Stochastic birth and death processes in Immunology

Emily Stirk (PhD)
Lythe and CMP (supervisors)

Modelling infectious diseases (workshop)
Institute of Mathematical Sciences (IMSc), Chennai, India
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carmen@maths.leeds.ac.uk

Outline

Outline

Useful references

- A wonderful book:

Linda J.S. Allen
An introduction to stochastic processes with applications to biology
CRC Press (2010).

- The mathematical model of T cell homeostasis was introduced in the following reference:

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).

- The mathematical model of bivariate clonotype competition was introduced in the following reference:

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, **265** 396–410 (2010).

Continuous time Markov chains (CTMC)

Let $\{\mathbb{X}(t)\}$, where $t \in [0, +\infty)$, be a collection of discrete random variables with values in a finite $S = \{0, 1, 2, \ldots, N\}$ or infinite $S = \{0, 1, 2, \ldots\}$ state space. The index set, time, is continuous: $[0, +\infty)$.

Definition

The stochastic process $\{\mathbb{X}(t)\}$, where $t \in [0, +\infty)$, is called a continuous time Markov chain (CTMC) if it satisfies the following condition: for any sequence of real numbers satisfying $0 \leq t_0 < t_1 < \ldots < t_n < t_{n+1}$ and $i_0, \ldots, i_{n+1} \in S$:

$$\mathbb{P}\left(\mathbb{X}(t_{n+1}) = i_{n+1} \mid \mathbb{X}(t_0) = i_0, \ldots, \mathbb{X}(t_n) = i_n\right) = \mathbb{P}\left(\mathbb{X}(t_{n+1}) = i_{n+1} \mid \mathbb{X}(t_n) = i_n\right) . \quad (1)$$

This is the Markov Property: the transition to state i_{n+1} at time t_{n+1} depends only on the value of the state at the most recent time t_n, and does not depend on the past (or history of the process).

Probability distribution

Each random variable $\{\mathbb{X}(t)\}$ has an associated probability distribution $\{p_i(t)\}_{i\in S}$, with $p_i(t) = \mathbb{P}\{\mathbb{X}(t) = i\}$ with $i \in S$.

Definition

For the random variables $\{\mathbb{X}(s)\}$ and $\{\mathbb{X}(t)\}$, where $s < t$, we define the transition probabilities as:

$$p_{ji}(t,s) = \mathbb{P}\{\mathbb{X}(t) = j \mid \mathbb{X}(s) = i\} \text{ for } i,j \in S\,.$$

Definition

For $i, j \in S$ and $s < t$, we say that the transition probabilities are stationary or homogeneous if they do not depend explicitly on s or t, but depend only on the length of the time interval, $t - s$, that is:

$$p_{ji}(t-s) = \mathbb{P}\{\mathbb{X}(t) = j \mid \mathbb{X}(s) = i\} = \mathbb{P}\{\mathbb{X}(t-s) = j \mid \mathbb{X}(0) = i\}\,.$$

Transition probabilities

We denote the matrix of transition probabilities (or the transition matrix) as

$$\mathbf{P}(t) = (p_{ji}(t)) \,, \tag{2}$$

which is a stochastic matrix for all $t \geq 0$.

Properties of the transition probabilities

- $p_{ji}(t) \geq 0 \,, \quad \forall t \in [0, +\infty[\,, \quad \forall i, j \in S \,.$
- For a fixed, but fiducial $i \in S$, we have

$$\sum_{j \in S} p_{ji}(t) = 1 \text{ for } t \geq 0 \,, \ \forall i \in S \,.$$

- The probability that there is a transition from state i to some other state at time t equals one, for all $t \in [0, +\infty[$ and for all $i \in S$.

Transition probabilities: solutions of the Kolmogorov equations

Theorem

The transition probabilities

$$p_{ji}(t+\Delta t) = \mathbb{P}\{\mathbb{X}(t+\Delta t) = j \mid \ \mathbb{X}(0) = i\}$$

satisfy the forward and backward Kolmogorov equations.

$$\begin{aligned} p_{ji}(t+\Delta t) &= \sum_{k\in S} p_{jk}(\Delta t)\ p_{ki}(t) \quad \textit{forward Kolmogorov equations ,} \\ &= \sum_{k\in S} p_{jk}(t)\ p_{ki}(\Delta t) \quad \textit{backward Kolmogorov equations .} \end{aligned} \tag{3}$$

Proof of the forward Kolmogorov equations

$$p_{ji}(t+\Delta t) = \mathbb{P}\{\mathbb{X}(t+\Delta t) = j \mid \mathbb{X}(0) = i\} = \sum_{k\in S} \mathbb{P}\{\mathbb{X}(t+\Delta t) = j, \mathbb{X}(t) = k \mid \mathbb{X}(0) = i\}$$

here we make use of the conditional probability property to get

$$= \sum_{k\in S} \mathbb{P}\{\mathbb{X}(t+\Delta t) = j \mid \mathbb{X}(t) = k \text{ and } \mathbb{X}(0) = i\}\, \mathbb{P}\{\mathbb{X}(t) = k \mid \mathbb{X}(0) = i\}$$

now we use the Markov property

$$= \sum_{k\in S} \mathbb{P}\{\mathbb{X}(t+\Delta t) = j \mid \mathbb{X}(t) = k\}\, \mathbb{P}\{\mathbb{X}(t) = k \mid \mathbb{X}(0) = i\}$$

we now use the general definition for the transition probabilities to get

$$= \sum_{k\in S} p_{jk}(\Delta t)\; p_{ki}(t)\;.$$

We obtain the forward Kolmogorov equations: $p_{ji}(t+\Delta t) = \sum_{k\in S} p_{jk}(\Delta t)\; p_{ki}(t)\;.$

Homework: Derive the backward Kolmogorov equations

$$p_{ji}(t+\Delta t) = \sum_{k\in S} p_{jk}(t)\; p_{ki}(\Delta t) \quad \text{backward Kolmogorov equations .} \tag{4}$$

Outline

Birth and death processes: special type of Markov processes

- Birth and death processes are a special type of Markov processes.
- Transitions are only allowed as follows in the infinite case:

$$0 \underset{\lambda_0=0}{\overset{\mu_1}{\leftrightharpoons}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightharpoons}} 2 \underset{\lambda_2}{\overset{\mu_3}{\leftrightharpoons}} 3 \underset{\lambda_3}{\overset{\mu_4}{\leftrightharpoons}} \cdots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftrightharpoons}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftrightharpoons}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftrightharpoons}} n+1 \cdots$$

- Transitions are only allowed as follows in the finite case:

$$0 \underset{\lambda_0}{\overset{\mu_1}{\leftrightharpoons}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightharpoons}} 2 \underset{\lambda_2}{\overset{\mu_3}{\leftrightharpoons}} 3 \underset{\lambda_3}{\overset{\mu_4}{\leftrightharpoons}} \cdots \underset{\lambda_{N-2}}{\overset{\mu_{N-1}}{\leftrightharpoons}} N-1 \underset{\lambda_{N-1}}{\overset{\mu_N}{\leftrightharpoons}} N$$

Birth and death process

- A continuous time birth and death process is a CTMC, $\mathbb{X}(t)$, with either a finite $\{0, 1, 2, \ldots, N\}$ or infinite $\{0, 1, 2, \ldots, \}$ state space.
- A birth and death process has the following transition probabilities as $\Delta t \to 0^+$:

$$p_{ji}(\Delta t) = \mathbb{P}\{\mathbb{X}(t + \Delta t) = j \mid \mathbb{X}(t) = i\}$$
$$= \begin{cases} \lambda_i \Delta t + o(\Delta t) & j = i + 1 \ , \\ \mu_i \Delta t + o(\Delta t) & j = i - 1 \ , \\ 1 - (\lambda_i + \mu_i)\Delta t + o(\Delta t) & j = i \\ o(\Delta t) & j \neq i - 1, i, i + 1 \ . \end{cases} \tag{5}$$

- We denote λ_i= birth rate and μ_i= death rate, when the population has size i. $\lambda_i, \mu_i \geq 0$ and $o(\Delta t)$ is the Landau order symbol:

$$\lim_{\Delta t \to 0^+} \frac{o(\Delta t)}{\Delta t} = 0 \ . \tag{6}$$

Forward Kolmogorov equations: birth and death process I

- Let $p_n(t) = \mathbb{P}\{\mathbb{X}(t) = n \mid \mathbb{X}(t_0 = 0) = n_0\} \quad \forall n \in S$ and with initial condition $n_0 \in S$ at time $t_0 = 0$.
- The forward Kolmogorov differential equations for $p_n(t)$ can be derived directly from the transition probabilities of Eq. (5).
- Assuming Δt is sufficiently small, we consider $p_n(t + \Delta t)$, and make use of the forward Kolmogorov equations:

$$\begin{aligned} p_n(t+\Delta t) &= p_{n-1}(t)[\lambda_{n-1}\Delta t + o(\Delta t)] + p_{n+1}(t)[\mu_{n+1}\Delta t + o(\Delta t)] \\ &\quad + p_n(t)[1 - (\lambda_n + \mu_n)\Delta t + o(\Delta t)] + \sum_{k \neq n-1,n,n+1} p_k(t) o(\Delta t) \\ &= p_{n-1}(t)\lambda_{n-1}\Delta t + p_{n+1}(t)\mu_{n+1}\Delta t \\ &\quad + p_n(t)[1 - (\lambda_n + \mu_n)\Delta t] + o(\Delta t) \ , \quad \forall n \in S \quad \text{except} \quad n = 0, N \ . \end{aligned} \tag{7}$$

- If $n = 0$ and assuming $\mu_0 = 0$, we can write

$$p_0(t + \Delta t) = p_1(t)\mu_1 \Delta t + p_0(t)(1 - \lambda_0 \Delta t) + o(\Delta t) \ . \tag{8}$$

Forward Kolmogorov equations: birth and death process II

- In the case of a finite state space, where $n = N$ is the maximum population size and assuming that $\lambda_N = 0$, we have

$$p_N(t + \Delta t) = p_{N-1}(t)\lambda_{N-1}\Delta t + p_N(t)(1 - \mu_N \Delta t) + o(\Delta t) \ . \tag{9}$$

- We can now derive the forward Kolmogorov differential equations making use of the transition probabilities of the previous slides.
- We obtain from Equation (7)

$$\frac{p_n(t + \Delta t) - p_n(t)}{\Delta t} = p_{n-1}(t)\lambda_{n-1} + p_{n+1}(t)\mu_{n+1} - p_n(t)(\lambda_n + \mu_n) + \frac{o(\Delta t)}{\Delta t} \ .$$

Forward Kolmogorov equations: birth and death process III

- We then take the limit as $\Delta t \to 0^+$, where $\lim_{\Delta t \to 0^+} \frac{o(\Delta t)}{\Delta t} = 0$

$$\begin{aligned} \frac{dp_n(t)}{dt} &= \lim_{\Delta t \to 0} \frac{p_n(t+\Delta t) - p_n(t)}{\Delta t} \\ &= \lambda_{n-1} p_{n-1}(t) + \mu_{n+1} p_{n+1}(t) - (\lambda_n + \mu_n) p_n(t) \ , \end{aligned} \tag{10}$$

  for $1 \leq n \leq N-1$.
- Using Equation (8) we obtain:

$$\frac{dp_0(t)}{dt} = \mu_1 p_1(t) - \lambda_0 p_0(t) \ . \tag{11}$$

- Using Equation (9) we obtain:

$$\frac{dp_N(t)}{dt} = \lambda_{N-1} p_{N-1}(t) - \mu_N p_N(t) \ . \tag{12}$$

Stationary probability distribution

- A positive stationary probability distribution can be defined for a general continuous time birth and death chain:

$$\pi = (\pi_0, \pi_1, \pi_2, \dots,)^T \ ,$$

where the transition probability matrix, $\mathbf{P}$ satisfy:

$$\mathbf{P}(t)\pi = \pi \ , \qquad \sum_{n \in S} \pi_n = 1 \ , \quad \text{and } \pi_n \geq 0 \ ,$$

for $t \geq 0$ and $n \in S$.

- If the state space, S, of the birth and death process is infinite, a unique positive stationary probability distribution, $\{\pi_n\}_{n \in S}$, exists under certain conditions.

Theorem

Suppose the continuous time Markov chain $\{\mathbb{X}(t)\}$, $t \geq 0$, *is a general birth and death process satisfying Equation* (5). *If the state space is infinite* $\{0, 1, 2, \ldots\}$, *a unique positive stationary probability distribution,* $\{\pi_n\}_{n \in S}$, *exists iff (if and only if)* $\mu_n > 0$ *and* $\lambda_{n-1} > 0$ *for* $n = 1, 2, \ldots,$ *and*

$$\sum_{n=1}^{+\infty} \frac{\lambda_0 \lambda_1 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} < +\infty \ . \tag{13}$$

The stationary probability distribution is given by

$$\pi_n = \frac{\lambda_0 \lambda_1 \ldots \lambda_{n-1}}{\mu_1 \mu_2 \ldots \mu_n} \pi_0 \ , \quad \text{for } i = 1, 2, \ldots \tag{14}$$

and

$$\pi_0 = \frac{1}{1 + \sum_{n=1}^{+\infty} \frac{\lambda_0 \lambda_1 \cdots \lambda_{n-1}}{\mu_1 \mu_2 \cdots \mu_n}} \ . \tag{15}$$

Theorem

If the state space is finite $\{0, 1, 2, \ldots, N\}$*, then a unique positive stationary probability distribution,* $\{\pi_n\}_{n \in S}$*, exists if and only if*

$$\mu_n > 0 \,, \qquad \lambda_{n-1} > 0 \,,$$

for $n = 1, 2, \ldots, N$*. The stationary probability distribution is given by Equations* (14) *and* (15)*, where the index* n *and the summation on* n *extend from 1 to* N*.*

Outline

Stochastic extinction

- In a simple birth and death process with $\lambda_0 = 0$ (remember $\mu_0 = 0$), the zero state, $n = 0$, is absorbing.
- Eventually the distribution for the total population size is concentrated at zero.
- A positive stationary probability distribution does not exist in this case.
- Furthermore, the zero state is absorbing and eventually the total population will become extinct as $t \to +\infty$. If $p_0(t) = \mathbb{P}(\mathbb{X}(t) = 0 | \mathbb{X}(0) = n_0 \geq 1)$, we have

$$\lim_{t \to +\infty} p_0(t) = 1 \, .$$

- What are the conditions for total population extinction in a general birth and death process?

Theorem

Let $\mu_0 = 0 = \lambda_0$ *in a general birth and death process with* $\mathbb{X}(0) = n_0 \geq 1$. *Suppose* $\mu_n > 0$ *and* $\lambda_n > 0$ *for* $n = 1, 2, \ldots$. *Then, if*

$$\sum_{n=1}^{+\infty} \frac{\mu_1 \mu_2 \ldots \mu_n}{\lambda_1 \lambda_2 \ldots \lambda_n} = +\infty \ , \tag{16}$$

we have $\lim_{t \to +\infty} p_0(t) = 1$, *and if*

$$\sum_{n=1}^{+\infty} \frac{\mu_1 \mu_2 \ldots \mu_n}{\lambda_1 \lambda_2 \ldots \lambda_n} < +\infty \ , \tag{17}$$

then we have

$$\lim_{t \to +\infty} p_0(t) = \frac{\sum_{k=n_0}^{+\infty} \frac{\mu_1 \mu_2 \ldots \mu_k}{\lambda_1 \lambda_2 \ldots \lambda_k}}{1 + \sum_{n=1}^{+\infty} \frac{\mu_1 \mu_2 \ldots \mu_n}{\lambda_1 \lambda_2 \ldots \lambda_n}} \ . \tag{18}$$

Expected times to extinction

- Suppose $\{\mathbb{X}(t)\}$, $t \geq 0$, is a continuous time birth and death process with $\mathbb{X}(0) = n_0 \geq 1$, satisfying $\lambda_0 = 0 = \mu_0$ and $\lambda_n > 0$ and $\mu_n > 0$ for $n = 1, 2, \ldots$.
- Furthermore, we assume that $\lim_{t \to +\infty} p_0(t) = 1$.
- The expected time to extinction $\tau_{n_0} = \mathbb{E}(\tau_{0,n_0})$ satisfies:

$$\tau_{n_0} = \begin{cases} \frac{1}{\mu_1} + \sum_{n=2}^{+\infty} \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{\mu_1 \cdots \mu_n} \ , & n_0 = 1 \ , \\ \tau_1 + \sum_{n=1}^{n_0 - 1} \left[\frac{\mu_1 \cdots \mu_n}{\lambda_1 \cdots \lambda_n} \sum_{k=n+1}^{+\infty} \frac{\lambda_1 \cdots \lambda_{k-1}}{\mu_1 \cdots \mu_k} \right] , & n_0 = 2, 3, \ldots \ . \end{cases} \tag{19}$$

- The extinction time is finite if $\sum_{n=2}^{+\infty} \frac{\lambda_1 \lambda_2 \ldots \lambda_{n-1}}{\mu_1 \ldots \mu_n} < +\infty$.

The limiting conditional probability distribution

- Prior to extinction at $n = 0$ occurring, the probability distribution of a birth and death process may remain approximately stationary for a long period of time, if extinction times are relatively large.
- We define the following conditional probabilities:

$$q_n(t) = \mathbb{P}(\mathbb{X}(t) = n \mid \mathbb{X}(t) \neq 0) = \frac{p_n(t)}{1 - p_0(t)} \quad \forall n \geq 1 \ . \tag{20}$$

- These conditional probabilities satisfy:

$$\begin{aligned} \frac{dq_n(t)}{dt} &= \frac{1}{1-p_0}\frac{dp_n}{dt} + \frac{p_n}{1-p_0}\frac{1}{1-p_0}\frac{dp_0}{dt} \\ &= \lambda_{n-1}q_{n-1} - (\lambda_n + \mu_n)q_n + \mu_{n+1}q_{n+1} + q_n(\mu_1 q_1) \ , \quad \text{for } n > 1 \ . \end{aligned} \tag{21}$$

- In the case $n = 1$, we have

$$\frac{dq_1}{dt} = q_2\mu_2 - q_1(\lambda_1 + \mu_1) + q_1(q_1\mu_1) \ . \tag{22}$$

Quasi-stationary probability distribution

- A distribution $\{\bar{q}_n\}_{n\geq 1}$ is called a quasi-stationary probability distribution (QSD) if it is a solution of the previous equations, where the time derivatives are set equal to zero.

Limiting conditional probability distribution

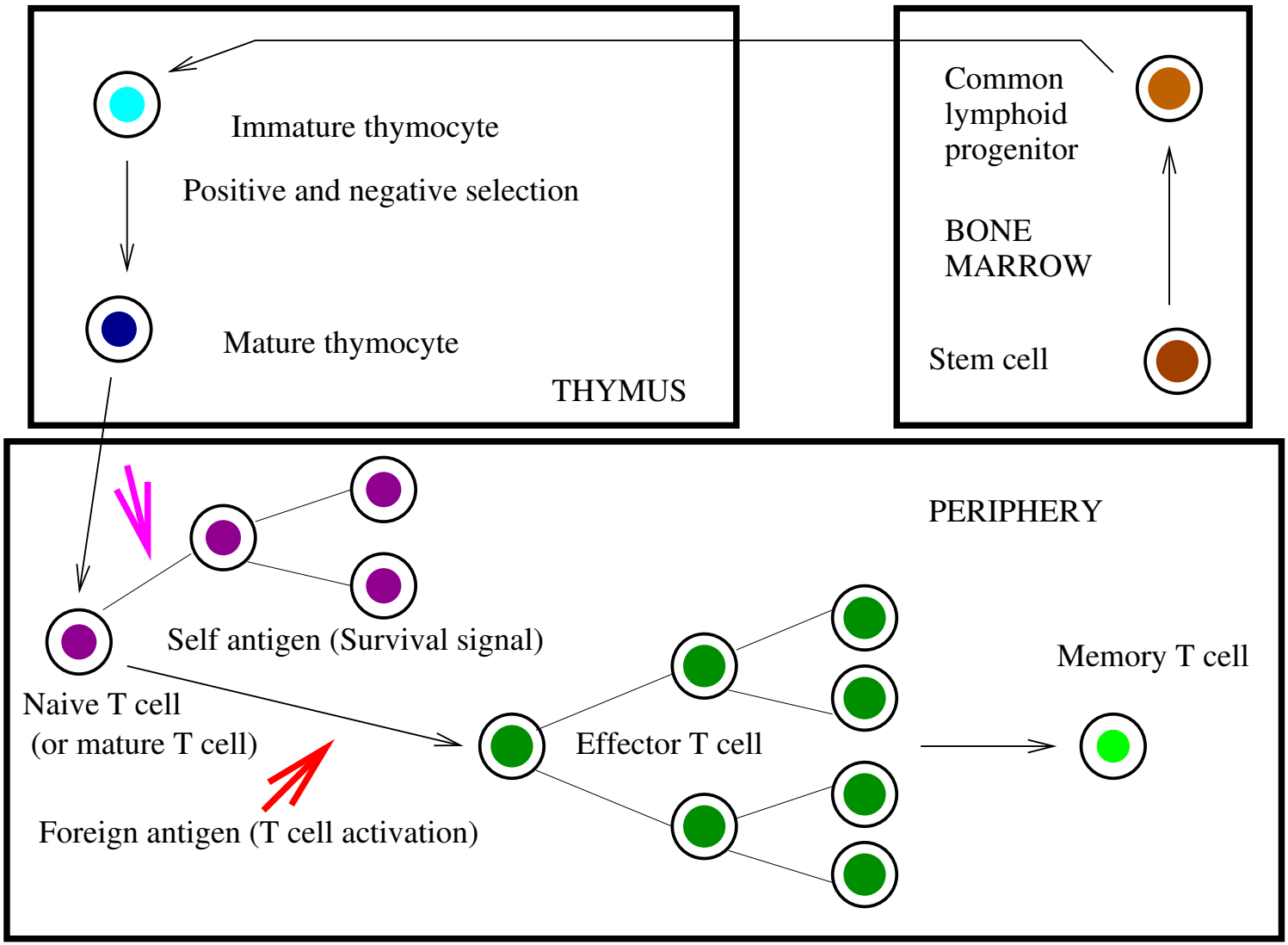
- The limiting conditional probability distribution (LCD) of the process is defined as $\lim_{t\to+\infty} q_n(t) \quad \forall n \geq 1$.
- Since the LCD is independent of time, it is also a QSD.
- If state space, S, is infinite, there may be no QSD, and if a QSD does exist, it is not necessarily unique.
- The LCD can be approximated analytically by making two different assumptions.

