

Stochastic modelling: T cell repertoire diversity

Carmen Molina-París

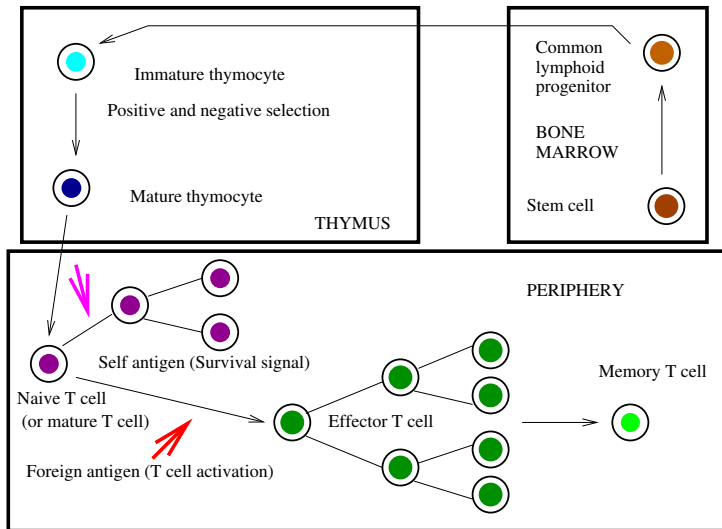
I²M Summer School, School of Mathematics, Leeds

4th of September 2009

Outline

- 1 Background: immunology
- 2 Mathematical model
- 3 Results
- 4 Conclusions and work in progress

History of a T cell



Immunological evidence

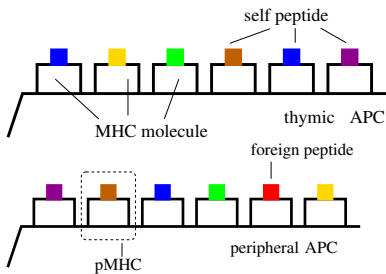
- 1 A protective immune system requires a T cell population that can respond to foreign antigens.
- 2 The host cannot predict the precise pathogen-derived antigens that will be encountered in the future.

Homeostatic regulation of naïve T cells in the periphery

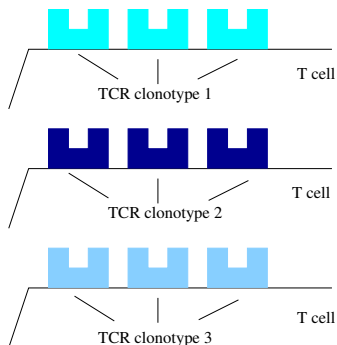
- 1 The mature T cell repertoire consists of a constant number of cells distributed over a large number of different T cell clonotypes.
- 2 T cells compete for signals to divide provided by professional cells. The immune system guarantees coexistence and persistence of different T cell clonotypes.
- 3 Centenarians have an extremely low number of naïve T cells and compromised diversity \Rightarrow **T cell clonotype extinction.**

Antigen presenting cells (APCs)

- 1 APCs present peptides (or antigens) on their surface by means of an MHC molecule.
- 2 We denote by pMHC the complex formed by a peptide-MHC molecule.
- 3 We denote by APP the antigen presentation profile of an APC.



T cells: T cell receptor (TCR)



- 1 T cells have on their surface receptors (TCRs) for ligand pMHC. Each T cell expresses only one type of TCR \equiv clonotype.
- 2 TCR diversity $\approx 10^7 - 10^8$ is randomly generated by genetic recombination.
- 3 Inevitably some clonotypes (all T cells with identical TCR molecules), recognise one or more self peptides and can generate autoimmune responses.

Mathematical setup of the model

- 1 We want to model the number of T cells (of a given clonotype) with a stochastic description.
- 2 The variable that describes the number of T cells (of the given clonotype) at time t is represented as $\mathbb{X}(t)$, with $t = 0$ the initial time.
- 3 The state space is $S = \{0, 1, 2, 3, \dots\}$. This represents the values $\mathbb{X}(t)$ can take at any time (number of cells).
- 4 The stochastic (Markov process) model can be determined uniquely with the transition probabilities:

$$\mathbb{P}(\mathbb{X}(t + \Delta t) = m \mid \mathbb{X}(t) = n) \quad \text{with} \quad n, m \in S.$$

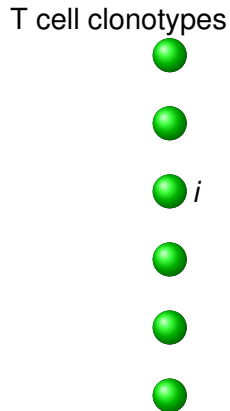
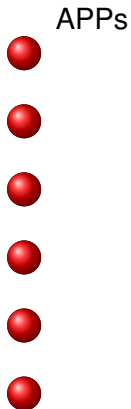
- 5 Birth and death Markov process:

$$0 \begin{array}{c} \xrightarrow{\mu_1} \\ \xleftarrow{\lambda_0=0} \end{array} 1 \begin{array}{c} \xrightarrow{\mu_2} \\ \xleftarrow{\lambda_1} \end{array} 2 \begin{array}{c} \xrightarrow{\mu_3} \\ \xleftarrow{\lambda_2} \end{array} 3 \begin{array}{c} \xrightarrow{\mu_4} \\ \xleftarrow{\lambda_3} \end{array} \dots \begin{array}{c} \xrightarrow{\mu_{n-1}} \\ \xleftarrow{\lambda_{n-2}} \end{array} n-1 \begin{array}{c} \xrightarrow{\mu_n} \\ \xleftarrow{\lambda_{n-1}} \end{array} n \begin{array}{c} \xrightarrow{\mu_{n+1}} \\ \xleftarrow{\lambda_n} \end{array} n+1 \dots$$

