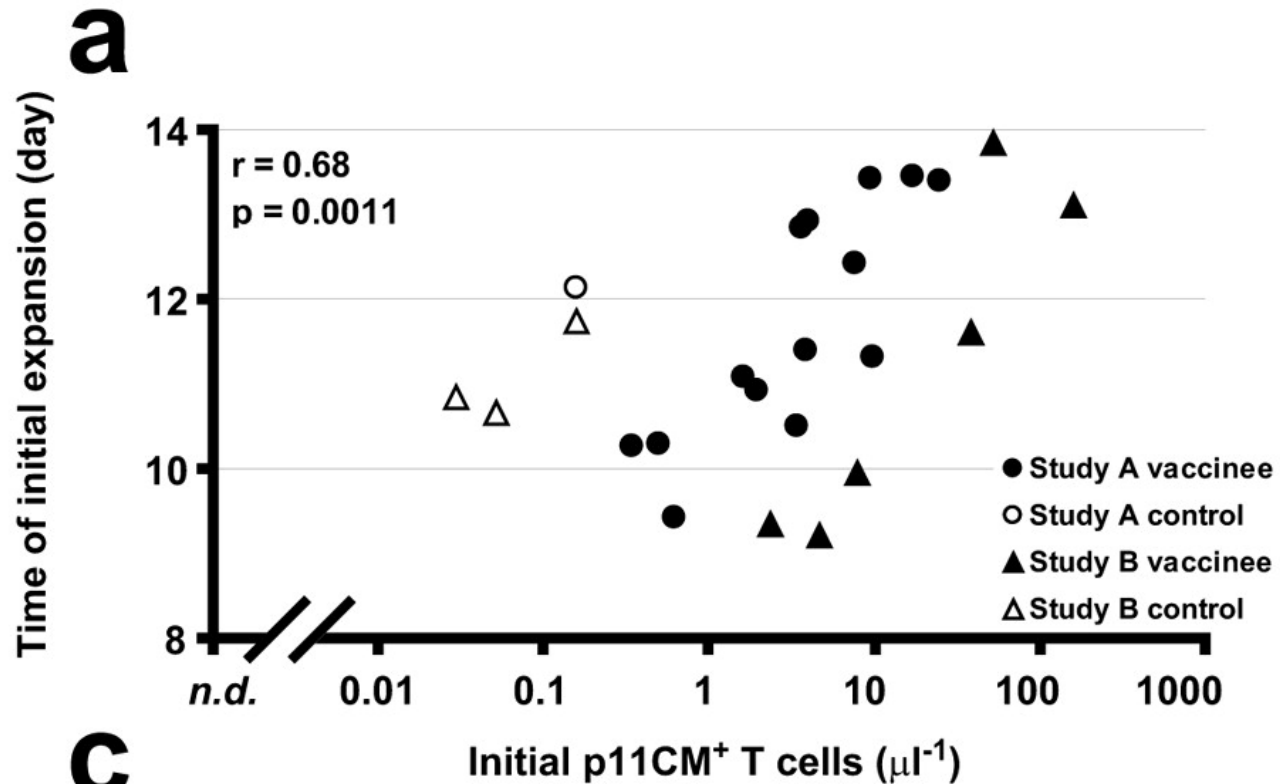
Data: Shiver.n02, Figure: Davenport.jv05

Model with competitive recruitment of memory cells

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{rV}{1 + \epsilon I} - dI - \gamma I \ ,$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \gamma I - \delta P - \frac{kEP}{h_k + P + E} \ ,$$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -\frac{aNP}{h_a + N + P} \ ,$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \frac{aNP}{h_a + N + P} + \frac{mEP}{h_m + E + P} - d_E E \ ,$$

where $V = pP$ is the quasi-steady-state viral load.

