Evaluating the Logic of Selection in Germinal Centers

Bertrand Ottino-Löffler & Gabriel Victora

Rockefeller University

March 10, 2023

What is a Germinal Center?

GC: Small Scale Evolutionary Optimization Alg.

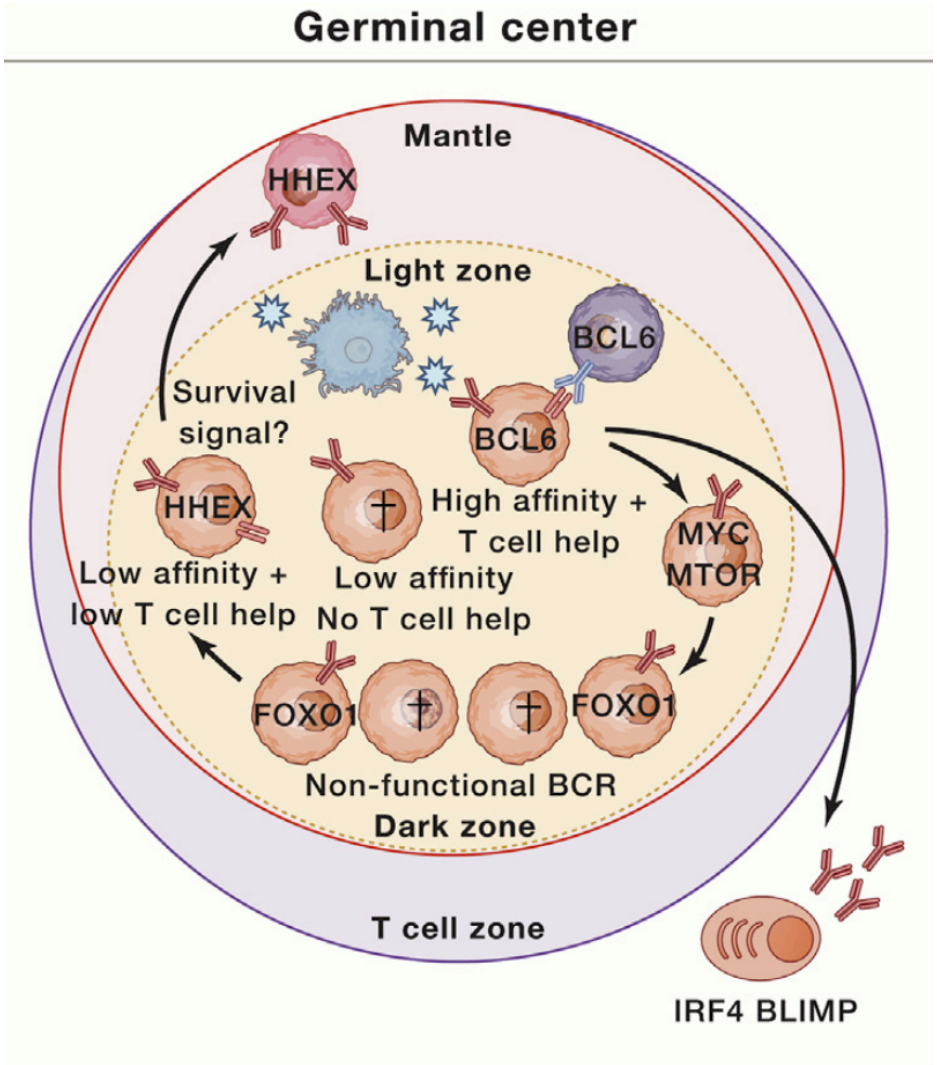


Figure: Young (2021)