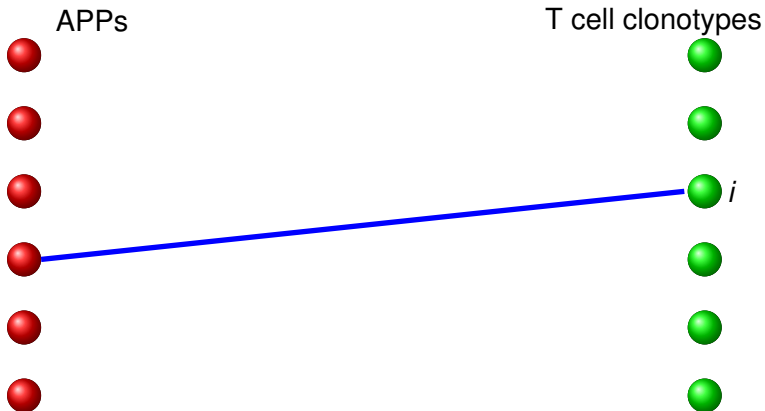
T cells require signals from self APCs to divide

- 1 T cells are defined by their clonotype i (TCR molecule).
- 2 $n_i(t)$ is the number of T cells of clonotype i at time t .
- 3 μ_i is the death rate per single T cell of clonotype i .
- 4 λ_i is the birth rate per single T cell of clonotype i .
- 5 APCs are defined by their antigen presentation profile (APP) and labelled by index q .
- 6 \mathcal{Q}_i is the set of APPs from which T cells of clonotype i receive a signal that triggers one round of cell division.
- 7 \mathcal{C}_q is the set of T cells that receive a signal to divide from APP q .

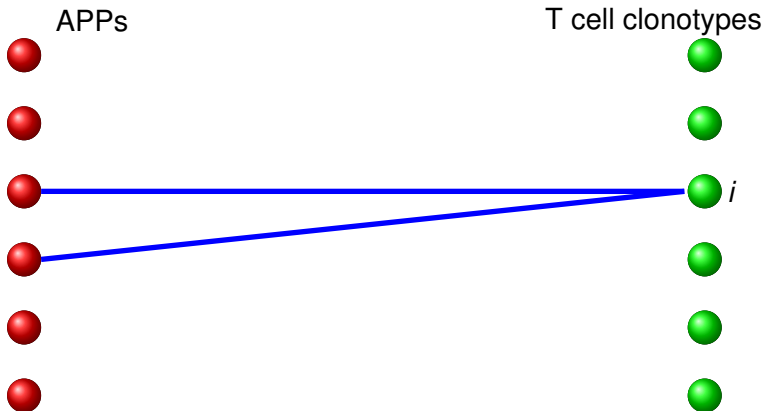
Antigen presentation profiles and T cell clonotypes



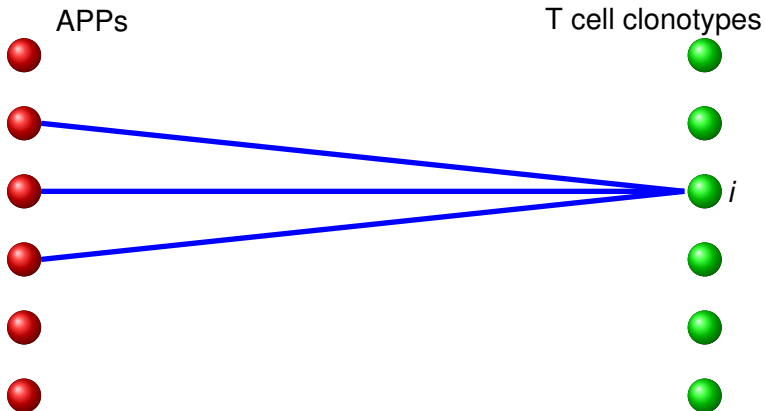
Antigen presentation profiles and T cell clonotypes



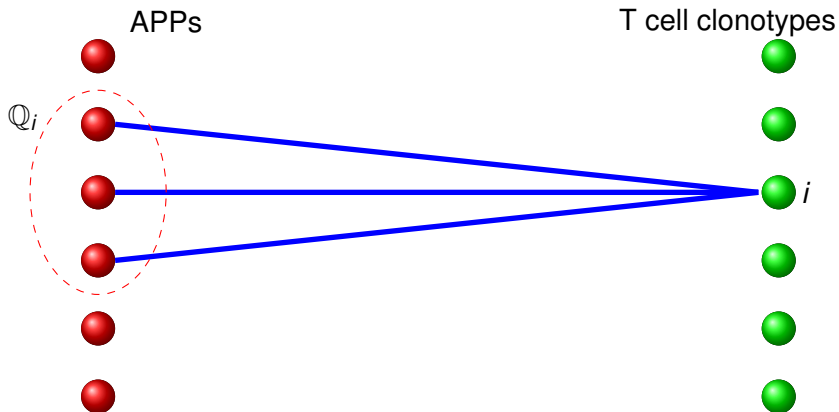
Antigen presentation profiles and T cell clonotypes



