Immune system: from principles to epidemiology

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Outline

- What are principles?
- What is the immune system?
- An organising principle of the immune system with relevance to epidemiology

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What are principles?

Fundamental truths...that serve as the foundation for a behavior...

Oxford English Dictionary

What are principles?

Reflect causal relationships [that are] fundamental to reality...

Wikipedia

My working definition

A mechanism/rule/structure that is:

- fundamental to the behaviour or functioning of a particular system
- generalizable to systems belonging to the same functional class

Benefits of principles

- Give fundamental insights into how biology works
- Provide a solid foundation for using math to deduce additional biological insights
- New fundamental insights → new drugs, vaccines, health policies, drought-resistant crops, protocols for mitigating effects of climate change, etc

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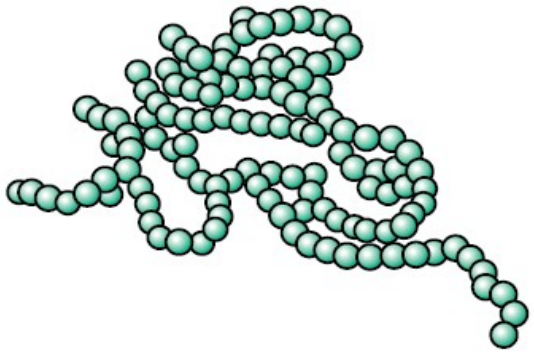
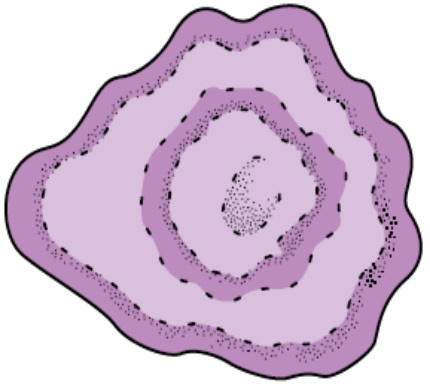
What is the immune system?

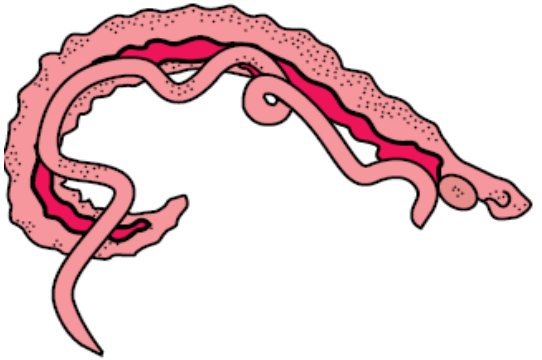
- A system of cells, tissues, organs that protect the body against disease
  - Fights pathogens (e.g. causative agents of AIDS, malaria), cancers, repairs tissues, etc



Bacteria:
streptococci



Viruses:
herpes virus



Parasites:
schistosome

Figures: NIH *Understanding the Immune System* 2003

Branches of the immune system

- There are two main conceptual divisions:
  - Innate immune system
    - mostly pathogen-nonspecific
    - first-line defense against pathogens
  - Adaptive immune system
    - mostly pathogen-specific
    - recalls previously encountered pathogens, enabling faster and stronger subsequent response

