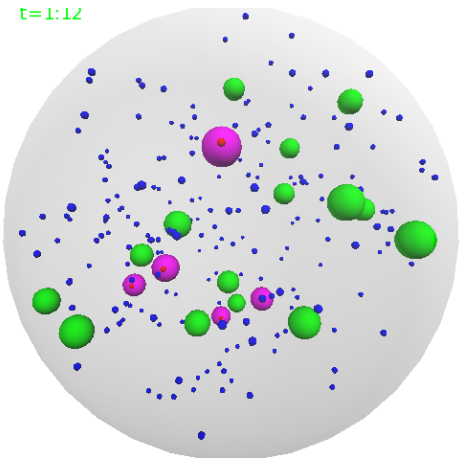
Mathematical Immunology at the molecular, cellular and population scales

Currie, Day, Reynolds and Stirk (PhD)
Palmer, Bousso, Celli, Amado and Freitas (experiments)
van den Berg, Castro, Lythe and CMP (models)



KITP (UCSB)
Quantitative Immunology
10th of December 2012

Carmen Molina-Paris, Univ. of Leeds

Outline

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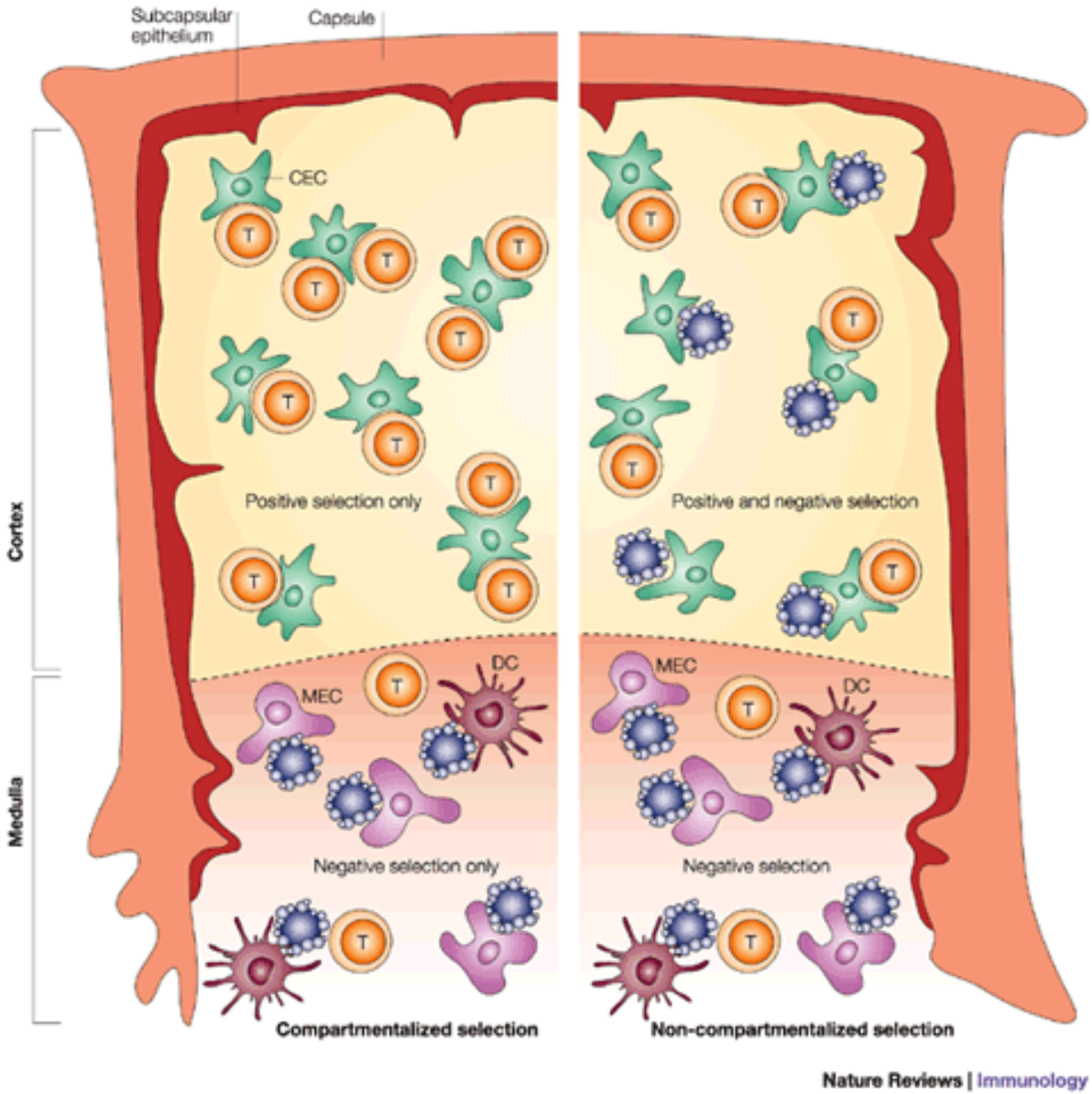
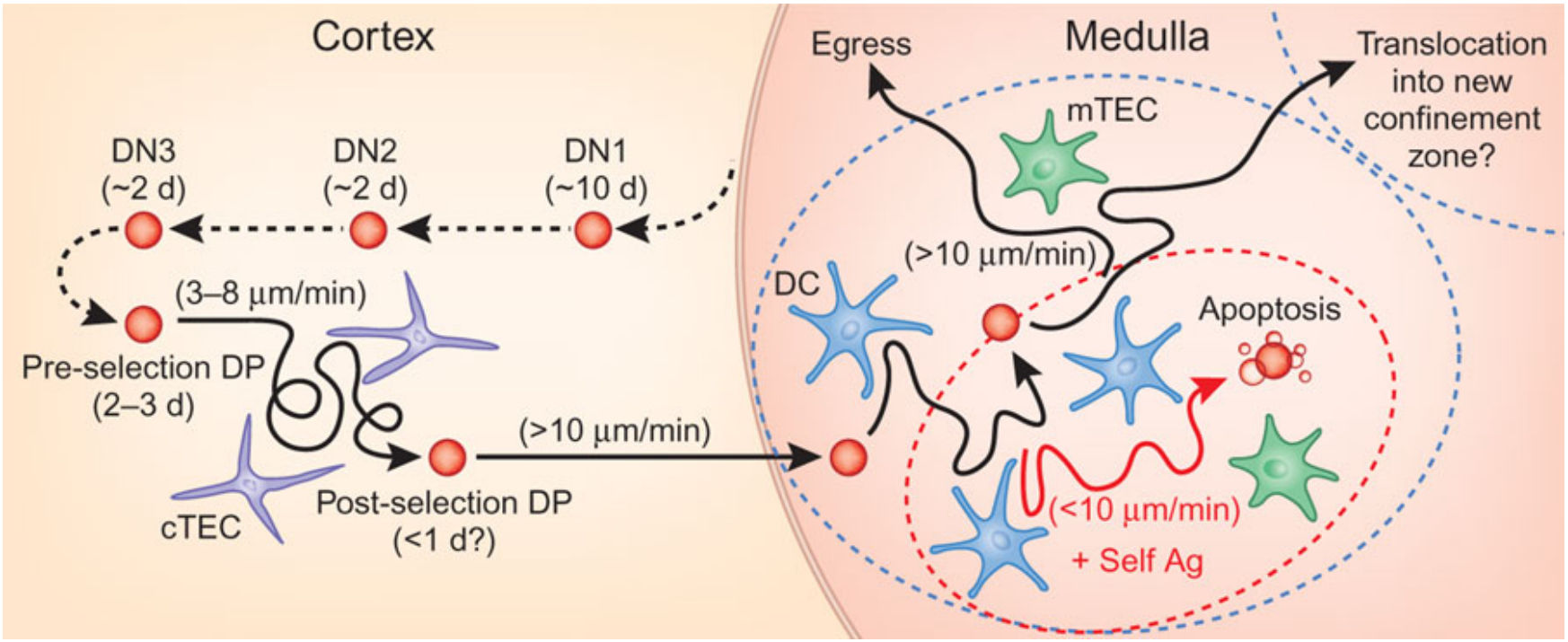
The T cell receptor and T cell development





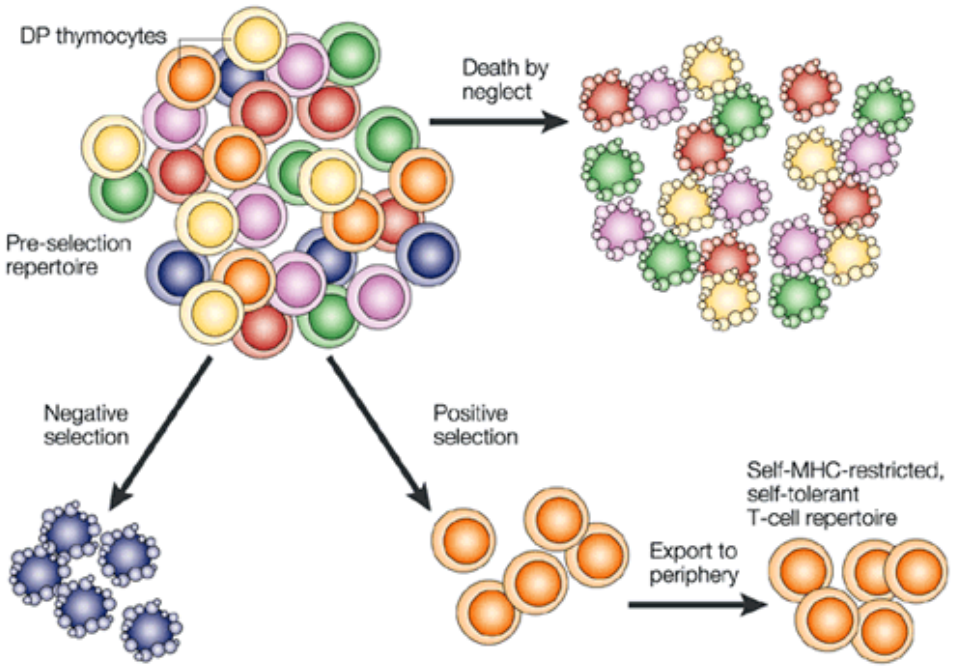
T cell development in the thymus: space and time

Developing T cells spend at most two weeks in the thymus.