Antigen presentation profiles and T cell clonotypes



Antigen presentation profiles and T cell clonotypes



T cells that receive signal delivered by APP q

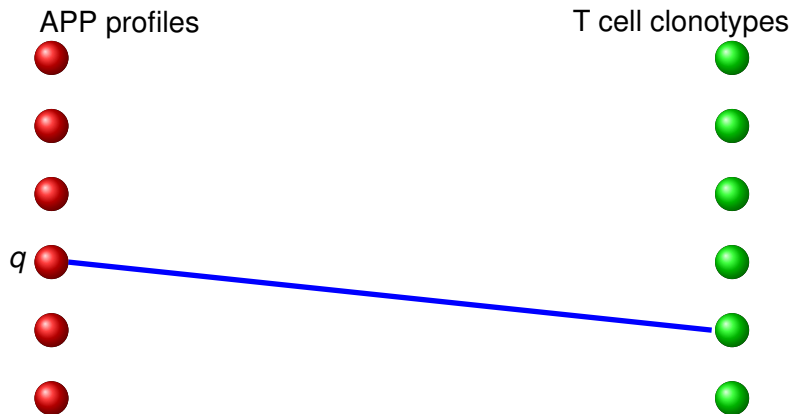
APP profiles



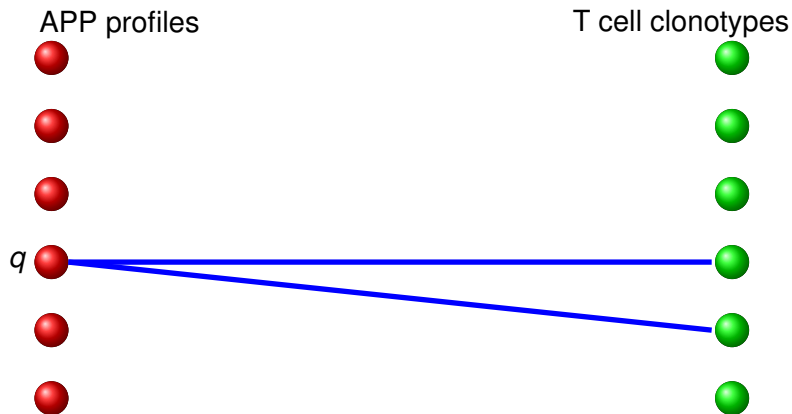
T cell clonotypes



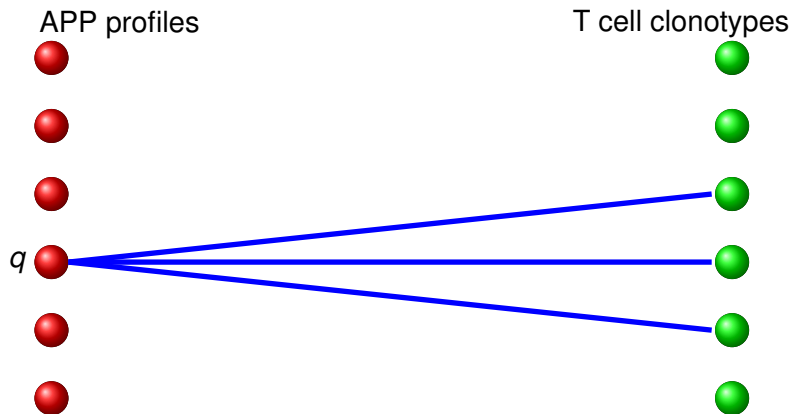
T cells that receive signal delivered by APP q



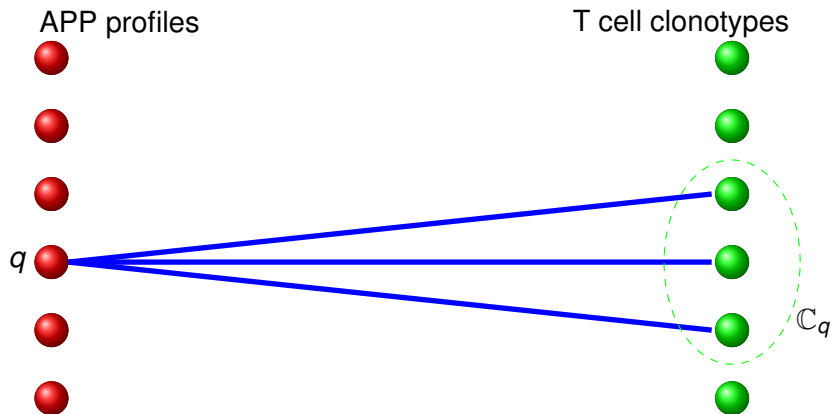
T cells that receive signal delivered by APP q



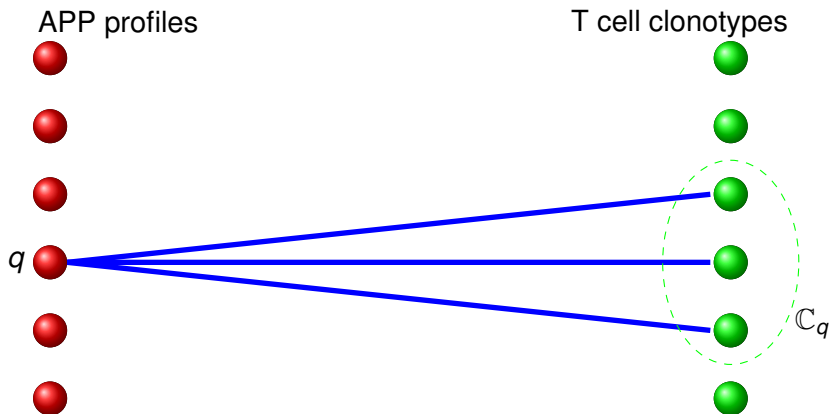
T cells that receive signal delivered by APP q



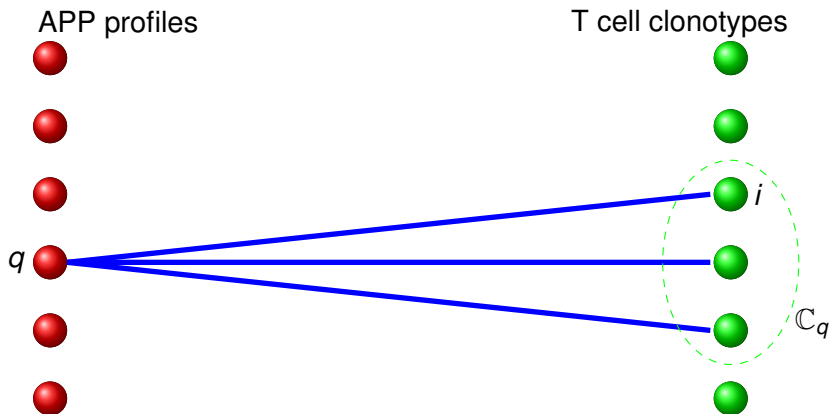
T cells that receive signal delivered by APP q