Approximations to the LCD

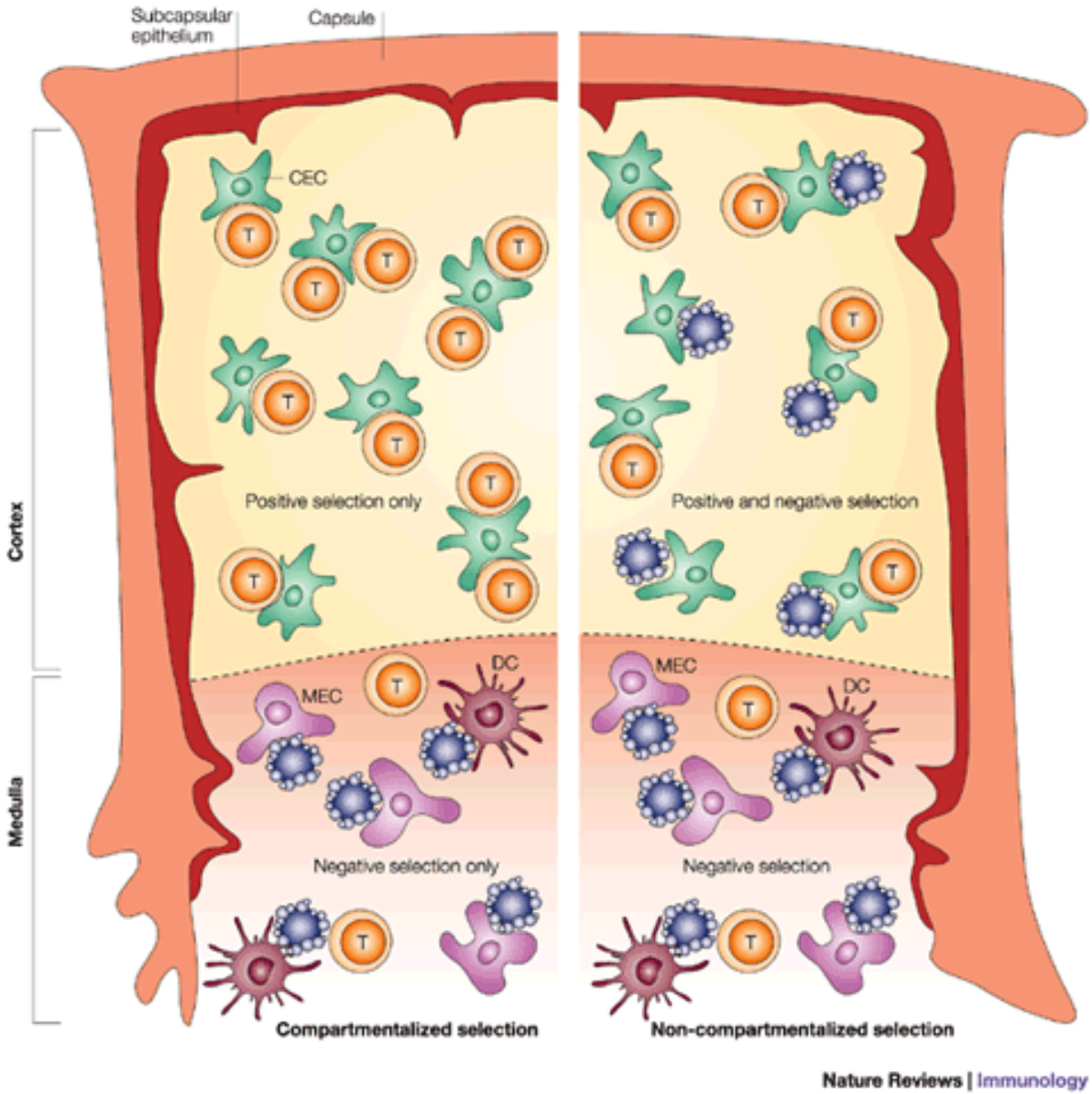
- Assume $\mu_1 = 0$.
- This is a good approximation when the mean time to extinction is long.
- Replace the death rate μ_n by μ_{n-1} to allow for one immortal individual.
- Allowing for one immortal individual is a better approximation when the mean extinction time is short.

Outline

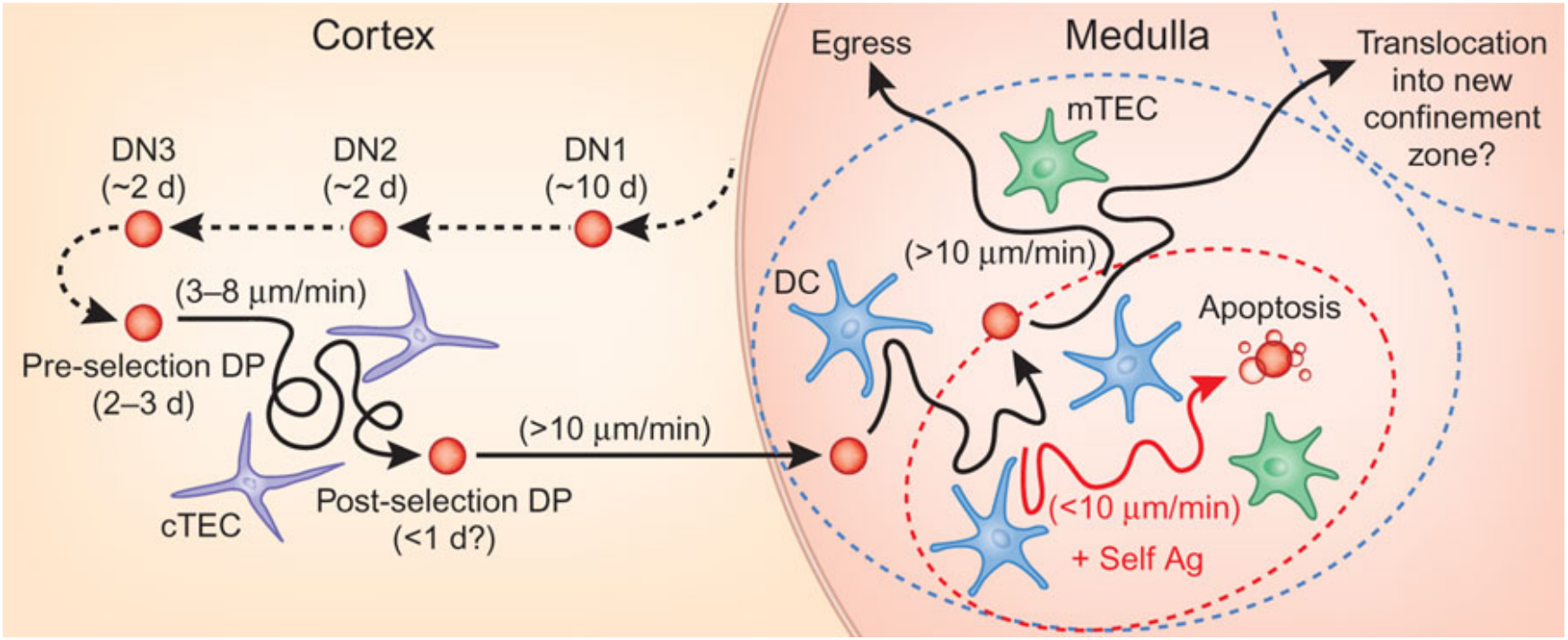
History of a T cell



Development of T cells in the thymus



The T cell receptor and T cell development



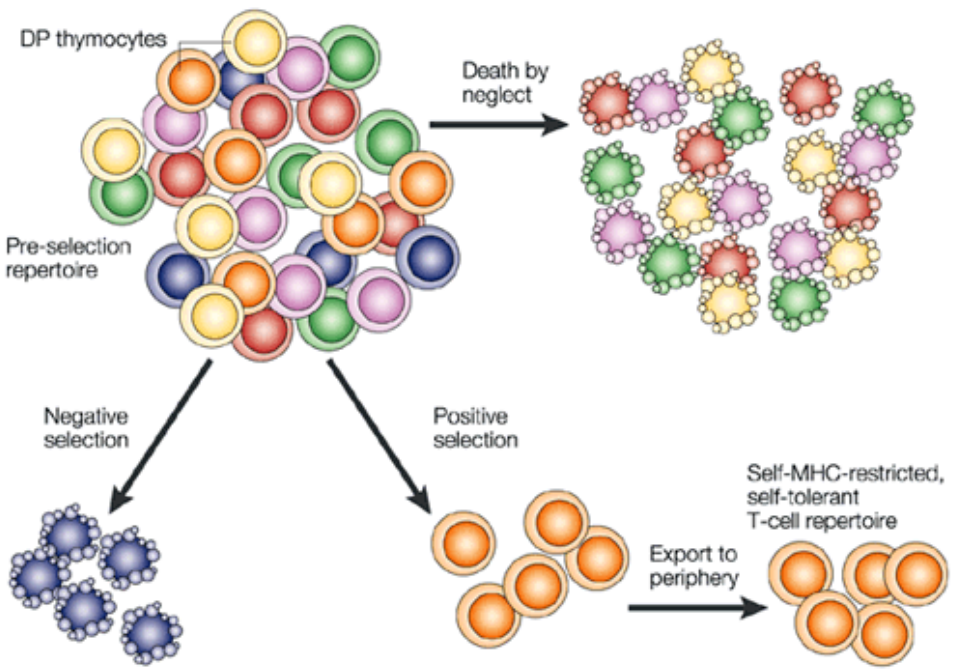
T cell development in the thymus: space and time

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).



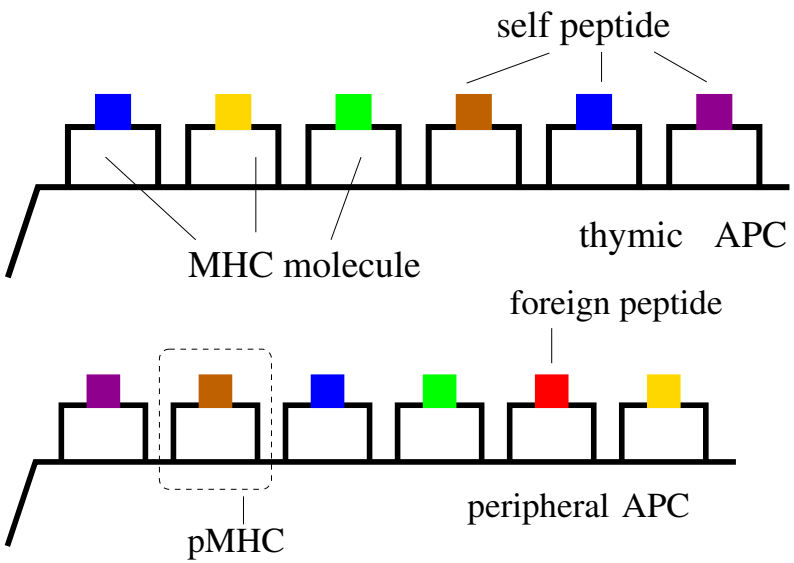
Immunological evidence

- 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.

Homeostatic regulation of naïve T cells in the periphery

- 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.

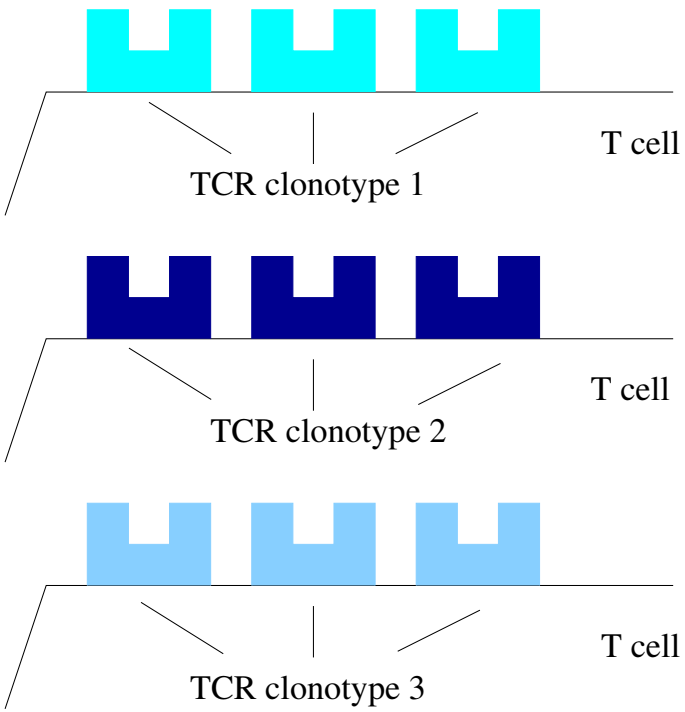
Surface of APCs



Antigen presenting cells (APCs)

- APCs present peptides (or antigens) on their surface by means of an MHC molecule.
- We denote by pMHC the complex formed by a peptide-MHC molecule.
- We describe APCs as a collection of arrays of pMHCs, each of them denoted an antigen presentation profile of the APC (APP).

Surface of T cells: TCRs



T cells: T cell receptor (TCR)

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

Outline

Mathematical setup of the multi-variate stochastic model

- We want to model the number of T cells (of a given clonotype) with a stochastic approach.
- 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.
- The state space is $S = \{0, 1, 2, 3, \ldots\}$. This represents the values $\mathbb{X}(t)$ can take at any time (number of cells).
- The stochastic (Markov process) model is determined uniquely by the transition probabilities:

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

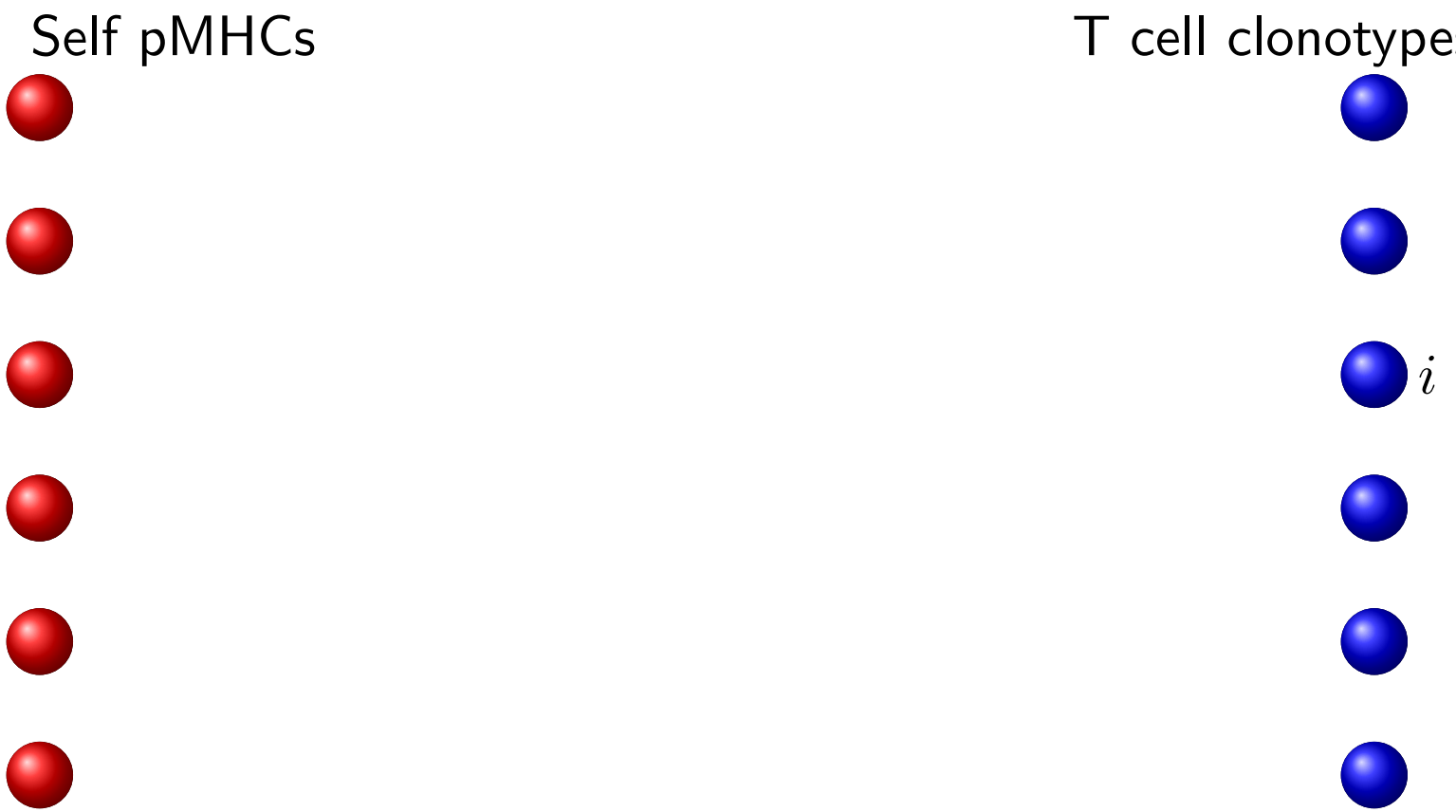
- Birth and death Markov process:

$$0 \underset{\lambda_0=0}{\overset{\mu_1}{\leftrightharpoons}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightharpoons}} 2 \underset{\lambda_2}{\overset{\mu_3}{\leftrightharpoons}} 3 \underset{\lambda_3}{\overset{\mu_4}{\leftrightharpoons}} \cdots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftrightharpoons}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftrightharpoons}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftrightharpoons}} n+1 \cdots$$

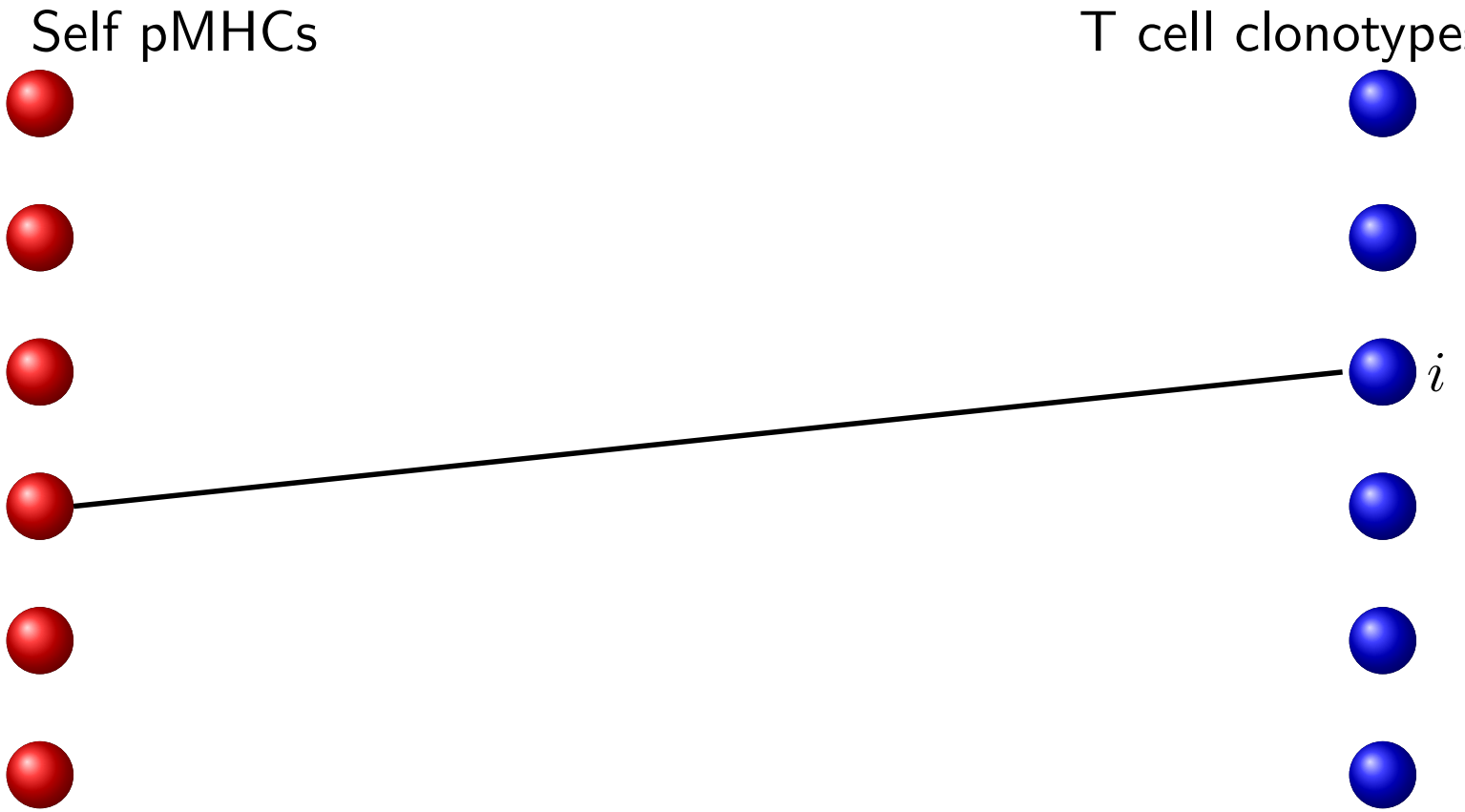
T cells require homeostatic signals from self pMHCs to proliferate

- T cells are defined by their clonotype i (TCR molecule).
- $n_i(t)$ is the number of T cells of clonotype i at time t.
- μ_i is the death rate per single T cell of clonotype i.
- λ_i is the birth rate per single T cell of clonotype i.
- A given self peptide-MHC molecule (pMHC) is labelled by index $q \in \mathbb{Q}$, with $\mathbb{Q}$ the set of all self pMHCs.
- $\mathbb{Q}_i$ is the set of self pMHCs from which T cells of clonotype i receive a signal, which triggers one round of cell division.
- $\mathbb{C}_q$ is the set of T cells that receive a signal to divide from self pMHC q.