An exquisitely stringent test: less than 5% chance to pass

T cells interact with special cells that present ligand (that can bind to TCR) on their surface:

- if no TCR signal $\Rightarrow$ death by neglect,
- if strong TCR signal $\Rightarrow$ death by apoptosis (negative selection), and
- if intermediate TCR signal $\Rightarrow$ export to the periphery (positive selection).



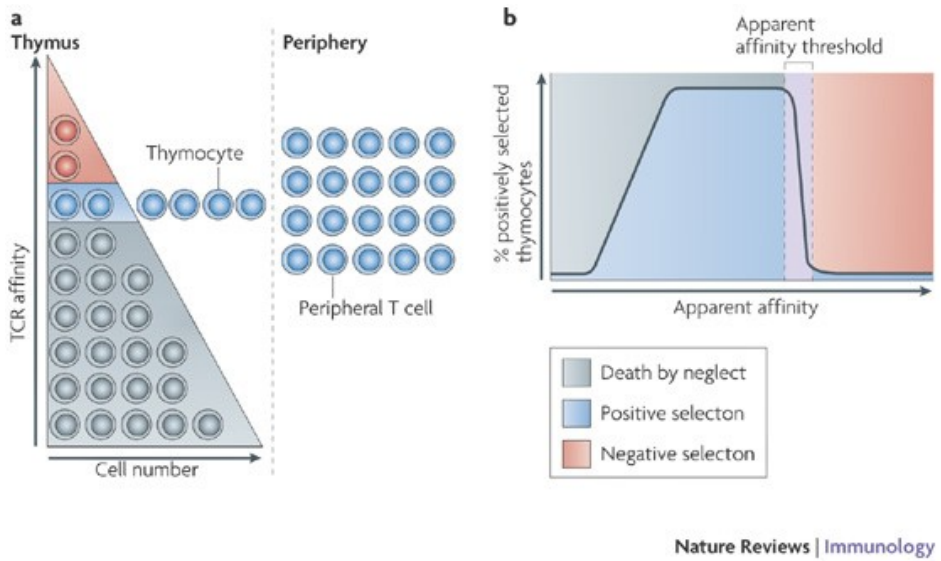
Problem A: Time scales of T cell responses **(molecular)**

Where are we now?

- Timescales: TCR-pMHC binding (seconds) and TCR-mediated signal transduction (hours).
- TCR-pMHC engaged for sufficiently long to initiate the signalling cascade, resulting in productive signal transduction.
- T cells can integrate signals: counting devices are at work in T cells to allow signal accumulation, decoding and translation into biological responses.

Valitutti, Coombs and Dupré.
The space and time frames of T cell activation at the immunological synapse.
FEBS Letters, **584** 4851–4857 (2010).

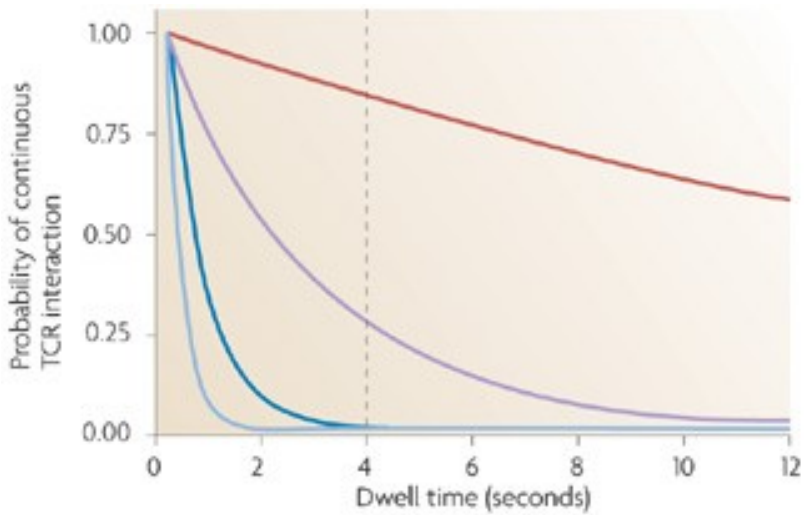
Affinity thresholds in negative selection



Naeher, Daniels, Hausmann, Guillaume, Luescher and Palmer.
A constant affinity threshold for T cell tolerance.
The Journal of Experimental Medicine **204** 2553–2559 (2007).

Probability of a productive binding event

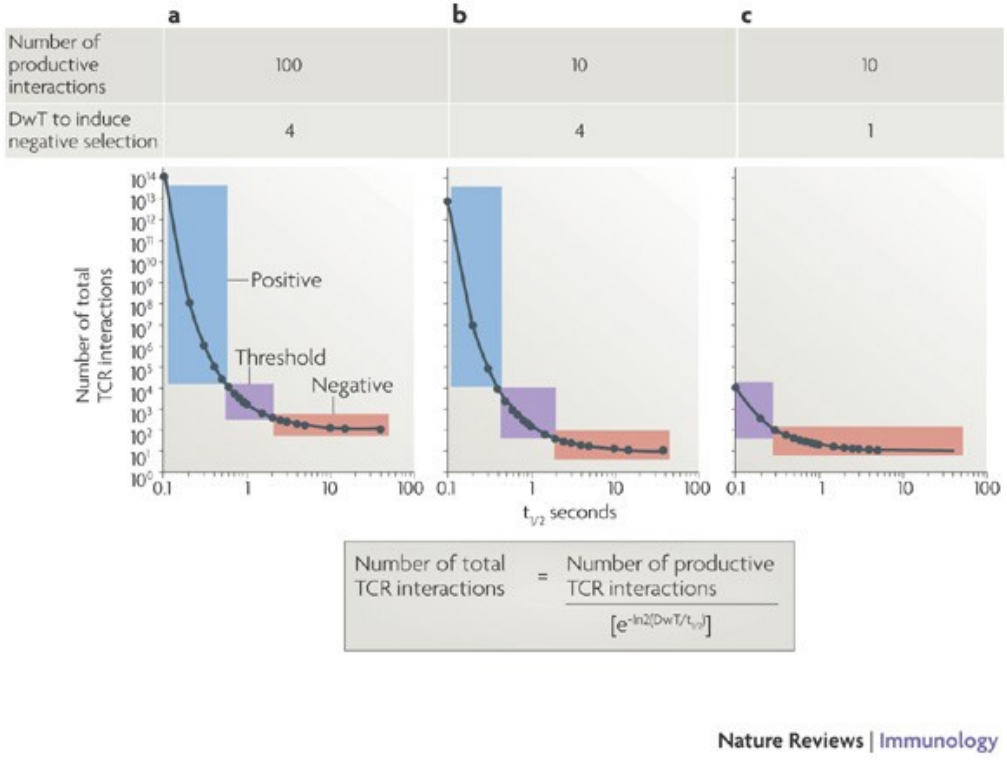
Palmer, E. and Naeher, D.
Affinity threshold for thymic selection through a T cell receptor–co-receptor zipper.
Nature Reviews Immunology **9** 207–213 (2009).



Probability of continuous TCR interaction $= e^{-\ln 2(DwT/t_{1/2})}$

	Half-life ($t_{1/2}$)	Probability of binding for 4 seconds	Outcome
—	15 sec	0.83	Negative-selection signalling
—	2 sec	0.25	Threshold signalling
—	0.5 sec	4×10^{-3}	Positive-selection signalling
—	0.2 sec	$\sim 10^{-6}$	Positive-selection signalling

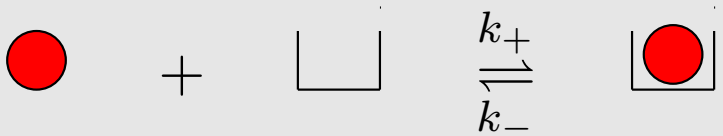
Counting productive binding events



Palmer, E. and Naeher, D.
Affinity threshold for thymic selection through a T cell receptor–co-receptor zipper.
Nature Reviews Immunology **9** 207–213 (2009).

Stochastic mathematical model

- TCR and pMHC binding



- Palmer's hypothesis: affinity threshold $\Rightarrow$ hierarchy of ligands for a given TCR and ligand discrimination.
- **H:** T cell responses take place once a given number of TCRs, N, has been bound to ligand, for at least a time, τ, each.
- First passage time (FPT) analysis implies:

$$T(N,\tau) = \tau + \frac{N\ \mathrm{e}^{\tau k_-}}{k_+ N_{\mathrm{R}} N_{\mathrm{L}}}\ .$$

- Published work by J. Currie (Royal Society Interface, 2012).

Calculation of mean time to N productive bindings

- Let N' be the mean total number of binding events before the Nth productive one $\Rightarrow$ $N' = \exp(\tau k_{\text{off}})\, N$.
- Let t_n be the time when the nth ligand-receptor complex is formed.

$$\text{FPT}(N,\tau) = \tau + t_{N'} \quad \text{and} \quad T(N,\tau) = \tau + \mathbb{E}(t_{N'}) \,.$$

- Each of the N' times between binding events, $t_{n+1} - t_n$, is exponentially-distributed.
- The time $t_{N'}$ is a sum of exponentially-distributed random times with mean $(k_+ N_{\text{R}} N_{\text{L}})^{-1}$.

$$\mathbb{E}(t_{N'}) = \frac{N'}{k_+ N_{\text{R}} N_{\text{L}}} \quad \text{and} \quad \mathbb{V}(t_{N'}) = \frac{N'}{(k_+ N_{\text{R}} N_{\text{L}})^2} \,.$$

- $T(N,\tau) = \tau + \frac{N\, \mathrm{e}^{\tau k_-}}{k_+ N_{\text{R}} N_{\text{L}}}$.