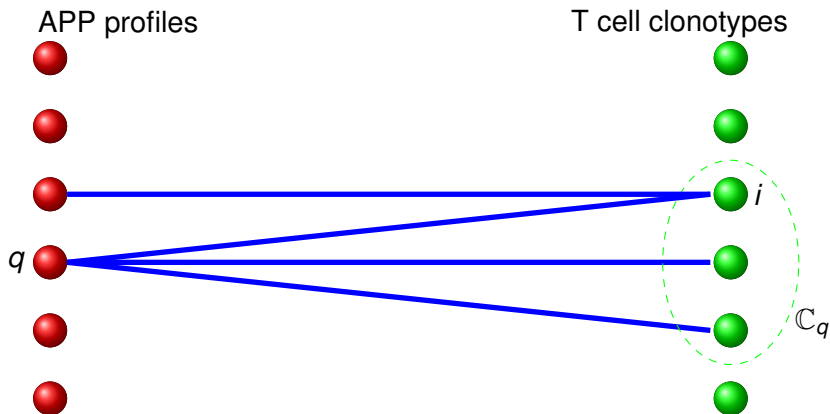
T cell clonotype competition for APPs



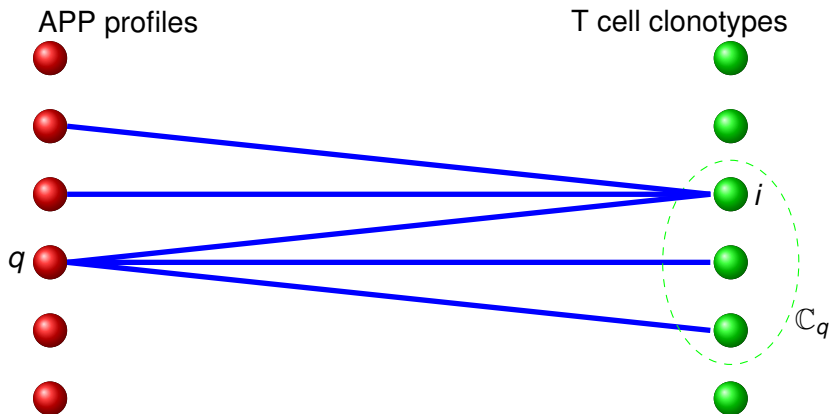
T cell clonotype competition for APPs



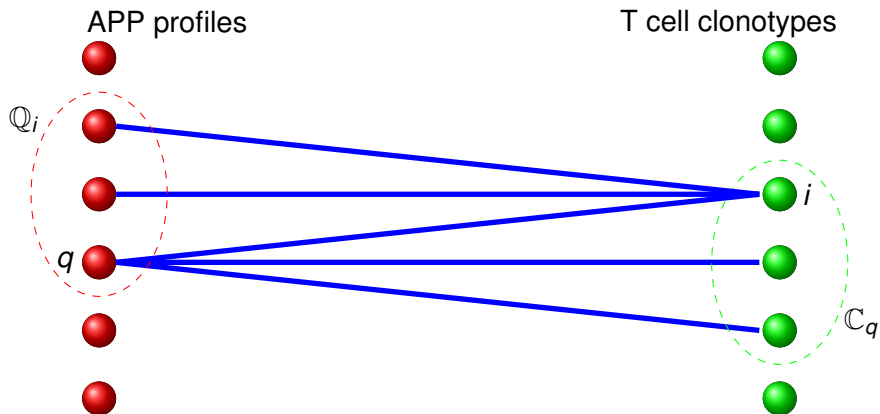
T cell clonotype competition for APPs



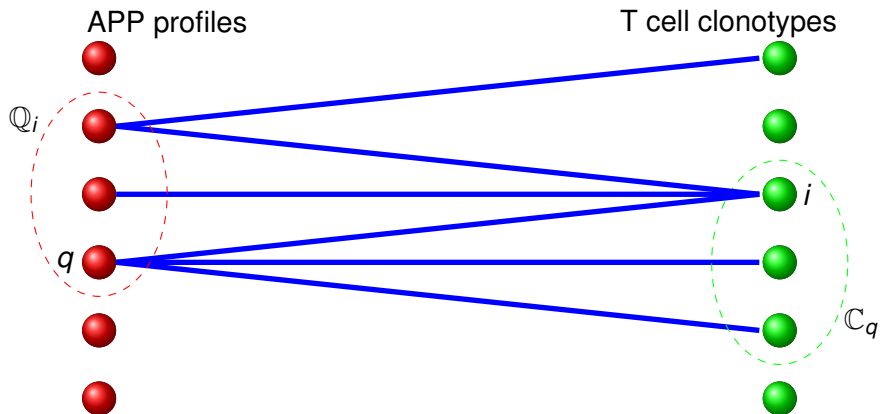
T cell clonotype competition for APPs



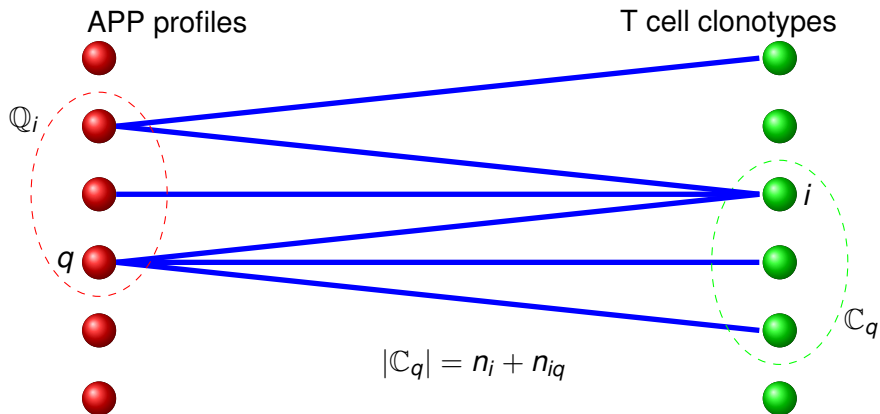
T cell clonotype competition for APPs



T cell clonotype competition for APPs

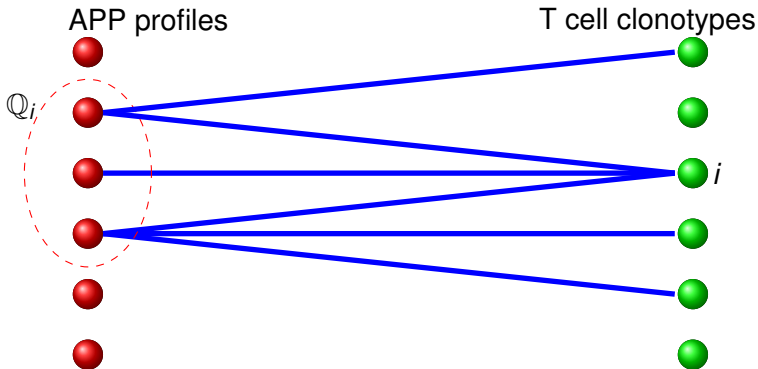


T cell clonotype competition for APPs



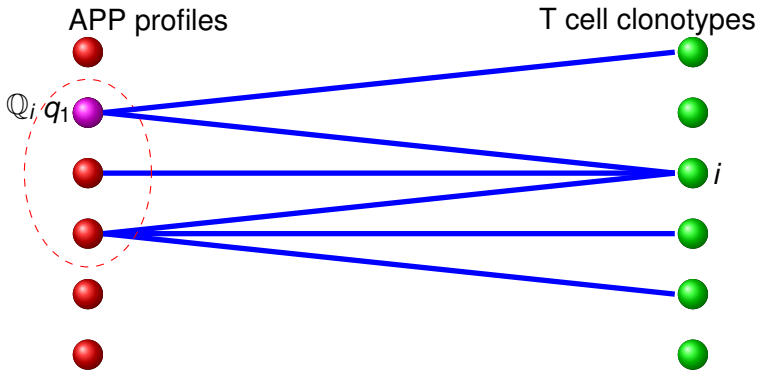
