Stochastic modelling and immunology: How many populations? how many cells? how many encounters?

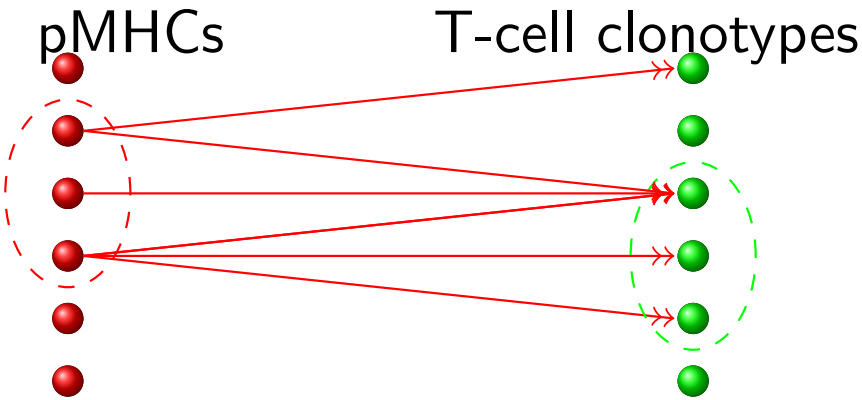
Grant Lythe and Carmen Molina-París (Leeds)
Robin Callard and Rollo Hoare (UCL)

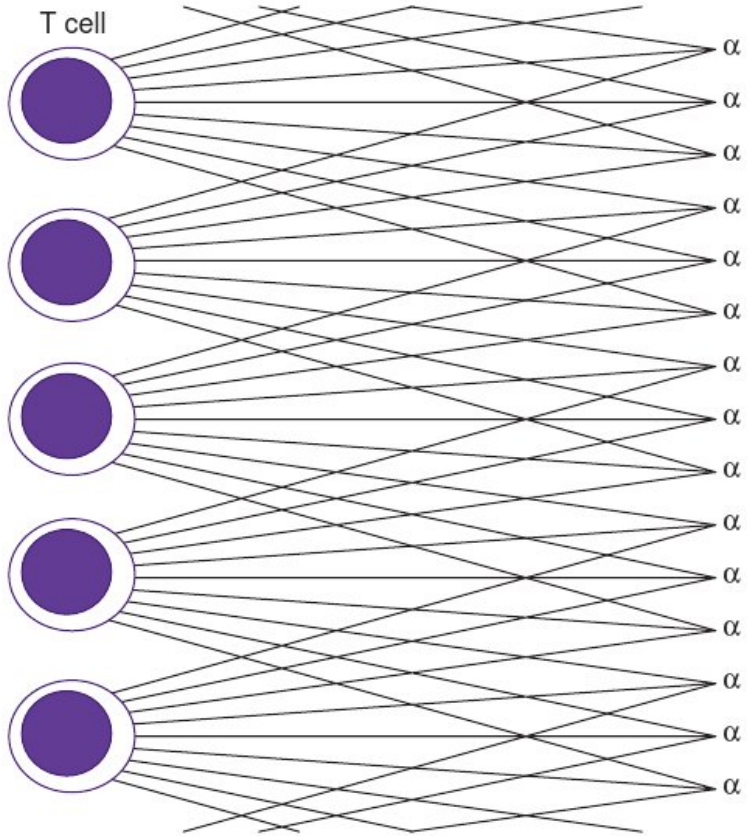
Thanks to: Hugo van den Berg, Nigel Burroughs, David Rand, Jochen Voss

2014

The T cell repertoire and self pMHC universe

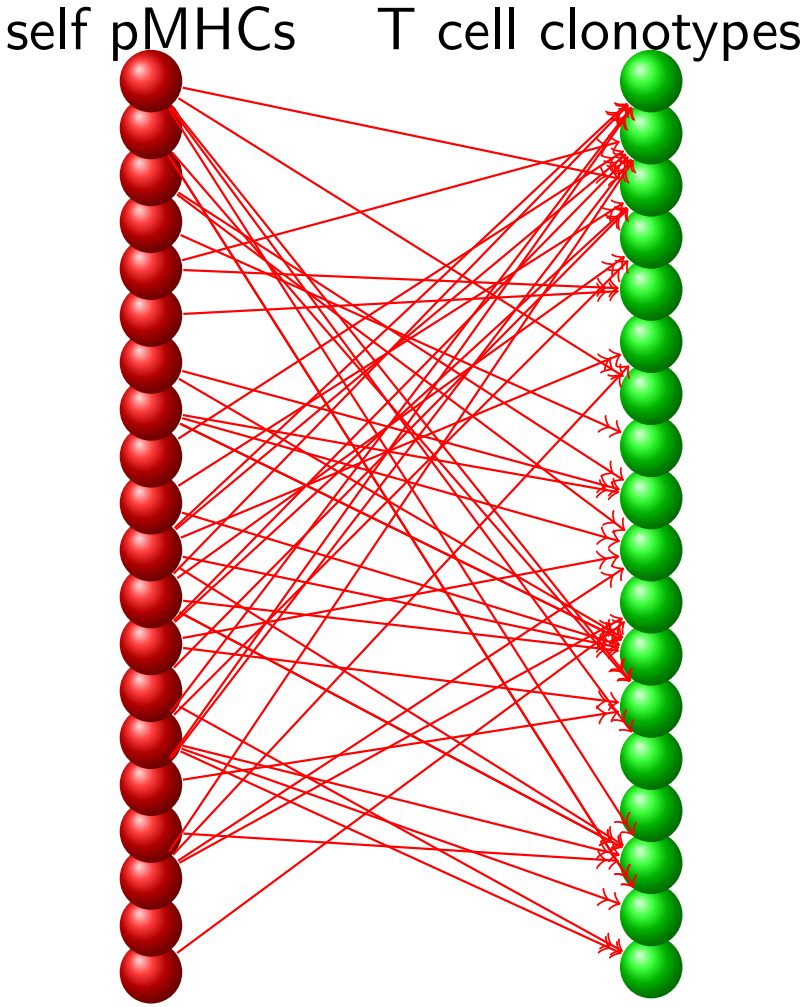
The human body maintains a diverse repertoire of T cells, about 10^{11} total cells classified by their T cell receptor into clonotypes. New T cells from the thymus or division of cells in the periphery compensate for cell death.





Mathematical Models and Immune Cell Biology, Springer (2011) ↑
D. Mason, Immunology Today **19** (1998)→

Cross-reactivity and clonal identity



Each clonotype is assigned a pattern of interaction with the set of M pMHCs. In the simplest algorithm, each of the pMHC is recognised with probability p, so that the mean number of pMHC recognised (cross-reactivity) is pM . The number of possible combinations is sufficiently large that each recognition profile is a unique signature.

Singh, Bando and Schwartz, Immunity **37** (2012)
Sewell, Nature Reviews Immunology **12** (2012)
Nikolich-Žugich et al Nature Reviews Immunology **4** (2004)