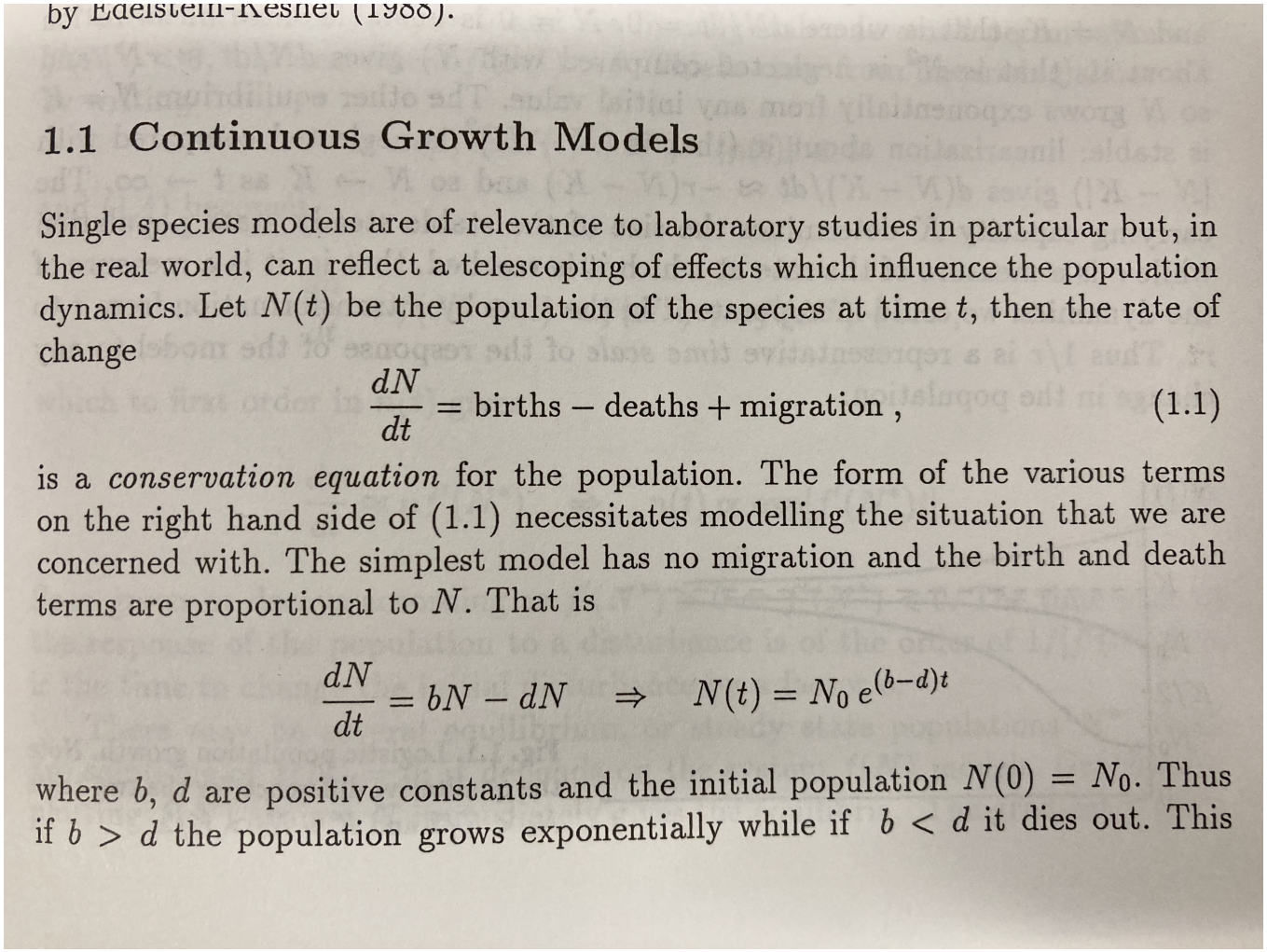
Question: How *Does* the Selection Take Place?

Standard Models: Single Parameter

Traditional population growth model:

$$\frac{dn}{dt} = (\text{birth rate} - \text{death rate})n$$

Normal models: Single Parameter



by Edelstein-Keshet (1988).

1.1 Continuous Growth Models

Single species models are of relevance to laboratory studies in particular but, in the real world, can reflect a telescoping of effects which influence the population dynamics. Let $N(t)$ be the population of the species at time t, then the rate of change

$$\frac{dN}{dt} = \text{births} - \text{deaths} + \text{migration}\,, \tag{1.1}$$

is a *conservation equation* for the population. The form of the various terms on the right hand side of (1.1) necessitates modelling the situation that we are concerned with. The simplest model has no migration and the birth and death terms are proportional to N. That is

$$\frac{dN}{dt} = bN - dN \quad \Rightarrow \quad N(t) = N_0\, e^{(b-d)t}$$

where b, d are positive constants and the initial population $N(0) = N_0$. Thus if $b > d$ the population grows exponentially while if $b < d$ it dies out. This