Experimental data from Ed Palmer's laboratory

TCR and peptide variants

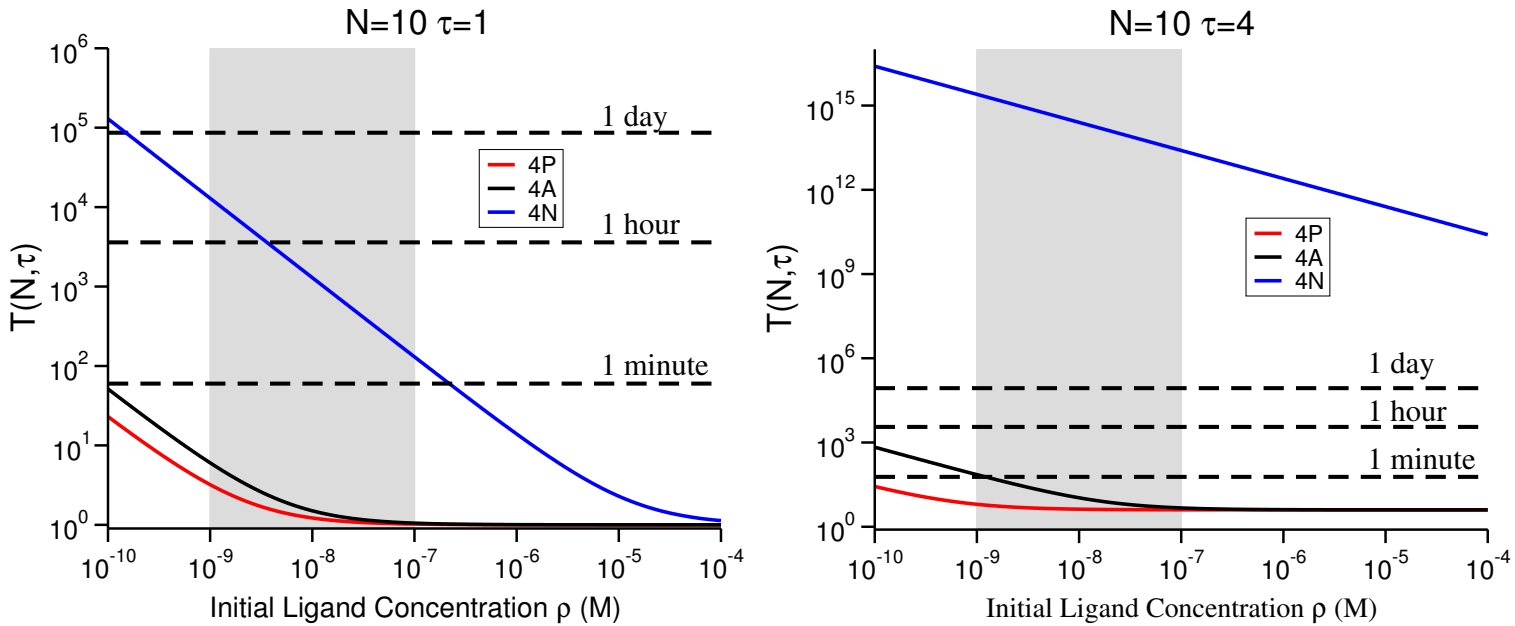
- Transgenic mice: CD8 T cells with T1 TCR.
- SYIPSAEK(ABA)I is the agonist peptide with a proline residue at position 4 (4P).
- Two peptide variants: alanine (4A) and asparagine (4N).

Cell type	Ligand	K_D (M)	$t_{1/2}$ (s)
SP thymocyte	4P at 37°C	1.1×10^{-7}	41
SP thymocyte	4A at 37°C	5.5×10^{-6}	0.8
SP thymocyte	4N at 37°C	5.8×10^{-5}	0.08

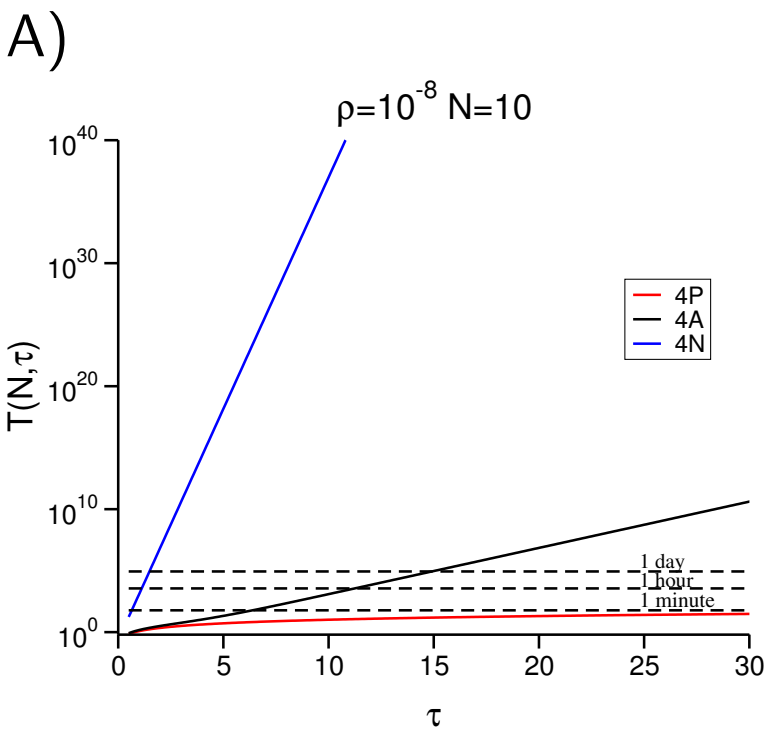
Luescher, I.F., Cerottini, J.C. and Romero, P.
Photoaffinity labelling of the T cell receptor on cloned cytotoxic T lymphocytes by covalent photoreactive ligand.
Journal of Biological Chemistry **8** 5574 (1994).

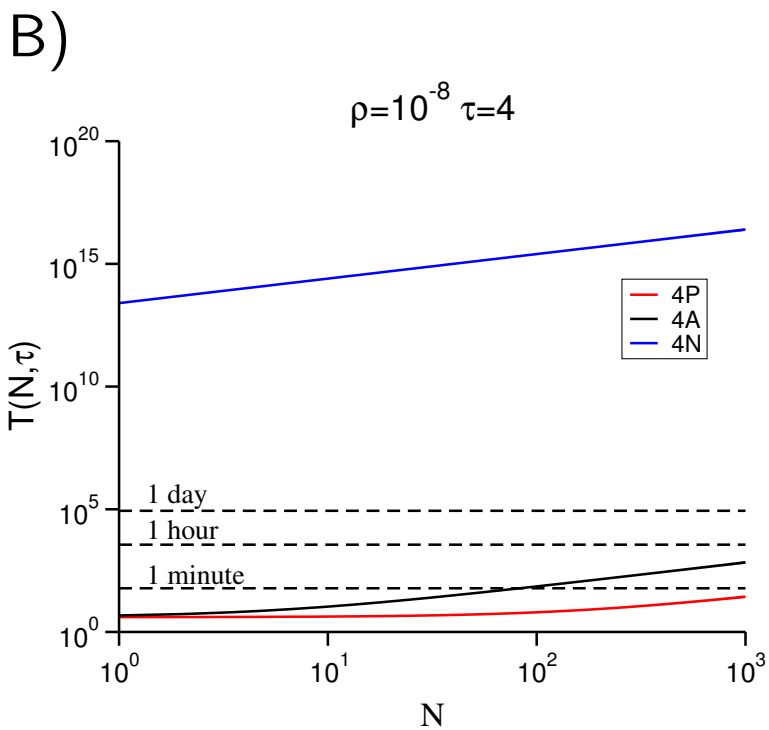
Implications of stochastic model: hierarchy of ligands

- Negative selecting ligand —
- Threshold ligand —
- Positive selecting ligand —



Implications of stochastic model: N and τ





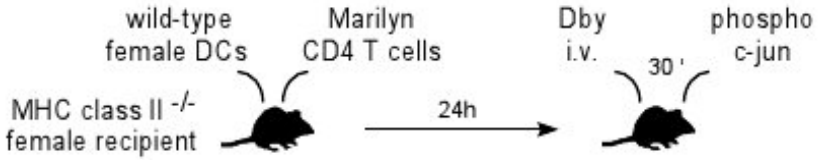
Outline

Problem B: APC-T cell interactions in the lymph nodes **(cellular)**

Quantifying the probability of T cell activation

1. Adaptive immune responses are initiated through encounters between rare naive Ag-specific T cells and Ag-bearing dendritic cells (DCs).
2. The number of Ag-presenting DCs in the draining lymph node (LN) should influence the chance that rare Ag-specific T cells become activated.
3. Using two experimental approaches and one in silico model, we measured the probability of T cell-DC encounters as a function of the number of DCs in the LN.

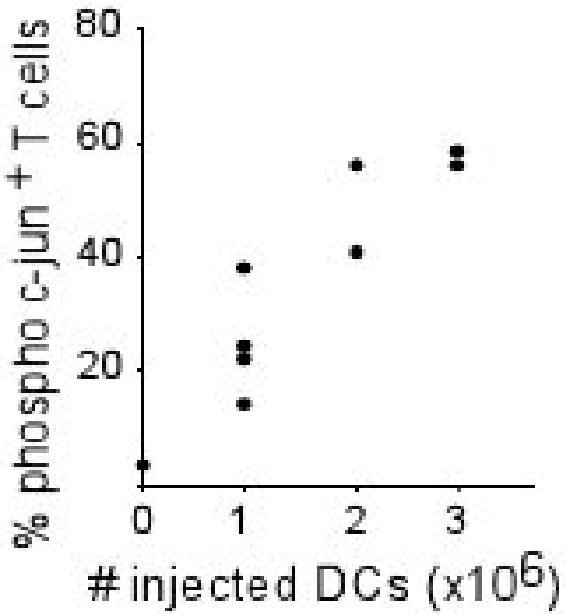
Experiments carried out at Pasteur (Bousso, Celli and Müller)

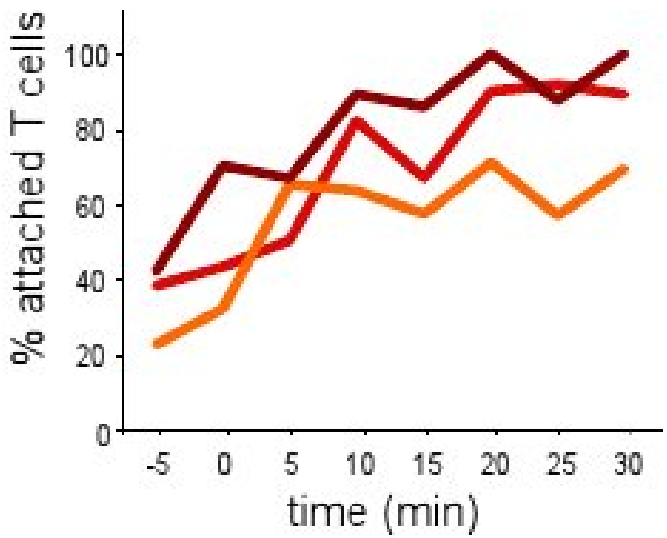


1. MHC class II$^{-/-}$ recipients received GFP^{+} DCs in the footpad.
2. Marilyn TCR CD4^{+} T cells, labelled with SNARF, injected intravenously.
3. After 24 hours Dby peptide was injected intravenously, resulting in Ag presentation in the draining LN by transferred DCs within minutes of peptide injection.