Stochastic system dynamics

Death

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

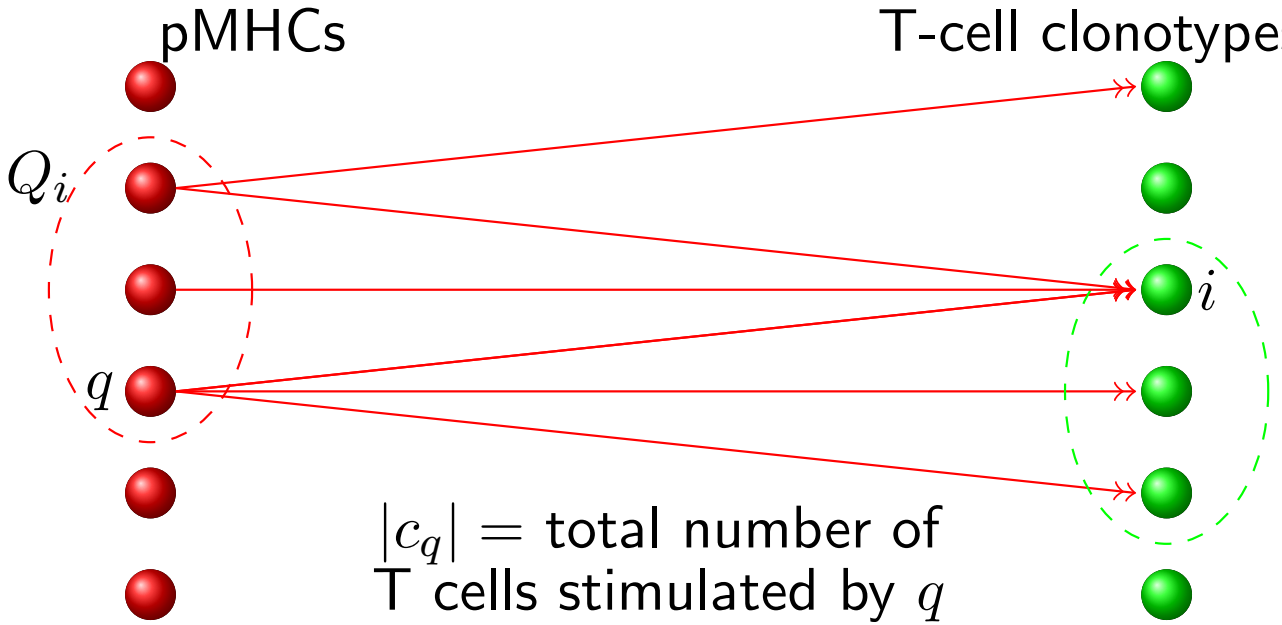
Division

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

The stimulus is divided into M subsets.
The number of T cells of type 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 $N(t)$.

Mathematical Models and Immune Cell Biology, Springer (2011)

Stimuli and cell division

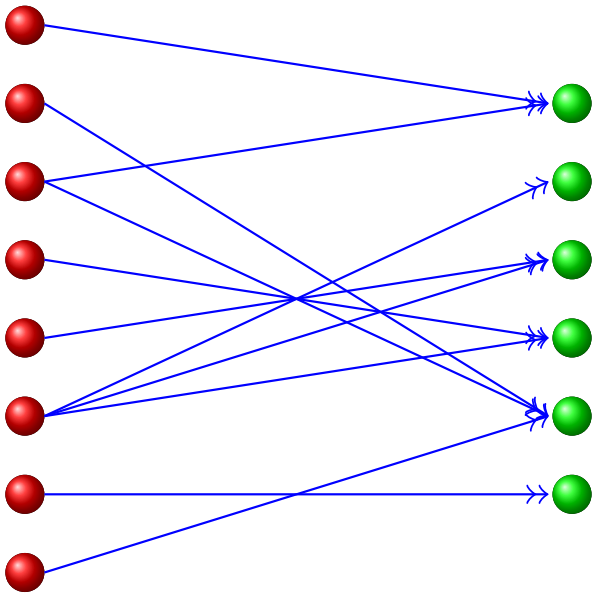


Birth rate for T cells of type i

$$\Lambda_i = \gamma \sum_{q \in Q_i} \frac{n_i}{|c_q|} \quad \leq \gamma \phi_i \text{ where } \phi_i = \text{number of pMHCs in } Q_i.$$

Stirk et al, Mathematical Biosciences **224** (2010)

Multidimensional Markov dynamics: example



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

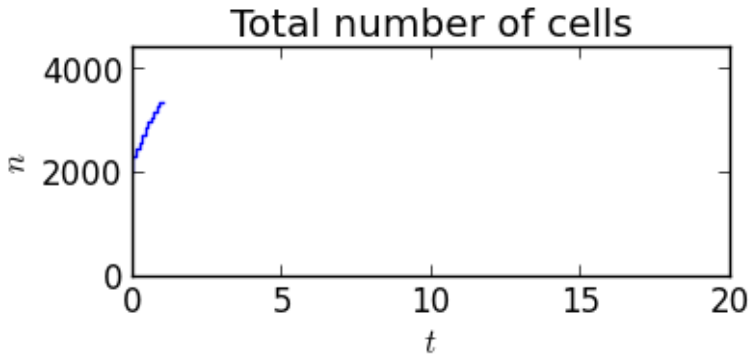
Suppose that $n(t) = (15, 7, 9, 0, 11, 1)$. Then

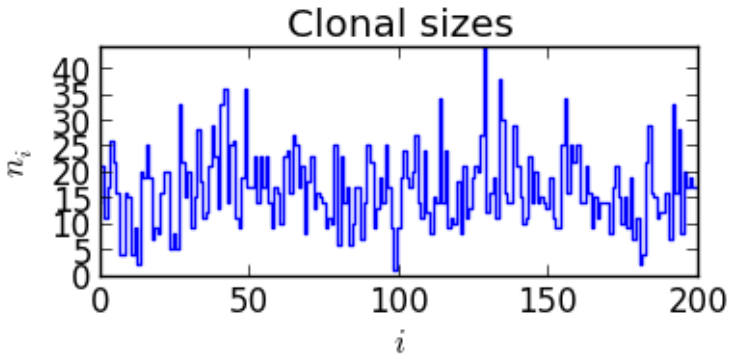
$$\Pr[\text{next event is a death}] = \frac{\Omega(t)}{\Omega(t) + \Lambda(t)}$$

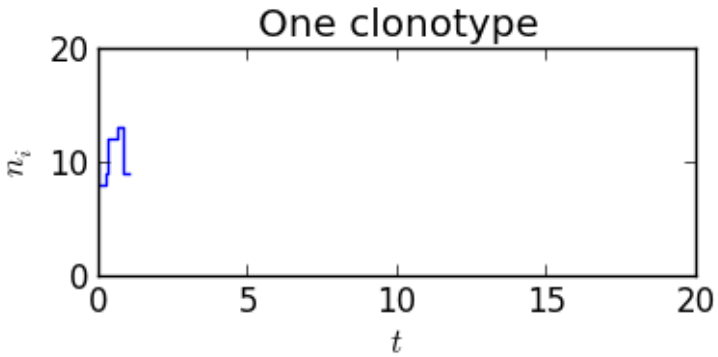
where $\Omega(t) = \mu(15 + 7 + 9 + 0 + 11 + 1)$
and
$\Lambda(t) = \Lambda_1(t) + \Lambda_2(t) + \Lambda_3(t) + \cdots + \Lambda_6(t)$,