Adaptive immune system's response

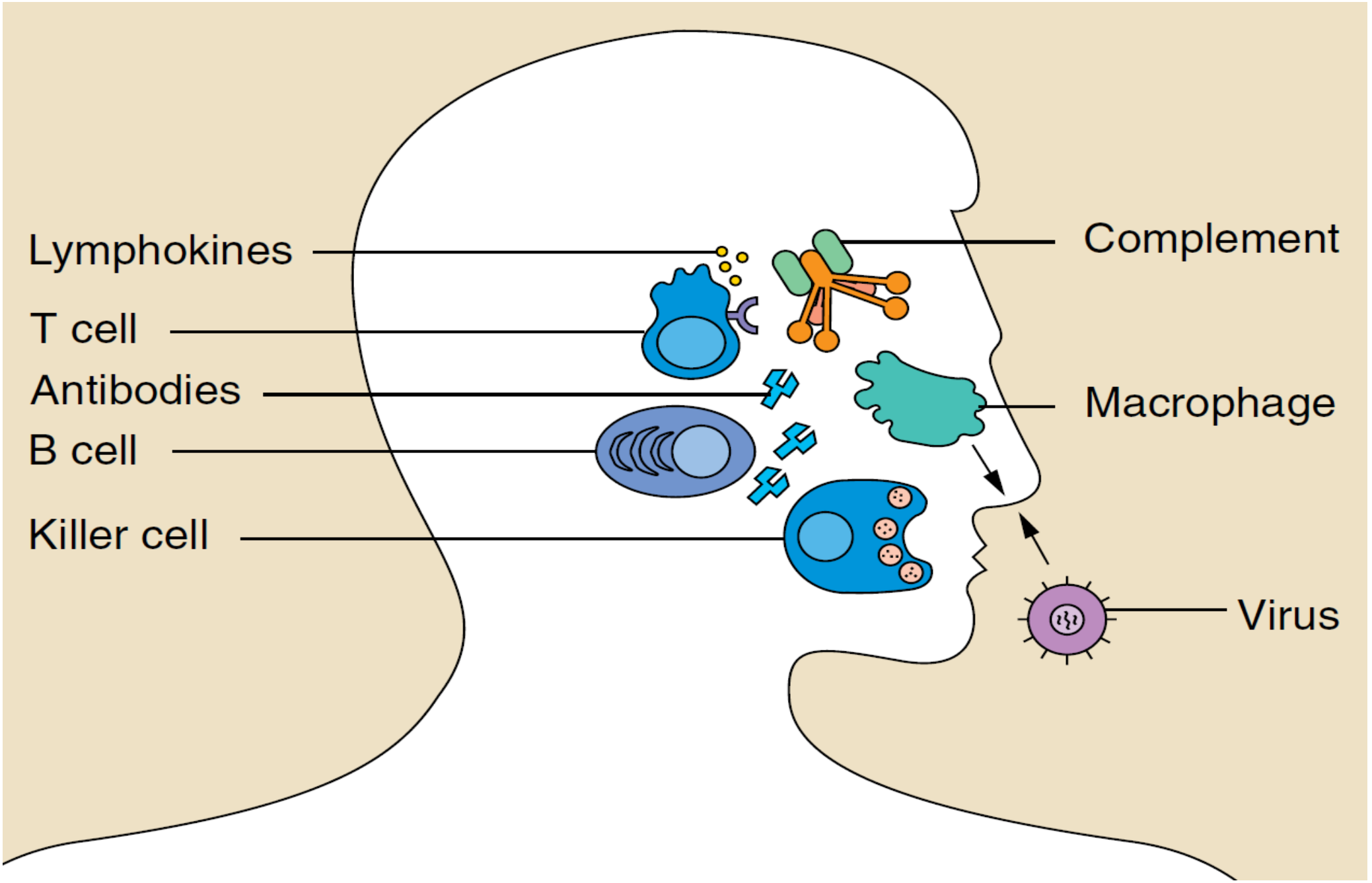


Figure: NIH *Understanding the Immune System* 2003

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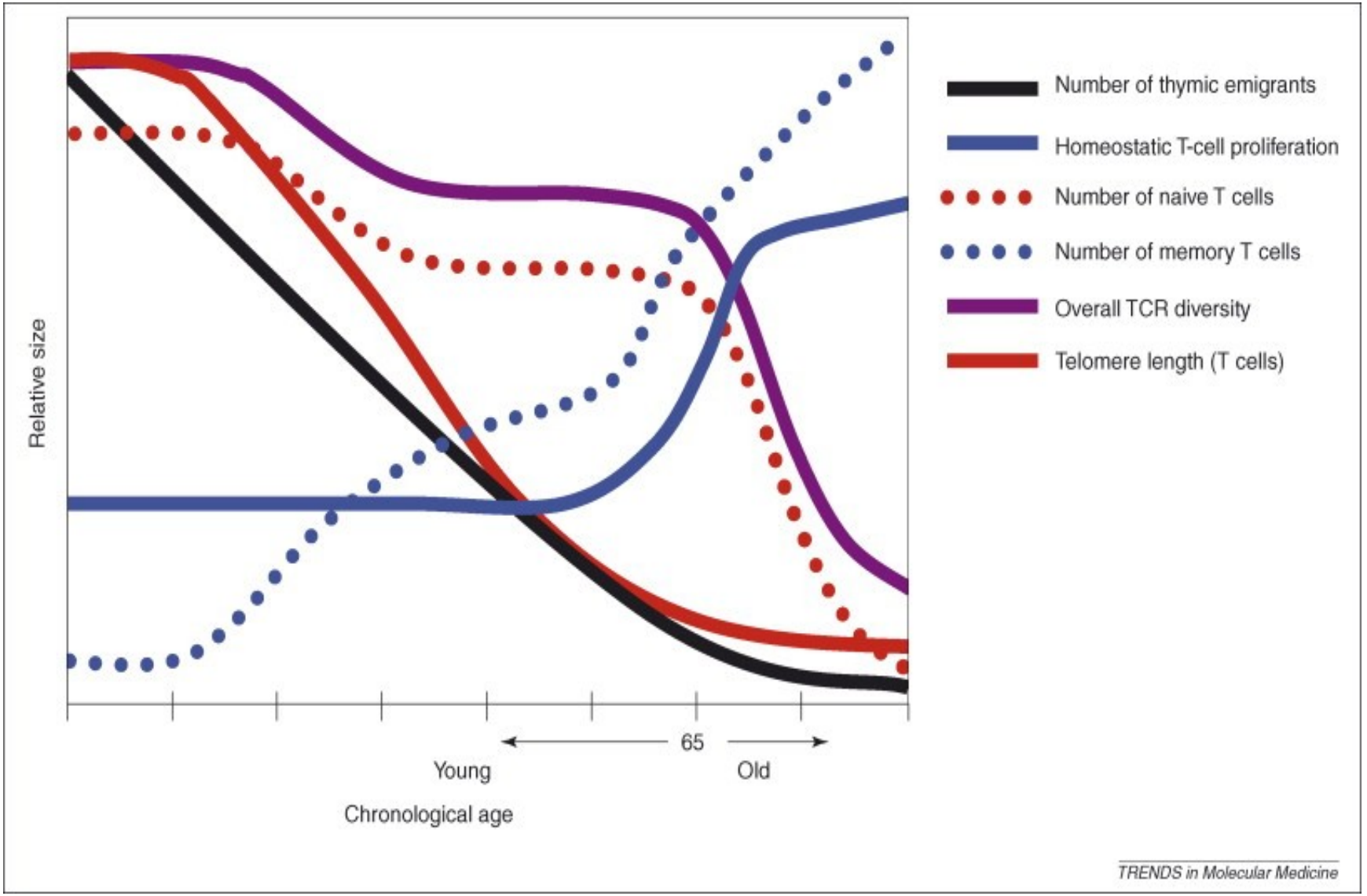
Immune system ages nonlinearly



Vallejo *Trends Mol Med*, 2007.

What causes TCR diversity to collapse in chronological old age?

Novel hypothesis: Diversity collapses because of the Hayflick limit