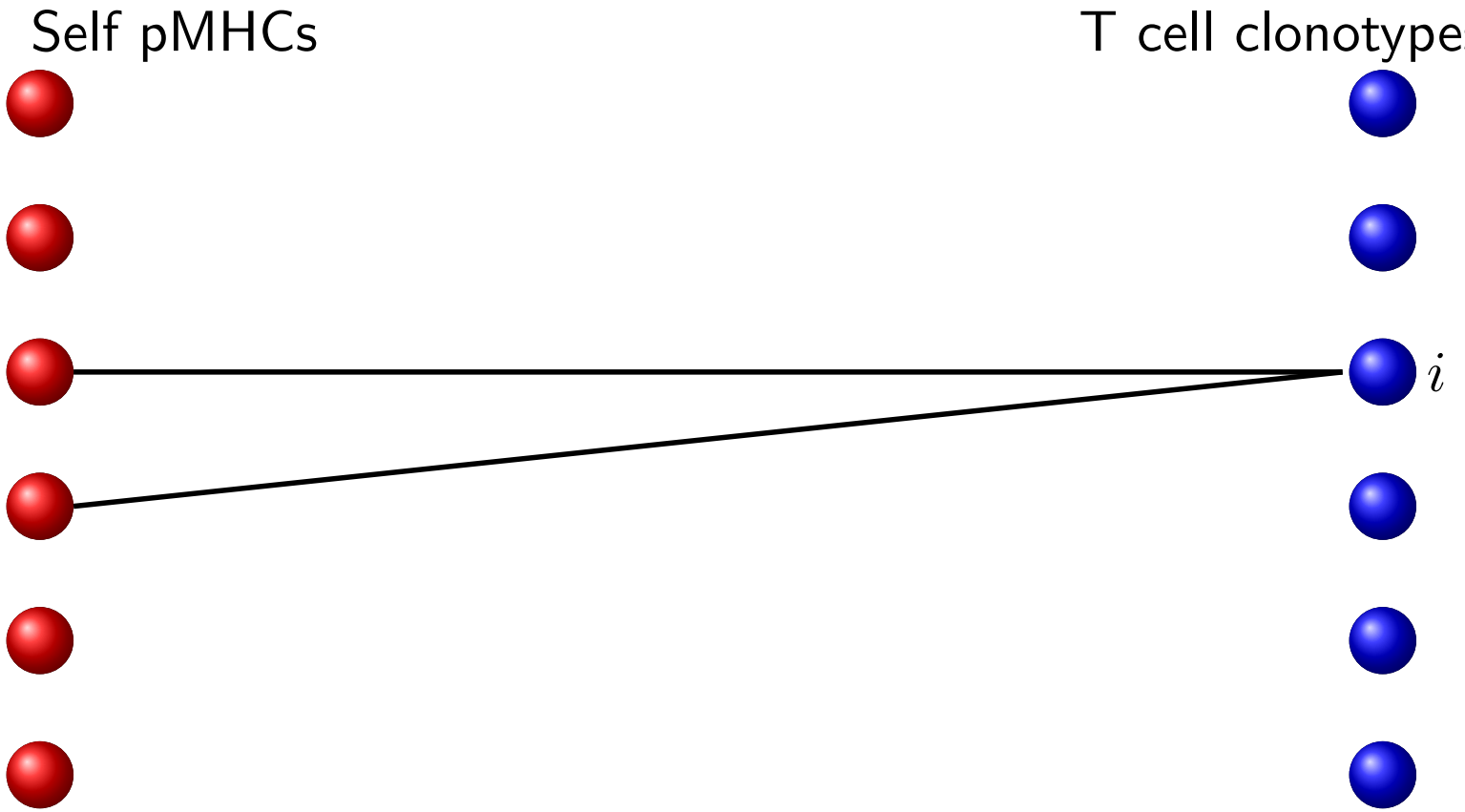
Self pMHCs and T cell clonotypes (T cells expressing identical TCRs)



Self pMHCs and T cell clonotypes (T cells expressing identical TCRs)



Self pMHCs and T cell clonotypes (T cells expressing identical TCRs)



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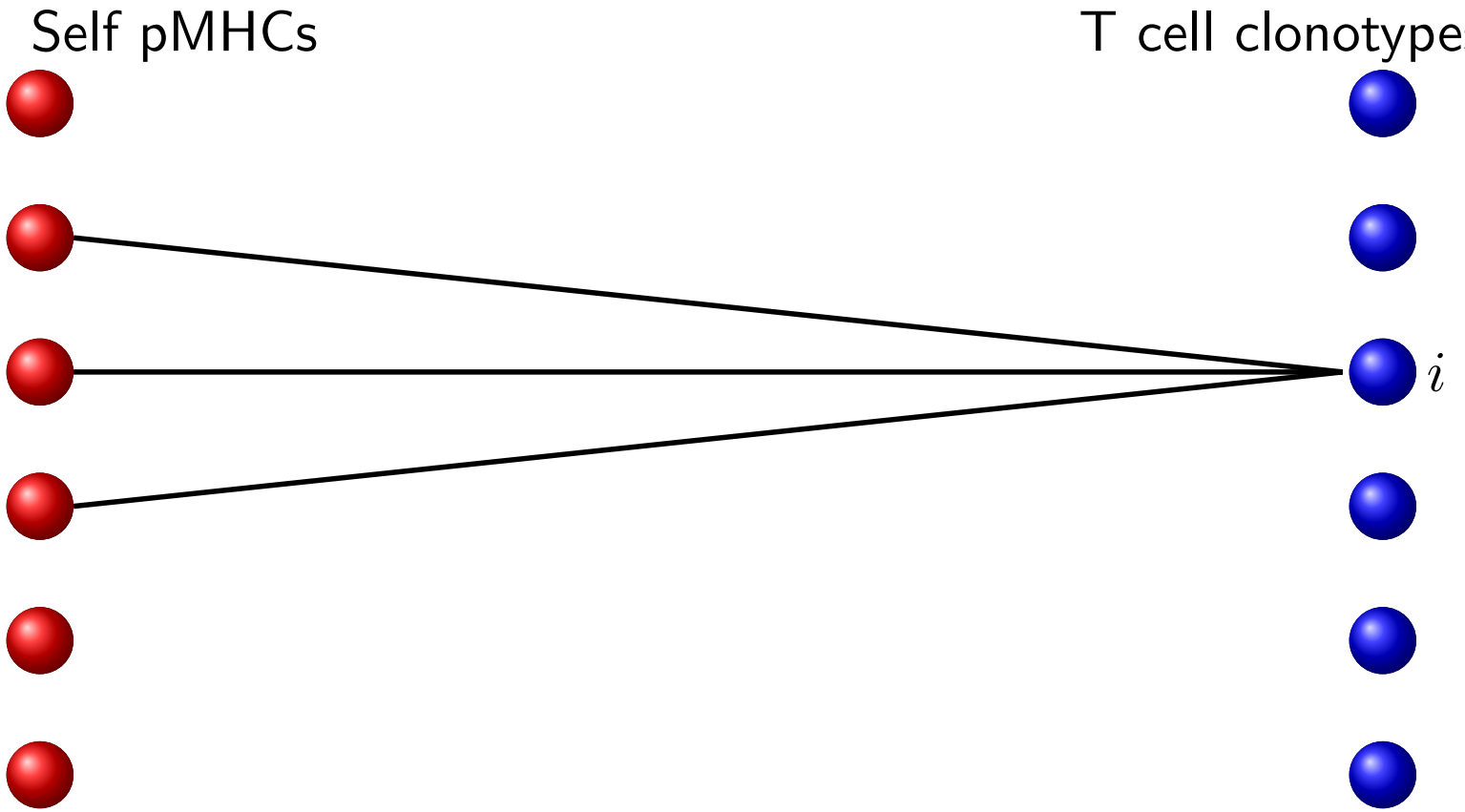

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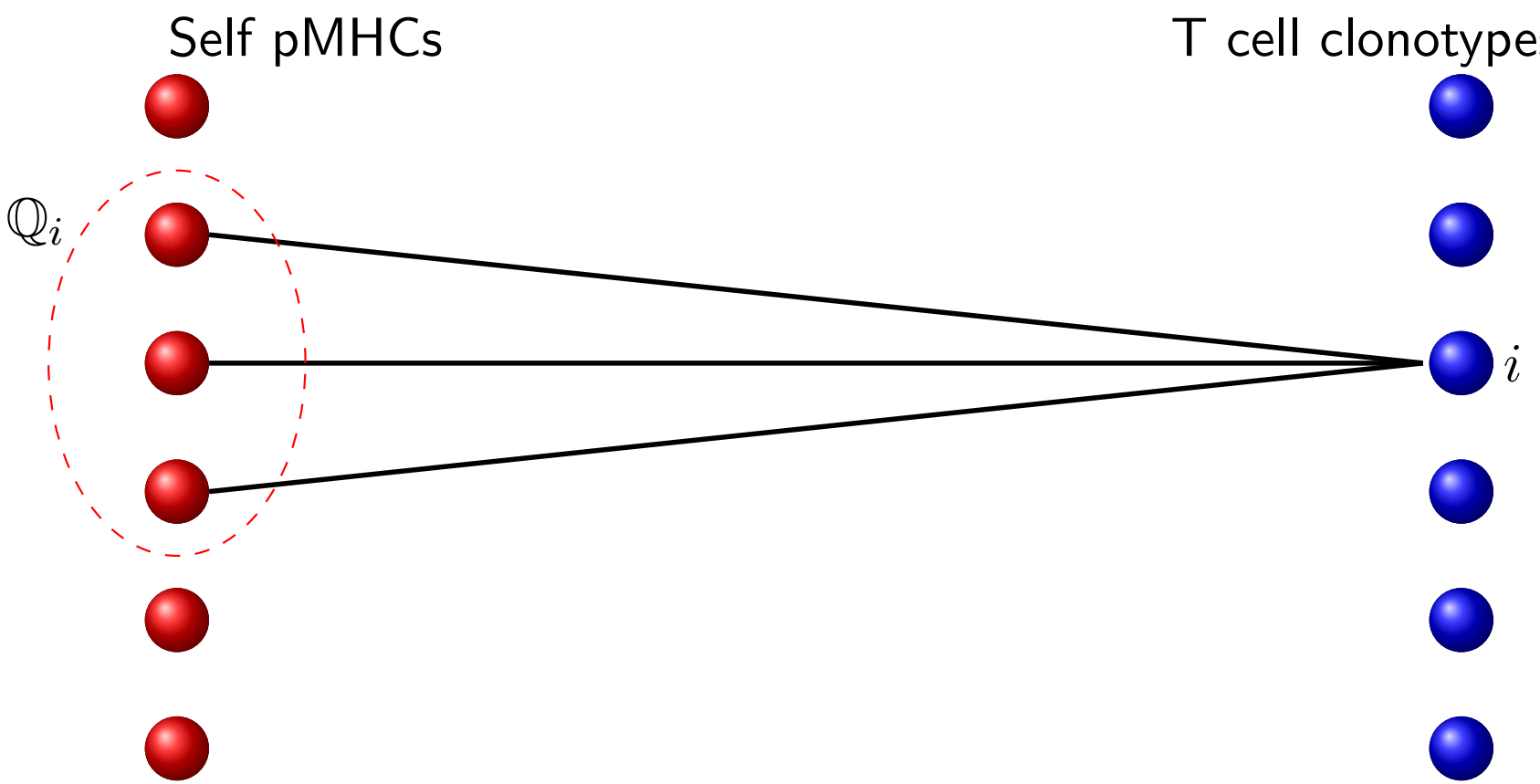
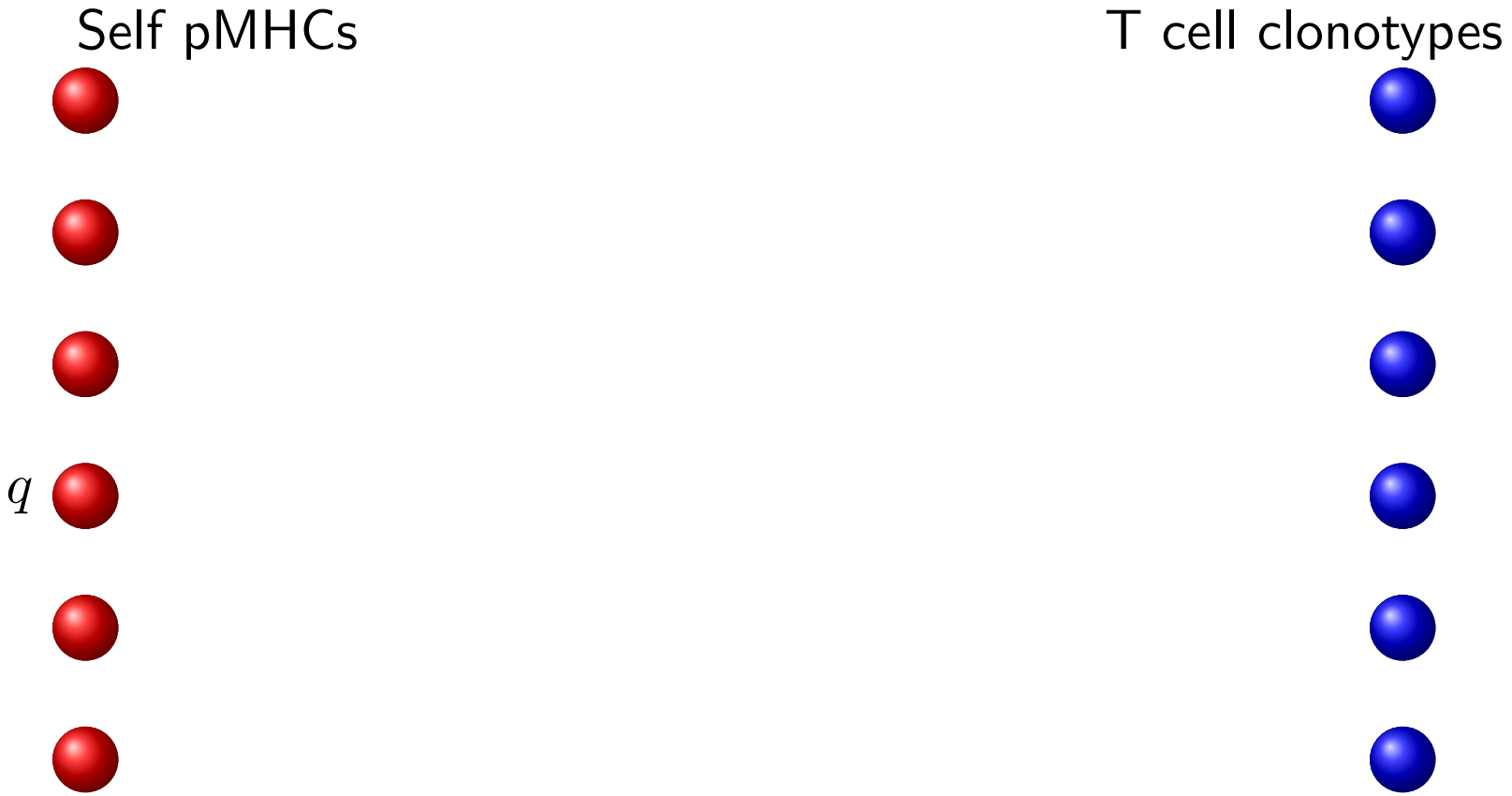


T cells that receive a signal from self pMHC q



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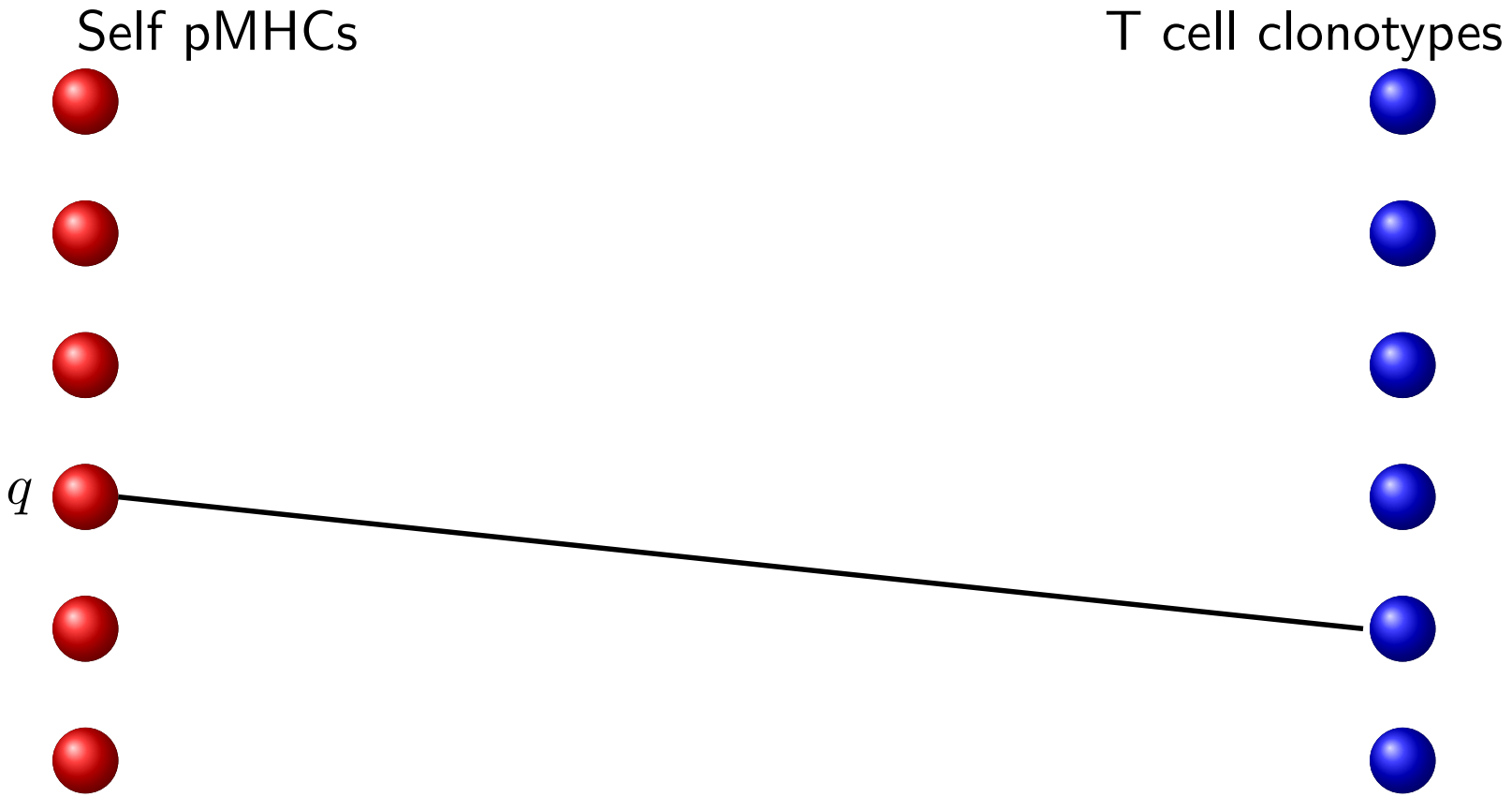

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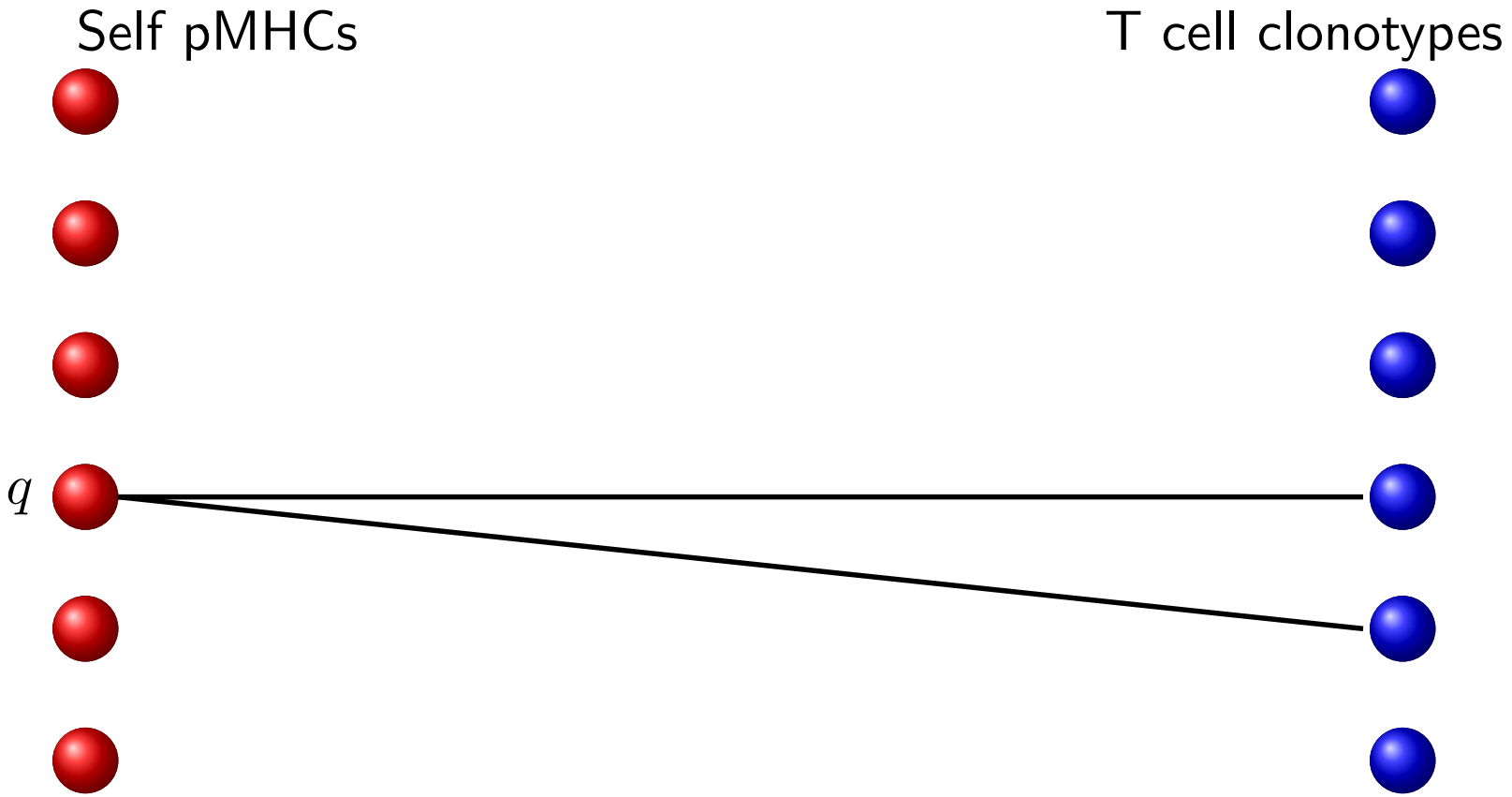