Vaccination in model with memory T cells
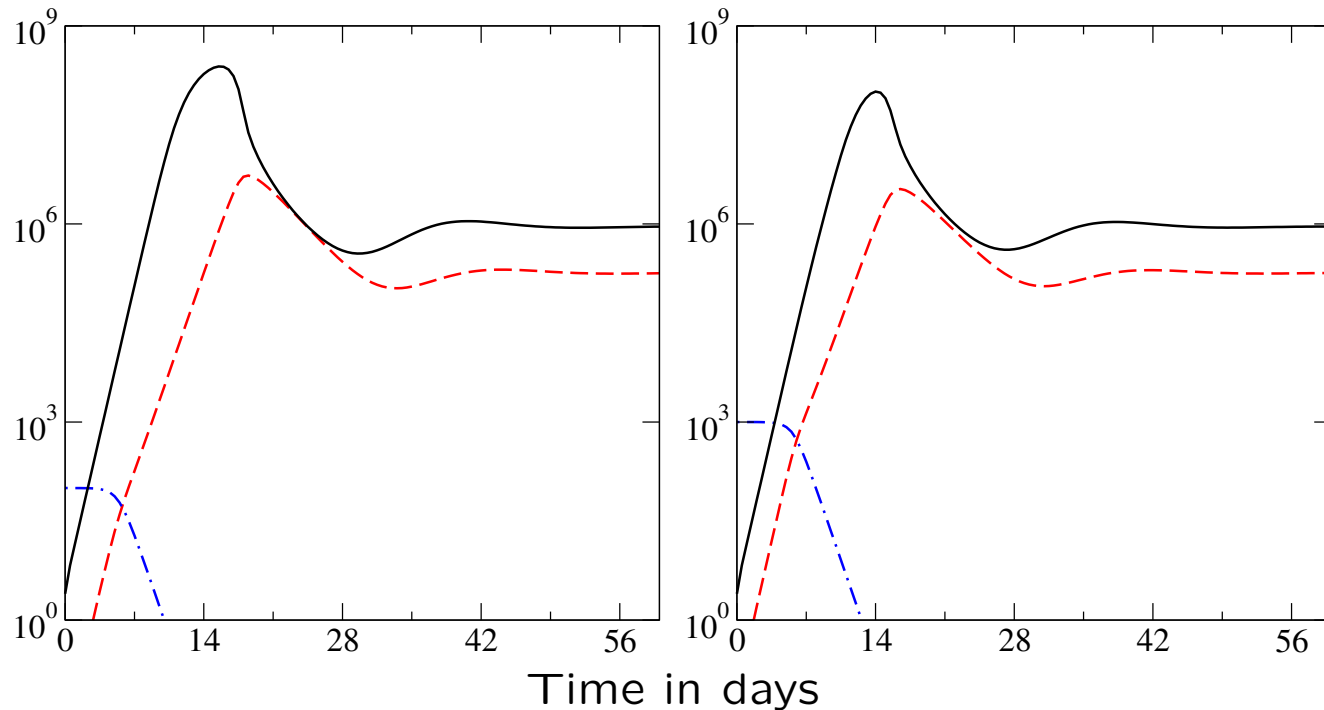
Starting with 10^2 or 10^3 memory CD8$^+$ T cells gives lower peak but similar up and down-slope rates.

SIV parameters: $r = 1.5$ d^{-1}, $\rho = 1$ d^{-1}, $k = 5$ d^{-1}.