Quantifying the probability of T cell activation (experiments)

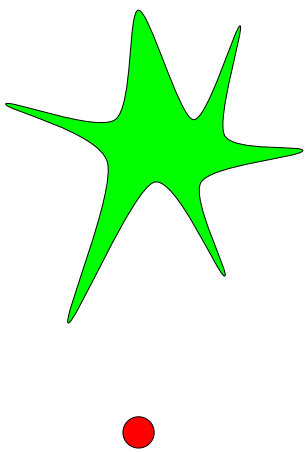
1. Measure T cell-DC encounter probability with two approaches.
2. Phosphorylated c-jun staining after 30 minutes.
3. Two-photon imaging during and after injection of peptide.

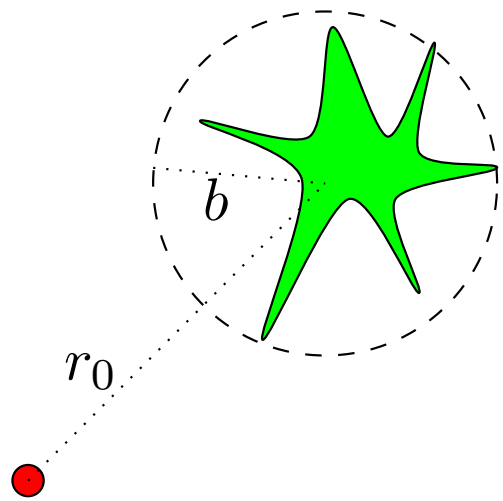




Cell-cell encounters confined to a volume

1. Take a DC to be stationary and with effective radius b.
2. Approximate a T cell by a diffusing point particle with diffusivity D.





Cell-cell encounters confined to a volume

1. Take a DC to be stationary and with effective radius b.
2. Approximate a T cell by a diffusing point particle with diffusivity D.

Mean time to collide

inside a sphere of radius R is

$$\frac{1}{3}\frac{R^3}{bD}$$

as $\frac{b}{R} \to 0$.

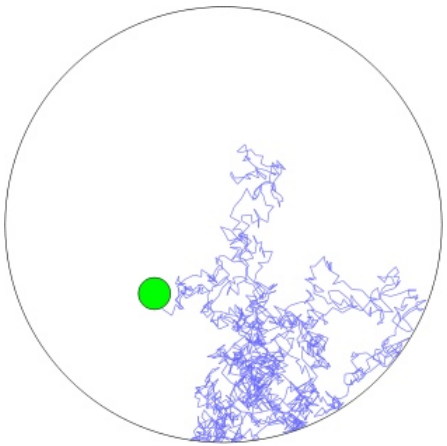


Figure: Path of Brownian motion, reflected inside the large sphere, run until it hits a spherical target (green).

Cell-cell encounters confined to a volume

1. Take a DC to be stationary and with effective radius b.
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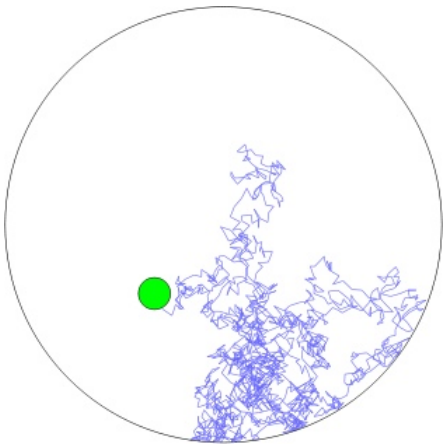


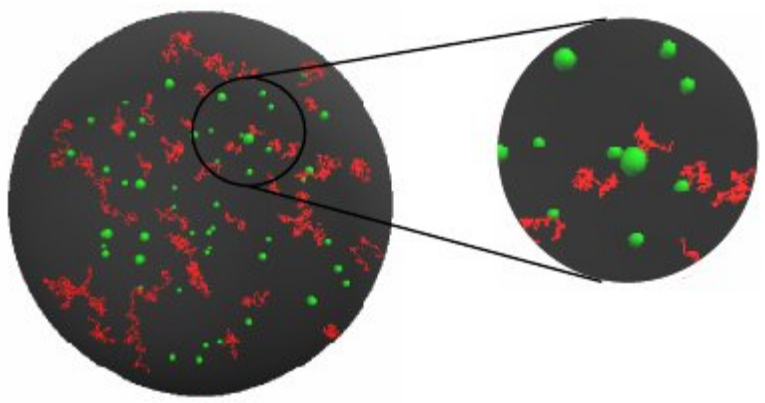
Let $\alpha = \frac{3Db}{R^3}$.

3. We assume:

$$\mathbb{P}(\text{T cell does not encounter DC before } t) = \mathrm{e}^{-\alpha t}.$$

Cell-cell encounters confined to a volume

1. Take a DC to be stationary and with effective radius b.
2. Approximate a T cell by a diffusing point particle with diffusivity D.



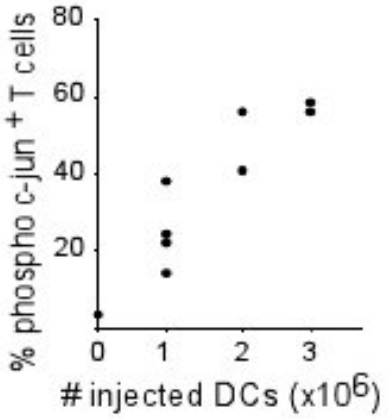
3. If there are A DCs, then the probability that one T cell chosen at random does not encounter any of the DCs in time t is assumed to be:

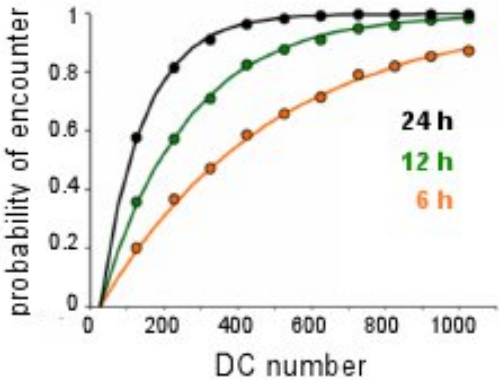
$$\mathbb{P}(\text{T cell does not encounter any DC}) = \mathrm{e}^{-\alpha A t}.$$

4. If there are N T cells then

$$\mathbb{P}(\text{No T cell encounters any DC}) = \mathrm{e}^{-\alpha N A t}.$$

Experiments and theory





From experiment to physiology: mathematical model

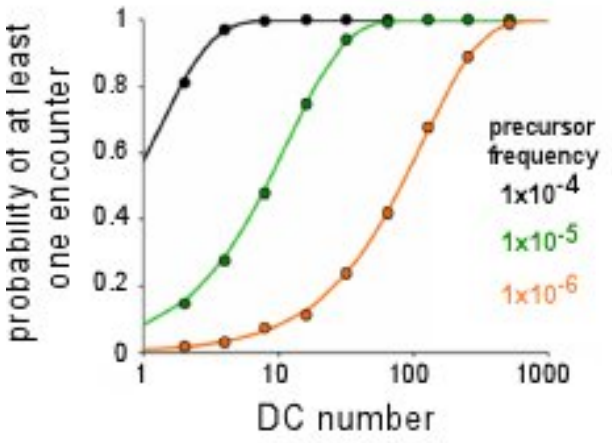
- $\mathbb{P}$(T cell does not encounter any DC) $= \mathrm{e}^{-\alpha A t}$.
- $\mathbb{P}$(T cell encounters at least one DC) $= 1 - \mathrm{e}^{-\alpha A t}$.
- Experiment: $t = 30$ minutes.
- Physiology: $t \simeq 24$ hours.
- Make use of the mathematical model to quantify number of APCs required for T cell activation.

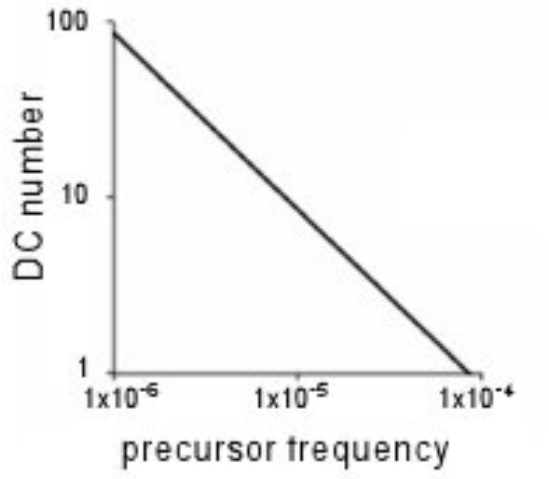
Quantifying the probability of T cell activation (mathematical model)

1. APCs fixed and of effective radius b, T cells move by Brownian motion with diffusion coefficient D and radius of the lymph node is $R \Rightarrow$ the rate of T cell-APC encounter is: $\alpha = \frac{3Db}{R^3}$.
2. The probability that a T cell hits an APC during the imaging period T is $\mathbb{P}_1 = 1 - e^{-\alpha AT}$.
3. The probability that at least one T cell hits an APC during the imaging period T is $\mathbb{P}_2 = 1 - e^{-\alpha ANT}$, with N the number of T cells in the imaging volume at the initial time.
4. The number of APCs that yields a 50% probability of at least one encounter in time t is given by $A^\star = \frac{\log 2}{4\pi Dbtnf_{\text{specific}}}$.
5. The T cell number density in the LN is n and f_{specific} is the precursor frequency.