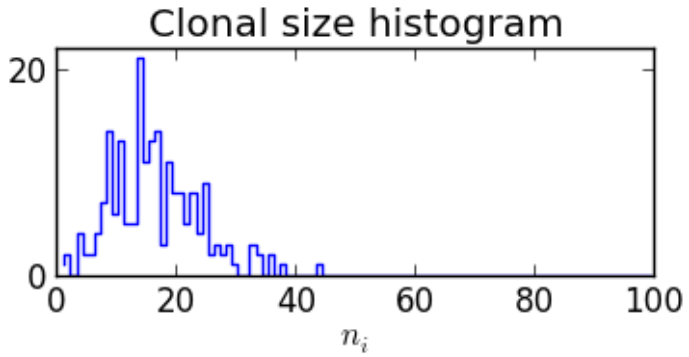
where

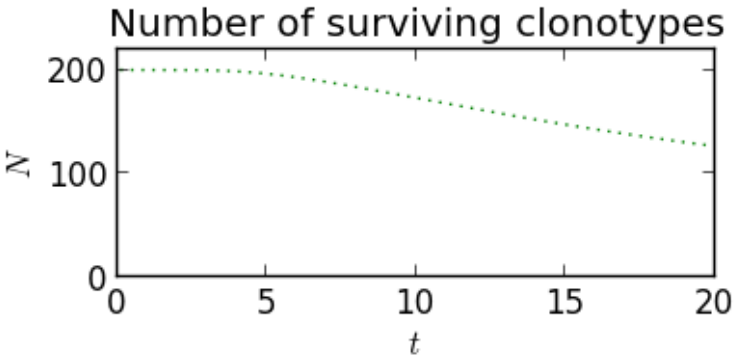
Model of large-scale clonal competition











γ=4.0 μ=1.0
M=1000 p=0.1
2013-08-29

Timescales

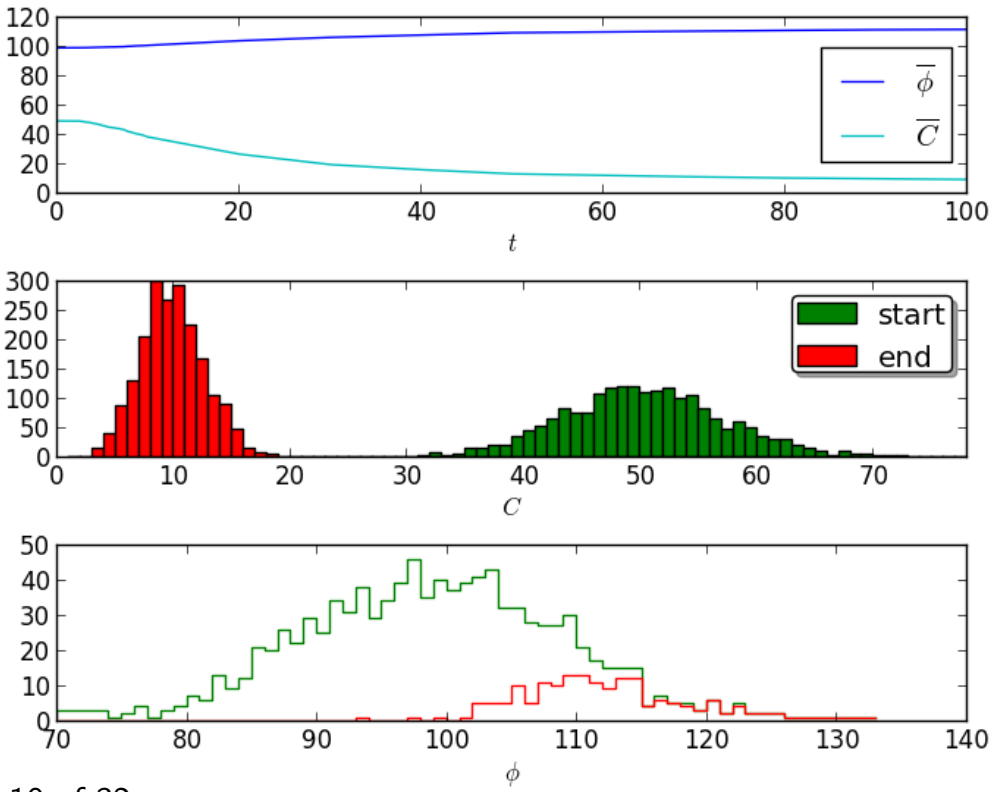
- The overall timescale for T-cell lifetimes is μ^{-1}.
  Mouse: $\mu = 1\text{month}^{-1}$ Human: $\mu = 1\text{year}^{-1}$
- Transient timescale: the mean total number of T cells finds the level $\frac{M\gamma}{\mu}$.
- Extinction timescale: the probability that a clone, initially with n_0 cells, survives up to time t is

$$\Pr(\text{survival}) = 1 - \exp(-\frac{n_0}{\mu t})$$

  That is, half of all clonotypes survive until $t_{1/2} = \frac{n_0}{\mu} \ln 2$.

Understanding clonotype competition

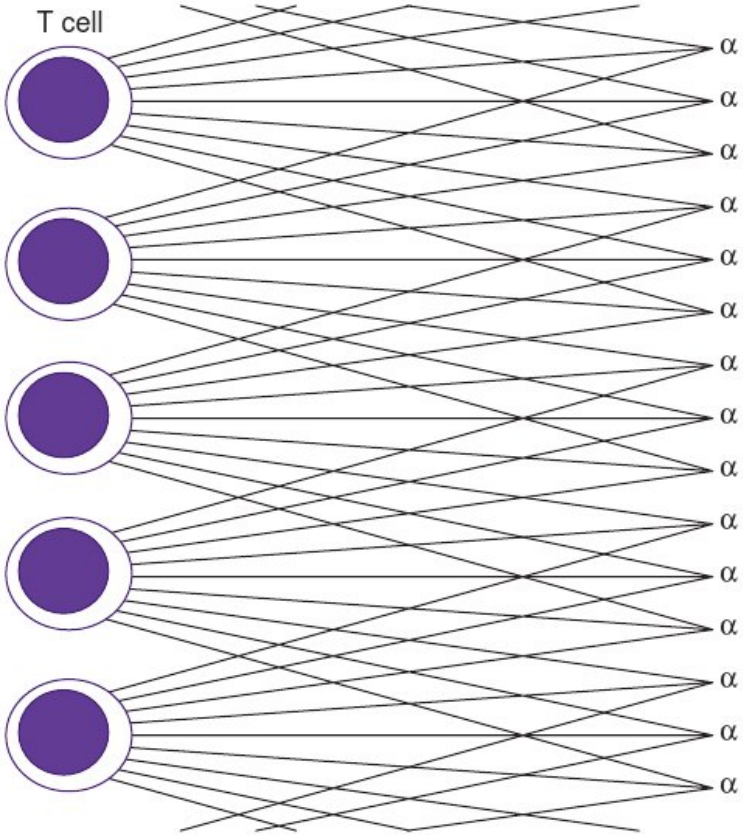
- For each clonotype i, we can define $\phi_i =$ number of q in Q_i.
- For each pMHC q we can define $|C_q|(t) =$ number of surviving clonotypes recognising q.



Numerical realization with $N = 1000$, $M = 2000$, $p = 0.05$, $\mu = 1.0$, $\gamma = 10.0$ and $n_i(0) = 10$.

- Green: initial distribution.
- Red: distribution at $T = 100$.

Mason relation



$$M\bar{C} = N\bar{\phi}$$

Fig. 3. *The derivation of the crossreactivity equation. Fifteen different MHC-associated peptides, 'α', are shown interacting with five different T cells. Each T cell reacts with nine different peptides and each peptide reacts with three different T cells. Evidently, 3 × 15 = 9 × 5 = 45, which is the number of peptide–T-cell interactions in the figure. Generalizing this result, T(p) × N = P(t) × T. Note that the value of T(p) will vary for different peptides and similarly the value of P(t) will not be the same for all T cells. However, the crossreactivity equation remains valid if the mean values of T(p) and P(t) are used.*