Starting with very many memory T cells
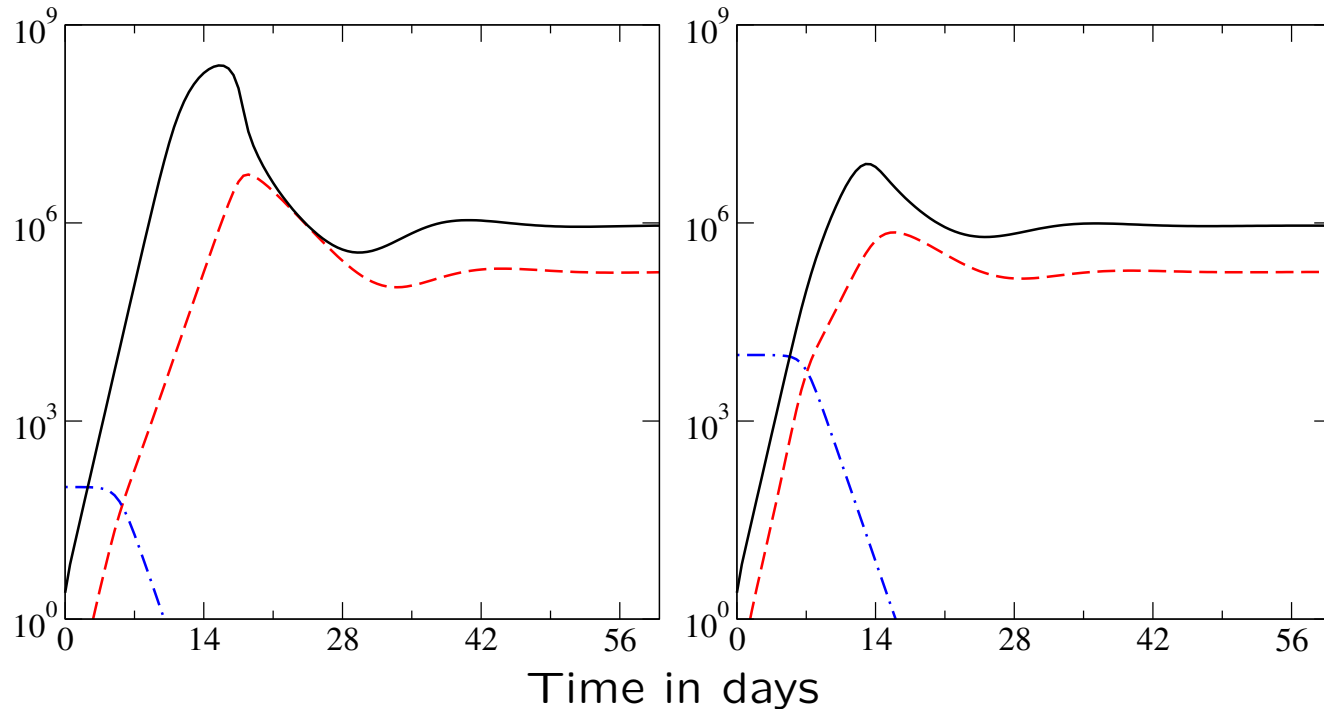
Initial viral replication rate is same, downslope similar, but peak is clearly blunted.

Same SIV parameters: $r = 1.5$ d^{-1}, $\rho = 1$ d^{-1}, $k = 5$ d^{-1}.

Numbers game

- CTL kill only a handful of target cells d^{-1} (2PM)
- in HIV$^+$ human patients 10% specific cells in blood
$\rightarrow 0.1 \times 10^{11} = 10^{10}$ HIV specific CD8$^+$ T cells
- in healthy CMV$^+$ human also 10% specific CD4$^+$ and CD8$^+$ memory T cells, i.e., also 10^{10} cells (Louis Picker)
$\rightarrow$ apparently this many effector cells are required to control set-point viremia in CMV and HIV

It takes time to grow 10^{10} CD8$^+$ effector/memory T cells from initially small precursor populations

CTL can only control after pathogen has slowed down?

CD8$^+$ T cell vaccination in HIV will remain a failure

Short lived (cross-reactive) memory

- although CTL numbers were boosted: no protection
→ effector response was too late and too little
- T cell memory response typically require re-expansion
- effector cells in local tissues relatively short lived
→ African sex workers contracted HIV after break
→ CTL persisting in airways after influenza infection would account for a cross-reactive memory waning on a time scale of months (Tjibbe Donker & Vitaly Ganusov)

Simple immune response models: do we need ODEs?
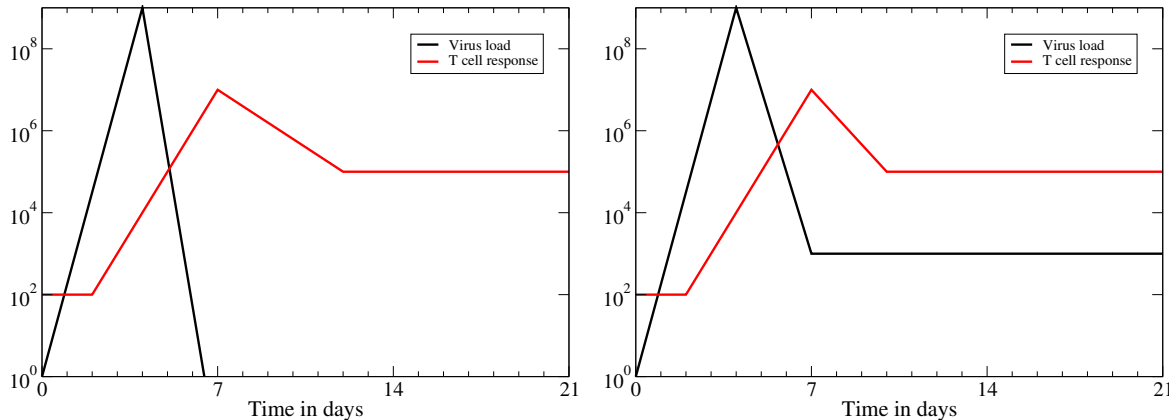
Acute infection requires $3 + 5$ parameters and chronic $4 + 5$ parameters only. Much less than any ODE model.