Quantifying the probability of T cell activation (Blood, 2012)

1. We find that A^* is proportional to $\frac{1}{f_{\text{specific}}}$.





2. The chance for a T cell residing 24 hours in a murine popliteal LN to interact with a DC was 8, 58 and 99% in the presence of 10, 100 and 1000 Ag-bearing DCs.
3. In both mice and humans, we estimate that a minimum of 85 DCs are required to initiate a T cell response when starting from a precursor frequency of 10^{-6}.

Outline

Problem C: Naive T cell homeostasis and maintenance **(population)**

- A protective immune system requires a T cell population that can respond to foreign antigens.
- The host cannot predict the precise pathogen-derived antigens that will be encountered in the future.
- The human mature naive T cell repertoire consists of a constant number of cells ($\approx 10^{11}$) distributed over a large number ($10^7 - 10^8$) of different T cell clonotypes.
- T cells compete for proliferation signals furnished by professional antigen-presenting cells. The immune system guarantees coexistence and persistence of different T cell clonotypes.
- A decline in the size and diversity of the T cell population is a hallmark of the ageing process $\Rightarrow$ T cell clonotype extinction.

Naive T cell homeostasis: mathematical model

Proliferation or cell division event (birth)

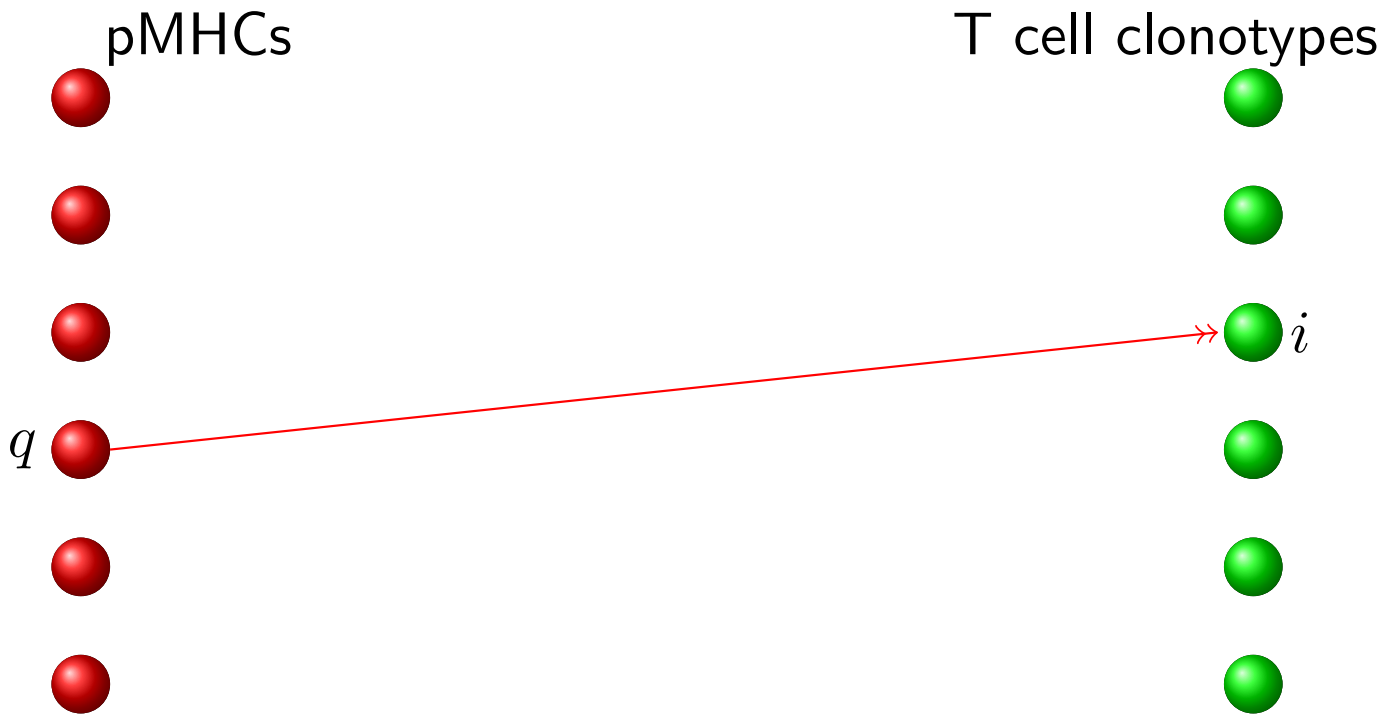
Each pMHC q stimulates at rate γ_q. The stimulus is equally likely to cause one round of cell division in any of the naive T cells capable of recognising it.

Death event

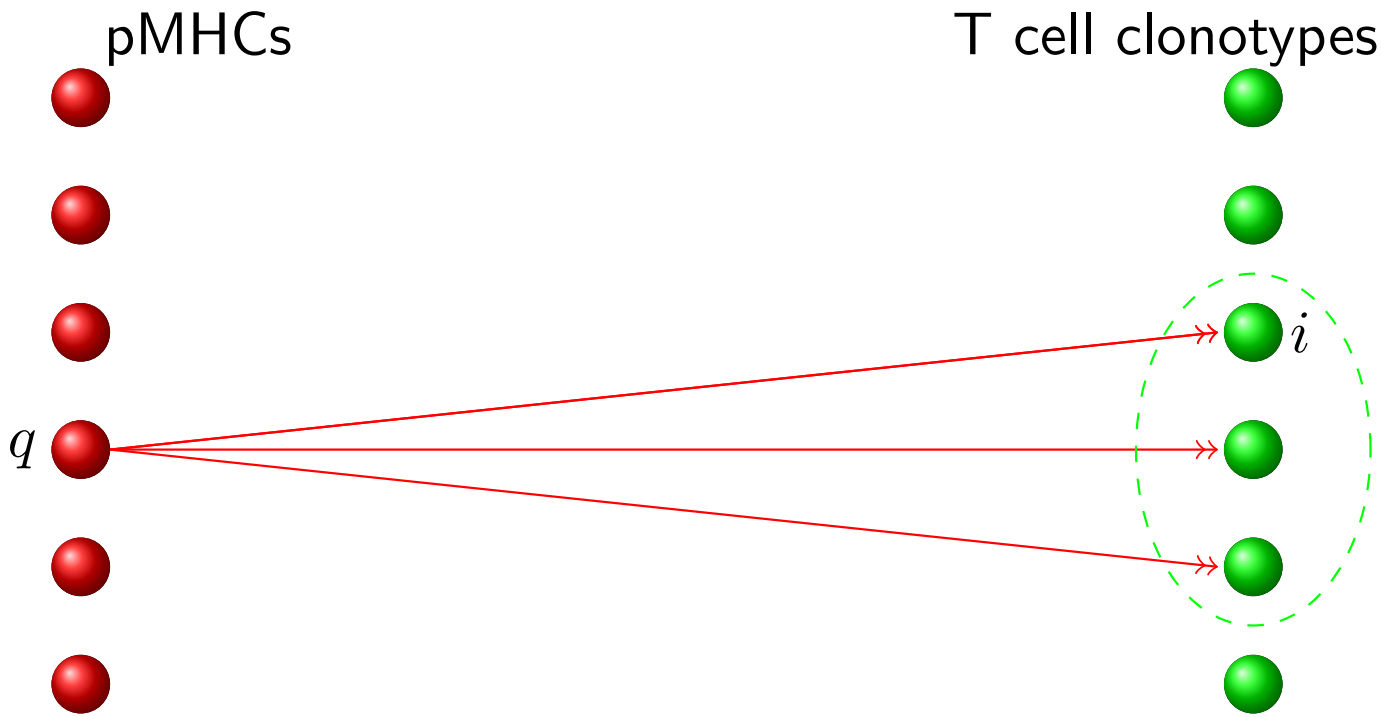
Every T cell has a constant probability per unit time μ of dying, independent of all others.

- The stimulus is divided into M pMHC subsets.
- The number of T cells of clonotype i at time t is $n_i(t) \geq 0$.
- A clonotype has survived to time t if $n_i(t) > 0$.
- The number of surviving clonotypes at time t is $N(t)$.