T cells are normally in quiescent phase of cell cycle (G_0/G_1)

Activated T cells divide – enter $S/G_2/M$ phase and produce two daughter cells

Cells can divide only finite number times (Hayflick limit), before being eliminated

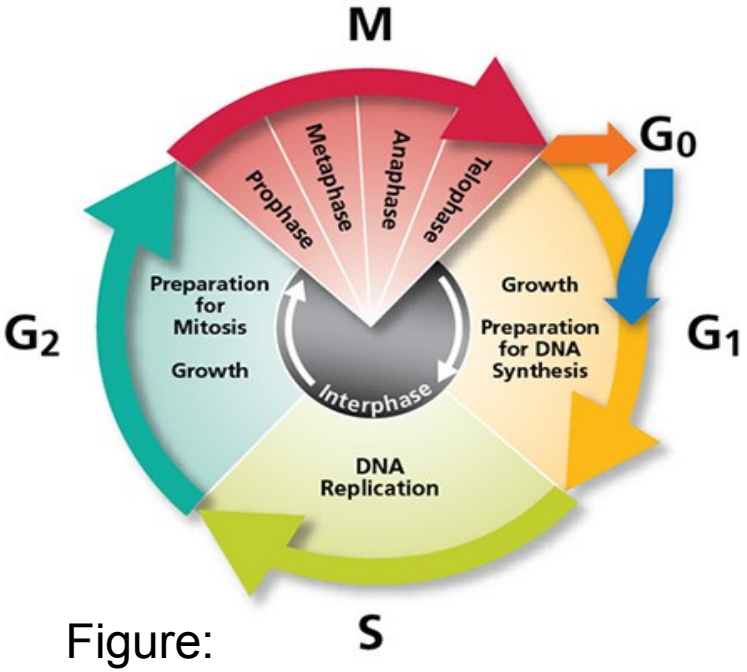


Figure: http://www.bdbiosciences.com/research/apoptosis/analysis/index.jsp

T-cell loss forces others to proliferate to maintain cell numbers (homeostasis)