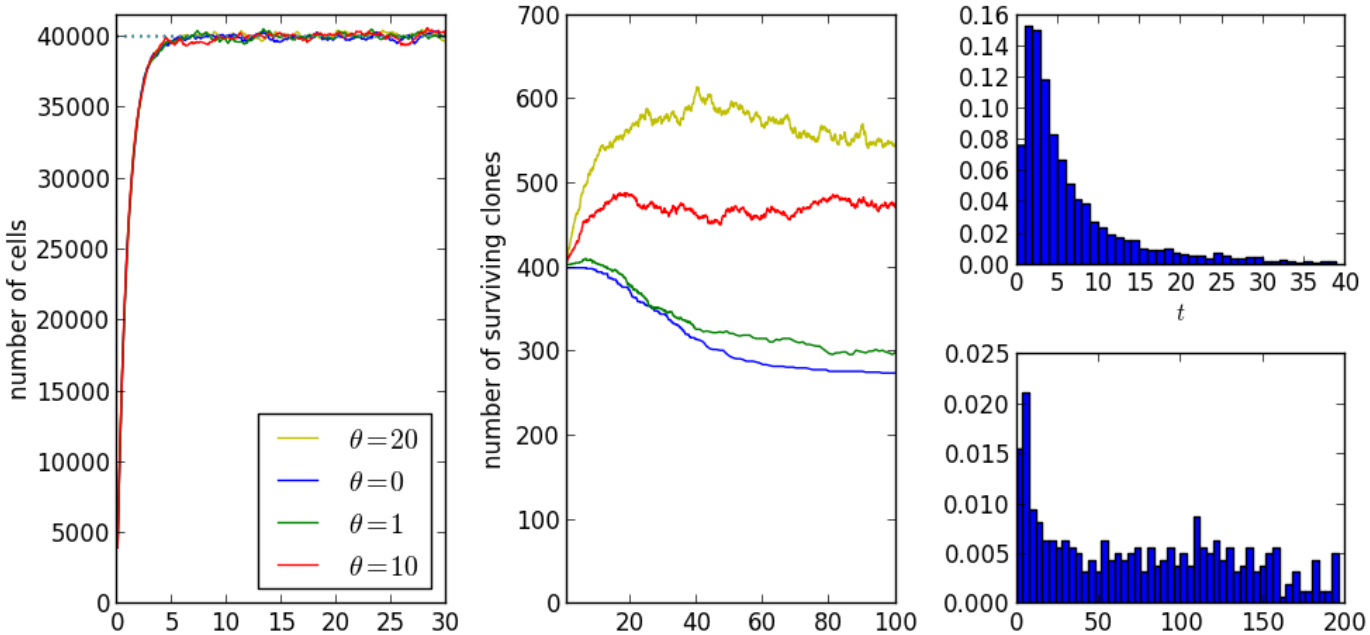
D. Mason, Immunology Today **19** (1998)
Zarnitsyna et al, Frontiers in Immunology (2013)

Thymic production: maintenance and reconstitution

At random times, with rate θ, new clonotypes are created with n_θ cells.

- The mean total number of cells is almost unaffected.
- Most thymic emigrant clonotypes do not survive for long, but those that do are important in maintaining diversity and coverage.

Berzins et al, Trends in Molecular Medicine **10** (2002)



Parameter value guesses for mice and humans

The steady mean total number of cells is $\mu^{-1}(\gamma M + n_\theta \theta)$.

Mice

$\mu = 1\text{month}^{-1}$

Total (naive CD4$^+$) T cells:
4×10^7

Thymic production:
$n_\theta \theta = 4 \times 10^7 \text{month}^{-1}$
$p = 10^{-6}$, $M = 10^9$,
$\gamma = 10^{-3}\text{month}^{-1}$
$N \simeq 2 \times 10^7 / n_\theta$

Humans

$\mu = 1\text{year}^{-1}$.

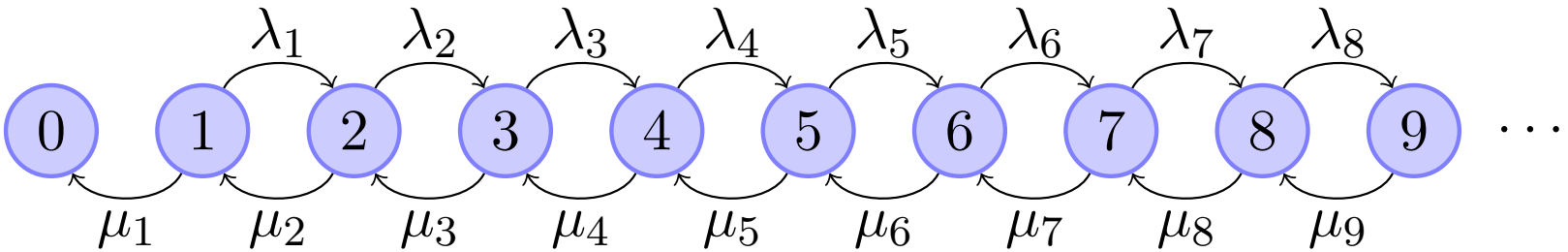
Total (naive CD4$^+$) T cells:
4×10^{11}.

Thymic production:
$n_\theta \theta = 10^{10}\text{year}^{-1}$
$p = 10^{-6}$, $M = 10^{10}$,
$\gamma = 10\text{year}^{-1}$
$N =$ no simple formula.

Bains, Antia, Callard and Yates, Blood **113** (2009)
Westera et al Blood (2013)
Vrisekoop et al PNAS **105** (2008)
Murray et al Immunology and Cell Biology (2003)
de Boer and Perelson, J Theoretical Biology (2013)

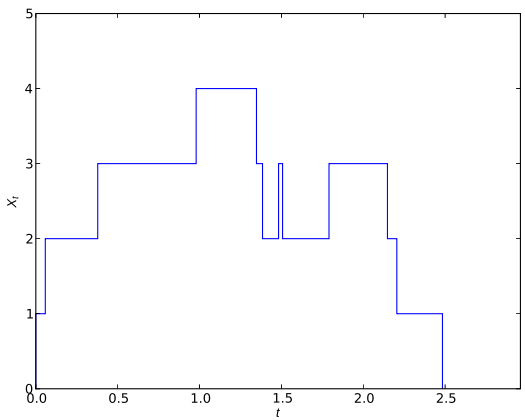
Markov chain model and extinction

$p_n(t)$ is the probability that, at time t, there are n T cells of clonotype i. The probability that, at time $t + \Delta t$, there are $n - 1$ T cells of clonotype i is $n\mu\Delta t$, as $\Delta t \to 0$. $\mu_n = n\mu$.



In the "mean-field" model, extinction occurs with probability 1.
Limiting conditional distribution:

$$q_n = \lim_{t\to\infty} \frac{p_n(t)}{1 - p_0(t)}.$$



Global competition model (one resource)

In any short time interval, a T cell either remains unchanged, dies, or divides into two cells of the same clonotype. The dynamics are thus governed by the birth (division) and death rates. For the latter, we adopt the simplest hypothesis: that each T cell, independently of all others, has a probability μ per unit time (rate) of death. Cell division results from a constant rate of stimulus γ that is equally likely to be received by each living cell.

- Each cell, independently, has a constant death rate, μ.
- The resource causes cell division at rate γ. All living cells are equally likely to receive stimulus and divide.

Stationary mean total number of cells

If the number of cells alive at time t is $n(t) > 0$ then the birth rate is γ and the death rate is $\mu n(t)$. That is,

$$\lim_{\Delta t \to 0} \Delta t^{-1} \Pr[n(t + \Delta t) - n(t) = 1] = \gamma \qquad \text{and,}$$

$$\lim_{\Delta t \to 0} \Delta t^{-1} \Pr[n(t + \Delta t) - n(t) = -1] = n(t)\mu.$$

Consider the quantities $p_k(t) = \Pr[n(t) = k]$, for each integer k. They satisfy

$$\frac{\mathrm{d}}{\mathrm{d}t} p_0 = \mu p_1$$

$$\frac{\mathrm{d}}{\mathrm{d}t} p_1 = -\mu p_1 + 2\mu p_2 - \gamma p_1$$

$$\frac{\mathrm{d}}{\mathrm{d}t} p_k = \gamma(p_{k-1} - p_k) + \mu((k+1)p_{k+1} - k p_k) \qquad k \geq 2.$$

Stationary mean total number of cells

Let the mean total number of cells be $x(t) = \mathbb{E}(n(t))$.
Then $x(t) = \sum_{k=1}^{\infty} k p_k(t)$ and

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}x(t) &= \mu\left(-p_1 + 2p_2 - \sum_{k=2}^{\infty} k^2 p_k + \sum_{k=2}^{\infty} k(k+1)p_{k+1}\right) \\
&\quad + \gamma\left(-p_1 - \sum_{k=2}^{\infty} k p_k + \sum_{k=2}^{\infty} k p_{k-1}\right) \\
&= \mu\left(-p_1 - \sum_{l=2}^{\infty} l p_l\right) + \gamma \sum_{k=0}^{\infty} p_k \\
&= -\mu x(t) + \gamma.
\end{aligned}$$

That is

$$\frac{\mathrm{d}}{\mathrm{d}t}x = \gamma - \mu x.$$

Clonotypes

The cell population is divided into clonotypes. Each cell has a clonotype label i and the number of cells with label i at time t is $n_i(t)$. Thus

$$n(t) = \sum_i n_i(t).$$

Now the birth and death rates for clonotype i are

$$\lim_{\Delta t \to 0} \Delta t^{-1} \Pr[n_i(t + \Delta t) - n_i(t) = 1] = \gamma \frac{n_i(t)}{n(t)},$$

and

$$\lim_{\Delta t \to 0} \Delta t^{-1} \Pr[n_i(t + \Delta t) - n_i(t) = -1] = n_i(t)\mu.$$

The competition for stimulus, between clonotypes and between cells of the same clonotype, is called **global or public** because of the factor $\frac{n_i(t)}{n(t)}$ in the birth rate for clonotype i.