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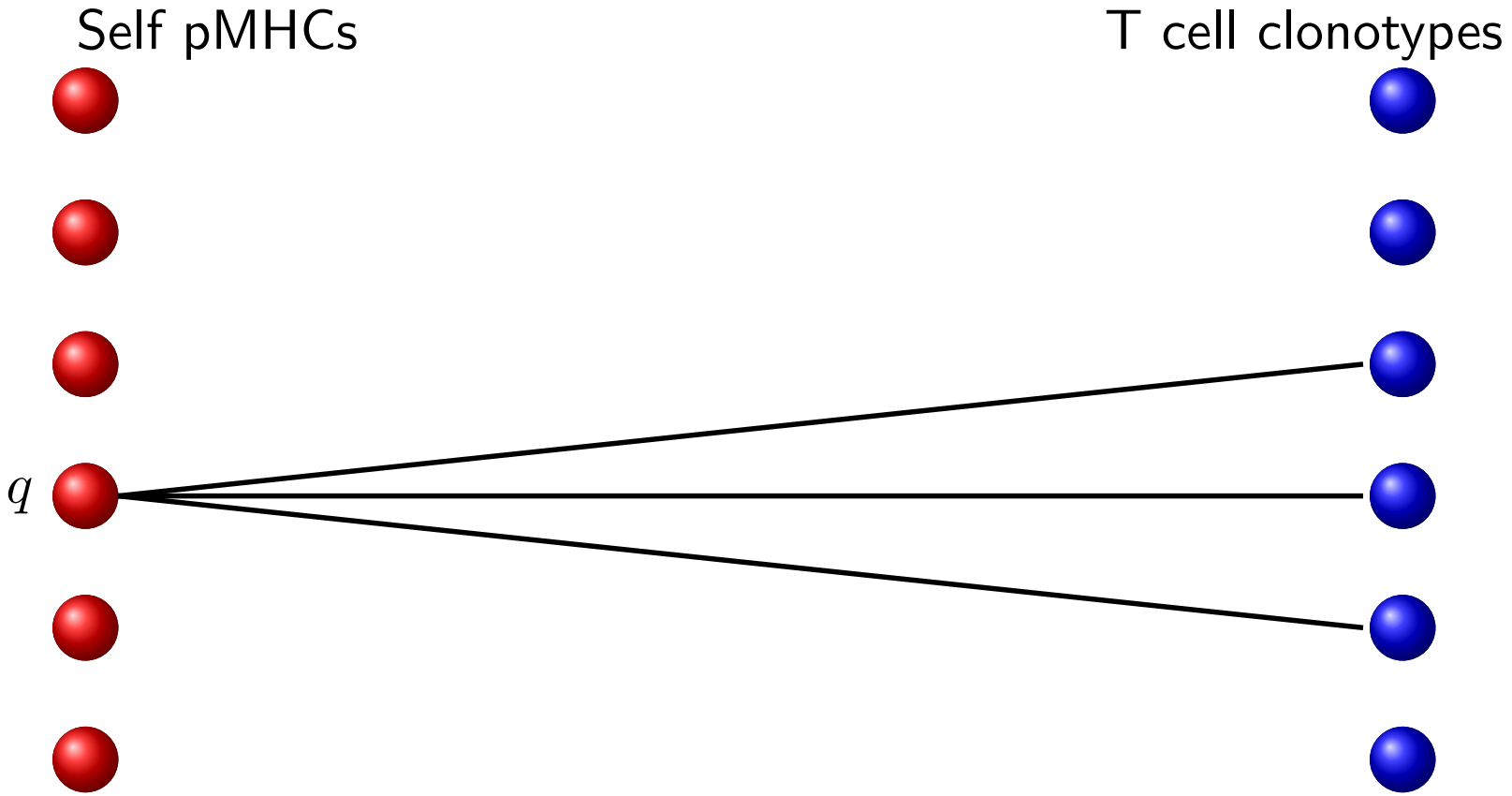

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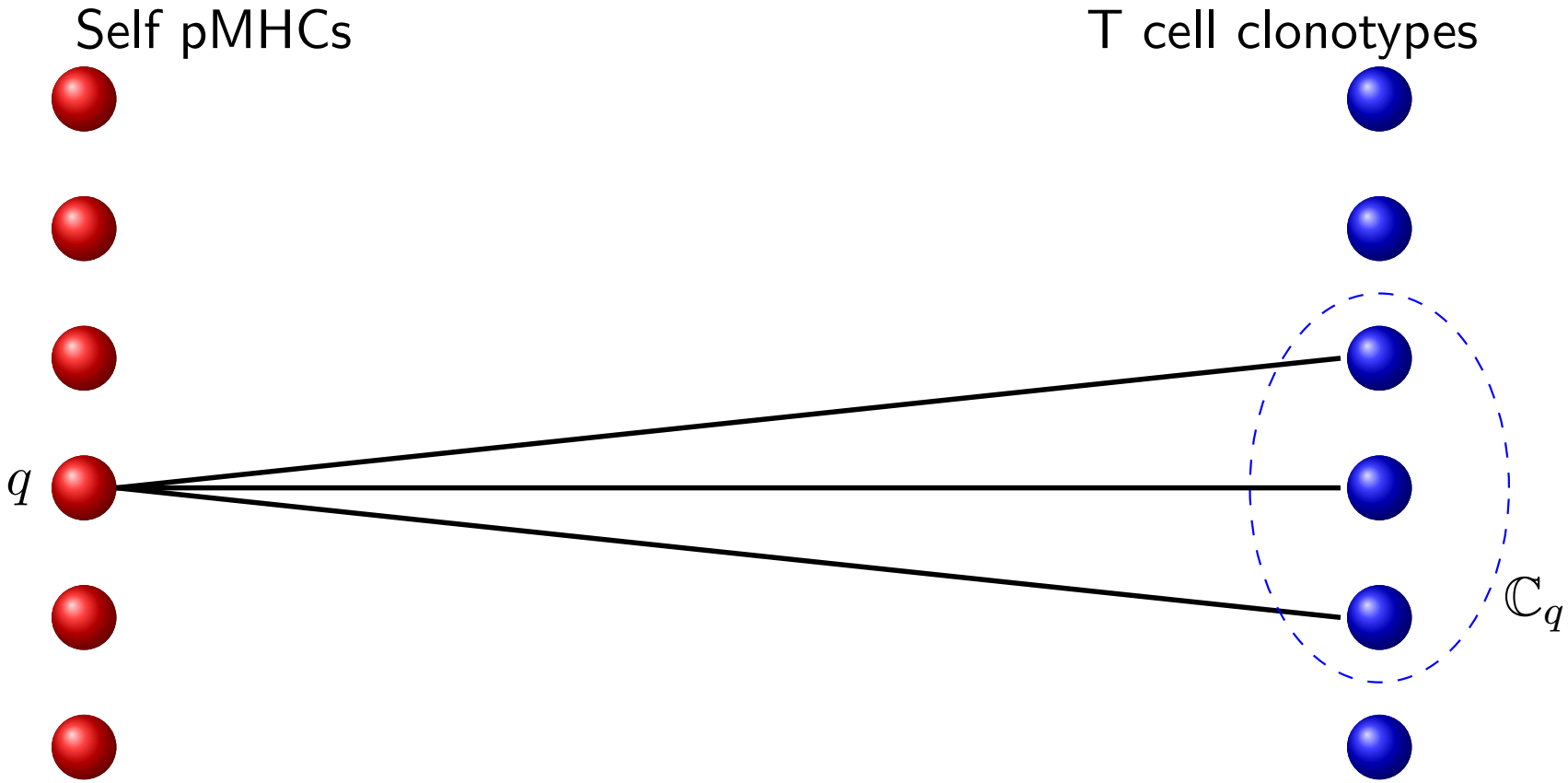
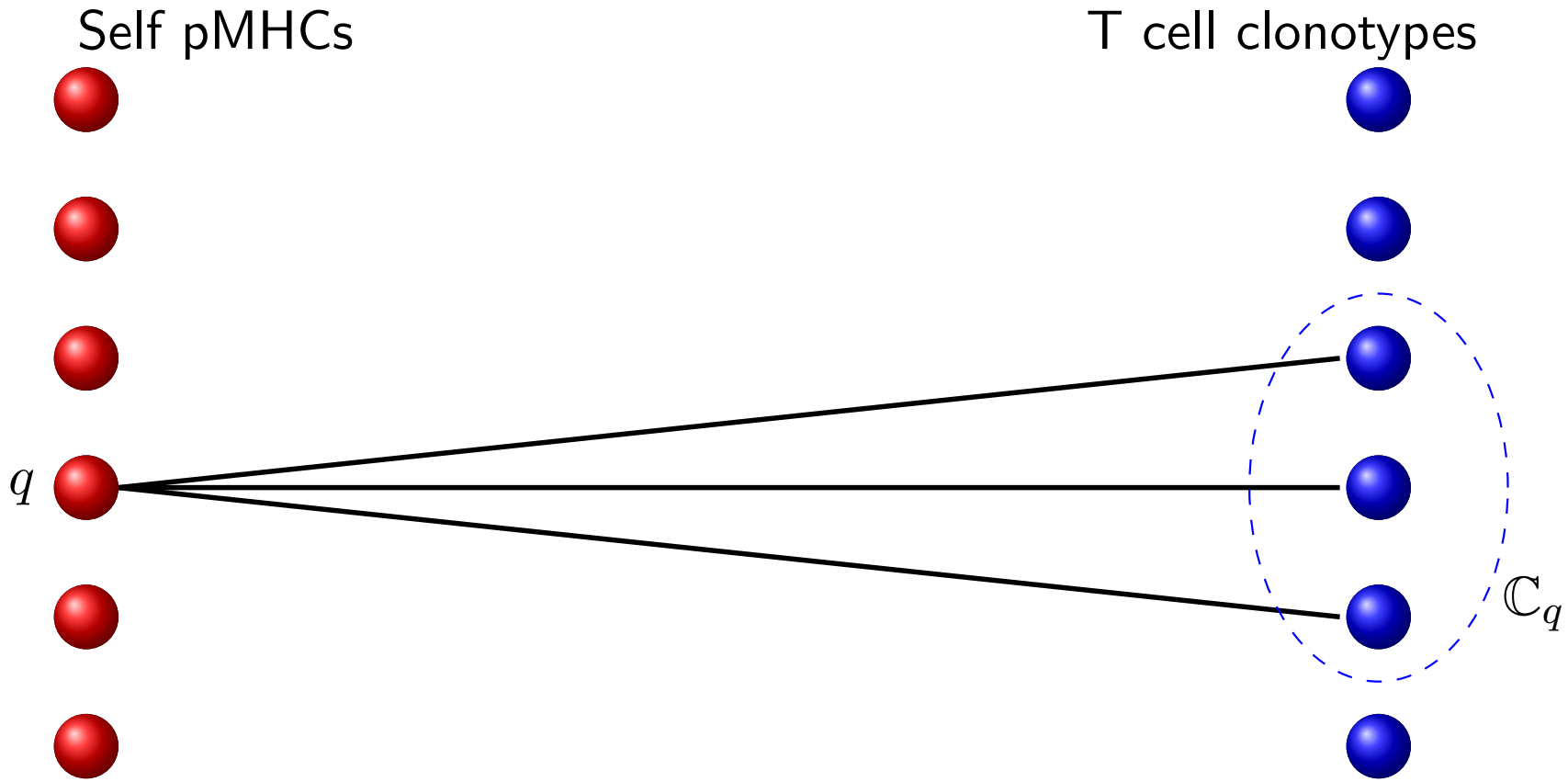


T cell clonotype competition for self pMHCs



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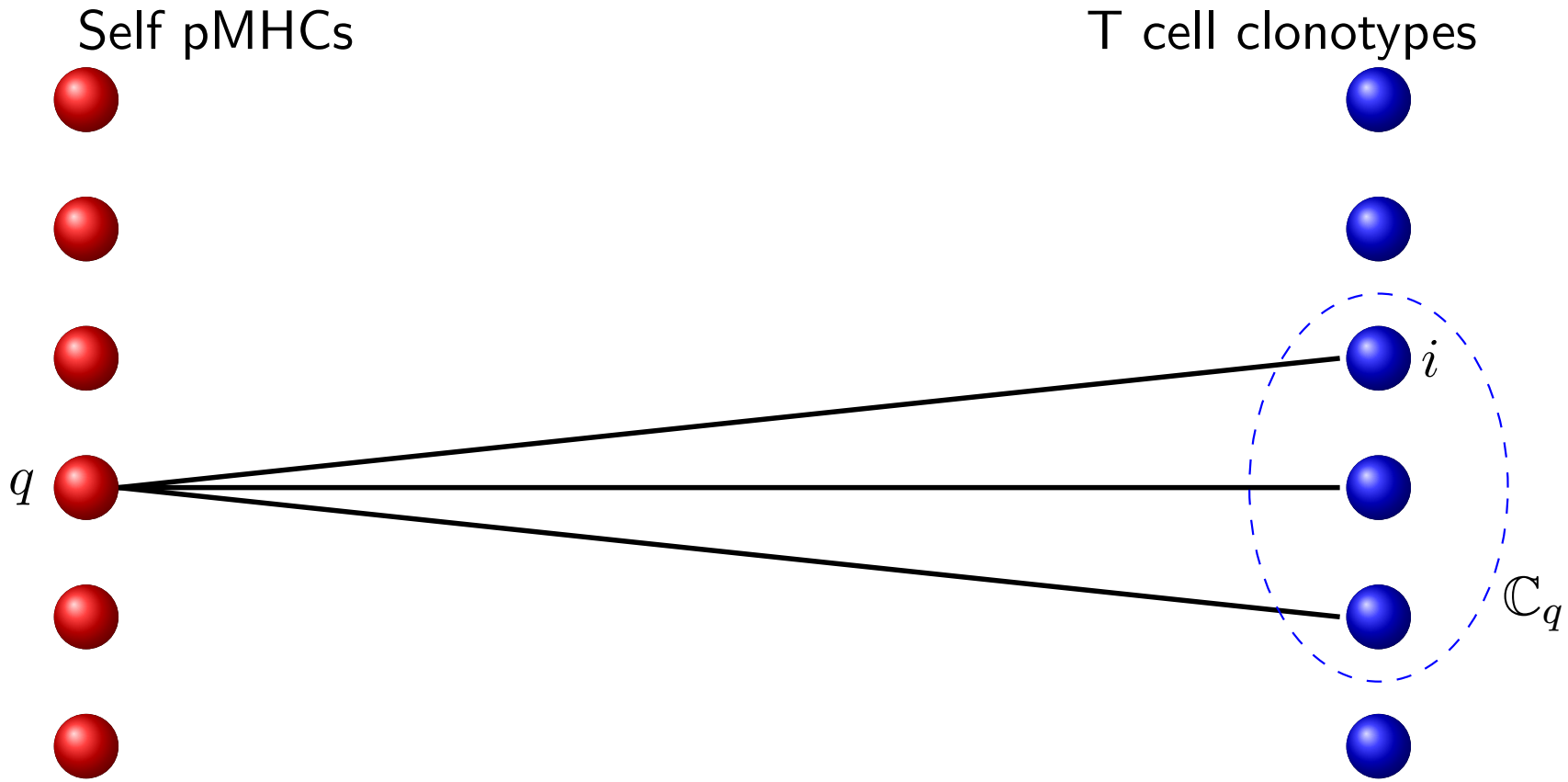

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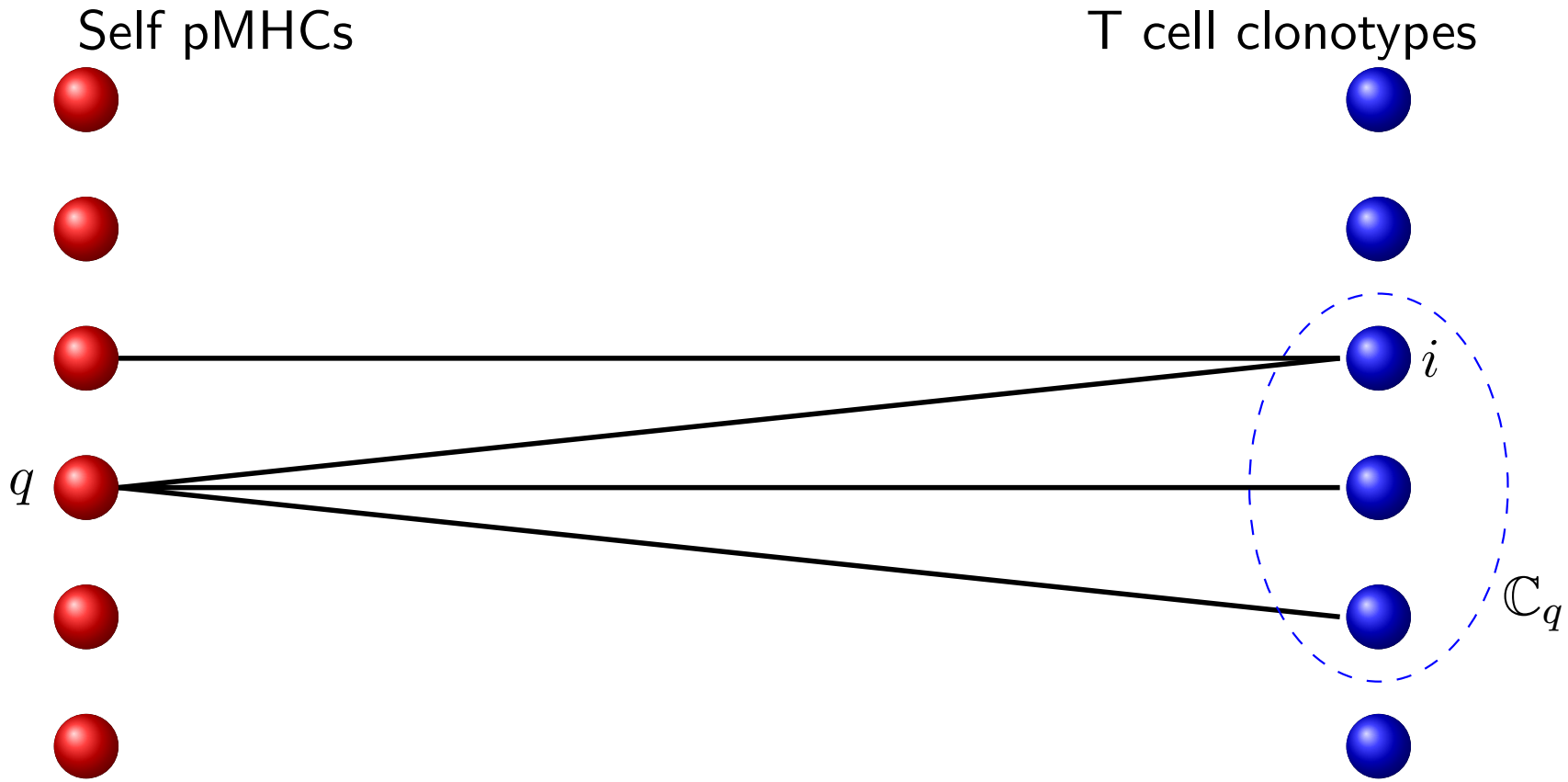