This dynamic leads to accerated rate of cell division and loss

Ndifon & Dushoff *J Immunol* 2016

Simple model predicts increase in homeostatic proliferation

$$\beta_t = \frac{\delta_t + \left(N_{t+1} - \int \varepsilon(x)\,dx \right) / N_t - 1}{1 - 2\,\acute{\mu}_t}$$

N_t total number of cells at time t

β_t rate at which cells are activated to divide

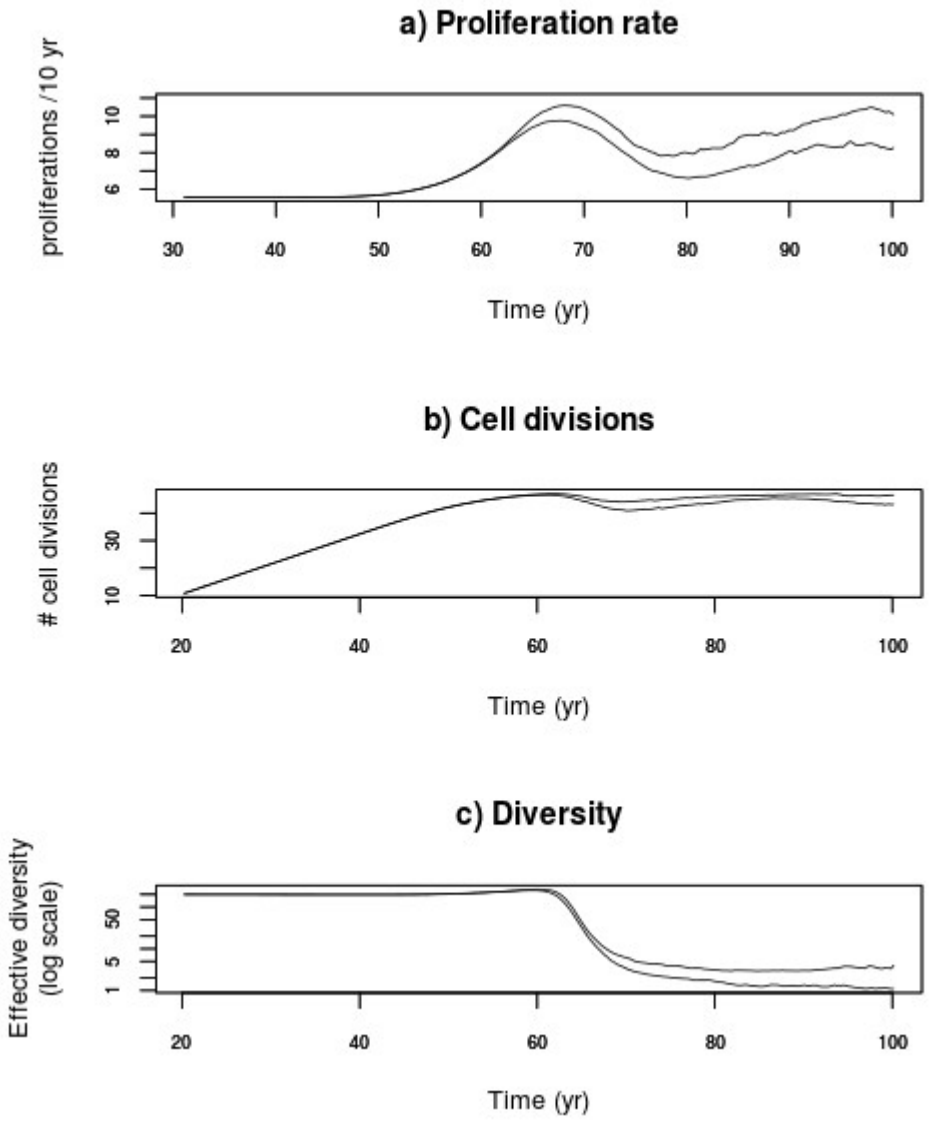
μ_t average rate of cell loss due to Hayflick limit