To know infectivity we need pathogen load parameters only (3–4); to appreciate memory, one would also need immune response parameters.

What parameters are influenced **most** by host variability?

Discussion

Mechanistic or statistical description of immune response?

Which parameters are influenced most by host variability?

Other questions?

Total quasi steady state assumption

For the general scheme

$$E_u + P_u \leftrightarrow C \rightarrow E_u + P_d \ ,$$

with the conservation equations

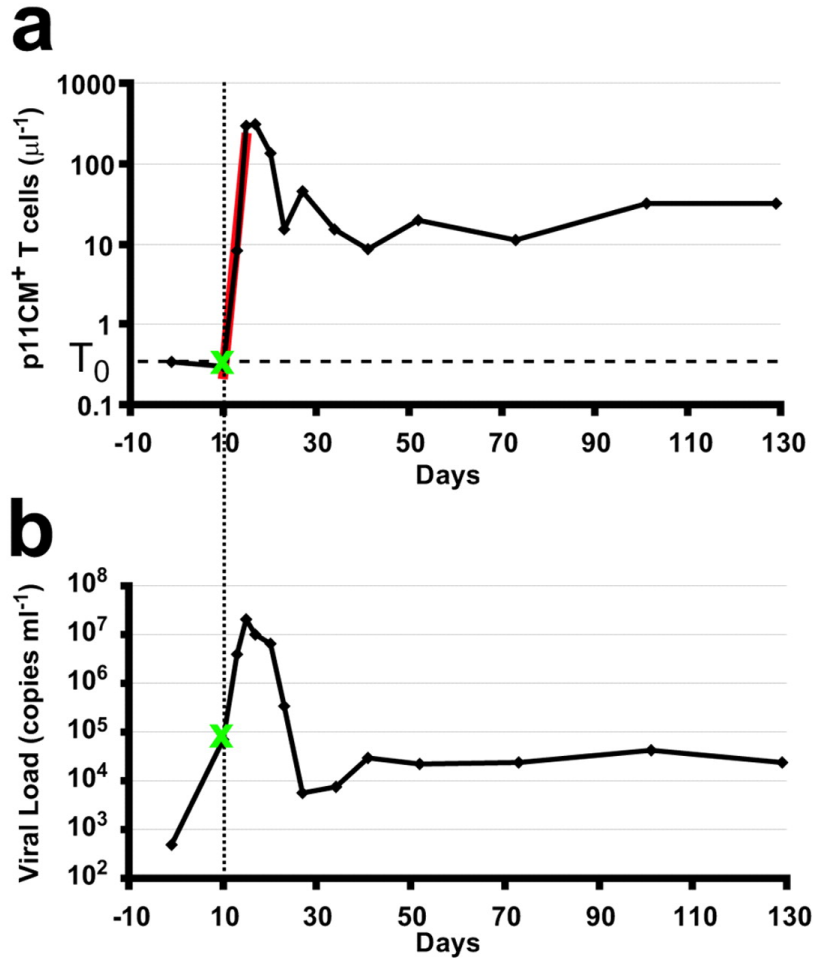$$E = E_u + C \quad \text{and} \quad P = P_u + C$$