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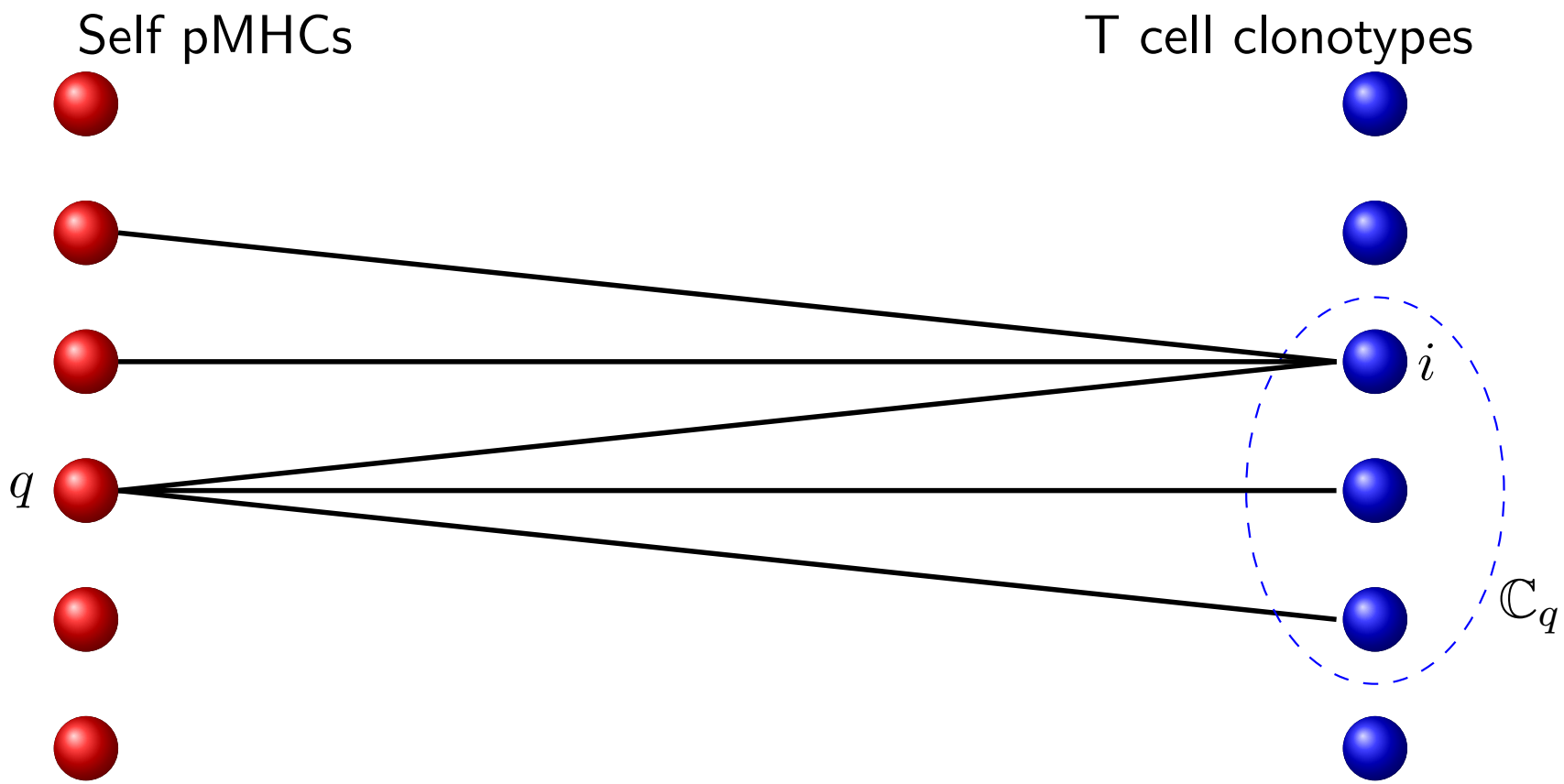

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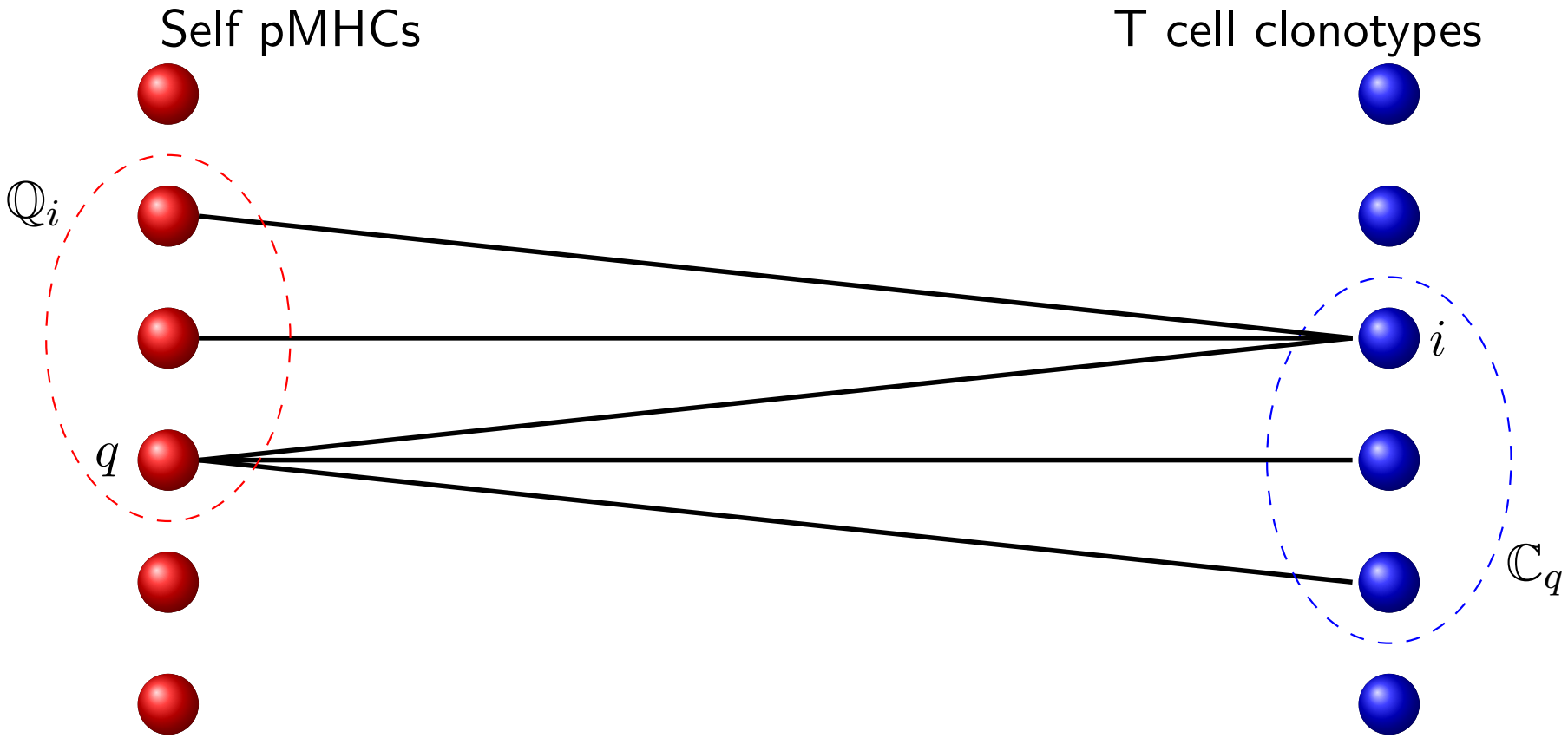

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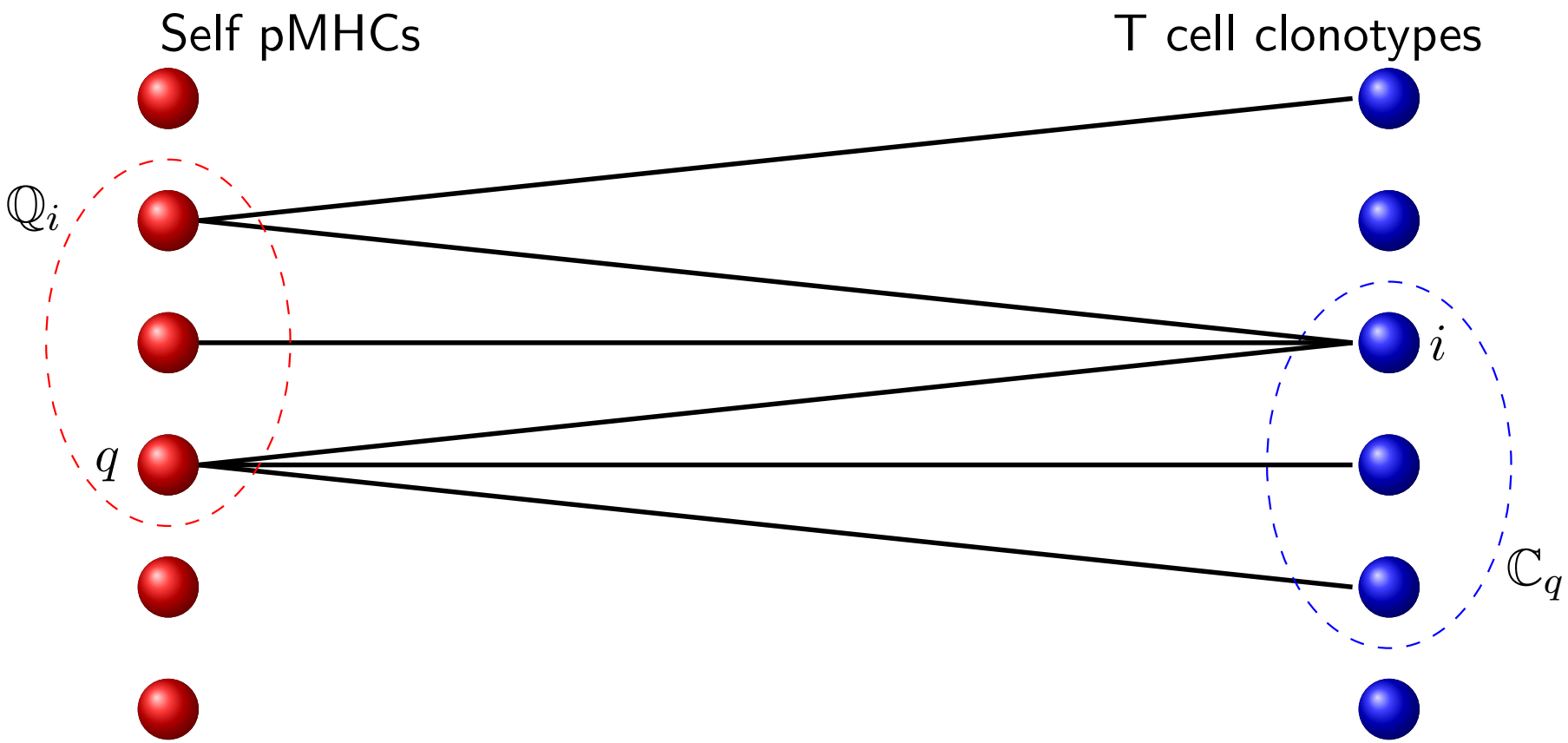

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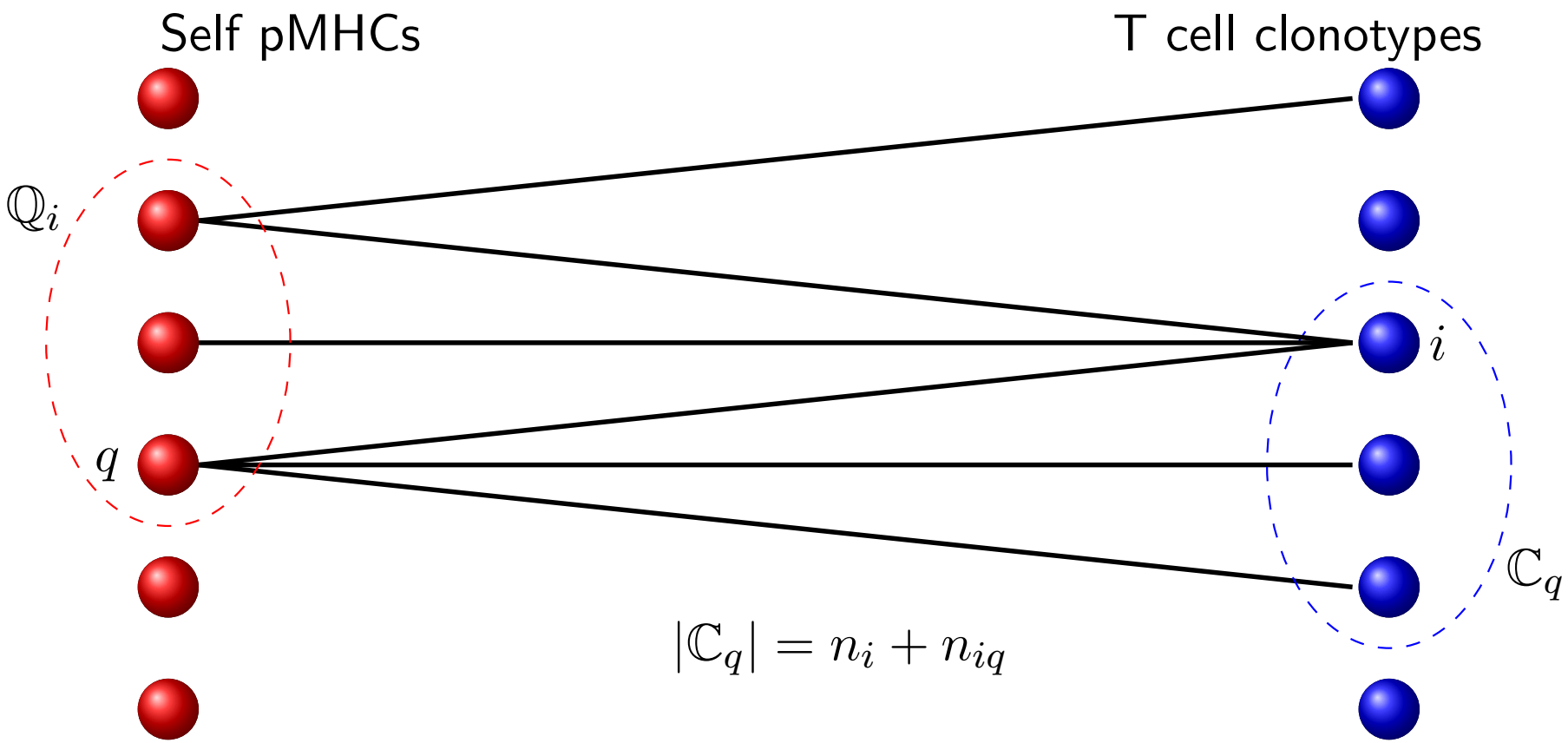

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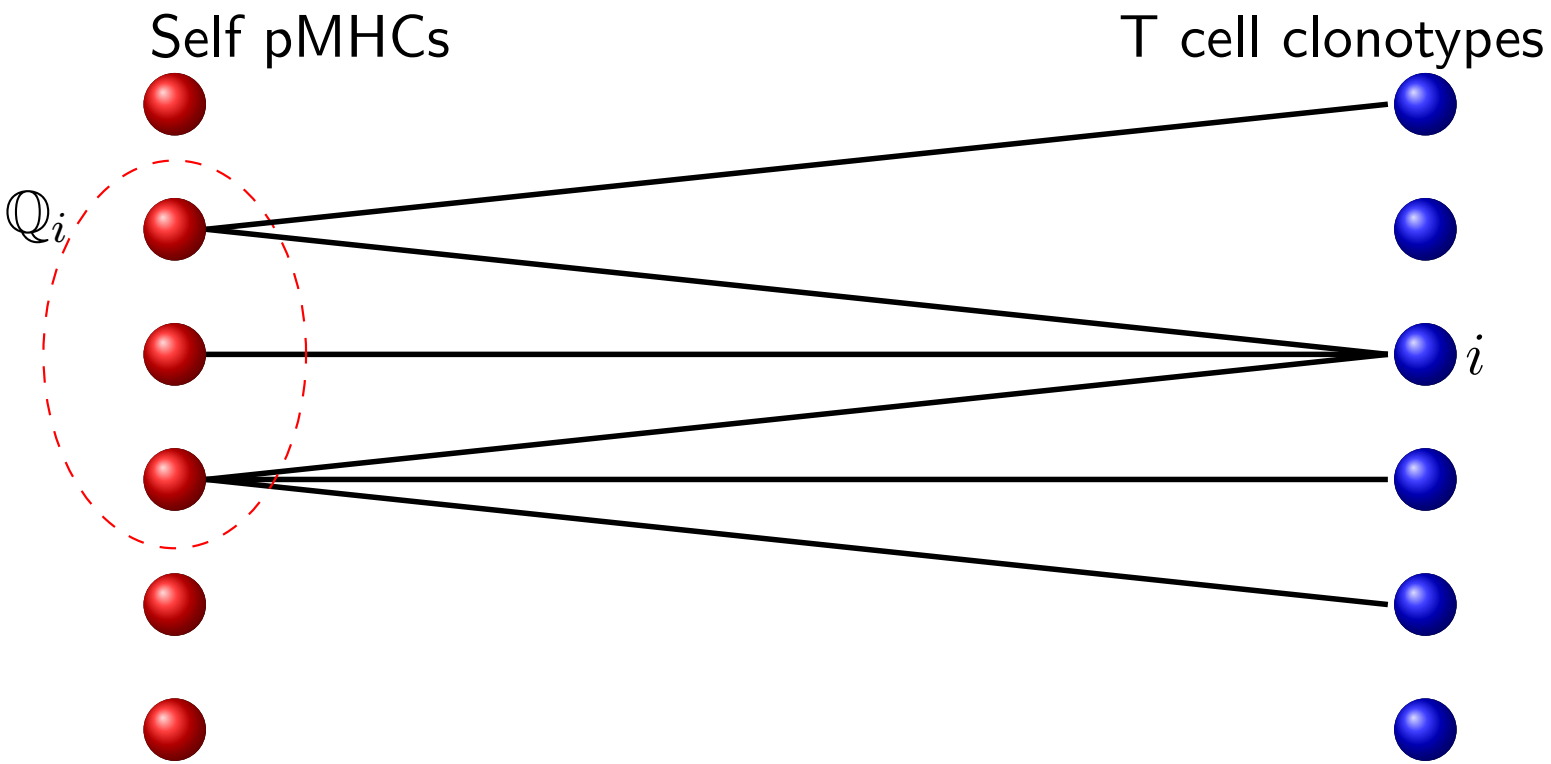

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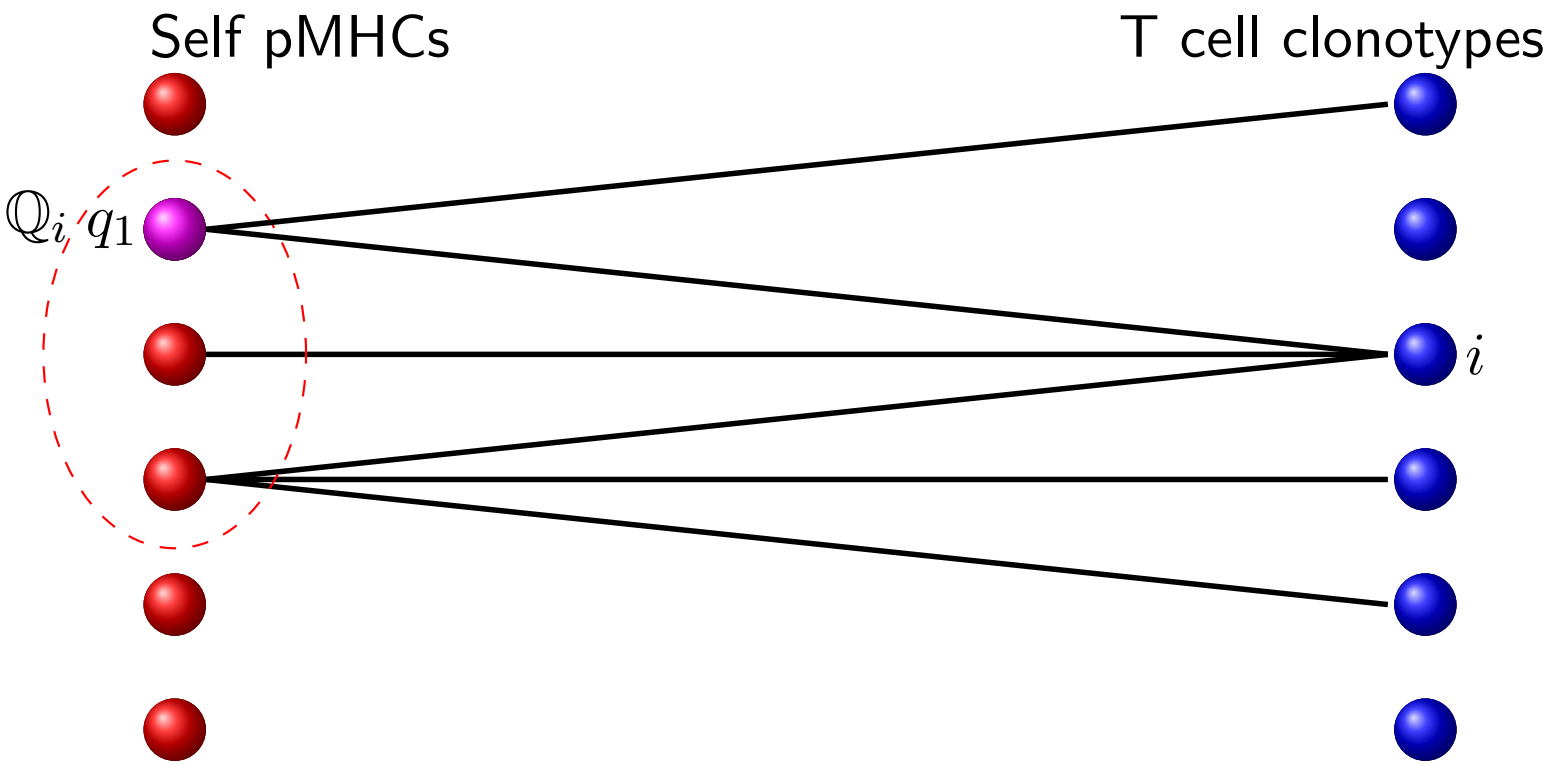