δ_t rate of cell turnover not directly linked to activation

ε_t thymic output of new T cells as a proportion of N_t

Ndifon & Dushoff *J Immunol* 2016

Simulations with experimental parameters confirm novel hypothesis



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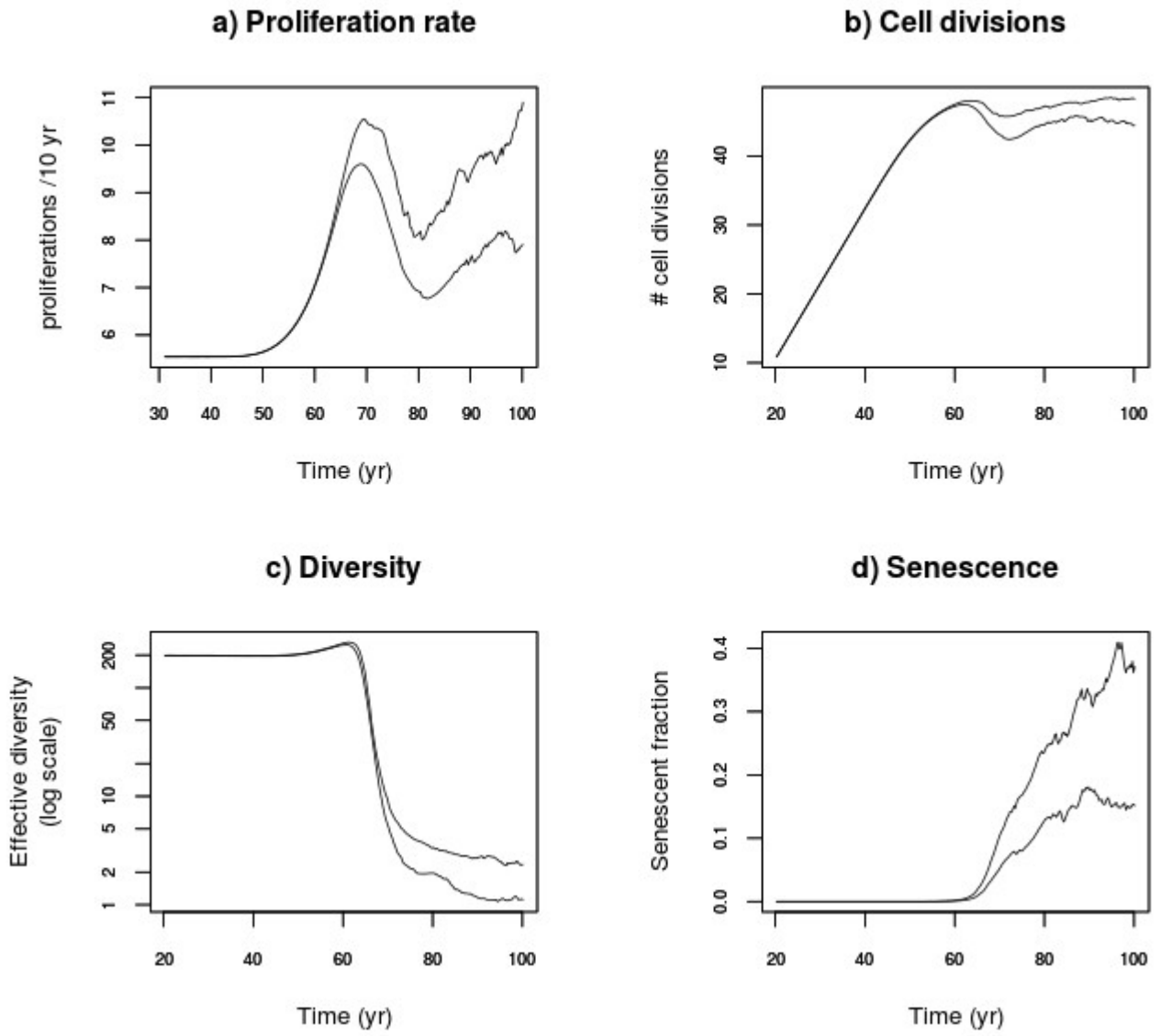
Simulation results are robust to assumptions



