How many TCR clones does the body maintain?

Competition model of T-cell repertoire

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How many TCRβ chains are there in a body?

10⁶ distinct β chains in the human blood extract and reverse transcribe mRNA from a pool of 10⁸ cells, amplify VB18 from a sample of cDNA, analyse the subfraction that has VJ1.4 and 12-aa-long CDR3. 17 different β chains found.

\[
\frac{17}{(0.093 \times 0.03 \times 0.008)} \approx 10^6. 
\]
25 α chains per β chain?

4 × 10⁶ distinct β chains in the human blood Direct counting of more than 10⁶ distinct β chains single-molecule DNA sequencing, millions of TCRβ determined, “unseen species” analysis. relative abundance, naive and memory repertoires compared
Homeostasis of naive T cells: size and TCR diversity

“The peripheral T-cell compartment is kept at a constant size as a consequence of homeostatic regulation, which requires the activity of cytokine and TCR signals.” (Seddon and Zamoyska, 2003).

Simple idea:

- IL-7, produced by stromal cells in lymph nodes, determines the overall size of the (naive) T-cell population. (Link et al 2007)

- TCR diversity of the T-cell population is determined by competition for (many different) self-pMHC ligands. (Mason 1998)
N\textsubscript{T} cell clonotypes
death rate per cell $\mu$

$M$ self pMHCs

stimulus rate $\gamma$

recognition probability $p$

thymic production $\theta$

cells per clone $n_\theta$

$N(t)$ T cell clonotypes
death rate per cell $\mu$

clonal extinction

Singh, Bando and Schwartz, Immunity 37 (2012)
Sewell, Nature Reviews Immunology 12 (2012)
Stochastic system dynamics

Death
Every T cell has a constant probability per unit time $\mu$ of dying, independent of all others.

Division
Each pMHC set stimulates at rate $\gamma$. 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)
Model of large-scale clonal competition

- 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

\[
\Pr(\text{survival}) = 1 - \exp\left(-\frac{n_0}{\mu t}\right)
\]
Stimuli and cell division

\[ \Lambda_i = \gamma \sum_{q \in Q_i} \frac{n_i}{|c_q|} \leq \gamma \phi_i \]

where \( \phi_i = \text{number of pMHCs in } Q_i \).

Birth rate for T cells of type \( i \)

\[ \left| c_q \right| = \text{total number of T cells stimulated by } q \]
Distribution of clonal extinction times

Now, if we assume \( n(t) \simeq \frac{\gamma}{\mu} \), then \( \lambda_i(t) = \sim \mu n_i \), so that birth rates and death rates are in balance. Let us, further, approximate \( n_i(t) \) by a diffusion process, \( X_t \).

\[
dX_t = \sqrt{2\mu X_t} dW_t.
\]

If \( F(t, b) \) is the probability of hitting 0 before time \( t \), starting with \( X_0 = b \), 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

\[
\Pr[X_t = 0|X_0 = b] = \exp(-\frac{b}{\mu t}).
\]
Thymic production

At rate $\theta$, new clonotypes are created with $n_\theta$ cells. The steady-state value of $N$ is the product of the rate of production of new clonotypes and the mean lifetime of a clonotype.

The steady-state fraction of T cells that are thymic emigrants is

$$\frac{n_\theta \theta}{\gamma M + n_\theta \theta}.$$

The parameter $\alpha = \frac{n_\theta \theta}{\gamma M}$ measures the strength of thymic production relative to peripheral division.

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**Figure:** Predicted steady-state number of distinct clonotypes. The dotted lines are valid in the weak-thymus limit. Three values of \( n_\theta \) are shown. We use \( \gamma M/\mu = 10^{11} \) cells, approximately equal to the number of naive CD4\(^+\) T cells in a human.
Parameter value guesses for mice and humans

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

Let $\alpha = \frac{n_\theta \theta}{\gamma M}$.

As $\alpha \to 0$, $N^* \to \frac{\gamma M}{\mu} \alpha (1 - 0.577 - \log(n_\theta \alpha))$.

Mice

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

Total (naive CD4$^+$) T cells: $4 \times 10^7$

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: $4 \times 10^{11}$.

Thymic production:

$n_\theta \theta = 10^{10} \text{year}^{-1}$

$p = 10^{-6}$, $M = 10^{10}$

$\gamma = 10 \text{year}^{-1}$

$N \simeq 10^{10}$.

Bains, Antia, Callard and Yates, Blood 113 (2009)
Westera et al Blood (2013)
Vrisekoop et al PNAS 105 (2008)
de Boer and Perelson, J Theoretical Biology (2013)
Cell by cell TCR analysis (Gonçalves and Rocha)

Using material obtained from T cell pools makes direct evaluation of clone sizes difficult, because identical Tcrs may correspond to different cells expressing the same receptor, or to several amplicons of the same T cell.

Gonçalves and Rocha (INSERM and Pasteur): TCRB expression in individual CD8 naive T cells from specific-pathogen-free adult mice. In each individual cell, a single primer pair is used for the PCR amplification of the Tcrb.

187 of the 188 single cells from mouse 1 expressed unique Tcrb chains, even though this cohort included CD44\(^+\) cells. All sequences had nibbling at the V-D-J junctions and 90% also had N additions. 2.9% of individual cells expressed two in-frame Tcrb chains. No sequences were shared between different mice.
Repertoire subsets: TCRBV and epitope-specific

CD44− T cells expressing only TRBV13 or only TRBV19.

CD44− CD8 T cells recognising the GP33 peptide from the Lymphocytic Choriomeningitis Virus (LCMV) (CD44-GP33+ CD8+ T cells), separated using GP33 dextramers.
Three types of hypotheses are:
that each clone has the same number of cells
that the clonal sizes follow a simple geometric distribution, where the probability of finding clones with small size is higher than that of finding large clones
that there are two types of clones in the repertoire, the majority of clones made up of only a few cells, and a small minority of clones that contain many cells
The observed distribution of clonal sizes

Our goal is to find the probability distribution of the number of instances of $k$ copies of a TCR in a random sample of $m$ cells. Firstly, consider the point of view of one cell in the total of $S$ cells in the repertoire. The probability, which we denote $q$, that this cell is one of the $m$ cells in the sample is equal to $m/S$. Next, let us define the Bernoulli random variable $B$:

$$\Pr[B = 0] = 1 - q \quad \text{and} \quad \Pr[B = 1] = q,$$

where $q = \frac{m}{S}$.

The probability generating function (pgf) of $B$ is $\phi_B(z) = 1 - q + qz$. If $n_i$ is the number of cells of a clonotype labelled $i$, then the number of cells of type $i$ in the sample is the random variable $Y_i$, which can be written $Y_i = B_1 + \cdots + B_{n_i}$. With the approximation that the $B_j$ are independent random variables, the pgf of $Y_i$ is

$$\phi_{Y_i}(z) = \phi_B(z)^{n_i} = (1 - q + qz)^{n_i}.$$
a word from ...

- Quantitative T cell Immunology (ITN)
- Mathematics for Health and Disease (FP7 IRSES)

http://www1.maths.leeds.ac.uk/Applied/QUANTI
http://www1.maths.leeds.ac.uk/Applied/INDOMATH
See you at ...

- ICI. Melbourne, August 2016
- Joint BSI and NVVI Congress. Liverpool, December 2016
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