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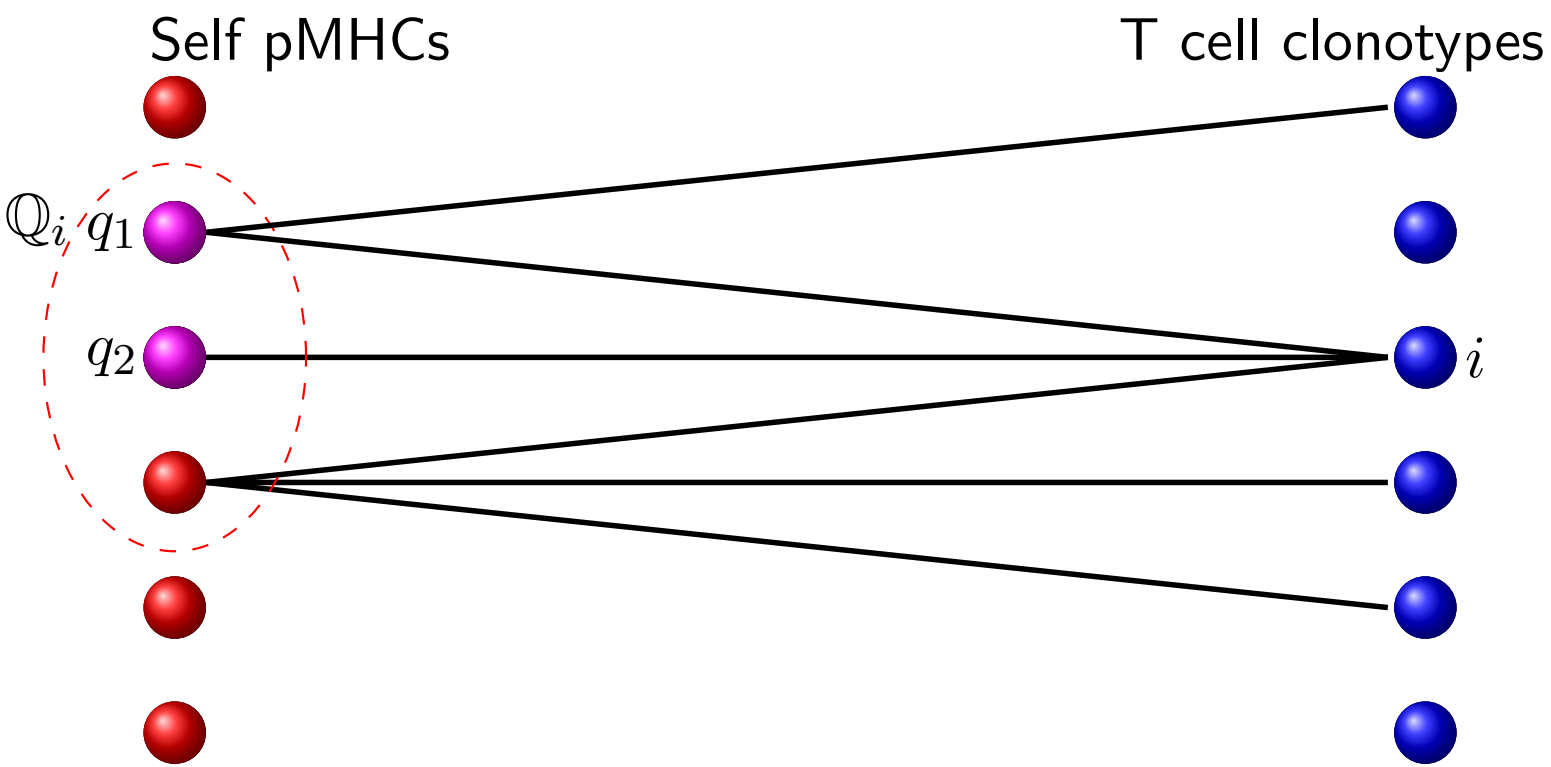

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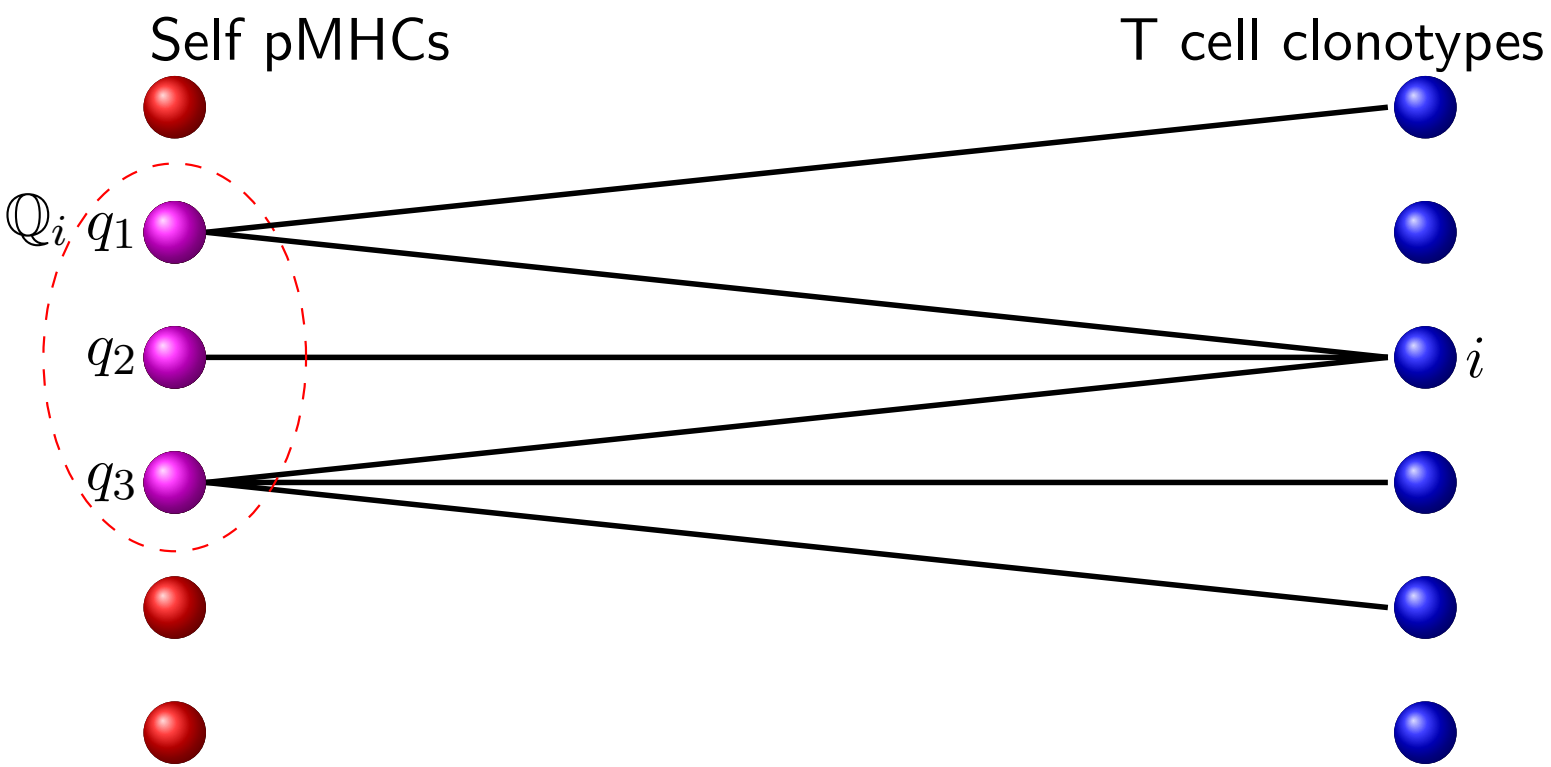

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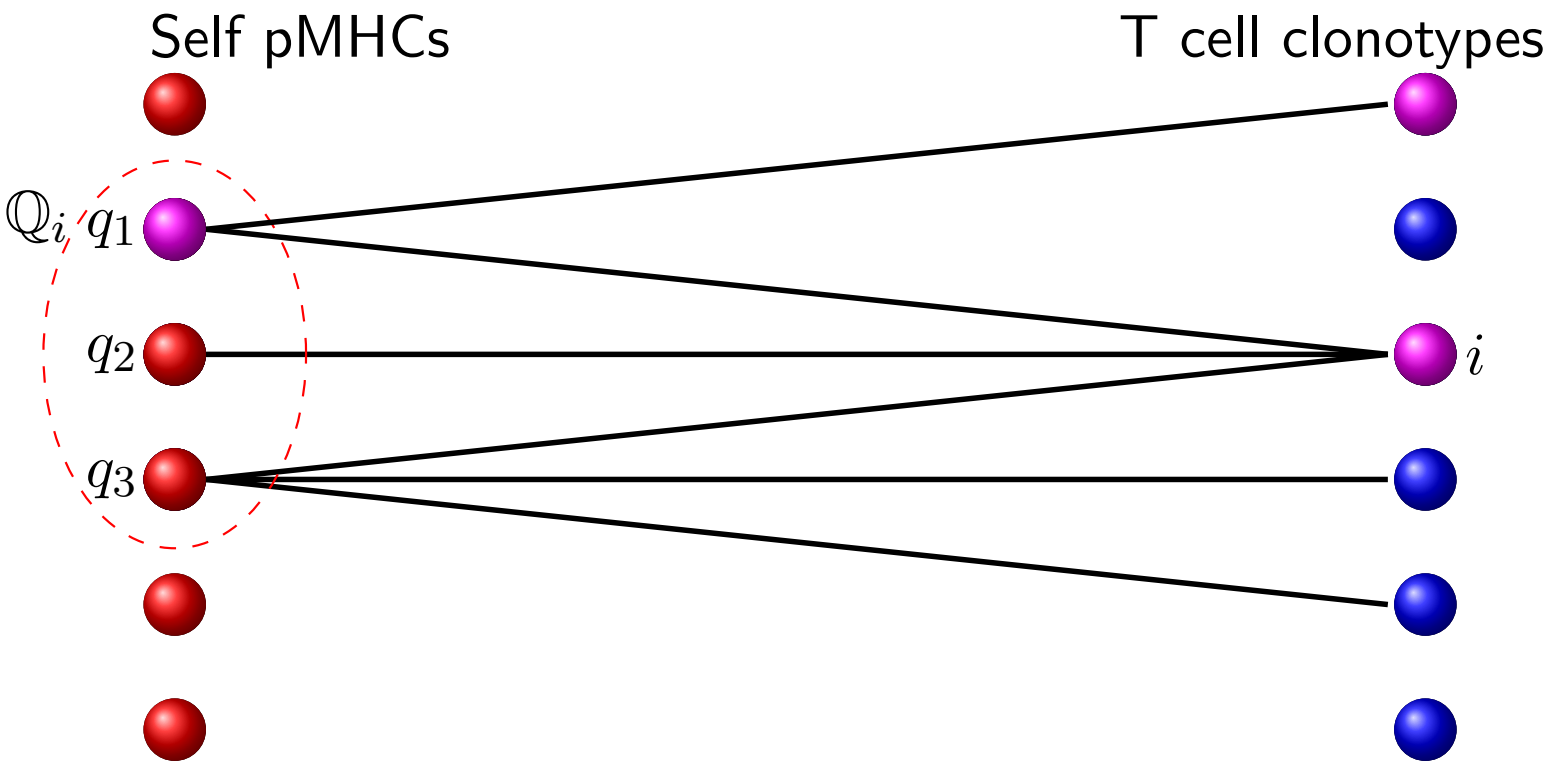

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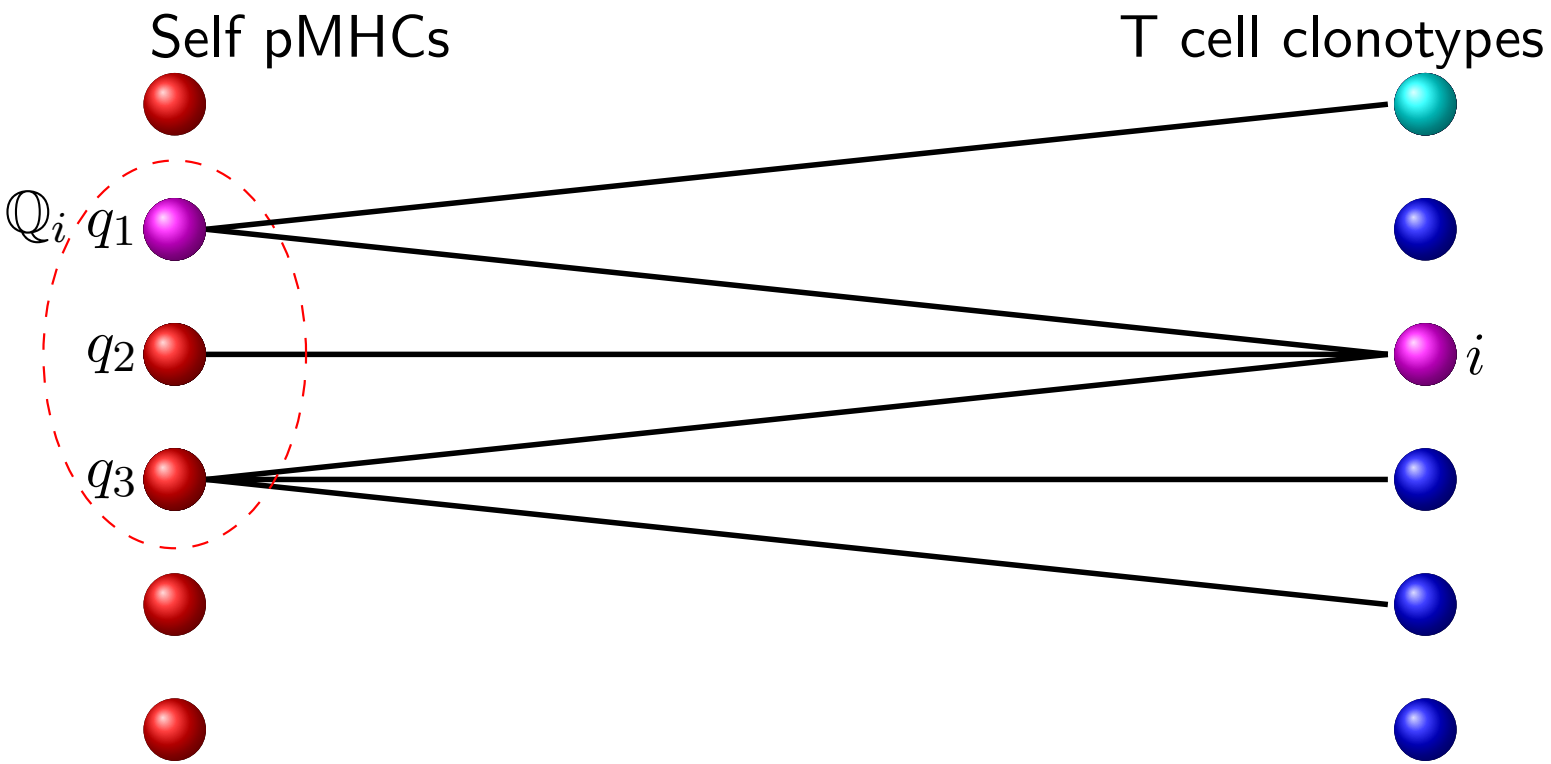

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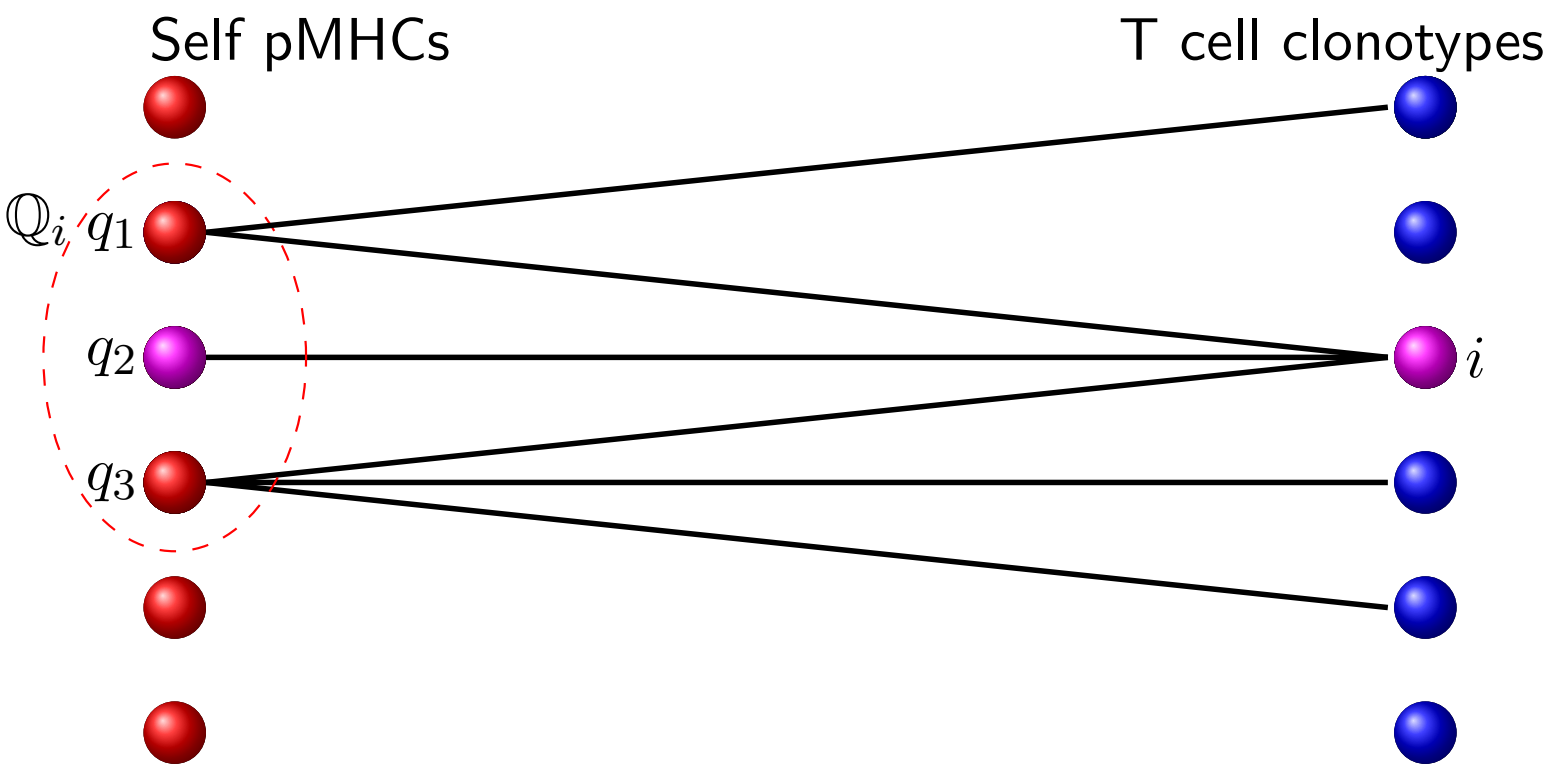

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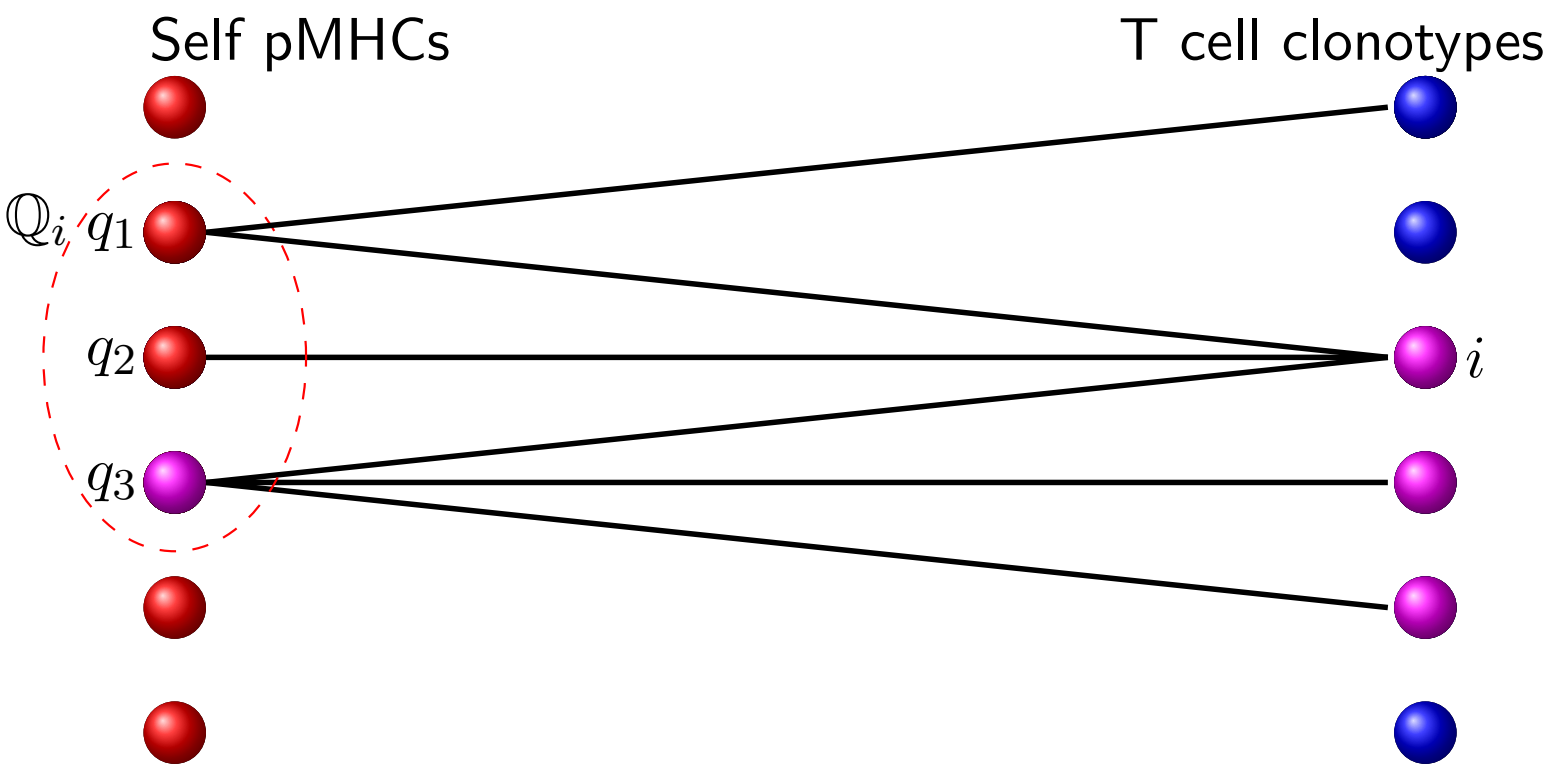