Distribution of extinction times

Now, if we assume $n(t) \simeq < n > = \frac{\gamma}{\mu}$, then

$$\lambda_i(t) = \simeq \mu n_i,$$

Let us approximate n_i by a diffusion process, $\mathbf{X}_t$.

$$\mathrm{d}\mathbf{X}_t = \sqrt{2\mu\mathbf{X}_t}\mathrm{d}\mathbf{W}_t.$$

If $F(t, b)$ is the probability of hitting 0 before time t, starting with $\mathbf{X}_0 = b$, then

$$\frac{\partial}{\partial t}F(t, b) = \frac{1}{2}\mu b\frac{\partial^2}{\partial b^2}F(t, b),$$

with $F(t, 0) = 1$. Thus $F(t, b) = 1 - \exp(-\frac{b}{\mu t})$ and

$$\Pr[\mathbf{X}_t = 0|\mathbf{X}_0 = b] = \exp(-\frac{b}{\mu t}).$$

Cells and interactions of the immune system

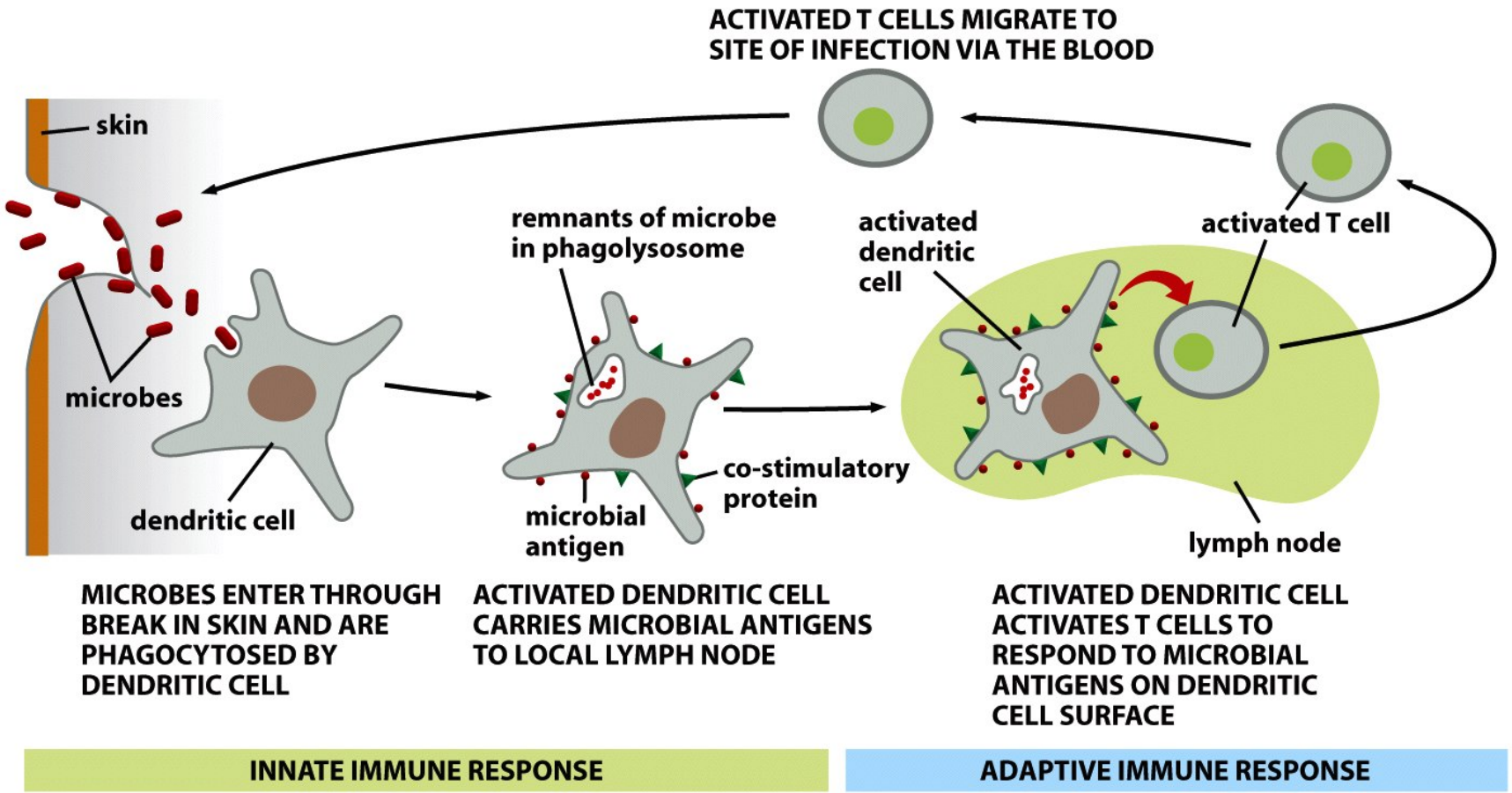


Figure 25-5 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cells and interactions of the immune system

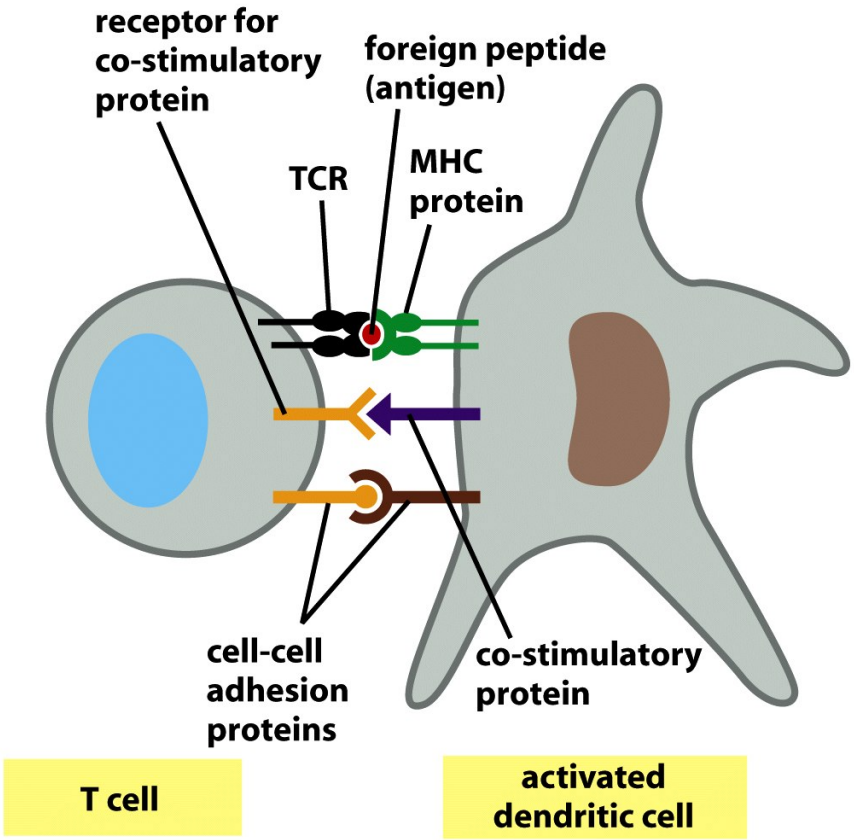
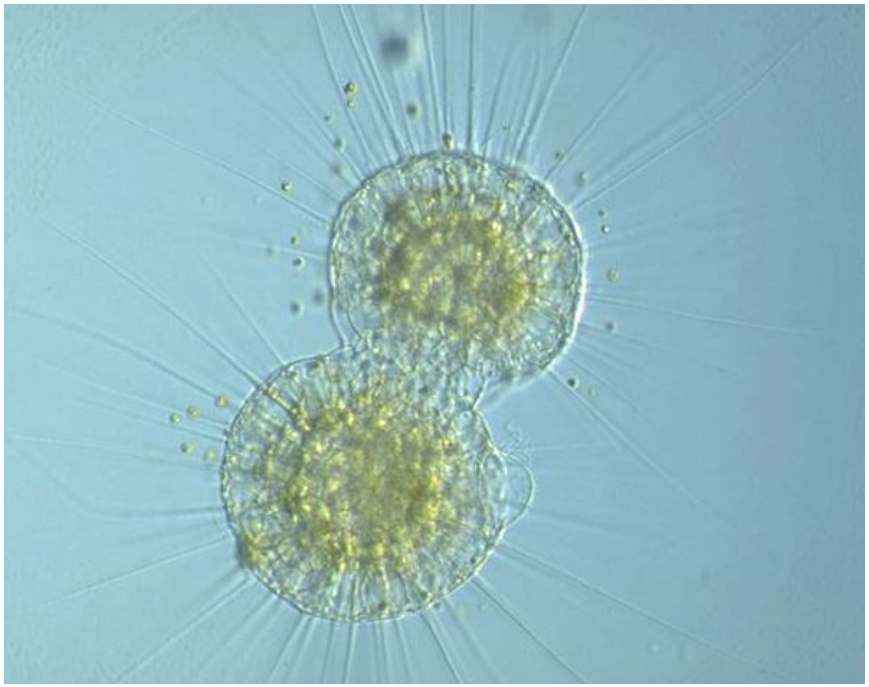