Figure: Murray (1993)

Birth and Death Are Not The Same

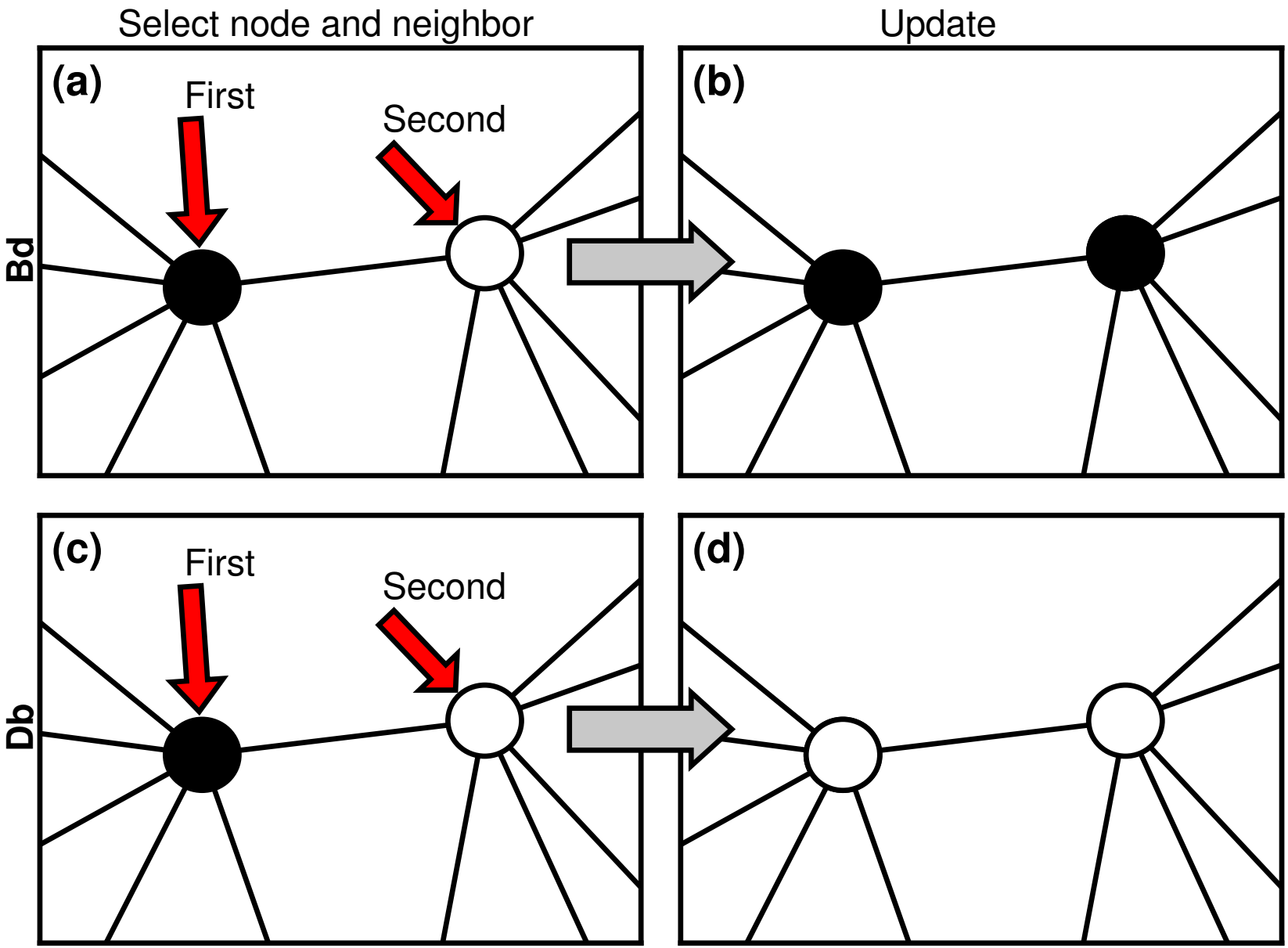
Previous Work: The Moran Model

Definition

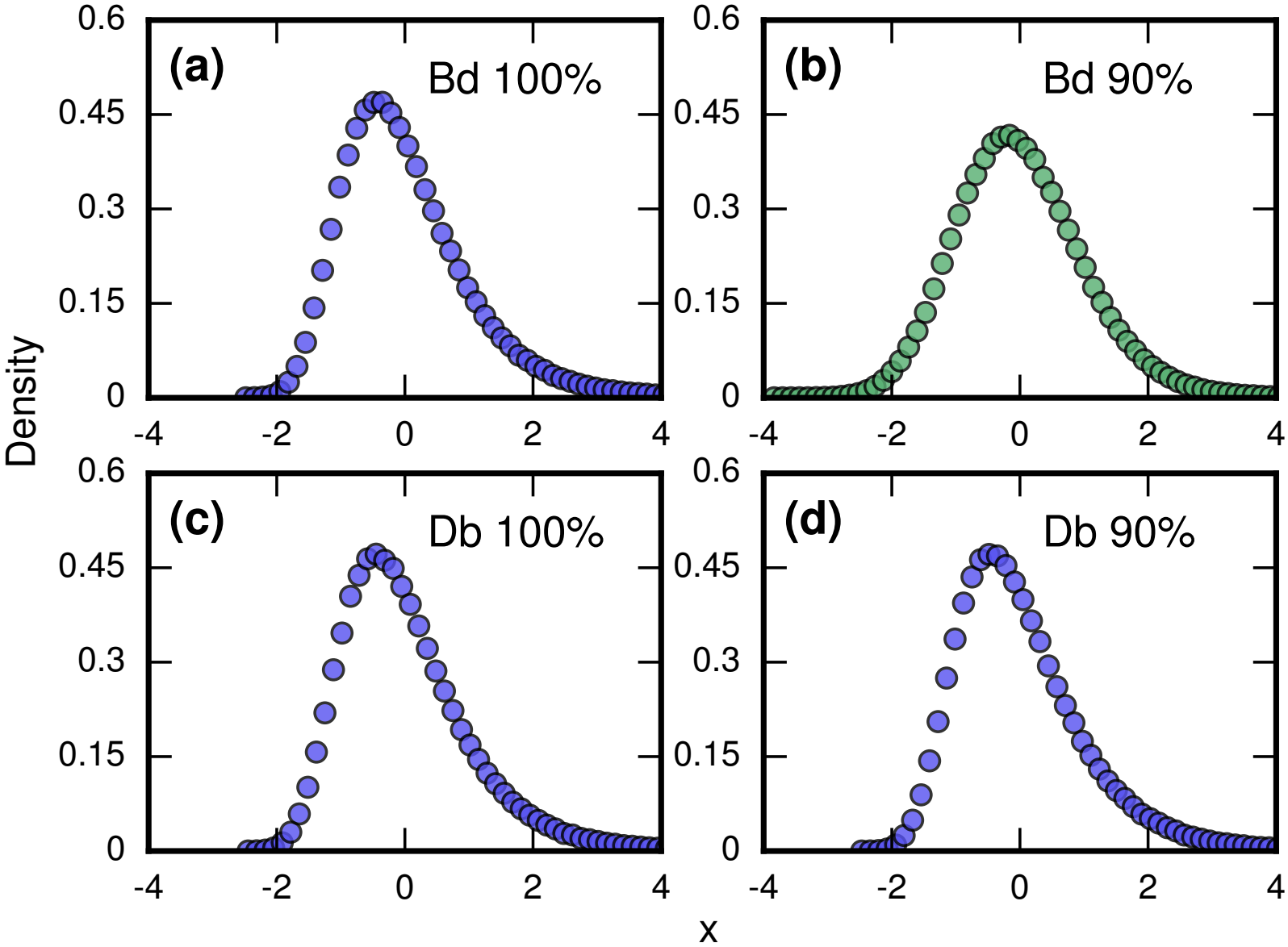
The **Moran Birth-death (Bd) model** consists of three steps:

1. With probability proportional to fitness (r), randomly select a cell to give birth.
2. Uniformly randomly select a neighbor of the first cell to die.
3. The dying cell takes on the type of the birthing cell.