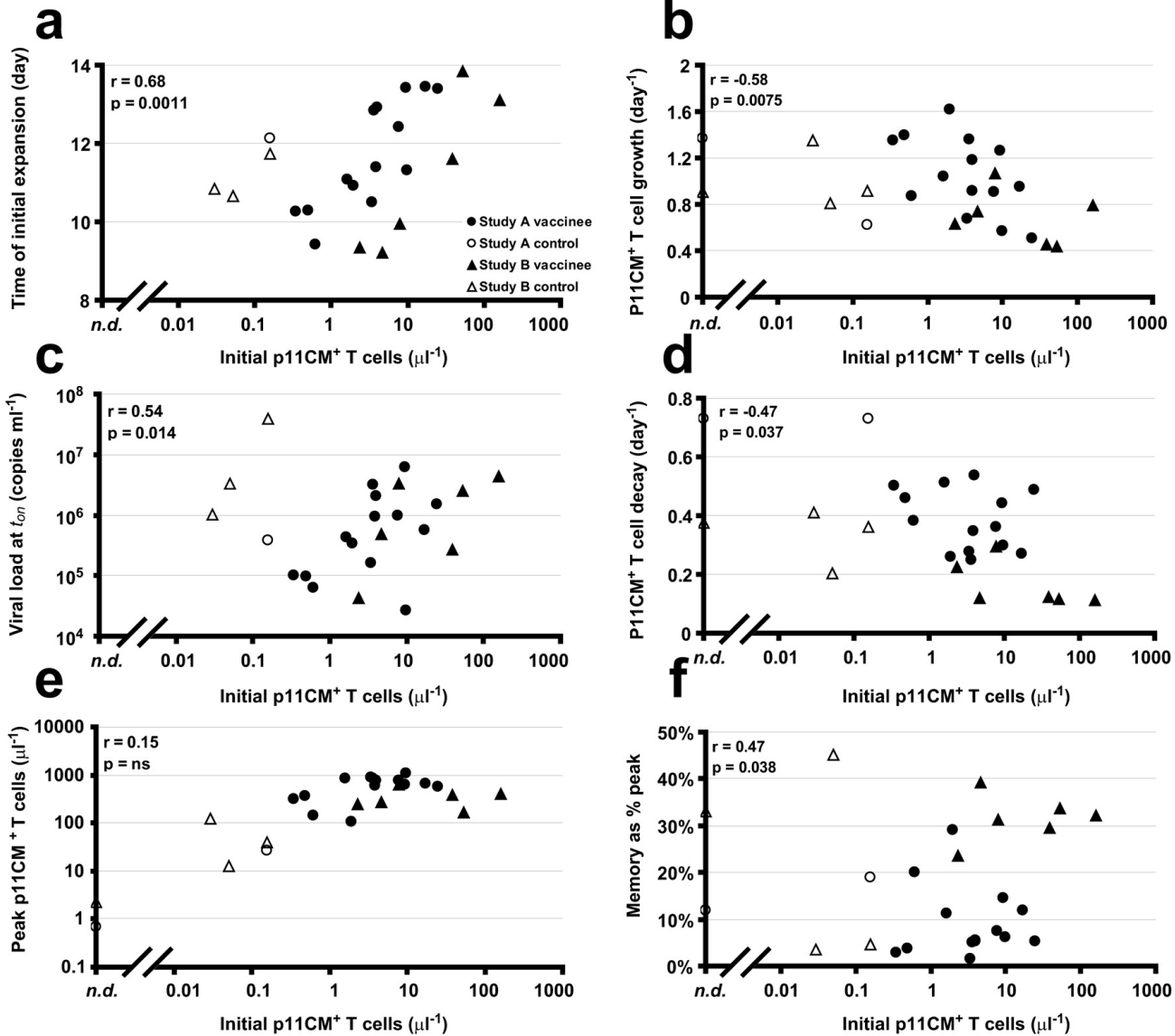one can make the tQSSA $dC/dt = 0$ and obtain