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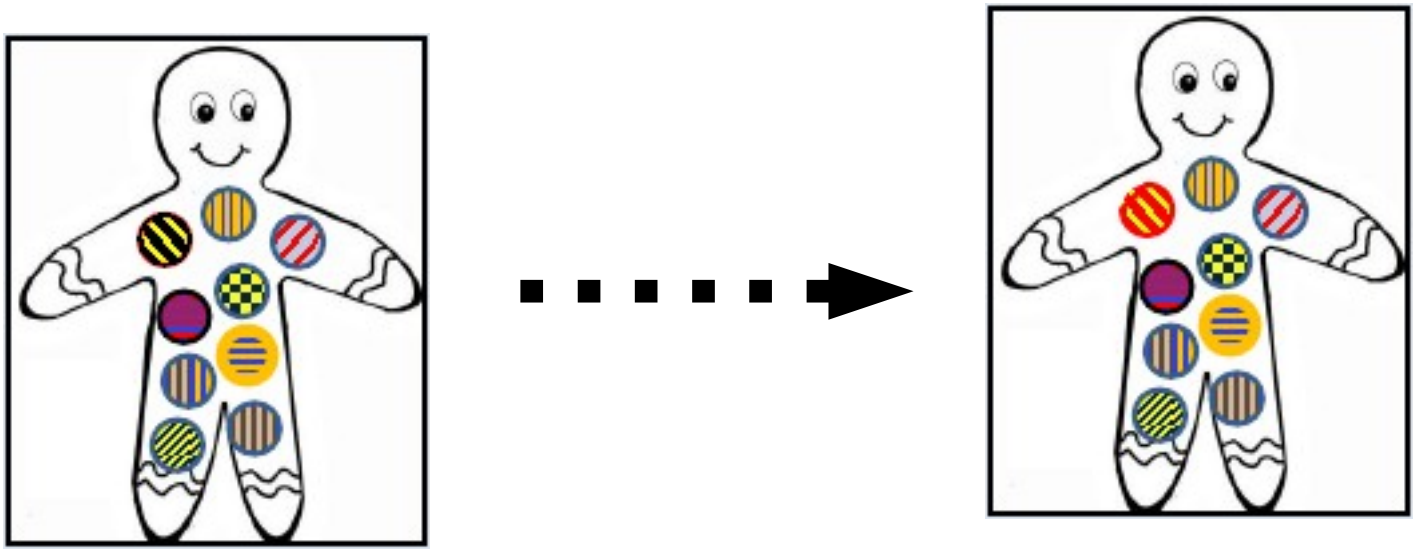
Summary

The Hayflick limit is one of the organising principles of T-cell diversity in humans

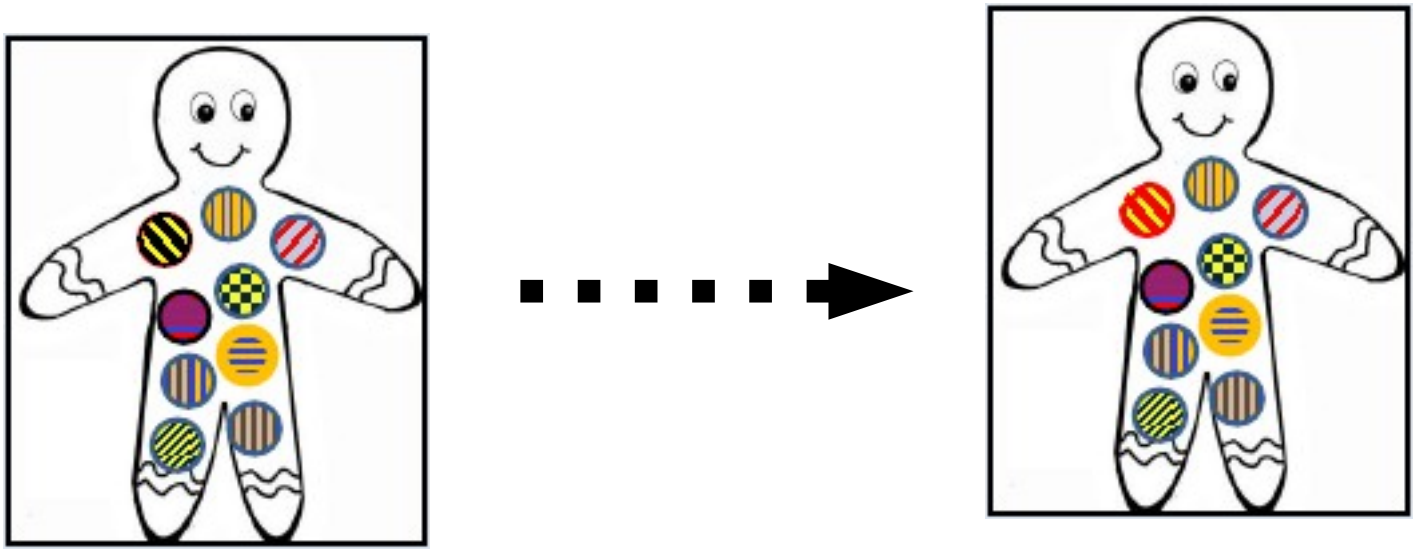
This principle is applicable to other long-lived animals in whom thymic production of new T cells declines significantly with age