Figure 25-45 Molecular Biology of the Cell 5/e (© Garland Science 2008)



Quantifying the probability of T cell activation

- Adaptive responses are initiated through encounters between rare naive Ag-specific T cells and Ag-bearing dendritic cells (DCs).
- The number of DCs in the draining Lymph node (LN) influences the chance that rare Ag-specific T cells are activated.
- Using two experimental approaches and one in silico model, we measured the probability of T cell-DC encounters.

Brief report

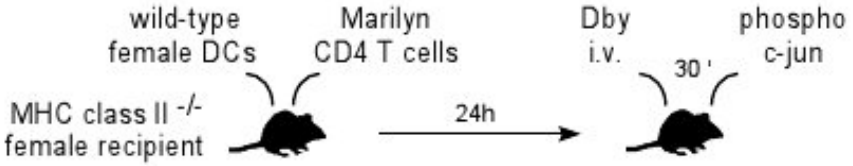
How many dendritic cells are required to initiate a T-cell response?

Susanna Celli,[1,2] Mark Day,[3] Andreas J. Müller,[1,2] Carmen Molina-Paris,[3] Grant Lythe,[3] and Philippe Bousso[1,2]

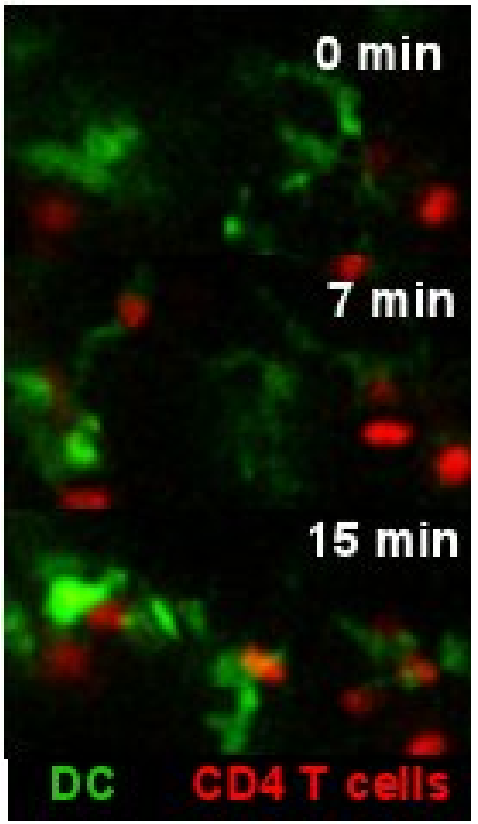
[1]Institut Pasteur, Dynamics of Immune Responses Unit, Paris, France; [2]Inserm U668, Paris, France; and [3]Department of Applied Mathematics, University of Leeds, Leeds, United Kingdom

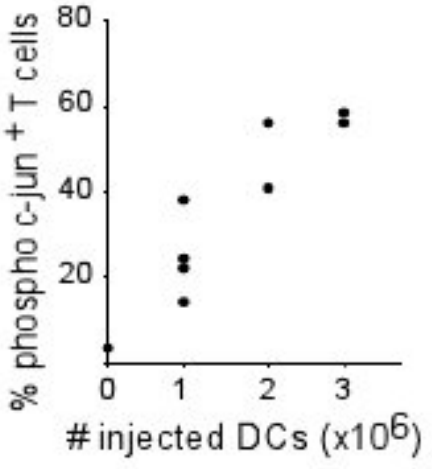
T-cell activation in lymph nodes relies on encounters with antigen (Ag)–bearing dendritic cells (DCs) but the number of DCs required to initiate an immune response is unknown. Here we have used a combination of flow cytometry, 2-photon imaging, and computational modeling to quantify the probability of T cell-DC encounters. We calculated that the chance for a T cell residing 24 hours in a murine popliteal lymph nodes to interact with a DC was 8%, 58%, and 99% in the presence of 10, 100, and 1000 Ag-bearing DCs, respectively. Our results reveal the existence of a threshold in DC numbers below which T-cell responses fail to be elicited for probabilistic reasons. In mice and probably humans, we estimate that a minimum of 85 DCs are required to initiate a T-cell response when starting from precursor frequency of 10^{-6}. Our results have implications for the rational design of DC-based vaccines. (*Blood*. 2012;120(00): 000-000)

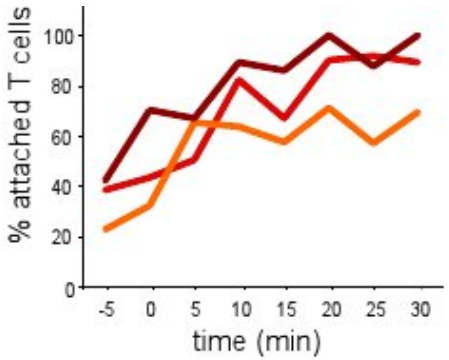
T cell - dendritic cell interactions in a lymph node



- Flow cytometry after 30 minutes (phospho-c-jun staining).
- Two-photon imaging during and after injection of peptide.