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



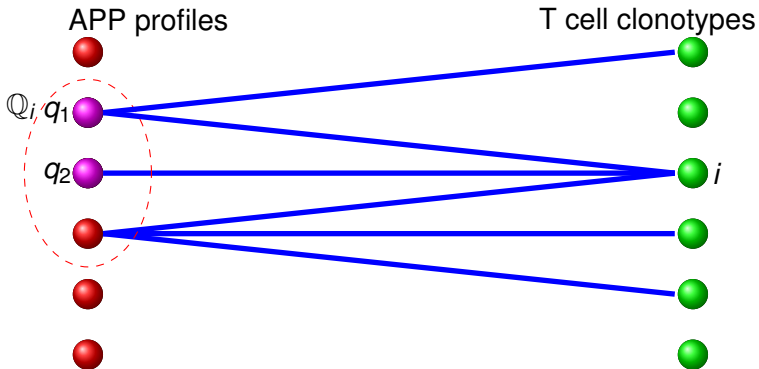
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



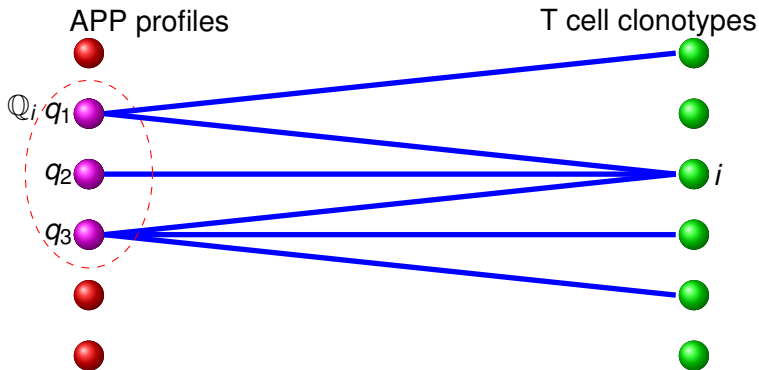
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



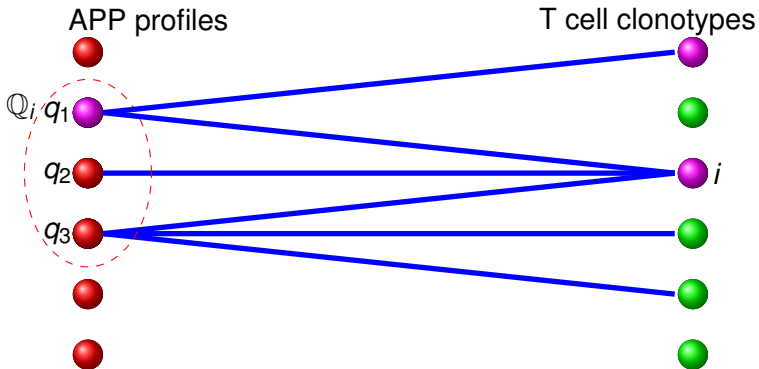
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



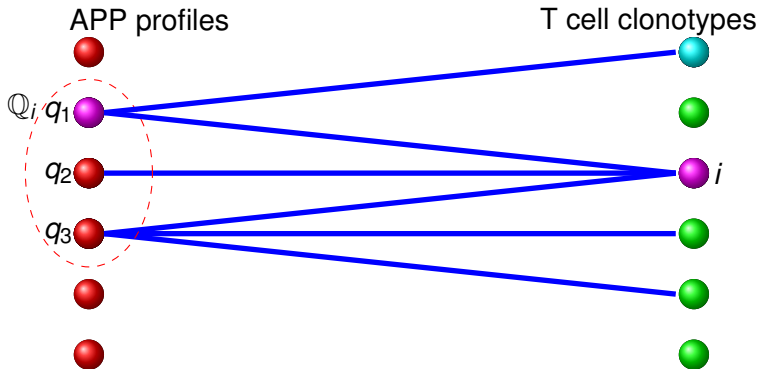
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



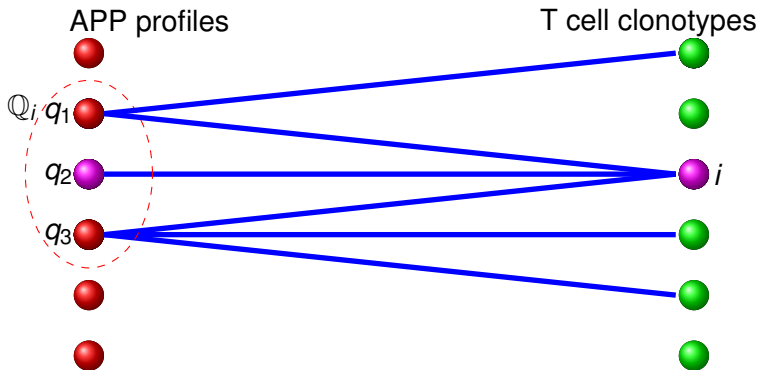
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