Implications for epidemiology



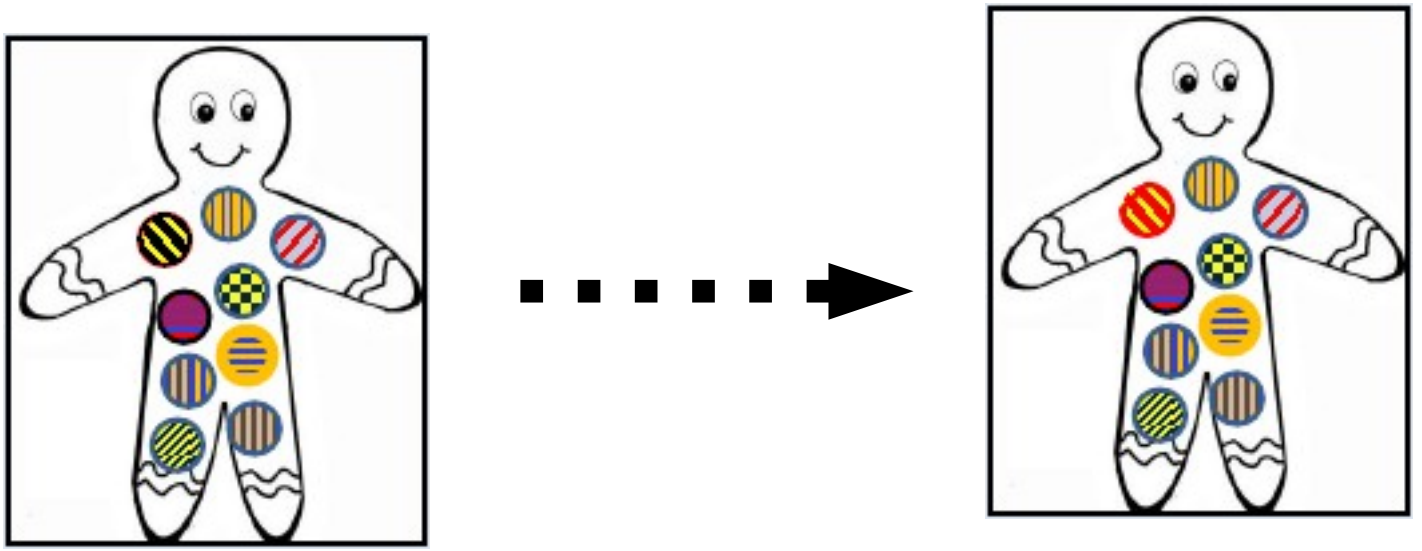
We now have a null model for human T-cell diversity for use in epidemiological studies

Challenges to applying model in epidemiology



1. Estimating T-cell diversity

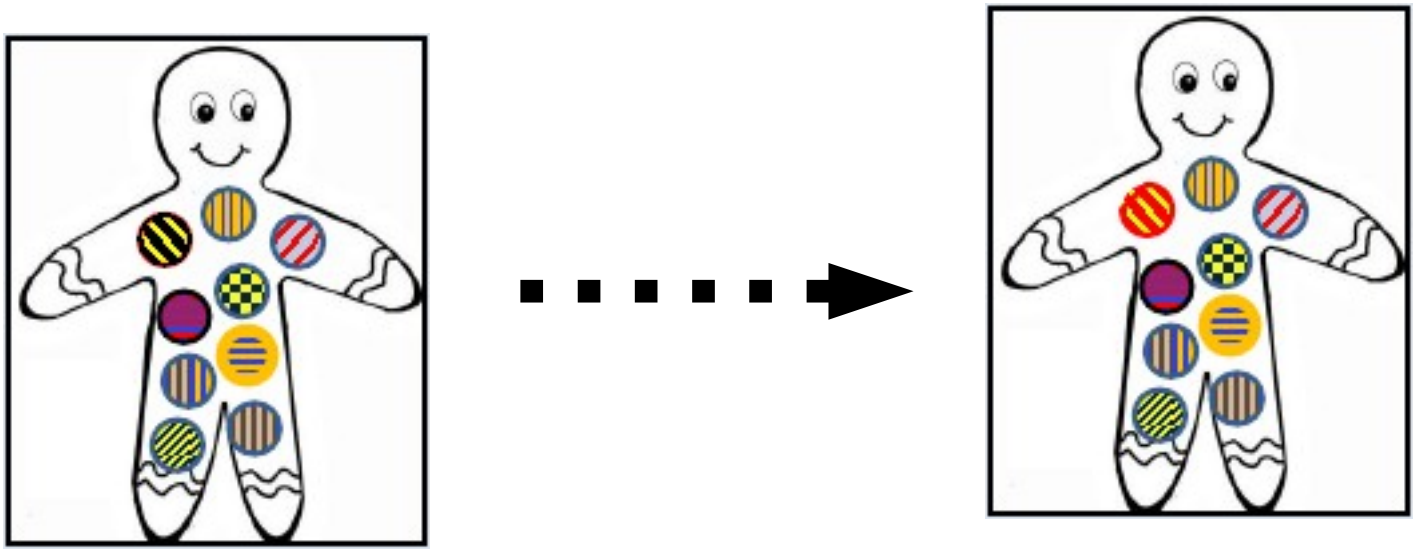
Challenges to applying model in epidemiology