Moran Model


Select node and neighbor
Update
(a)
First
Second
Bd
(b)
(c)
First
Second
Db
(d)

Fixation Times Distinguish Birth and Death



Birth and Death Are Not The Same

Intuition:

- Birth selection slows down near total fixation
- Death selection starts slow, but fixates fast,
- Truncation skip slow regime for Bd, changing the qualitative shape.

The Goal

Can we find a convenient signature of death selection in Germinal Centers?

A Model for Affinity Selection

Only two affinities, High (H) and Low (L) for maximum disparity.

h = fraction of population which is high affinity.

GC has three potential selection mechanisms:

- Birth Selection,
- Death Selection,
- Mutational Selection (will be explained later).

Birth Selection r_B

If a cell divides this timestep, then:

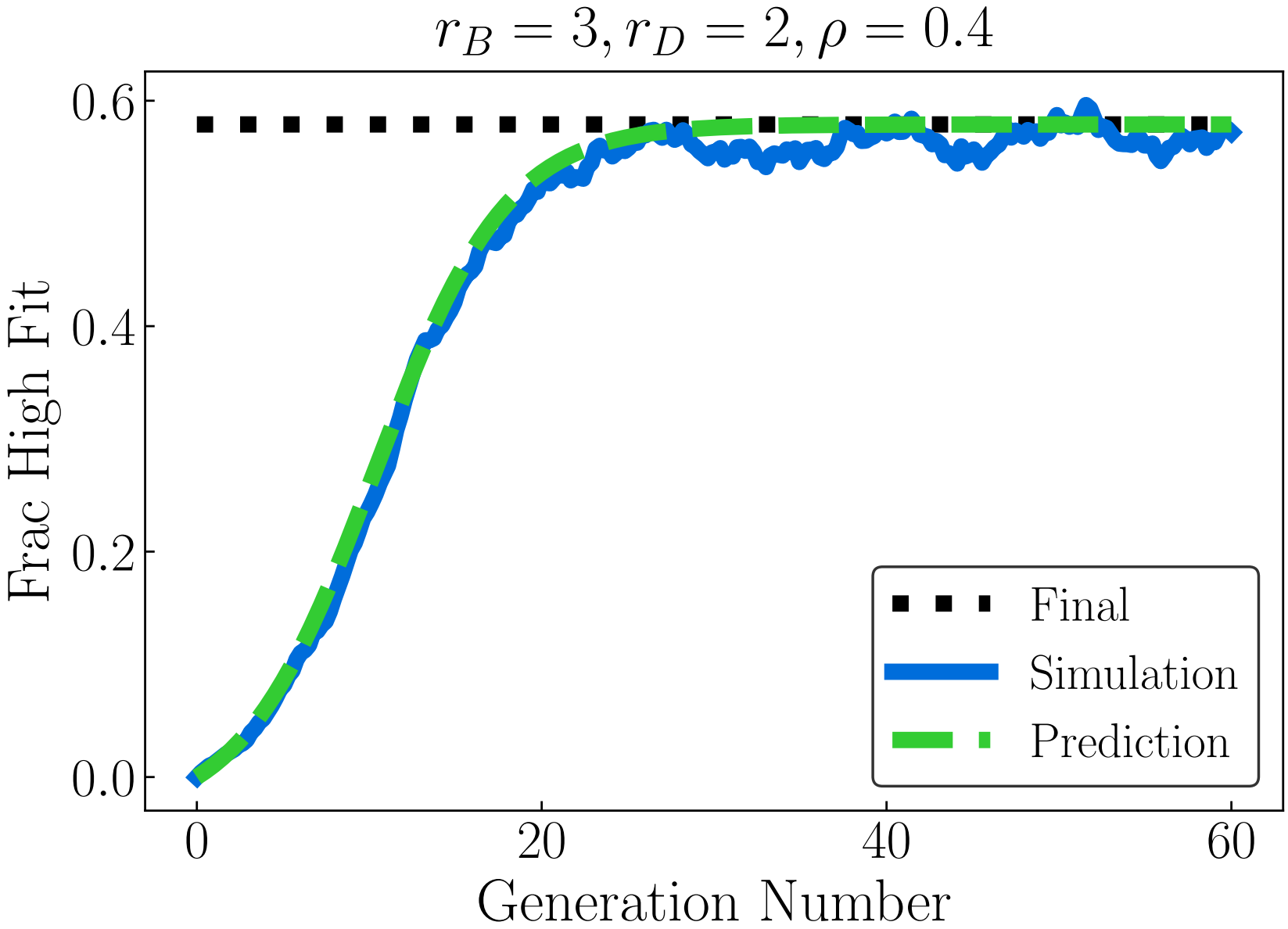
- The dividing cell is High affinity with prob $\propto r_B h$
- The dividing cell is Low affinity with prob $\propto 1 - h$