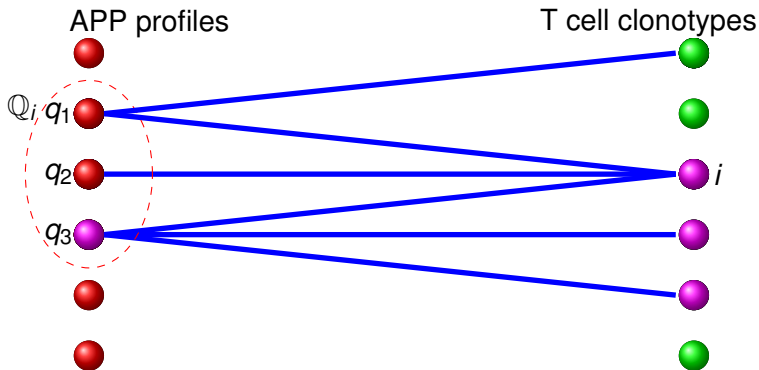
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



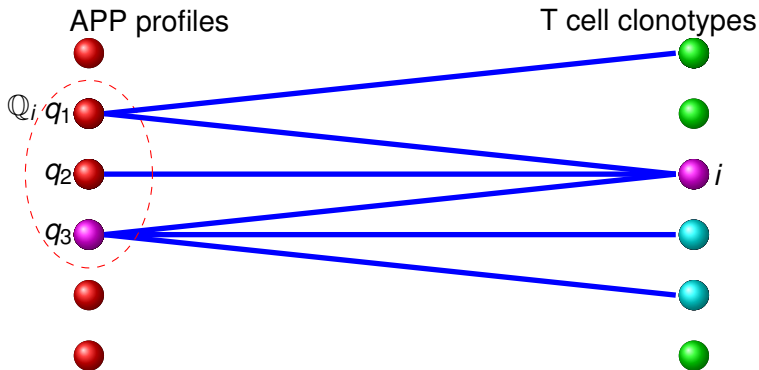
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



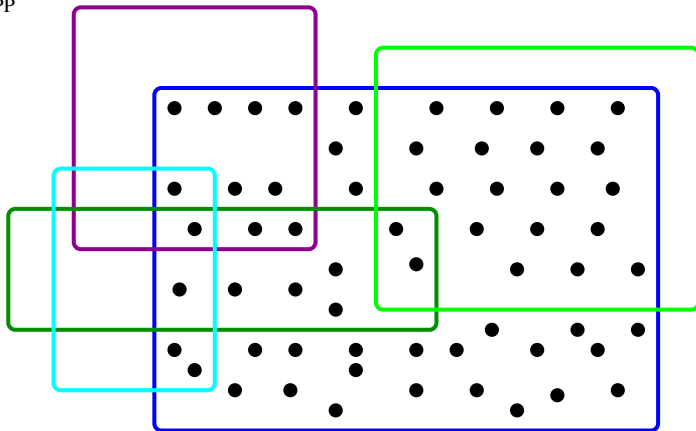
Competition for APPs that signal to clonotype i

- 1 Given i we need to identify the set Q_i .
- 2 Given $q \in Q_i$ we need to identify clonotypes that compete with i .