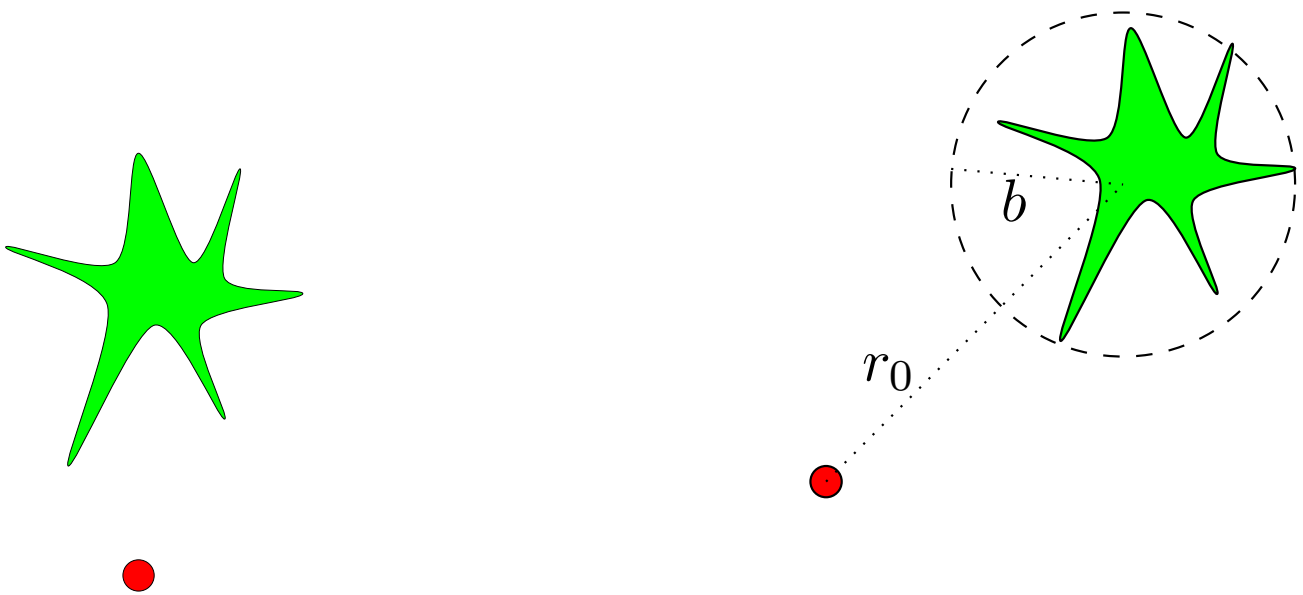






Cell-cell encounters confined to a volume

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



Preston, Waters, Jensen, Heaton and Pritchard. Physical Review E (2006)
Cheviakov and Ward. Mathematical and Computer Modelling (2011)
Mark Day and Grant Lythe, Springer (2012)

Estimate for α

In general, the mean hitting time, T, as a function of the initial location, x_0, satisfies $D\nabla^2 T(x_0) = -1$. If the DC is situated at the centre of the volume, the mean time is a function of $r_0 = |x_0|$ only, $T(x_0) = F(r_0)$, with $F(b) = 0$ and $\frac{\partial}{\partial r}F(R) = 0$.
If the T cell starts a distance r from the centre of the volume, then

$$F(r) = \frac{R^3}{3D}\left(\frac{1}{b} - \frac{1}{r}\right) - \frac{1}{6D}(r^2 - b^2).$$

The rate α is estimated the inverse of the mean hitting time, averaged over all available initial T-cell positions inside the volume, and expanding in powers of b/R:

$$\frac{1}{\alpha} = \frac{1}{\frac{4}{3}\pi(R^3 - b^3)} \int_b^R 4\pi r^2 F(r)\mathrm{d}r = \frac{R^3}{3Db} - \frac{3}{5}\frac{R^2}{D} + \cdots .$$

Experiment, numerics, formula

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

$$\text{Prob(T cell encounters at least one DC)} = 1 - \mathrm{e}^{-\alpha A t}.$$

With N T cells and A DCs,

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

Let the number of DCs that yields a 50 percent probability of at least one T cell-DC encounter in time t be denoted by A^*. Then

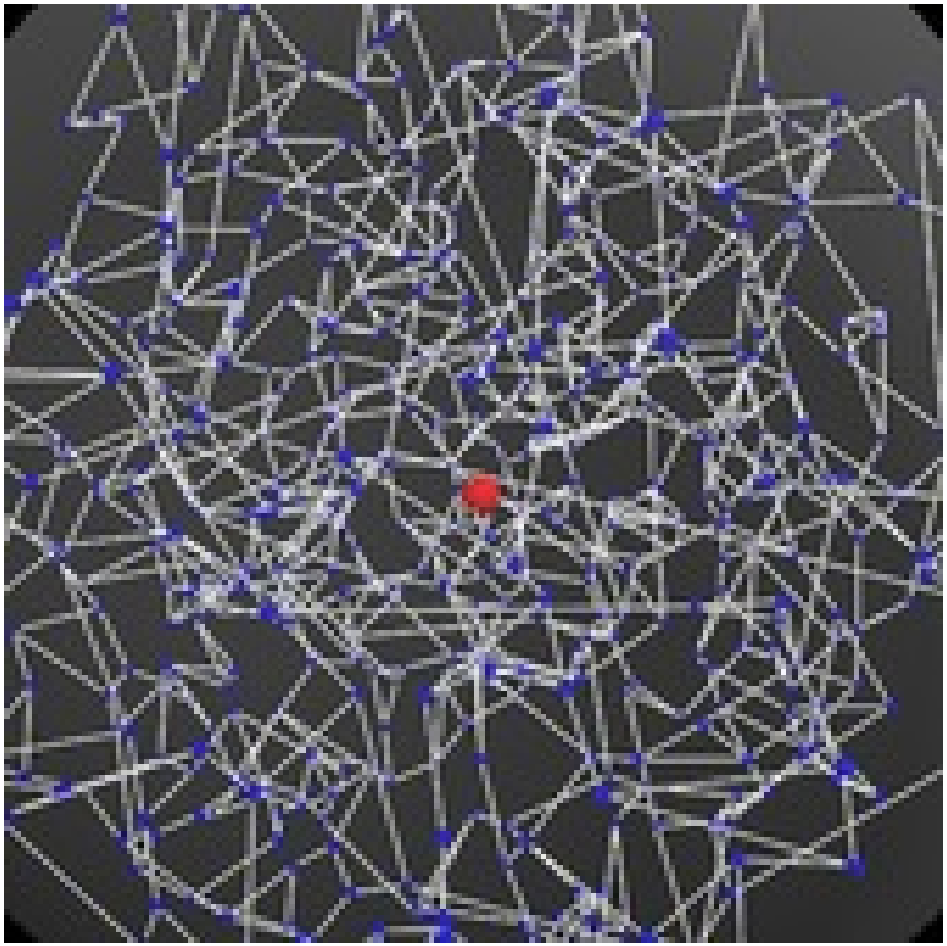
$$A^* = \frac{\ln 2}{\alpha N t}.$$

Choose $t = 24$hours.

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}.

Theory bol

Motion on a network resembles Brownian motion?



T cells can move on the network of reticular fibroblastic cells inside the lymph node, which may be haphazardly distributed, but is mostly static.