Death Selection r_D

If a cell dies this timestep, then:

- The dying cell is High affinity with prob $\propto h/r_D$
- The dying cell is Low affinity with prob $\propto 1 - h$

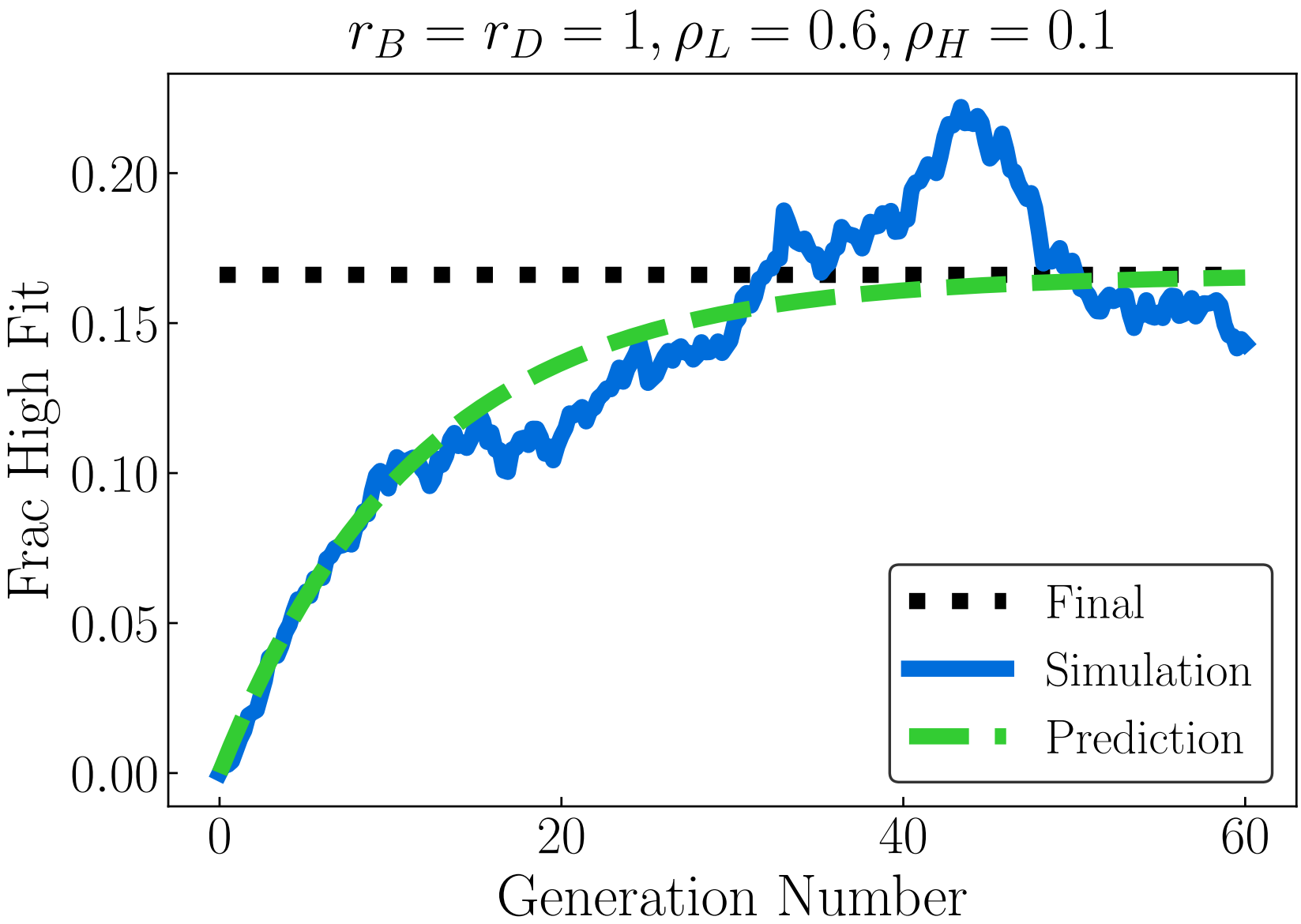
Typical Selection Curve



Mutational Selection?