Picture of partition of Q_i

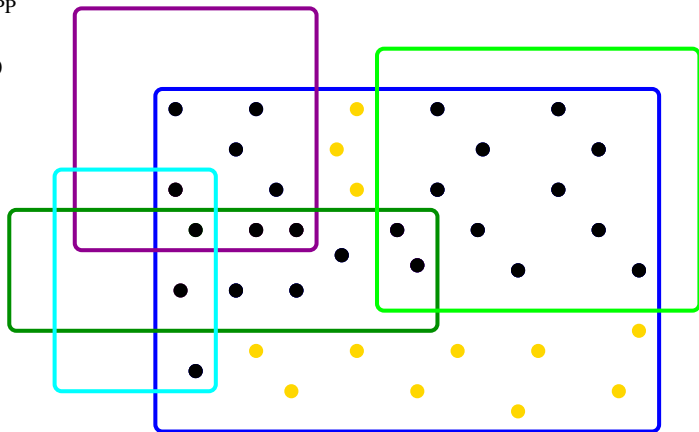
- APP



Picture of partition of Q_i

● APP

● $r=0$

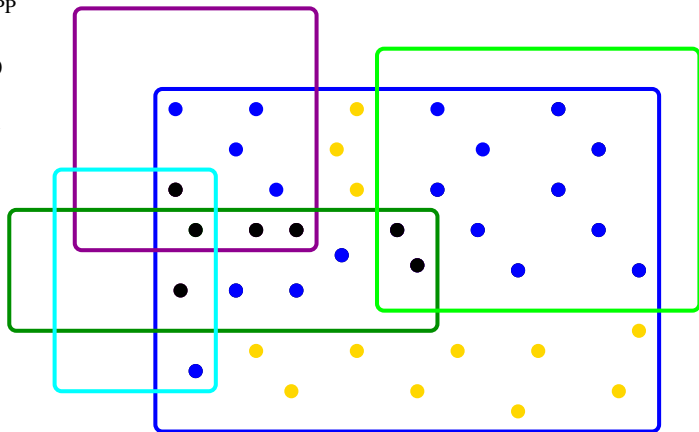


Picture of partition of Q_i

● APP

● $r=0$

● $r=1$



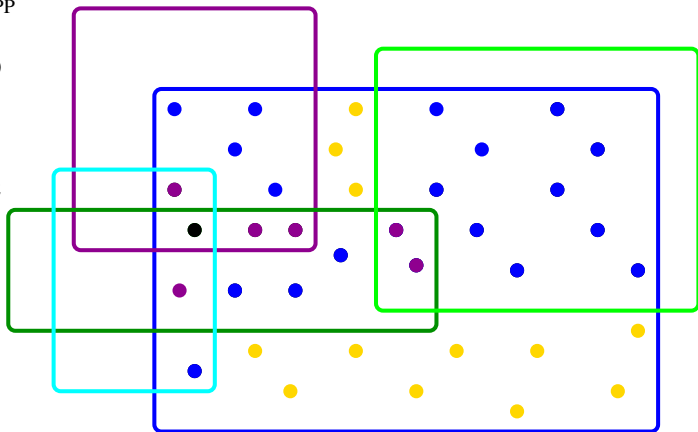
Picture of partition of Q_i

● APP

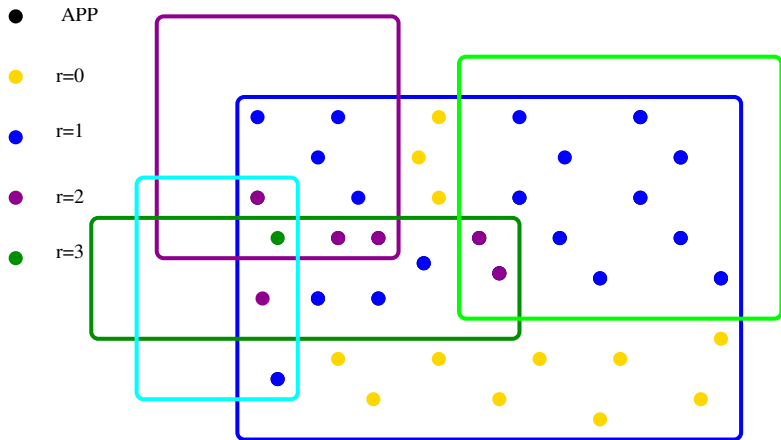
● $r=0$

● $r=1$

● $r=2$



Picture of partition of Q_i



More on this partition of Q_i

- 1 $Q_i = \bigcup_{r=0}^{+\infty} Q_{ir}$.
- 2 Q_{ir} is the subset of APPs in Q_i that provide signals to T cells of clonotype i and r other different T cell clonotypes in the peripheral repertoire.
- 3 $Q_{ir} \cap Q_{ir'} = \emptyset$, for $r \neq r'$.

More on this partition of \mathbb{Q}_i

- 1 $\mathbb{Q}_i = \bigcup_{r=0}^{+\infty} \mathbb{Q}_{ir}$.
- 2 \mathbb{Q}_{ir} is the subset of APPs in \mathbb{Q}_i that provide signals to T cells of clonotype i and r other different T cell clonotypes in the peripheral repertoire.
- 3 $\mathbb{Q}_{ir} \cap \mathbb{Q}_{ir'} = \emptyset$, for $r \neq r'$.

Mean field approximation

More on this partition of \mathbb{Q}_i

- 1 $\mathbb{Q}_i = \bigcup_{r=0}^{+\infty} \mathbb{Q}_{ir}$.
- 2 \mathbb{Q}_{ir} is the subset of APPs in \mathbb{Q}_i that provide signals to T cells of clonotype i and r other different T cell clonotypes in the peripheral repertoire.
- 3 $\mathbb{Q}_{ir} \cap \mathbb{Q}_{ir'} = \emptyset$, for $r \neq r'$.

Mean field approximation

- 1 $\mathbb{E}_{q \in \mathbb{Q}_{ir}} [n_{iq}] = r \langle n \rangle$, with $\langle n \rangle$ the average clonotype size (average number of T cells per clonotype). (*)
- 2 The cardinality of the set \mathbb{Q}_{ir} can be computed from the binomial distribution.

Meaning of the mean field approximation

- 1 The cells of clonotype i are competing with many T cells belonging to a large number of other clonotypes in the repertoire.
- 2 Individual competitive interactions with other clones are weak: access to any given APP does not have a significant impact on the fate of the clone.

Modelling the number of cells of a given clonotype

1 The number of T cells of a given clonotype is modeled as a continuous time birth and death process: $\mathbb{X}(t)$.

2 State space and transitions (birth and death events):

$$0 \xrightleftharpoons[\lambda_{0=0}]{\mu_1} 1 \xrightleftharpoons[\lambda_1]{\mu_2} 2 \xrightleftharpoons[\lambda_2]{\mu_3} 3 \xrightleftharpoons[\lambda_3]{\mu_4} \dots \xrightleftharpoons[\lambda_{n-2}]{\mu_{n-1}} n-1 \xrightleftharpoons[\lambda_{n-1}]{\mu_n} n \xrightleftharpoons[\lambda_n]{\mu_{n+1}} n+1 \dots$$

3 $\mu_n \equiv \mu n$ is the death rate from state n .

4 $\lambda_n \equiv \varphi n e^{-\nu} \sum_{r=0}^{+\infty} \frac{\nu^r}{r!} \frac{1}{r \langle n \rangle + n}$ is the birth rate from state n . (\star)

5 μ is the death rate per single T cell.

6 φ is the signal rate to divide per single T cell.

7 ν is the average number of clonotype competitors of the given clonotype.

8 $\langle n \rangle$ is the average number of T cells per clonotype.

Analytic results

- 1 Extinction takes places with certainty.
- 2 If extinction is certain, the mean time to extinction from state $m \geq 1$, τ_m , is finite and can be computed.
- 3 What can we say about $\mathbb{X}(t)$ before extinction?
- 4 Before extinction takes place, the following conditional probability distribution for $n \geq 1$ exists and can be computed:

$$q_n(t) = \mathbb{P}(\mathbb{X}(t) = n \mid \text{no extinction}) .$$

- 5 The limiting conditional probability distribution (LCD) is defined as

$$\lim_{t \rightarrow +\infty} q_n(t) = \bar{q}_n .$$

Expected time to extinction from state $n = 1$

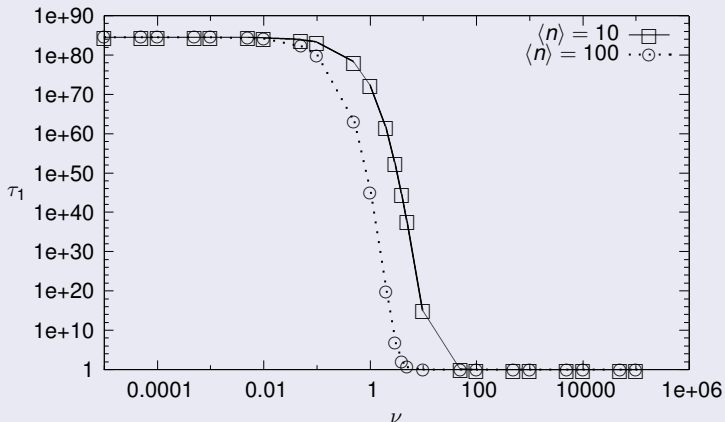


Figure: τ_1 as a function of ν with $\varphi = 200$, $\mu = 1$ and $\langle n \rangle = 10, 100$.