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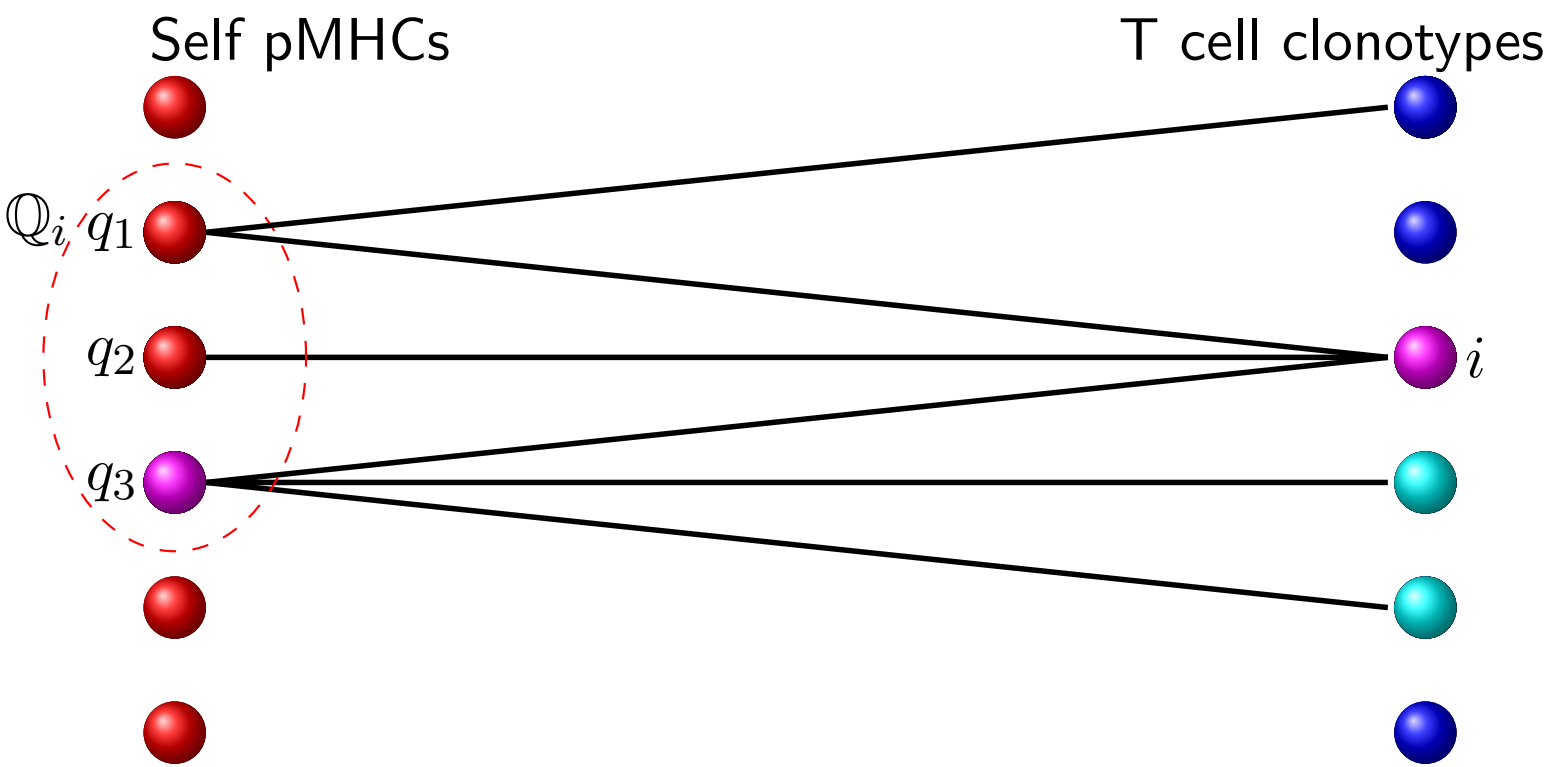
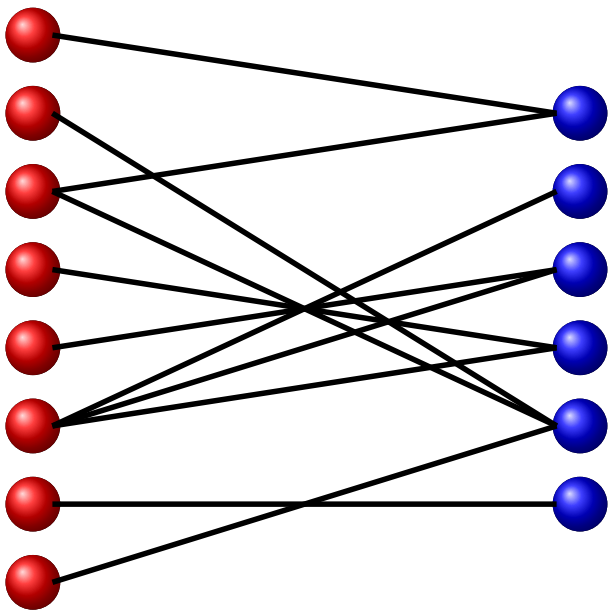


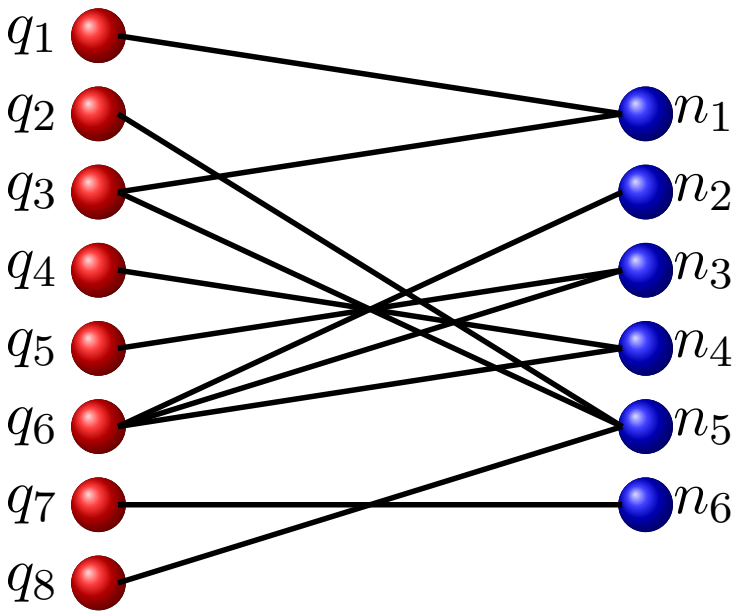
Outline

Multi-variate Markov dynamics: an example I



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

Multi-variate Markov dynamics: an example II

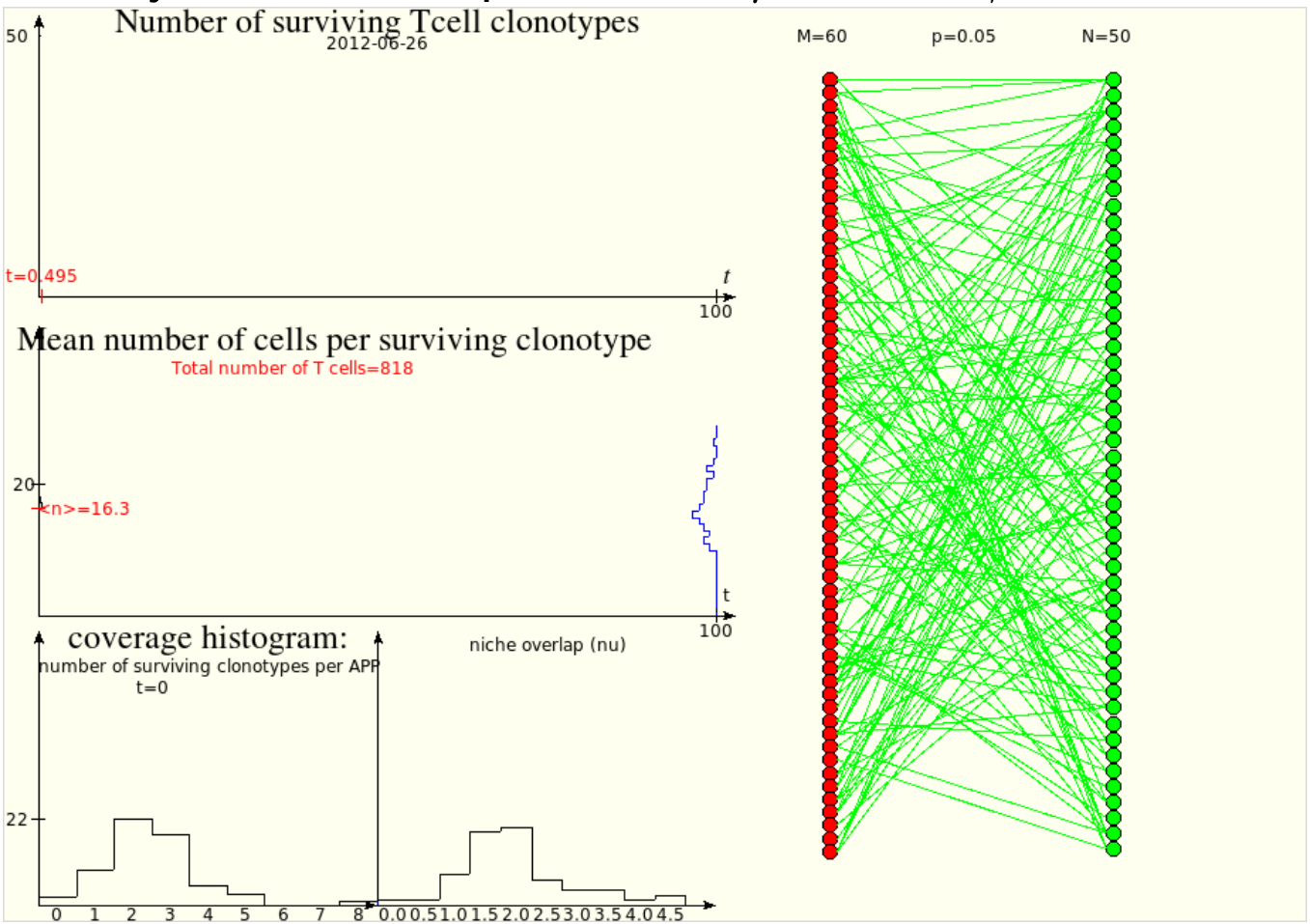


- Suppose that $n(t) = (15, 7, 9, 0, 11, 1)$.
- $\mathbb{P}(\text{next event is a death}) = \frac{\Omega(t)}{\Omega(t)+\Lambda(t)}$.
- $\Omega(t) = \mu\,(15 + 7 + 9 + 0 + 11 + 1)$.
- $\Lambda(t) = \Lambda_1(t) + \Lambda_2(t) + \cdots + \Lambda_6(t)$.

- $\Lambda_1(t) = \gamma\left(\frac{15}{15} + \frac{15}{15+11}\right), \Lambda_2(t) = \gamma\left(\frac{7}{7+9+0}\right), \Lambda_3(t) = \gamma\left(\frac{9}{9} + \frac{9}{7+9+0}\right),$
- $\Lambda_4(t) = 0, \Lambda_5(t) = \gamma\left(\frac{11}{11} + \frac{11}{15+11} + \frac{11}{11}\right), \Lambda_6(t) = \gamma\left(\frac{1}{1}\right)$.
- $\mathbb{P}(\text{birth in clonotype 1}) = \frac{\Lambda_1(t)}{\Omega(t)+\Lambda(t)}$.
- $\mathbb{P}(\text{death in clonotype 3}) = \frac{9\,\mu}{\Omega(t)+\Lambda(t)}$.
- 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. $\mu = 1.0$, $\gamma = 10.0$



Outline

Self pMHC signal: one round of T cell division

- γ_q is the proliferation rate from self pMCH q.
- $\mathbb{C}_q$ is the set of T cells that receive a proliferation signal (to go through one round of cell division) from self pMHC q.
- $\mathbb{Q}_i$ is the set of self pMHCs from which T cells of clonotype i receive a signal that triggers one round of cell division.
- If $q \in \mathbb{Q}_i$, then $|\mathbb{C}_q| = n_i + n_{iq} \geq n_i$.
- n_i is the number of T cells of clonotype i.
- n_{iq} is the number of T cells, other than clonotype i, that receive proliferation signal to divide once from self pMHC q.
- The birth rate per T cell of clonotype i is

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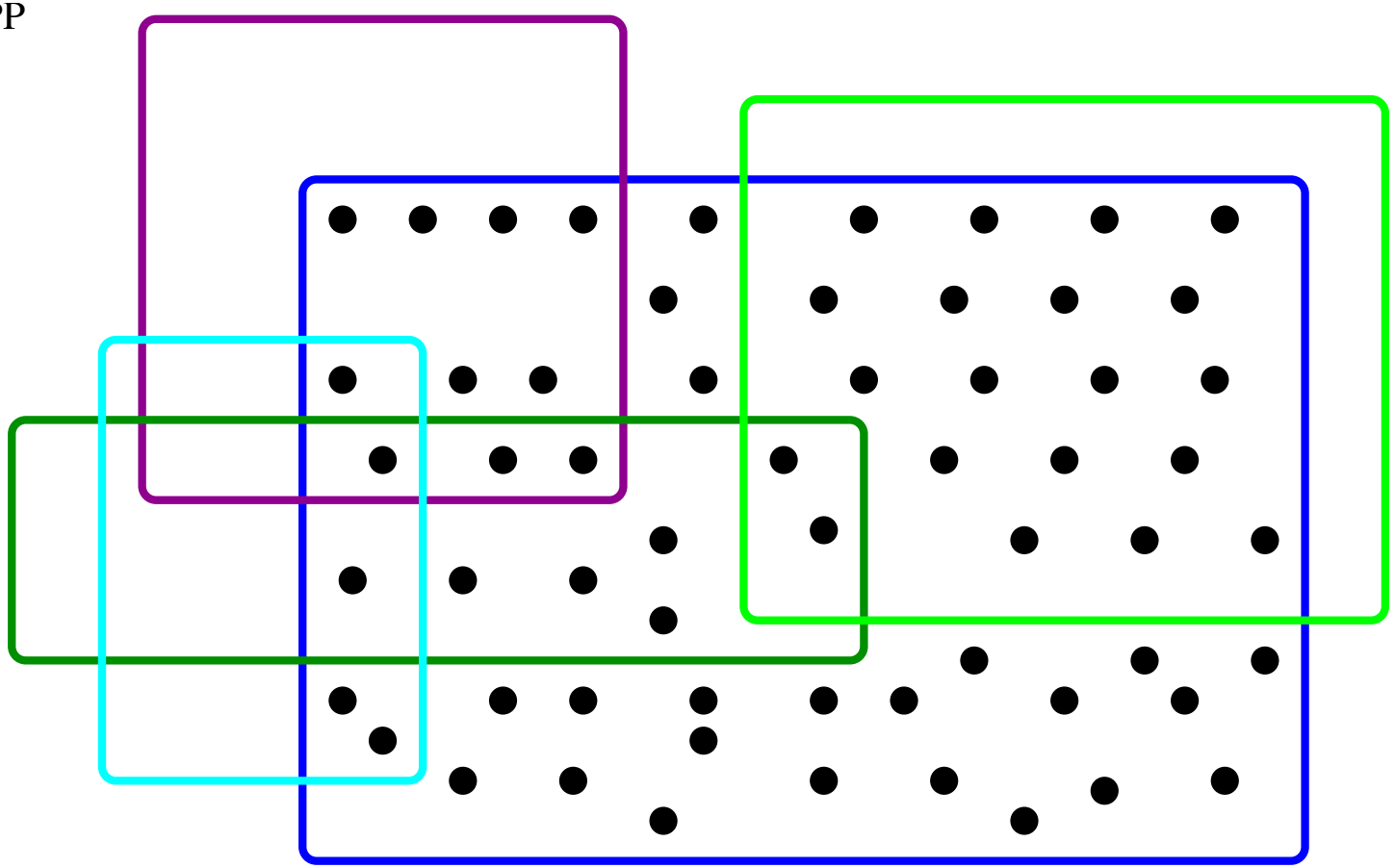
Partition of $\mathbb{Q}_i$

- APP



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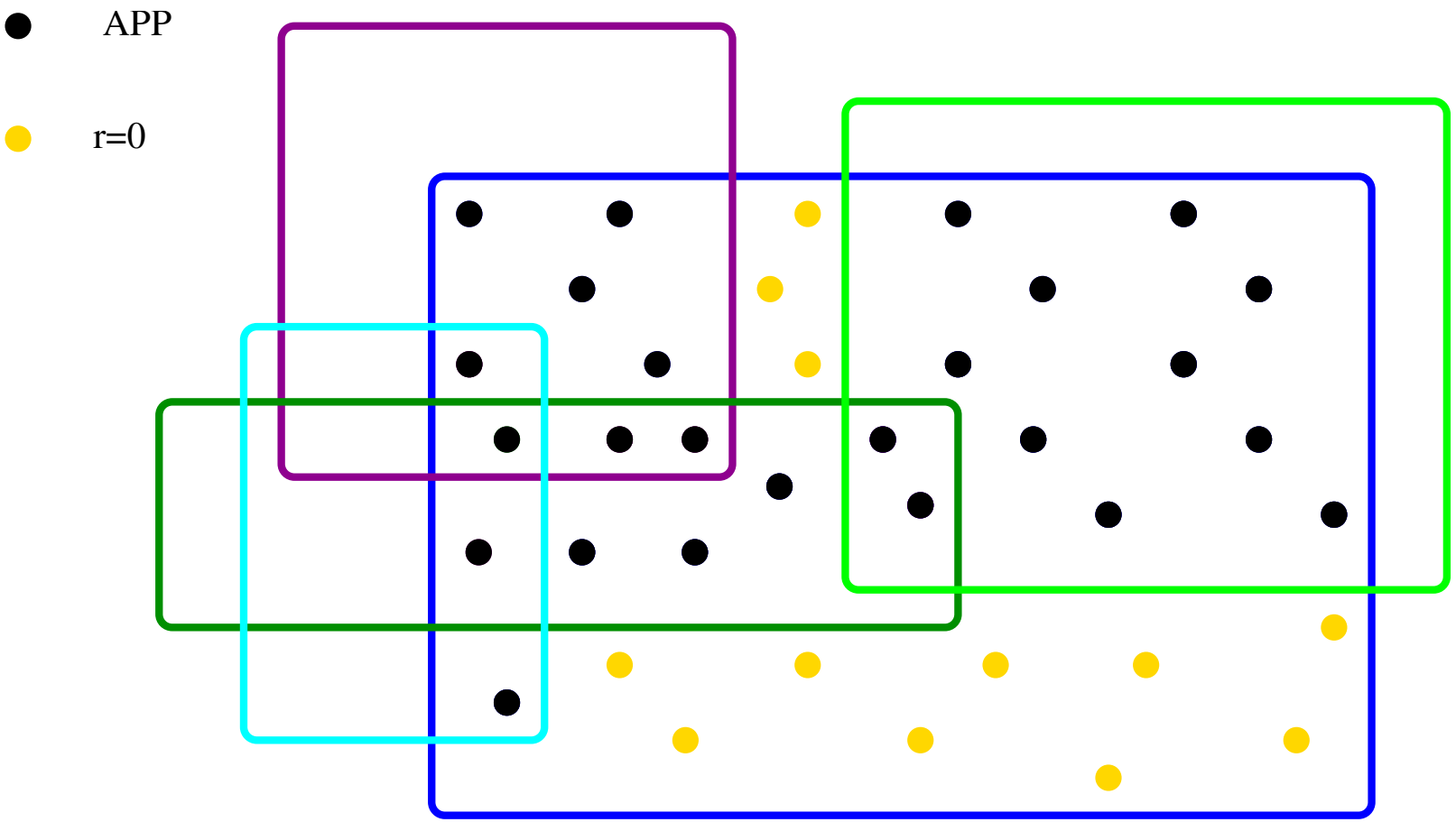

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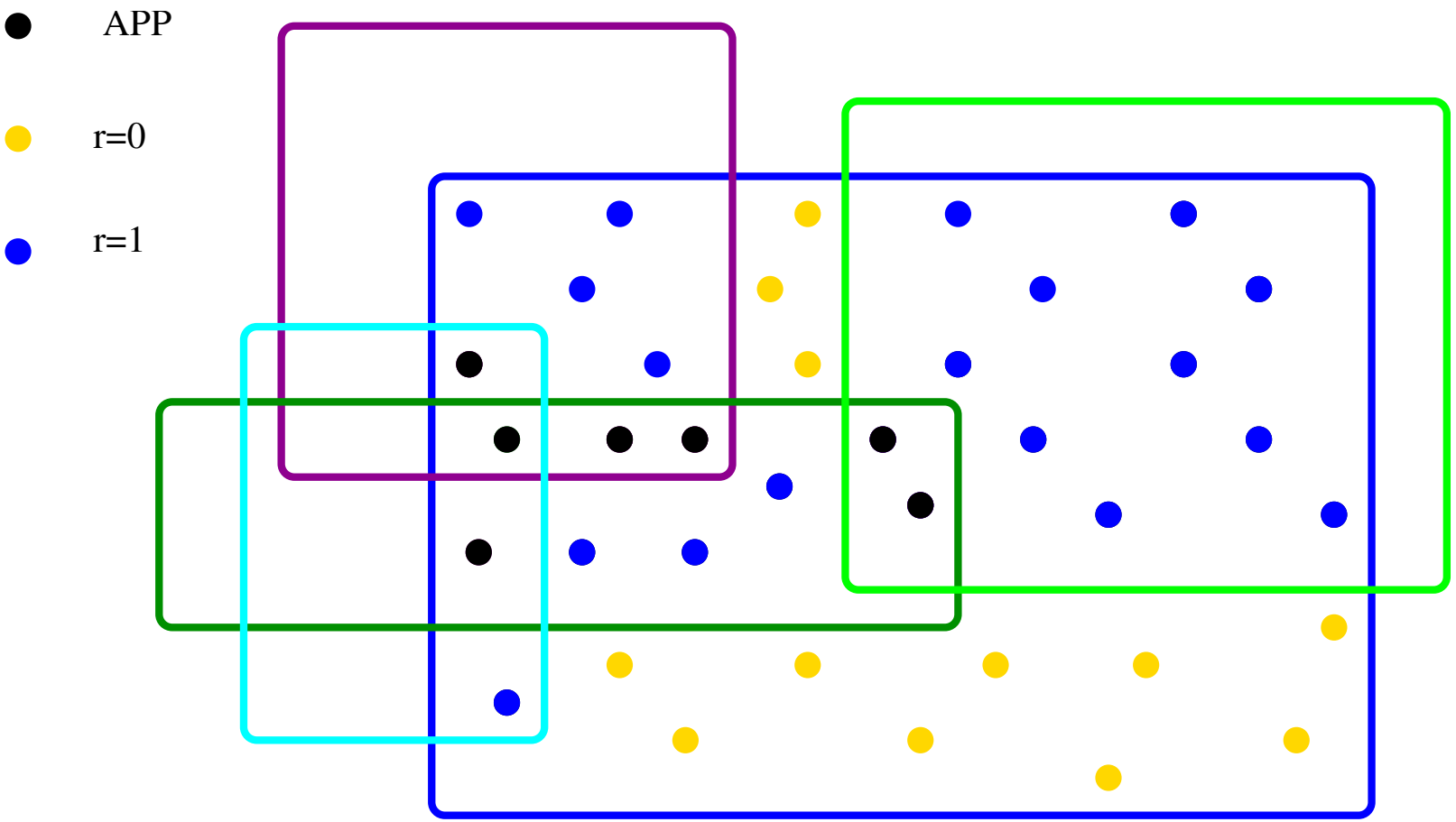