1. Estimating T-cell diversity

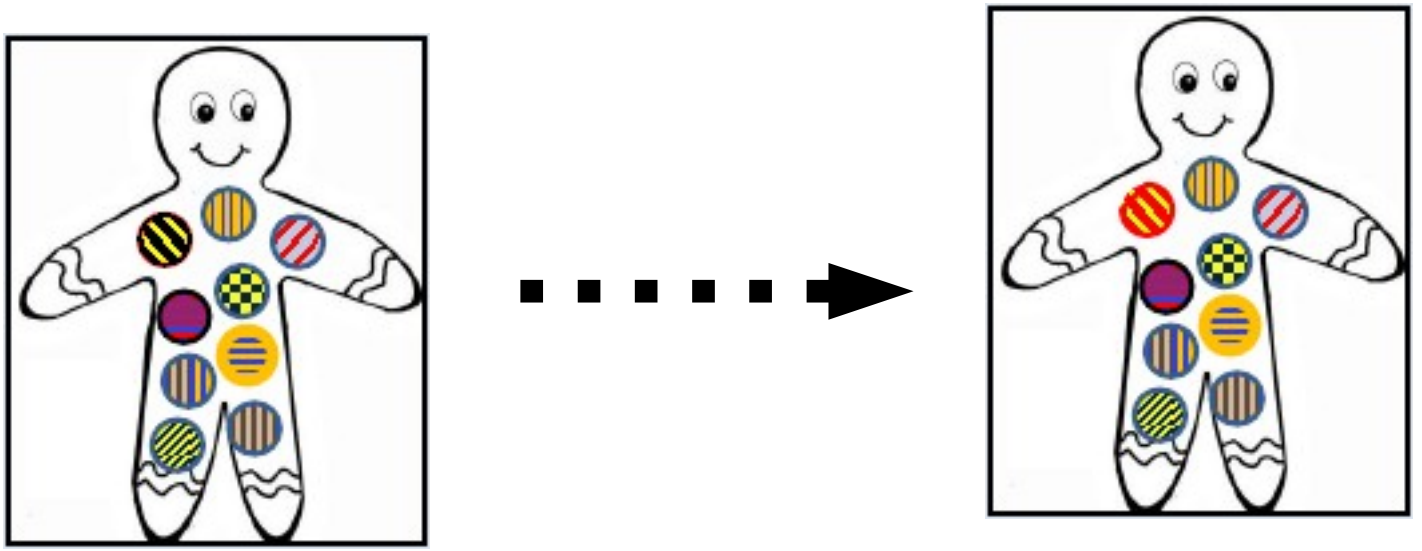
   Technologies exist for doing this (e.g. Robins et al. Blood 2009; Ndifon et a. PNAS 2012)

Challenges to applying model in epidemiology



2. Estimating distribution of cell divisions

Challenges to applying model in epidemiology



2. Estimating distribution of cell divisions

   A technology will be developed for doing this (by Zoe Gill)

Take-home messages

- Immune system is at intersection of many processes that determine health
- Principles give fundamental insight into how immune system works
- Discovery of principles can lead to new ways of treating and preventing diseases: drugs, vaccines, health policies, etc

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