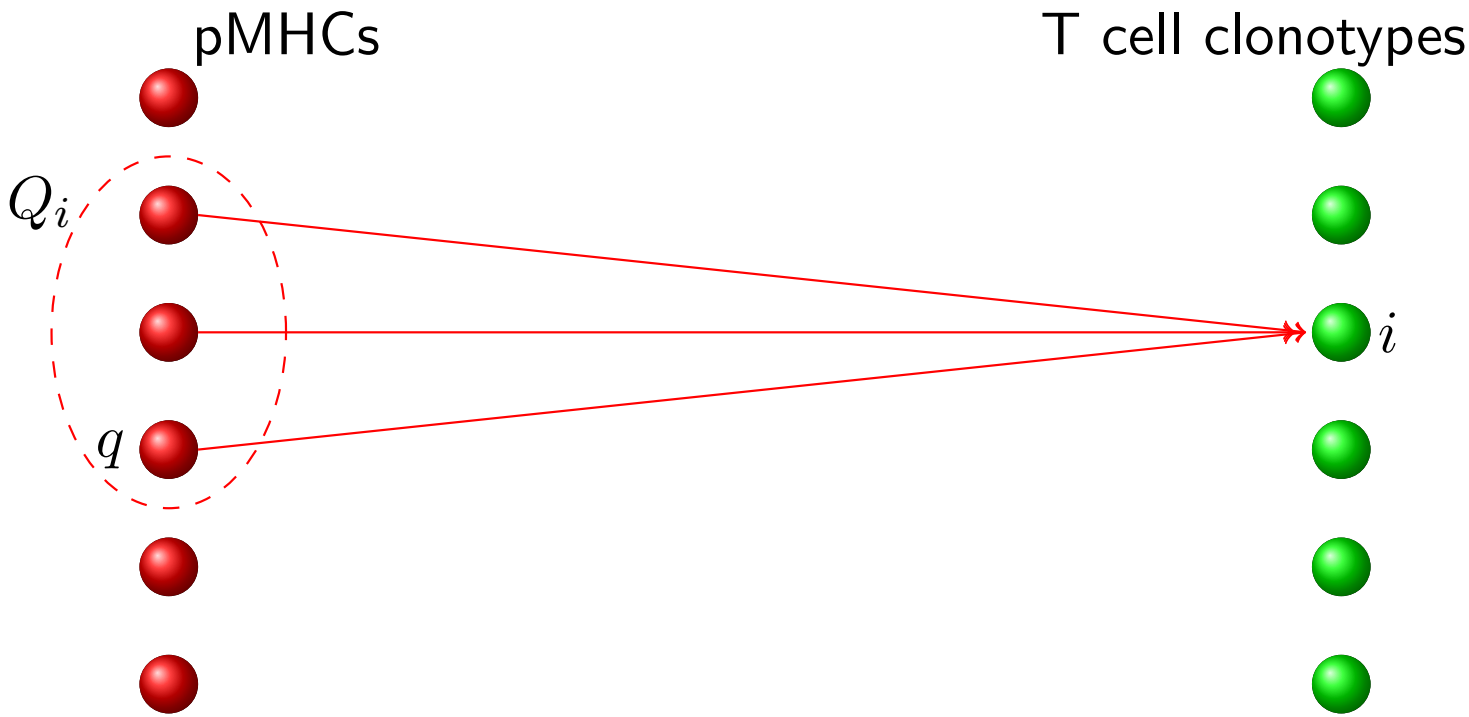
pMHC stimulus and naive T cell division



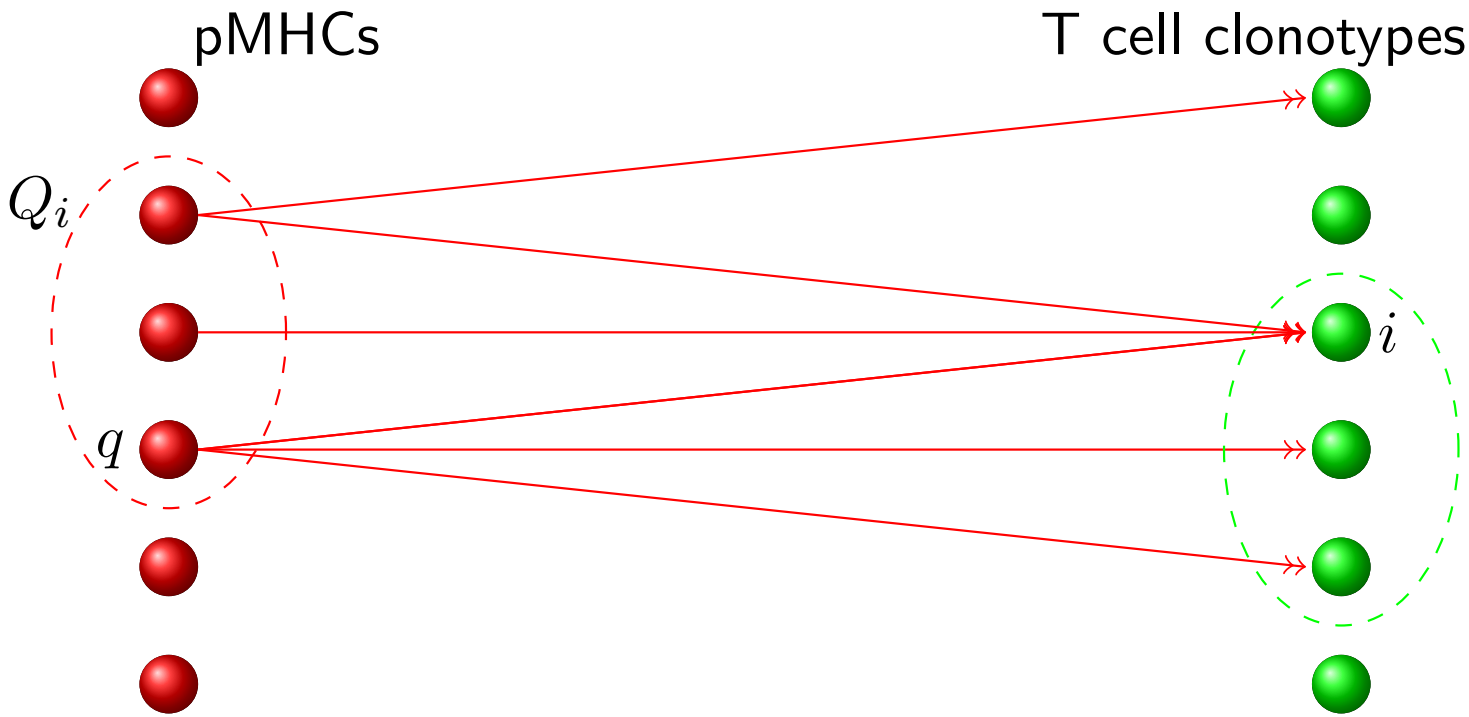
pMHC stimulus and naive T cell division



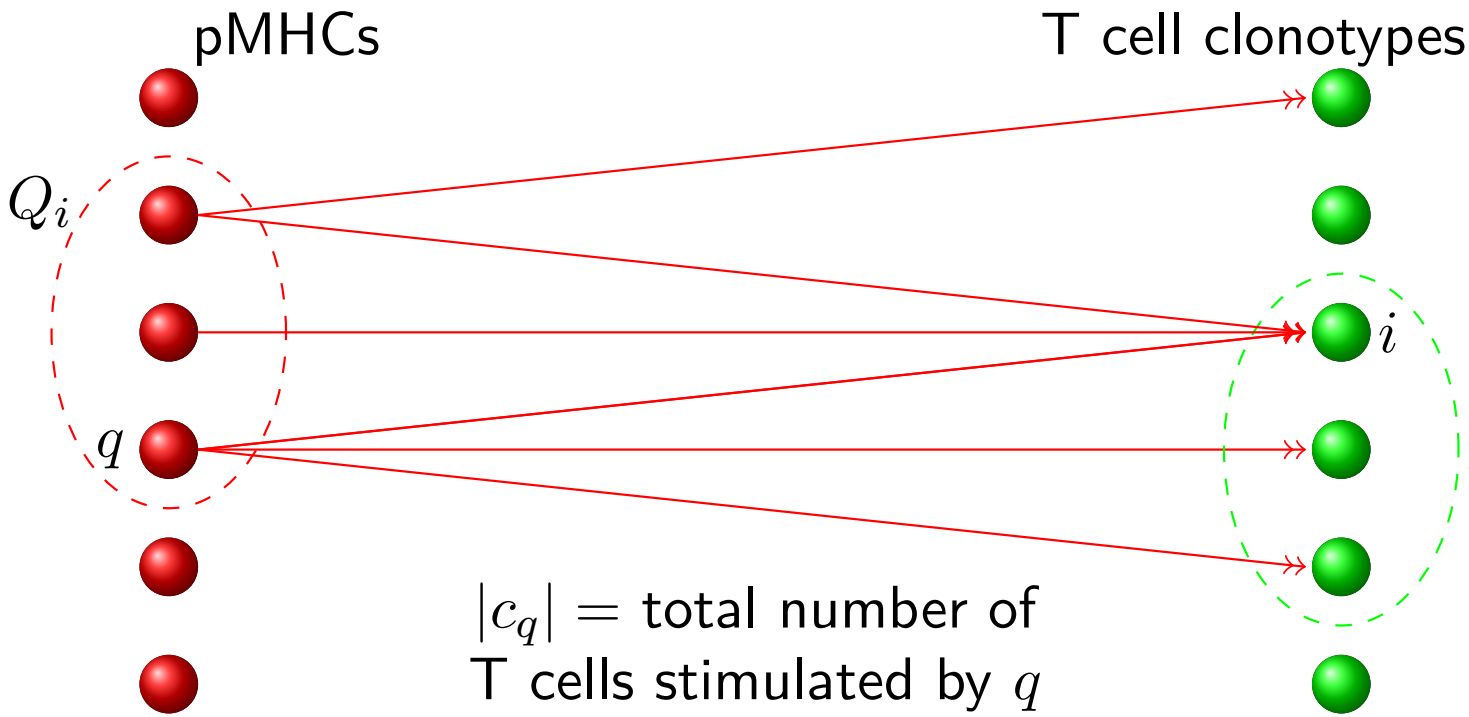
pMHC stimulus and naive T cell division



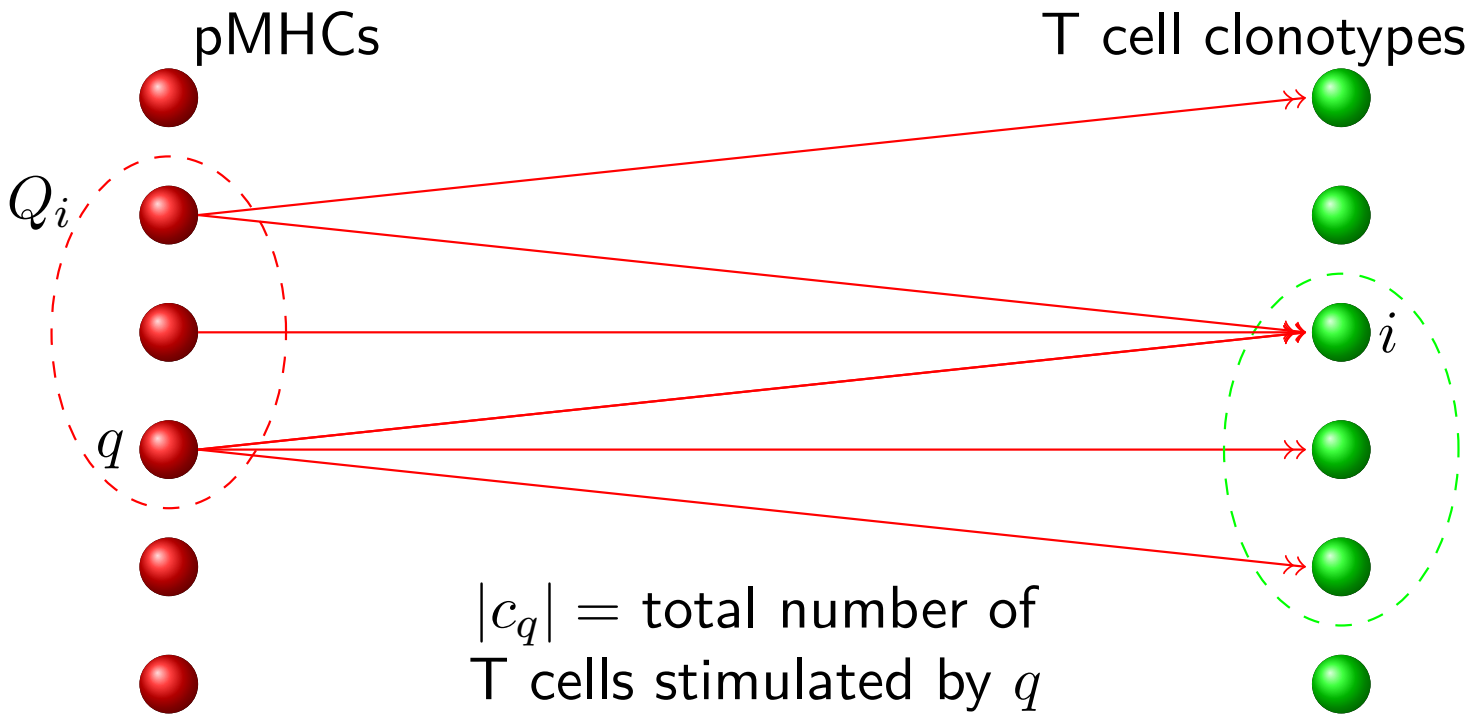
pMHC stimulus and naive T cell division



pMHC stimulus and naive T cell division



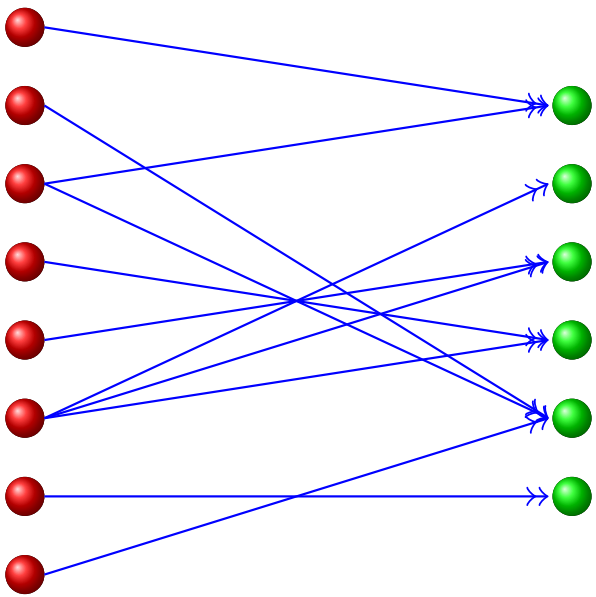
pMHC stimulus and naive T cell division



Birth rate for T cells of clonotype i

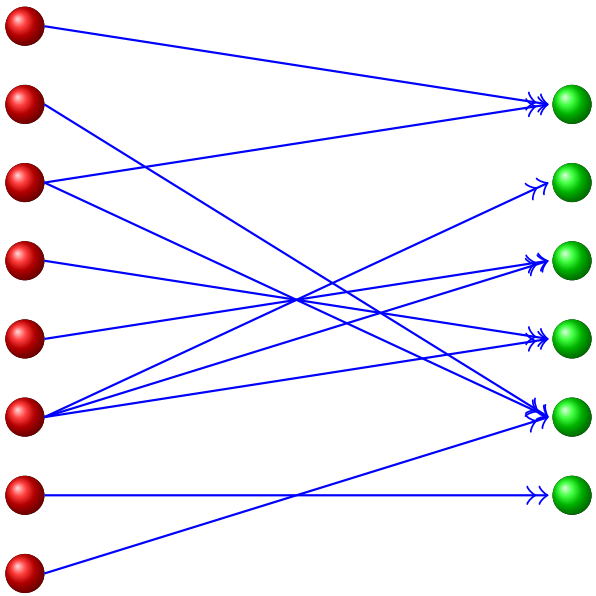
- $\Lambda_i = n_i \sum_{q \in Q_i} \frac{\gamma_q}{|c_q|} = n_i \sum_{q \in Q_i} \frac{\gamma}{|c_q|} \leq \gamma \phi_i$,
- ϕ_i = number of pMHCs in Q_i .

Multi-dimensional Markov dynamics: example



$$\begin{pmatrix} 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 1 & 1 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