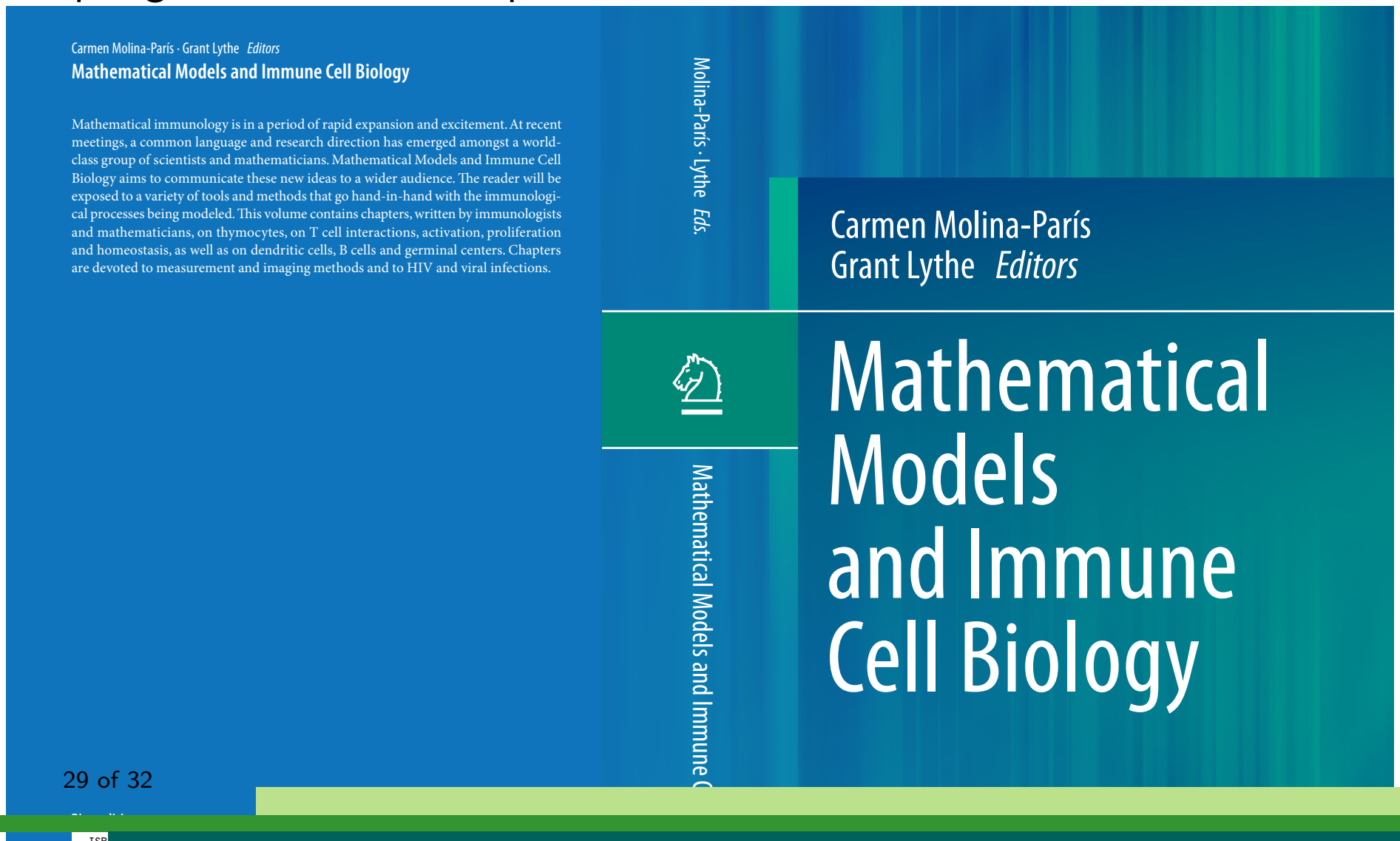
If the distribution of edges lengths l has $\beta = \mathbb{E}(l)$ and $\gamma = \mathbb{E}(l^2)$, and if a T cell moves with constant velocity v, then

$$D \propto v\frac{\gamma}{\beta}.$$

Graham Donovan and Grant Lythe
T-cell movement on the reticular network
Journal of Theoretical Biology **295** 59-67 (2012)

“Mathematical Models and Immune Cell Biology”

Springer volume, 19 Chapters.



MATHEMATICAL MODELLING AFFINITY GROUP

19 - 20 MAY 2014

Monday 19 May

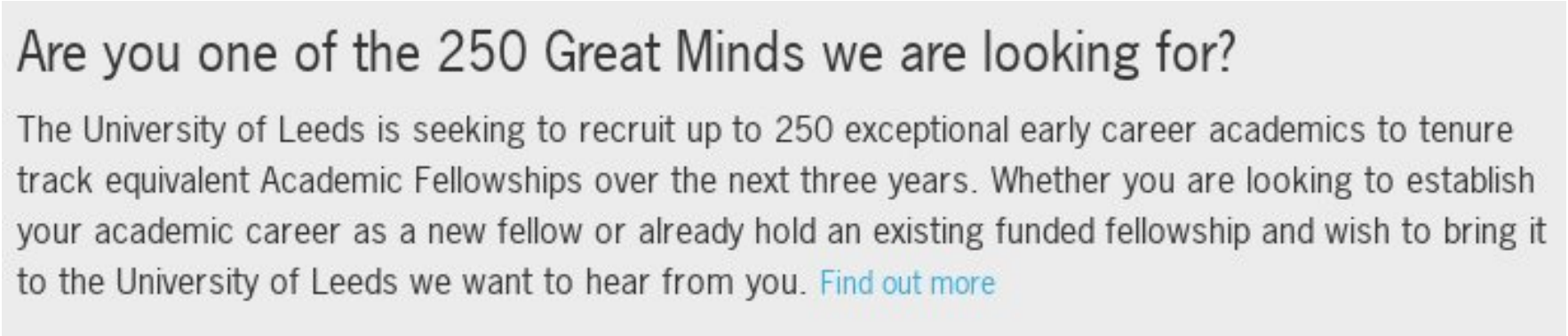
10:45-11:10	**REGISTRATION & COFFEE**
11:10-12:00	**Robin Callard (UCL)** *T cell homeostasis and immune reconstitution in HIV infected children on anti-retroviral therapy*
12:00-12:50	**Martin Turner (Babraham Institute)** *Molecular regulation of lymphocyte cell cycle*
12:50-14:00	**LUNCH**
14:00-14:50	**Klaus Okkenhaug (Babraham Institute)** *Signalling by PI3Ks in the immune system*
14:50-15:15	**Sitabhra Sinha (MISc, Chennai, India)** *Action-at-a-distance in cell signalling networks*
15:15-15:45	**COFFEE & BISCUITS**
15:45-16:10	**Benny Chain (UCL)** *Tracking global changes induced in the CD4 T cell receptor repertoire by immunisation with a complex antigen using short stretches of CDR3 protein sequences*
16:10-16:35	**Jennifer Benichou (Bar Ilan University, Israel)** *Restricted DH gene reading frame usage in the expressed human antigen repertoire is selected based on their amino acid content*
16:35-17:00	**Valentina Proserpio (EMBL, European Bioinformatics Institute)** *Transcriptomic dynamics in T helper 2 cells reveal a three state differentiation model*
17:00-17:25	**Andreas Bruckbauer (Cancer Research UK)** *From single molecules to nanoclusters: the spatio-temporal dynamics of the B cell receptor in the steady state*
18:30	**Dinner at St John's Chop House**

Tuesday 20 May

09:30-10:00	**REGISTRATION**
10:00-10:50	**Gerard Graham (University of Glasgow)** *Chemokines and the regulation of leukocyte migration in immunity*
10:50-11:15	**Niyaz Ahmed (University of Hyderabad)** *Immunology of novel bacterial survival mechanisms encoded by accessory genome content: from theoretical prediction to experiemental evidence*
11:15-11:45	**COFFEE AND BISCUITS**
11:45-12:10	**Joanna Lewis (UCL)** *Production and MHC-unbinding rates of viral peptides both affect the timing of epitope presentation by MHC-1*
12:10-13:00	**Simon Davis (University of Oxford(** *Unconventional receptor triggering in T cells: the kinetic-segregation model*
13:00 - 14:00	**LUNCH**
14:00-14:25	**Alistair Bailey (University of Southampton)** *Investigating the relationship between MHC-1 antigen processing and protein plasticity using molecular dynamics simulations*
14:25-14:50	**Hannah Mayer (University of Bonn)** *A mathematical justification for a specific recognition by T cells*
14:50-15:15	**Aridaman Pandit (University of Utrecht)** *Modelling cytotoxic T lymphocyte fate commitment dynamics*
15:15-15:45	**COFFEE AND BISCUITS**
15:45 - 16:10	**Thea Hogan (MRC & UCL)** *Cell-intrinsic and extrinsic factors combine to determine CTL killing efficiency in vivo*
16:10-17:00	**Carmen Molina-Paris (University of Leeds)** *IL-7 in T cell homeostasis: modelling at the molecular, cellular and population levels*
	- END -

Next meeting:
Microsoft Research, Cambridge
4-5 June 2015.
`http://www1.maths.leeds.ac.uk/applied/BSI/`

Academic fellowships



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a word from . . .

- Quantitative T cell Immunology (ITN)
- Mathematics for Health and Disease (FP7 IRSES)
- International Network on Theoretical Immunology (FP7 IRSES)
- Immunology, Imaging and Modelling (BBSRC MATSYB)

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