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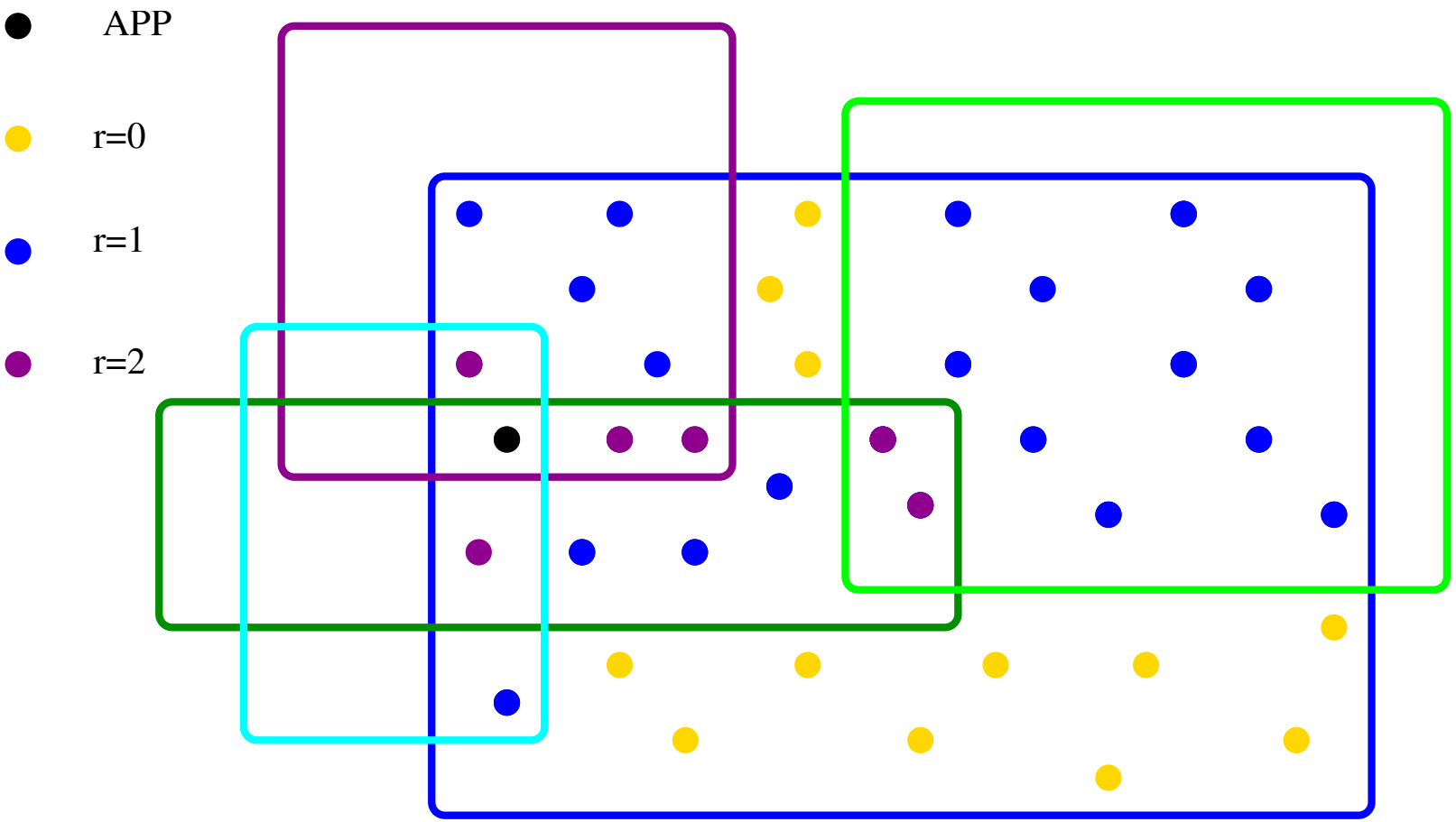

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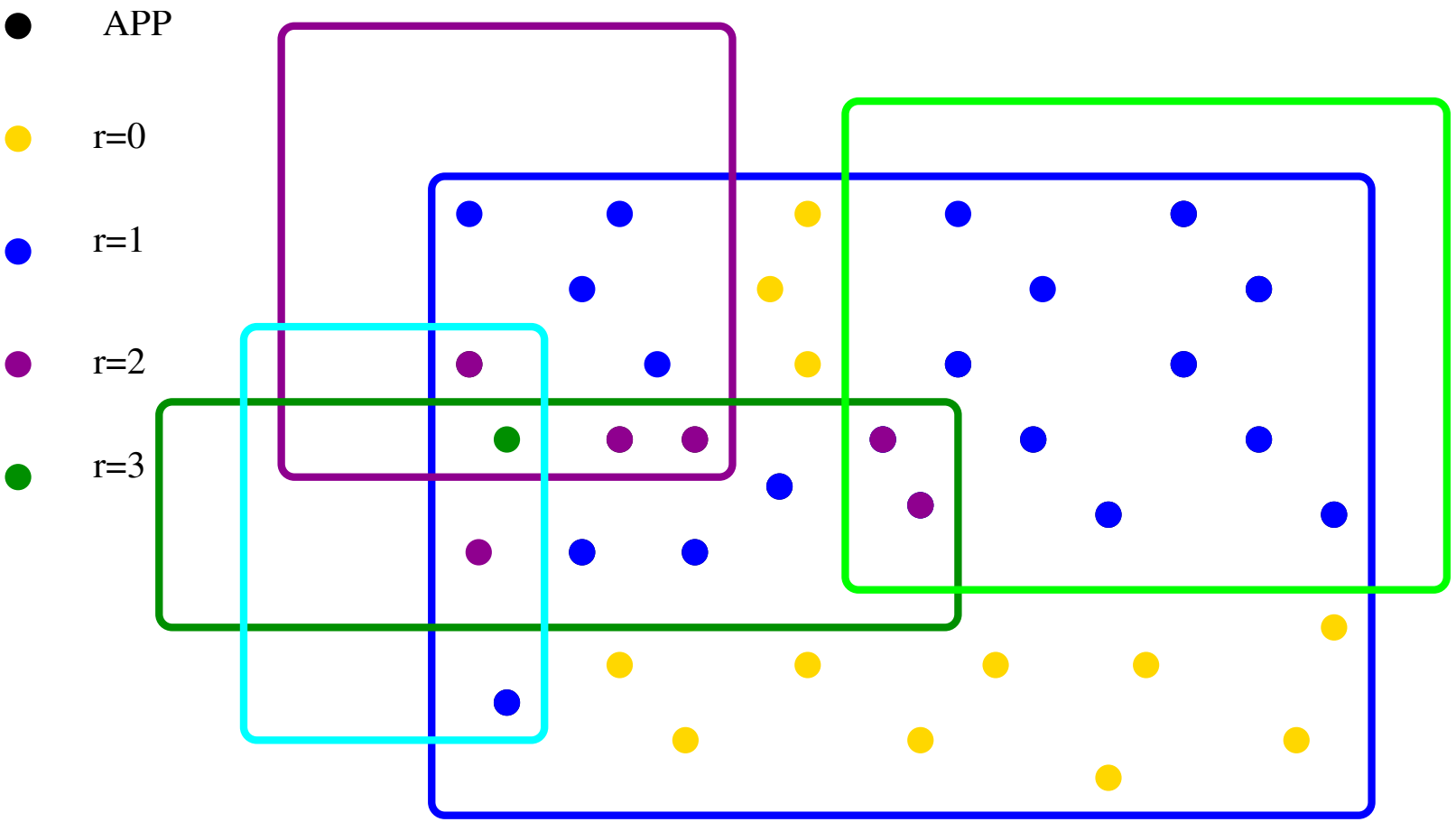

More on this partition

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Mean field approximation (two hypotheses)

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- $\mathbb{Q}_{ir} \cap \mathbb{Q}_{ir'} = \emptyset$, for $r \neq r'$, and $\sum_{q \in \mathbb{Q}_i} = \sum_{r=0}^{+\infty} \sum_{q \in \mathbb{Q}_{ir}}$.
- $\lambda_i = \sum_{q \in \mathbb{Q}_i} \frac{\gamma}{n_i + n_{iq}} = \sum_{r=0}^{+\infty} \sum_{q \in \mathbb{Q}_{ir}} \frac{\gamma}{n_i + n_{iq}}$.

Mean field approximation (two hypotheses)

- $\sum_{q \in \mathbb{Q}_{ir}} \frac{\gamma}{n_i + n_{iq}} = \gamma \, |\mathbb{Q}_{ir}| \, \mathbb{E}_{q \in \mathbb{Q}_{ir}} \left[\frac{1}{n_i + n_{iq}} \right]$.
- $\mathbb{E}_{q \in \mathbb{Q}_{ir}} \left[\frac{1}{n_i + n_{iq}} \right] \approx \frac{1}{\mathbb{E}_{q \in \mathbb{Q}_{ir}}[n_{iq}] + n_i}$. **(H1)**
- $\mathbb{E}_{q \in \mathbb{Q}_{ir}} [n_{iq}] = r \langle n \rangle$, with $\langle n \rangle$ the average clonotype size (average number of T cells per clonotype). $(\star)$ **(H2)**

More on this partition

- $\mathbb{Q}_i = \bigcup_{r=0}^{+\infty} \mathbb{Q}_{ir}$.
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- $\lambda_i = \sum_{q \in \mathbb{Q}_i} \frac{\gamma}{n_i + n_{iq}} = \sum_{r=0}^{+\infty} \sum_{q \in \mathbb{Q}_{ir}} \frac{\gamma}{n_i + n_{iq}}$.

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- $\sum_{q \in \mathbb{Q}_{ir}} \frac{\gamma}{n_i + n_{iq}} = \gamma \, |\mathbb{Q}_{ir}| \, \mathbb{E}_{q \in \mathbb{Q}_{ir}} \left[\frac{1}{n_i + n_{iq}} \right]$.
- $\mathbb{E}_{q \in \mathbb{Q}_{ir}} \left[\frac{1}{n_i + n_{iq}} \right] \approx \frac{1}{\mathbb{E}_{q \in \mathbb{Q}_{ir}}[n_{iq}] + n_i}$. **(H1)**
- $\mathbb{E}_{q \in \mathbb{Q}_{ir}} [n_{iq}] = r \langle n \rangle$, with $\langle n \rangle$ the average clonotype size (average number of T cells per clonotype). $(\star)$ **(H2)**
- The cardinality of the set $\mathbb{Q}_{ir}$ (for fixed i and r) can be computed from the binomial distribution.

Cardinality of $\mathbb{Q}_{ir}$

- N_C is the number of clonotypes in the periphery.
- $p_{\cdot|i}$ is the probability that a self pMHC randomly chosen from $\mathbb{Q}_i$ belongs to $\mathbb{Q}_{i'}$, with i' a different and random clonotype.
- $|\mathbb{Q}_{ir}|$ can be computed from the binomial distribution.

Competition for self pMHCs

- The different r clonotypes are chosen from $N_C - 1$ different ones. The probability of success is $p_{\cdot|i}$.
- $|\mathbb{Q}_{ir}| = |\mathbb{Q}_i| \binom{N_C-1}{r} p_{\cdot|i}^r \left(1 - p_{\cdot|i}\right)^{N_C-1-r}$.
- If $N_C \gg 1$ and $p_{\cdot|i} \ll 1$, we have $|\mathbb{Q}_{ir}| = |\mathbb{Q}_i| \frac{\nu_i^r \, e^{-\nu_i}}{r!}$.
- Define the niche overlap $\nu_i = p_{\cdot|i} \left(N_C - 1\right) \approx p_{\cdot|i} \, N_C$.

Meaning of the mean field approximation

- The cells of clonotype i are competing with many T cells belonging to a large number of other clonotypes in the repertoire.
- Individual competitive interactions with other clones are weak: access to any given self pMHC does not have a significant impact on the fate of the clone.
- The clone experiences interactions with very many other clones, each of which is virtually inconsequential by itself.
- The cross-reactivity of a given TCR can be 10^6, that is, a single TCR can "see" 10^6 different pMHCs.

Continuous time Markov chain for a given T cell clonotype

- The number of T cells of a given clonotype is modeled as a continuous time birth and death process: $\mathbb{X}(t)$.
- State space and transitions (birth and death events):
$$0 \underset{\lambda_0=0}{\overset{\mu_1}{\leftrightharpoons}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightharpoons}} 2 \underset{\lambda_2}{\overset{\mu_3}{\leftrightharpoons}} 3 \underset{\lambda_3}{\overset{\mu_4}{\leftrightharpoons}} \cdots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftrightharpoons}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftrightharpoons}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftrightharpoons}} n+1 \cdots$$
- $\mu_n \equiv \mu\, n$ is the death rate from state n.
- $\lambda_n \equiv \varphi n e^{-\nu} \sum_{r=0}^{+\infty} \frac{\nu^r}{r!} \frac{1}{r\langle n \rangle + n}$ is the birth rate from state n. $(\star)$
- μ is the death rate per single T cell.
- φ is the proliferation rate per single T cell.
- ν is the average number of clonotype competitors of the given clonotype.
- $\langle n \rangle$ is the average number of T cells per clonotype.

Extinction is certain

$$0 \underset{\lambda_0=0}{\overset{\mu_1}{\leftrightharpoons}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightharpoons}} 2 \underset{\lambda_2}{\overset{\mu_3}{\leftrightharpoons}} 3 \underset{\lambda_3}{\overset{\mu_4}{\leftrightharpoons}} \cdots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftrightharpoons}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftrightharpoons}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftrightharpoons}} n+1 \cdots$$

- We assume $\mathbb{X}(0) = n_0 > 0$, the thymic output at time $t = 0$.
- Denote by $p_m(t) = \mathbb{P}(\mathbb{X}(t) = m | \mathbb{X}(0) = n_0)$ for $m \geq 0$.
- $\sum_{m=0}^{+\infty} p_m(t) = 1$.
- It can be shown that (first lecture)

$$\frac{dp_n(t)}{dt} = -(\mu_n + \lambda_n)p_n(t) + \mu_{n+1}p_{n+1}(t) + \lambda_{n-1}p_{n-1}(t) \ .$$

- The probability of absorption into state 0 from any state $m \geq 1$ is one. Extinction is certain if (first lecture)

$$\sum_{k=1}^{+\infty} \prod_{n=1}^{k} \frac{\mu_n}{\lambda_n} = +\infty \ .$$

Expected time until extinction

- If extinction is certain, the mean time until extinction from state $m \geq 1$, τ_m, is finite if $\sum_{n=1}^{+\infty} \rho_n < +\infty$.
- $\tau_m = \sum_{n=1}^{+\infty} \rho_n + \sum_{s=1}^{m-1} a_s \sum_{k=s+1}^{+\infty} \rho_k$, where

$$a_k = \prod_{n=1}^{k} \frac{\mu_n}{\lambda_n} , \quad \rho_1 = \frac{1}{\mu_1} , \quad \text{and} \quad \rho_k = \frac{\lambda_1 \cdots \lambda_{k-1}}{\mu_1 \cdots \mu_k} \quad \forall k \geq 2 .$$

- The expected time to clonotype extinction given thymic output $\mathbb{X}(0) = n_0 > 0$ is τ_{n_0}.
- For $m \geq 1$, $\tau_m \geq \tau_1$. This implies that the time scale for extinction is determined by τ_1.

Theorem

Stationary probability distribution

- *The unique stationary solution of the forward Kolmogorov equations is characterised by* $\lim_{t\to+\infty} p_0(t) = 1$.
- *The stationary probability distribution is given by*

$$(p_0^*, p_1^*, p_2^*, \cdots) = (1, 0, 0, \cdots) .$$

Question

What can we say about the time evolution of $\mathbb{X}(t)$ before extinction takes place?

Conditional probability distribution

- Before extinction takes place, we define the conditional probability for $n \geq 1$

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

- $q_n(t) = \frac{p_n(t)}{1-p_0(t)} \ , \quad \forall n \geq 1 \ .$
- $\sum_{n=1}^{+\infty} \ q_n(t) = 1 \ .$
- It can be shown that

$$\begin{aligned} \frac{dq_n(t)}{dt} &= -(\lambda_n + \mu_n) \ q_n(t) + \mu_{n+1} \ q_{n+1}(t) + \lambda_{n-1} \ q_{n-1}(t) \\ &+ \mu_1 \ q_1(t) \ q_n(t) \ . \end{aligned}$$

Quasi-stationary probability distribution

- A sequence $\{q_1^*, q_2^*, q_3^*, \cdots\}$ is called a quasi-stationary probability distribution if

$$0 = -(\lambda_n + \mu_n)q_n^* + \mu_{n+1}q_{n+1}^* + \lambda_{n-1}q_{n-1}^* + \mu_1 q_1^* q_n^* \ ,$$

  with $q_0^* = 0$, for each $n \geq 1$, $q_n^* \geq 0$ and $\sum_{n=1}^{+\infty} q_n^* = 1$.
- For general birth and death population rates, there is no analytic solution.

Approximation I to the LSD – Ingemar Nasell

- Remove absorbing state and set $\mu_1 = 0$.
- $\Pi_m^{(1)} = \frac{\lambda_1 \lambda_2 \cdots \lambda_{m-1}}{\mu_2 \mu_3 \cdots \mu_m} \, \Pi_1^{(1)} \, , \quad \forall m \geq 2 \, .$
- τ_1 sets the time scale for absorption. This is a good approximation if $\tau_1 \gg \mu_1$.

$$1 \underset{\lambda_1}{\overset{\mu_2}{\leftharpoondown\rightharpoonup}} 2 \underset{\lambda_2}{\overset{\mu_3}{\leftharpoondown\rightharpoonup}} 3 \underset{\lambda_3}{\overset{\mu_4}{\leftharpoondown\rightharpoonup}} \cdots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftharpoondown\rightharpoonup}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftharpoondown\rightharpoonup}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftharpoondown\rightharpoonup}} n+1 \cdots$$

Approximation II to the LSD – Ingemar Nasell

- Remove absorbing state and replace μ_n by μ_{n-1} in the original Markov chain.
- $\Pi_m^{(2)} = \frac{\lambda_1 \lambda_2 \cdots \lambda_{m-1}}{\mu_1 \mu_2 \cdots \mu_{m-1}} \, \Pi_1^{(2)} \, , \quad \forall m \geq 2 \, .$
- τ_1 sets the time scale for absorption. This is a good approximation if $\tau_1 \approx \mu_1$.

$$1 \underset{\lambda_1}{\overset{\mu_1}{\leftharpoondown\rightharpoonup}} 2 \underset{\lambda_2}{\overset{\mu_2}{\leftharpoondown\rightharpoonup}} 3 \underset{\lambda_3}{\overset{\mu_3}{\leftharpoondown\rightharpoonup}} \cdots \underset{\lambda_{n-2}}{\overset{\mu_{n-2}}{\leftharpoondown\rightharpoonup}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_{n-1}}{\leftharpoondown\rightharpoonup}} n \underset{\lambda_n}{\overset{\mu_n}{\leftharpoondown\rightharpoonup}} n+1 \cdots$$

Two extreme competition limits

Hard niche ($\nu \ll 1$)

- On average, T cells of the given clonotype compete very little for self pMHC (small number of competitors).

Soft niche ($\nu \gg 1$)

- On average, T cells of the given clonotype compete a lot for self pMHCs (large number of competitors).

Analytic results

Hard niche ($\nu \ll 1$)

- Parameter $x = \frac{\varphi}{\mu}$.
- $\Pi_m^{(1)} = \frac{x^m}{m!(e^x-1)}$, $\forall m \geq 1$.
- $\langle n \rangle_{\Pi^{(1)}} = \frac{x}{1-e^{-x}}$.
- $\Pi_m^{(2)} = \frac{x^{m-1}}{(m-1)!e^x}$, $\forall m \geq 1$.
- $\langle n \rangle_{\Pi^{(2)}} = 1 + x$.
- $\tau_1\ \mu = \frac{e^x-1}{x}$.

Soft niche ($\nu \gg 1$)

- Parameter $y = \frac{\varphi}{\mu\nu\langle n \rangle} < 1$.
- $\Pi_m^{(1)} = -\frac{y^m}{m\log(1-y)}$, $\forall m \geq 1$.
- $\langle n \rangle_{\Pi^{(1)}} = -\frac{y}{(1-y)\log(1-y)}$.
- $\Pi_m^{(2)} = (1-y)y^{m-1}$, $\forall m \geq 1$.
- $\langle n \rangle_{\Pi^{(2)}} = \frac{1}{1-y}$.
- $\tau_1\ \mu = -\frac{\log(1-y)}{y}$.

Outline

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