Why are cell populations maintained via multiple intermediate compartments?
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Abstract There exist in nature many examples of cellular populations with a compartmental structure. For instance, T cell progenitors (thymocytes) in the thymus follow a structured journey of development. During this journey, they divide, die and differentiate [1]. Naive T cells in lymph nodes follow a structured journey of antigen-induced activation. During this journey, they divide, die and differentiate (to become effector and memory T cells) [2].

In this talk I introduce a mathematical compartmental model to characterise the structured journey of cellular populations, making use of a branching process approach. I discuss two cases: that of a single compartment, and that of multiple compartments (Figure 1). Each cellular compartment has its specific sets of rules (probabilities of division, differentiation and death) and function (Figure 2). I shall consider four types of single-cell events in compartment c ($1 \leq c \leq C$):

- **Symmetric division**, $p_b(c)$: both daughter cells remain in compartment c.
- **Asymmetric division**, $p_a(c)$: one daughter cell remains in compartment c and the other moves to compartment $c+1$.
- **Death**, $p_d(c)$: a cell in compartment c dies.
- **Exit**, $p_e(c)$: a cell in compartment c moves to compartment $c+1$.

Each cell in compartment c obeys the same rules and cells are independent; this allows us to make use of the theory of branching processes. The study is restricted to a time-independent analysis (Figure 1). We restrict ourselves to counting cells and ignore inter-event times; that is, we ignore the total time taken for progeny to disappear from all intermediate compartments and exit from the last one. We assume $p_b < p_d + p_e$, so that *extinction* is the ultimate fate of the population of intermediate cells. For the case $C = 1$ and arbitrary C intermediate compartments between progenitor and product cells, we are interested in the following two random variables : the total number of product cells from a single progenitor cell, and the number of divisions that separates each cell from the progenitor, so that we can classify cells by generation. These random variables are studied with first step arguments and probability generating functions.

Results We consider the maintenance of a population of *product* cells from *progenitor* cells via one or more intermediate compartments. We calculate the distribution of $\mathcal{R}$, the number of product cells per progenitor, and its mean, N. We also consider the random variable $\mathcal{G}$, the generation number of a randomly-selected product cell, and its mean, D. Thus, D is the mean age of the product cell population, measured in number of generations from the progenitor.

If $C = 1$, a large ratio of product cells to progenitors can only be achieved at the cost of the product cell population being dominated by large families of cells descended from individual progenitors, and large number of divisions separating product cells from progenitors. These undesirable features can be avoided if there are multiple intermediate compartments. A sequence of compartments is, in fact, an efficient way to maintain a product cell population from a progenitor population, avoiding excessive clonality and minimising the number of rounds of division *en route*.

I shall discuss the case when $p_a = 0$, but the results can be generalised to the case when asymetric division events are present ($p_a \neq 0$). For the symmetric case, we may express all single compartment quantities in terms of N and D.

$$p_b = \frac{1}{2}\frac{D}{D+1}, \text{ and } p_e = \frac{N}{D+1}.$$

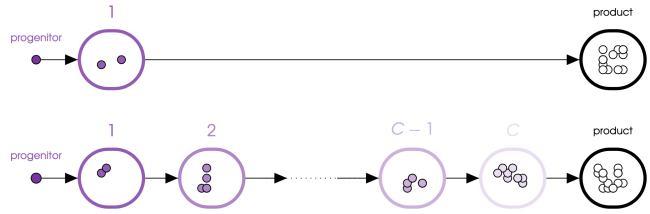

Fig. 1. A single intermediate compartment ($C = 1$). Multiple intermediate compartments ($C \geq 2$). From a single progenitor, how many cells exit a single compartment? From a single progenitor, how many cells exit a sequence of C different compartments?

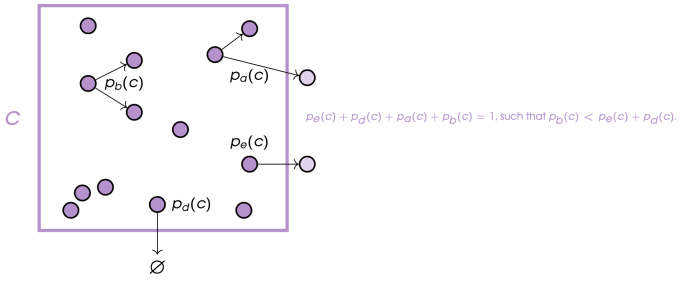

Fig. 2. Each cell in compartment c: same rules and independence ⇒ branching process.

[1] Klein, Kyewski, Allen and Hogquist. *Positive and negative selection of the T cell repertoire: what thymocytes see (and do not see)*. Nature Reviews Immunology 2014.

[2] Farber, Yudanin and Restifo. *Human memory T cells: generation, compartmentalization and homeostasis*. Nature Reviews Immunology 2014.