$$C \simeq \frac{v_{\mathsf{max}} E P}{K + E + P}$$

where v_{max} is the maximum reaction rate, and K is the Michaelis Menten constant.
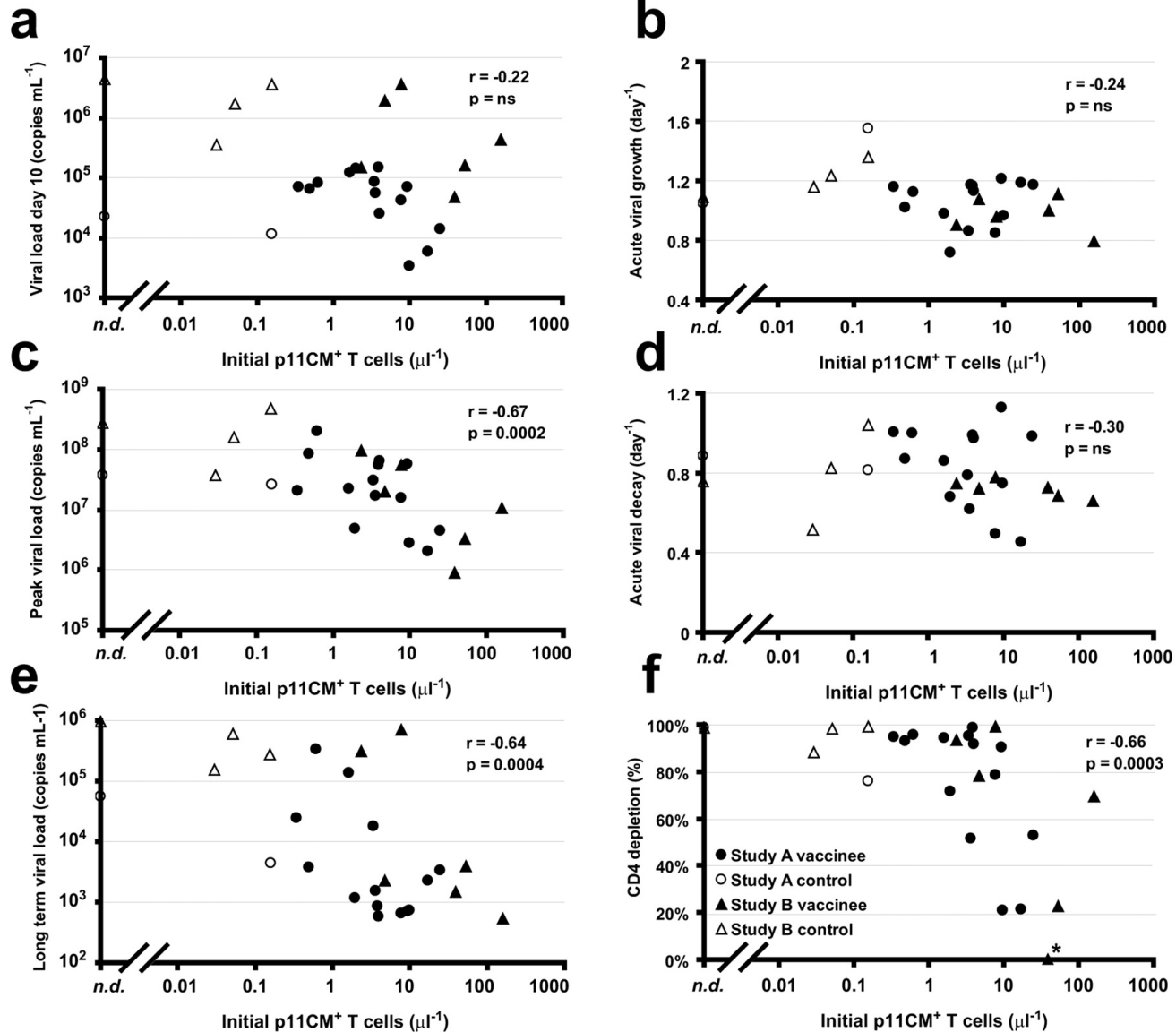
When $P \gg K + E$, the killing rate of an infected cell approaches the E:T ratio: $v_{\mathsf{max}} E / P$

Data: Shiver.n02, Figure: Davenport.jv05

a Time of initial expansion (day) vs Initial p11CM⁺ T cells (μl⁻¹); r = 0.68, p = 0.0011; legend: Study A vaccinee (●), Study A control (○), Study B vaccinee (▲), Study B control (△)

b P11CM⁺ T cell growth (day⁻¹) vs Initial p11CM⁺ T cells (μl⁻¹); r = -0.58, p = 0.0075

c Viral load at t_{on} (copies ml⁻¹) vs Initial p11CM⁺ T cells (μl⁻¹); r = 0.54, p = 0.014

d P11CM⁺ T cell decay (day⁻¹) vs Initial p11CM⁺ T cells (μl⁻¹); r = -0.47, p = 0.037

e Peak p11CM⁺ T cells (μl⁻¹) vs Initial p11CM⁺ T cells (μl⁻¹); r = 0.15, p = ns

f Memory as % peak vs Initial p11CM⁺ T cells (μl⁻¹); r = 0.47, p = 0.038

Data: Shiver.n02, Figure: Davenport.jv05

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Data: Shiver.n02, Figure: Davenport.jv05