Multi-dimensional Markov dynamics: example

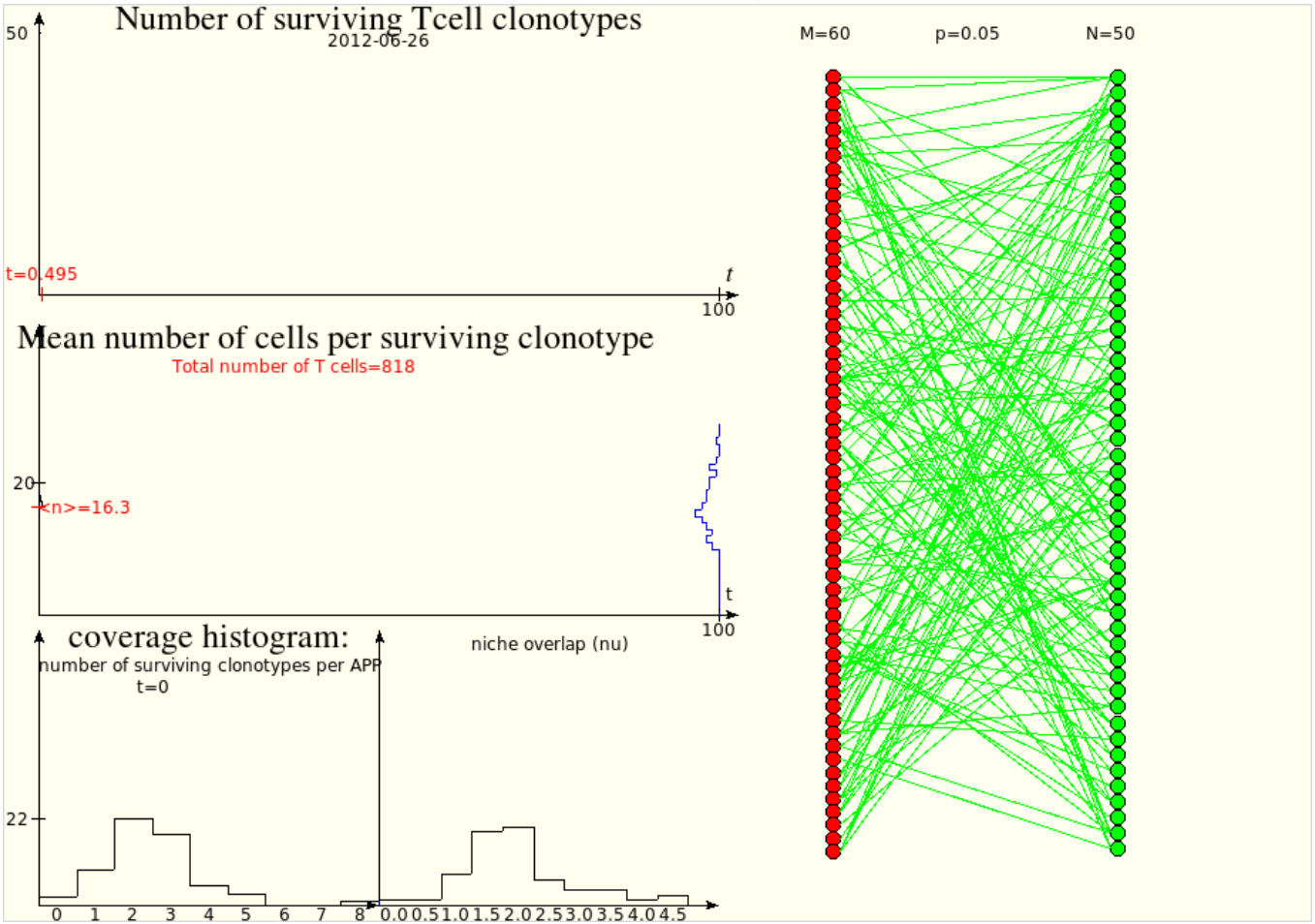


- Suppose that $n(t) = (15, 7, 9, 0, 11, 1)$.
- $\mathbb{P}(\text{next event is a death}) = \frac{\Omega(t)}{\Omega(t)+\Lambda(t)}$.
- $\Omega(t) = \mu(15 + 7 + 9 + 0 + 11 + 1)$.
- $\Lambda(t) = \Lambda_1(t) + \Lambda_2(t) + \cdots + \Lambda_6(t)$.

- $\Lambda_1(t) = \gamma\left(\frac{15}{15} + \frac{15}{15+11}\right)$, $\Lambda_2(t) = \gamma\left(\frac{7}{7+9+0}\right)$ $\cdots$
- $\mathbb{P}(\text{birth in clonotype 1}) = \frac{\Lambda_1(t)}{\Omega(t)+\Lambda(t)}$.
- $\mathbb{P}(\text{death in clonotype 3}) = \frac{9\mu}{\Omega(t)+\Lambda(t)}$.
- Gillespie algorithm: time is incremented by $\Delta t = \frac{-\log(\mathbf{u})}{\Omega(t)+\Lambda(t)}$.