Expected T cell number in LCD

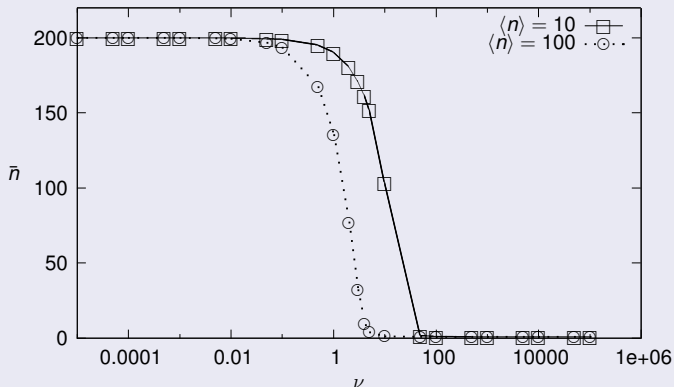
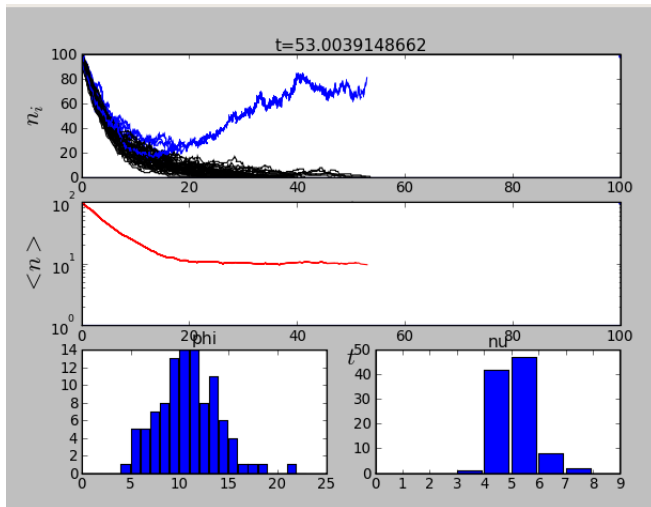


Figure: LCD expected T cell number in a clonotype as a function of ν with $\varphi = 200$, $\mu = 1$ and $\langle n \rangle = 10, 100$.

Visualisation of exact T cell competition model



Results and conclusions

- 1 Based on immunological evidence, we propose a stochastic model of peripheral naïve T cell competition for APC signals to divide.
- 2 The model requires four parameters: μ , φ , ν and $\langle n \rangle$.
- 3 Extinction is certain for any value of the parameters.
- 4 We can calculate expected extinction times \Rightarrow clones with a mean niche overlap greater than one have a short repertoire lifespan.
- 5 Existence of the limiting conditional probability distribution is guaranteed \Rightarrow homeostatic regulation of T cell numbers.
- 6 If the average number of T cells per clonotype decreases, the LCD expected T cell number increases \Rightarrow qualitative explanation of lymphopenia.
- 7 Minimal self pMHC recognition commonality between different TCRs (clonotypes) results in a diverse T cell repertoire.

Work in progress (still a lot to do!)

- 1 Consider continuous thymic output.
- 2 Compute competition probabilities **from scratch** $\Rightarrow \nu$.
- 3 $\langle n \rangle$ should be computed self-consistently. This requires knowledge of the thymic distribution of ν .
- 4 If $|\mathbb{Q}_i \cap \mathbb{Q}_{i'}| \approx |\mathbb{Q}_i|$ we need to study a **bi-variate competition processes** \Rightarrow multi-variate competition processes.
- 5 Use the large N approximation to derive deterministic equations for the average number of cells in a clonotype.
- 6 T cell homeostasis: cytokine signalling, $CD4^+$ T cells versus $CD8^+$ T cells, memory T cells versus naïve T cells, etc.
- 7 Extend the model to study B cell repertoire diversity.

Other immunology projects at Leeds

- 1 Develop stochastic models of in vivo two-photon microscopy imaging of cellular interactions between T cells and dendritic cells (Glasgow, Birmingham and Leeds).
- 2 Develop stochastic models of multivalent receptor-ligand binding (TCR-pMHC) (Heidelberg, Madrid and Leeds).

Visualisation of multivalent receptor-ligand engagement

Interested in experimental/theoretical immunology?

Interested in experimental/theoretical immunology?

I²M MATSYB BBSRC Network

I²M MATSYB BBSRC Network

- 1 Immunology Imaging and Modelling Research Network.

Interested in experimental/theoretical immunology?

I²M MATSYB BBSRC Network

- 1 Immunology Imaging and Modelling Research Network.
- 2 Join the network!

I²M MATSYB BBSRC Network

- 1 Immunology Imaging and Modelling Research Network.
- 2 Join the network!
- 3 <http://www.maths.leeds.ac.uk/Applied/I2M/>

Interested in experimental/theoretical immunology?

I²M MATSYB BBSRC Network

- 1 Immunology Imaging and Modelling Research Network.
- 2 Join the network!
- 3 <http://www.maths.leeds.ac.uk/Applied/I2M/>
- 4 Any questions? Simply ask me!

Interested in experimental/theoretical immunology?

I²M MATSYB BBSRC Network

- 1 Immunology Imaging and Modelling Research Network.
- 2 Join the network!
- 3 <http://www.maths.leeds.ac.uk/Applied/I2M/>
- 4 Any questions? Simply ask me!
- 5 Network Summer School, School of Mathematics, University of Leeds, 31st August - 4th September 2009.

Thank You!

- 1 Hugo van den Berg (for all this joint work).
- 2 Emily Stirk and Grant Lythe.
- 3 The audience (for your patience).
- 4 Support is acknowledged from the University of Leeds through a WUN Research Fund for International Collaboration and BBSRC through a MATSYB Network.