Model of large-scale clonal competition

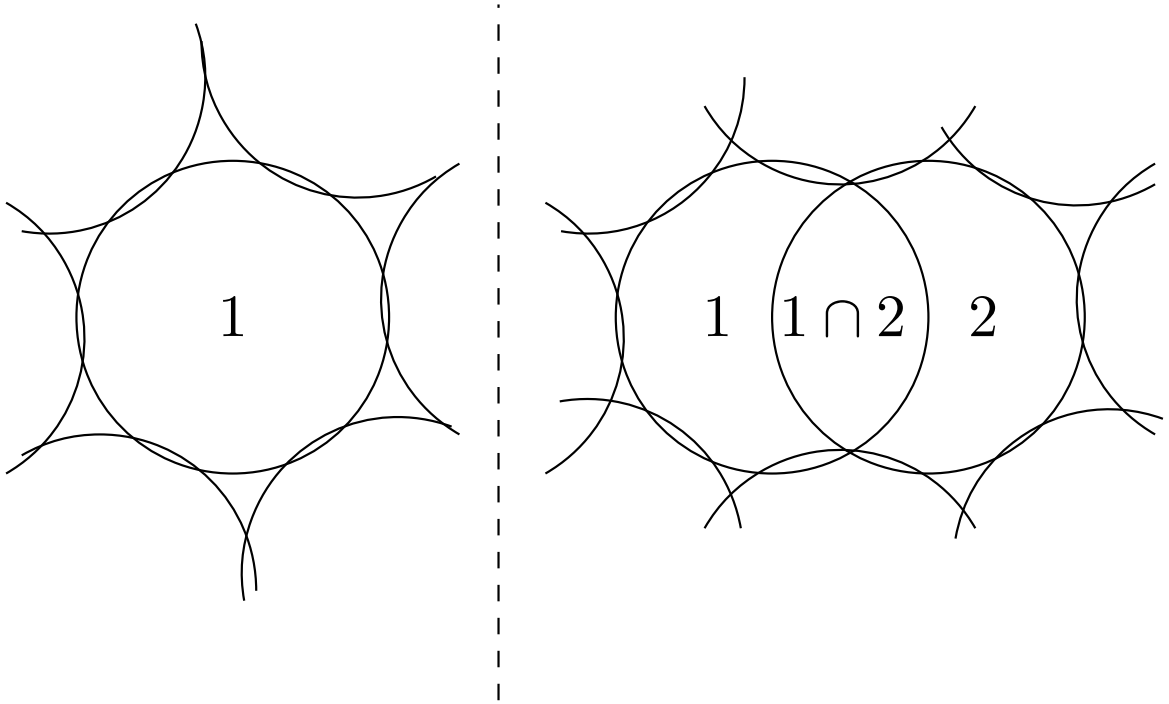
With probability p, pMHC q is recognised by T cell clonotype i, independently of all other pairs. $\mu = 1.0$, $\gamma = 10.0$



Observations (work in progress)

- The mean total number of naive T cells is constant and equal to $\frac{\gamma}{\mu}M$.
- The number of clonotypes that survive does not depend on the initial TCR repertoire diversity $N(0)$.
- Competition between clonotypes leads to a more even covering of epitope space than would be produced by a uniform random distribution.
- The system scales with the combination of parameters pM, that is, the number of pMHCs times the probability of TCR recognition.
- If we introduce thymic output, the mean total number of naive T cells is almost unaffected.
- Most thymic emigrant clonotypes do not survive for long, but those that do, are important in maintaining diversity and coverage.

Uni-variate and bi-variate approximations



E.R. Stirk, CM-P and H.A. van den Berg
Stochastic niche structure and diversity maintenance in the T cell repertoire
Journal of theoretical biology **255** 237–249 (2008)

E.R. Stirk, G. Lythe, H.A. van den Berg and CM-P
Stochastic competitive exclusion in the maintenance of the naive T cell repertoire
Journal of theoretical biology, – (2010)

Clonal sizes and stochastic descriptors: future work

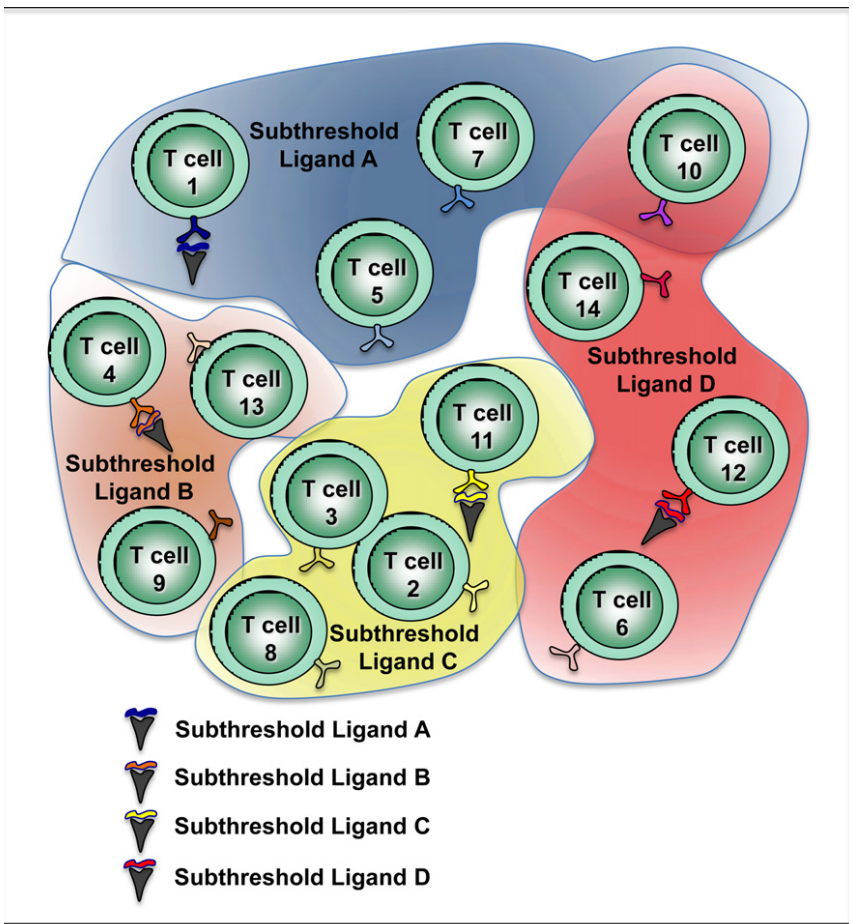
- Study the distribution of clonal sizes.
- Study stochastic descriptors: time to reach a given size.

New rules for peripheral T cell homeostasis

- Peripheral T cell pool: subsets dictated by recognition of a common sub-threshold ligand.
- T cell numbers controlled primarily by competition between members of the subset.

Singh, Bando, and Schwartz
Subsets of non-clonal neighboring $CD4^+$ T cells specifically regulate the frequency of individual antigen-reactive T cells
Immunity (2012).

Walker
Maintaining a competitive edge: new rules for peripheral T cell homeostasis
Immunity **37** 598–600 (2012).



Outline

Thanks

- **Organisers and KITP:** for the kind invitation.
- **Post-graduate students at the University of Leeds:** James Currie, Mark Day, Joseph Reynolds and Emily Stirk.
- **Theoretical collaborators:** Stuart Barber, Hugo van den Berg, Mario Castro and Grant Lythe.
- **Experimental collaborators:** Amado and Freitas (Pasteur), Bousso, Celli and Müller (Pasteur) and Palmer (Basel).
- The audience (for your patience).
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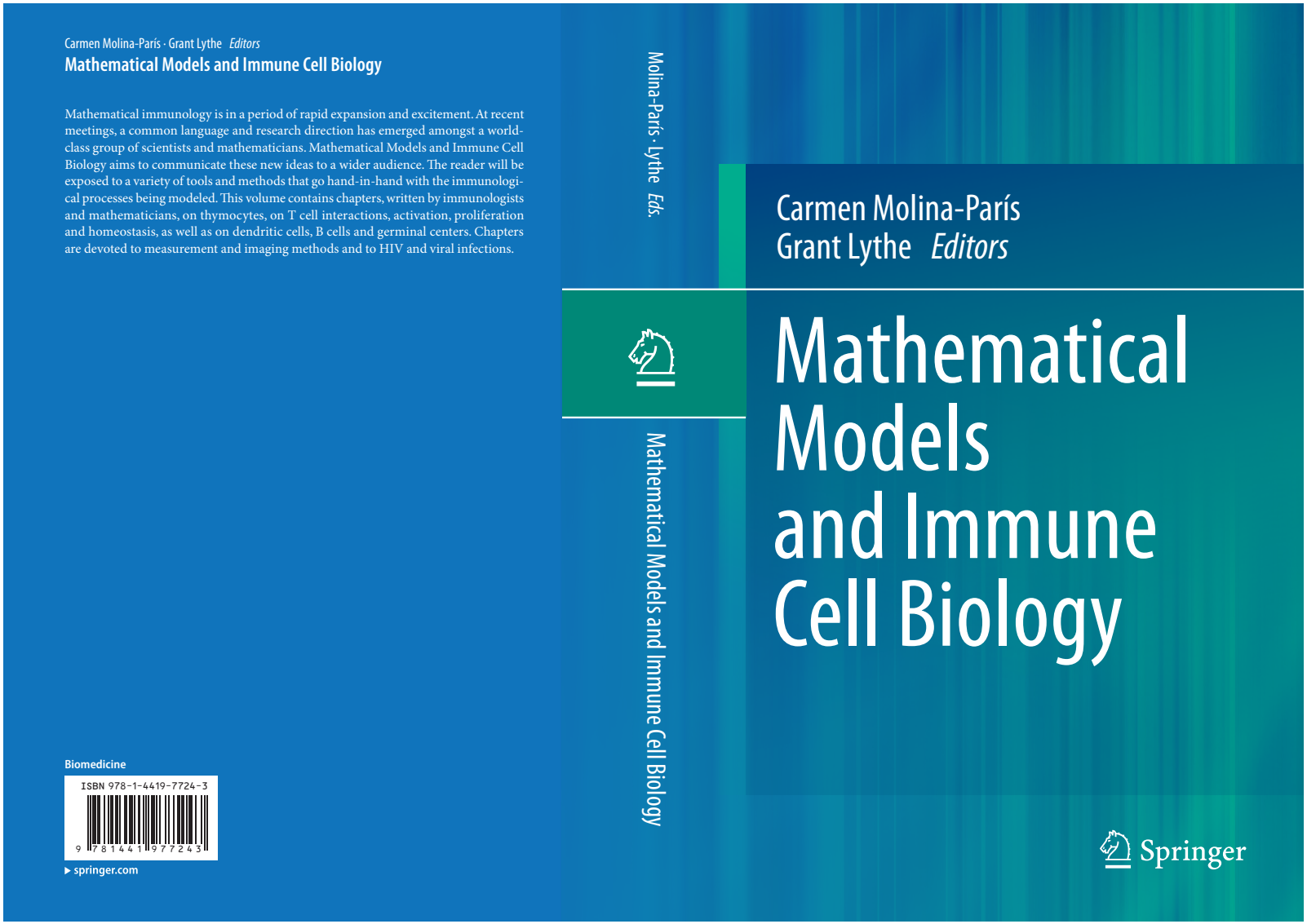
a word from . . .

- Quantitative T cell Immunology (FP7 ITN)
- Mathematics for Health and Disease (FP7 IRSES)
- Post-doctoral position at Leeds (3 years).

`http://www1.maths.leeds.ac.uk/Applied/QUANTI`
`http://www1.maths.leeds.ac.uk/Applied/INDOMATH`

Book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