- GCs occasionally have **Clonal Bursts**, where one cell line repeatedly divides.
- When bursting, the line has a *notably lower* mutation rate than normal.
- This opens the possibility of a *tunable mutation rate*.

Pure Mutational Selection



Skew Hypothesis

Skew Hypothesis

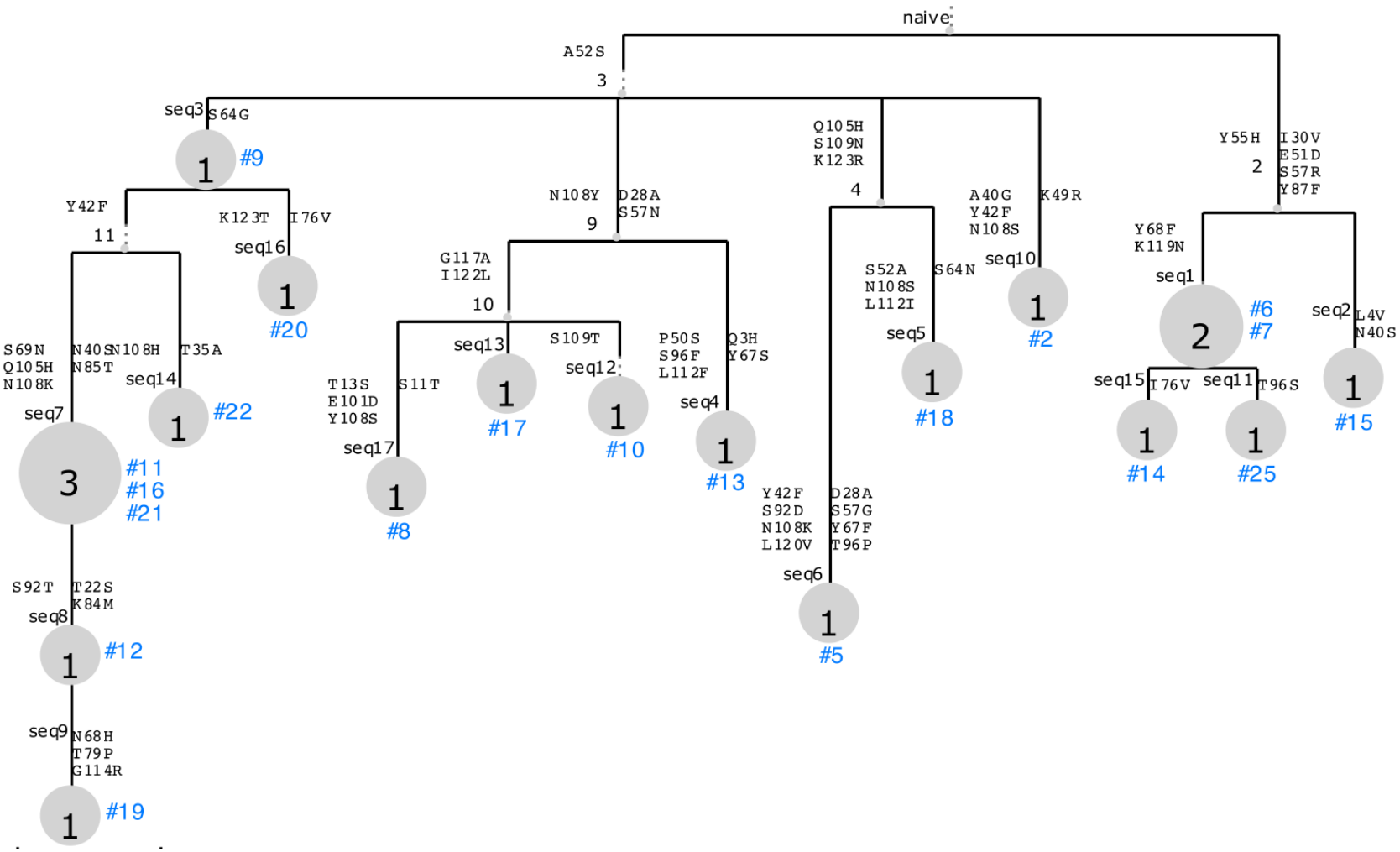
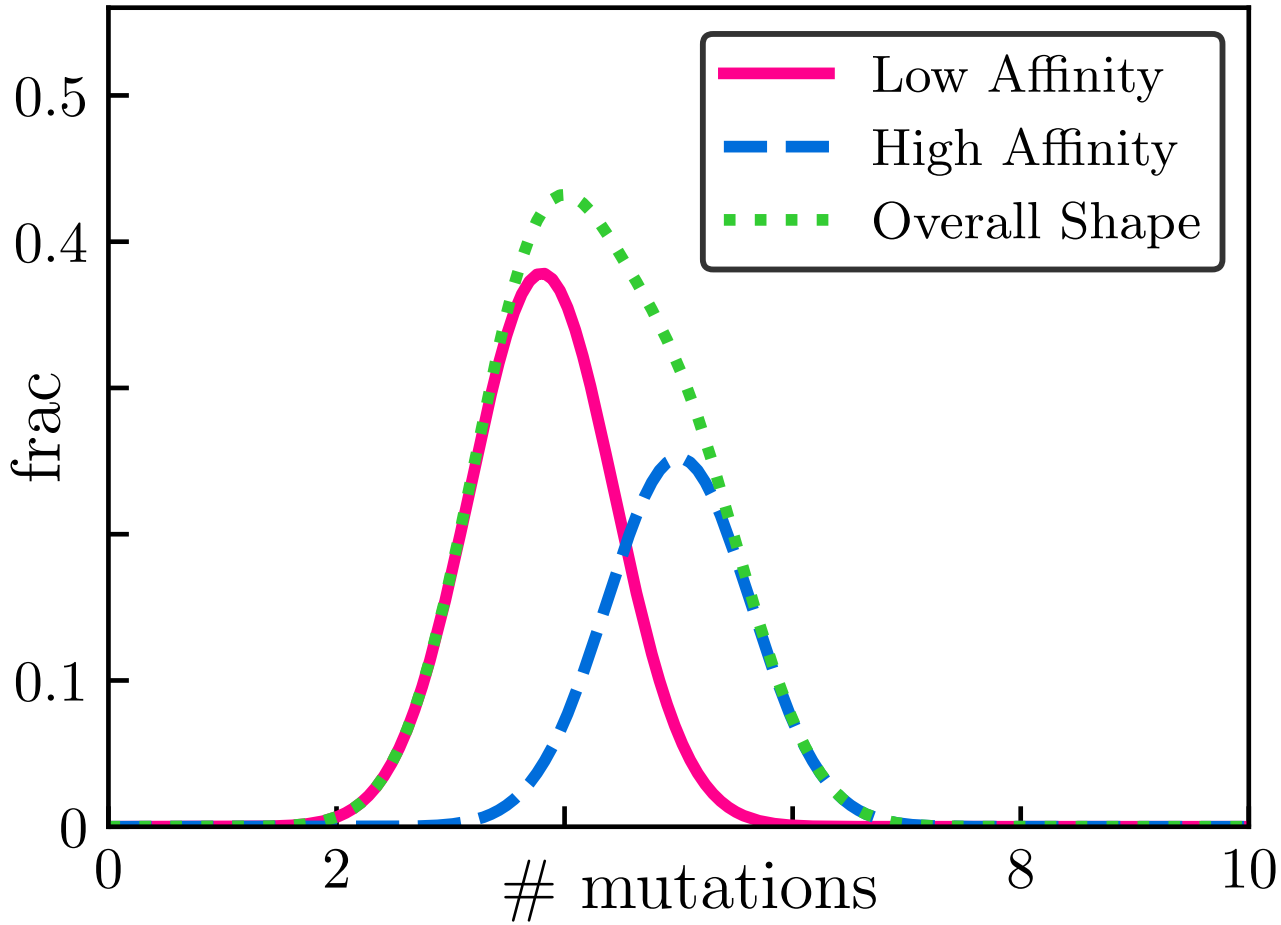


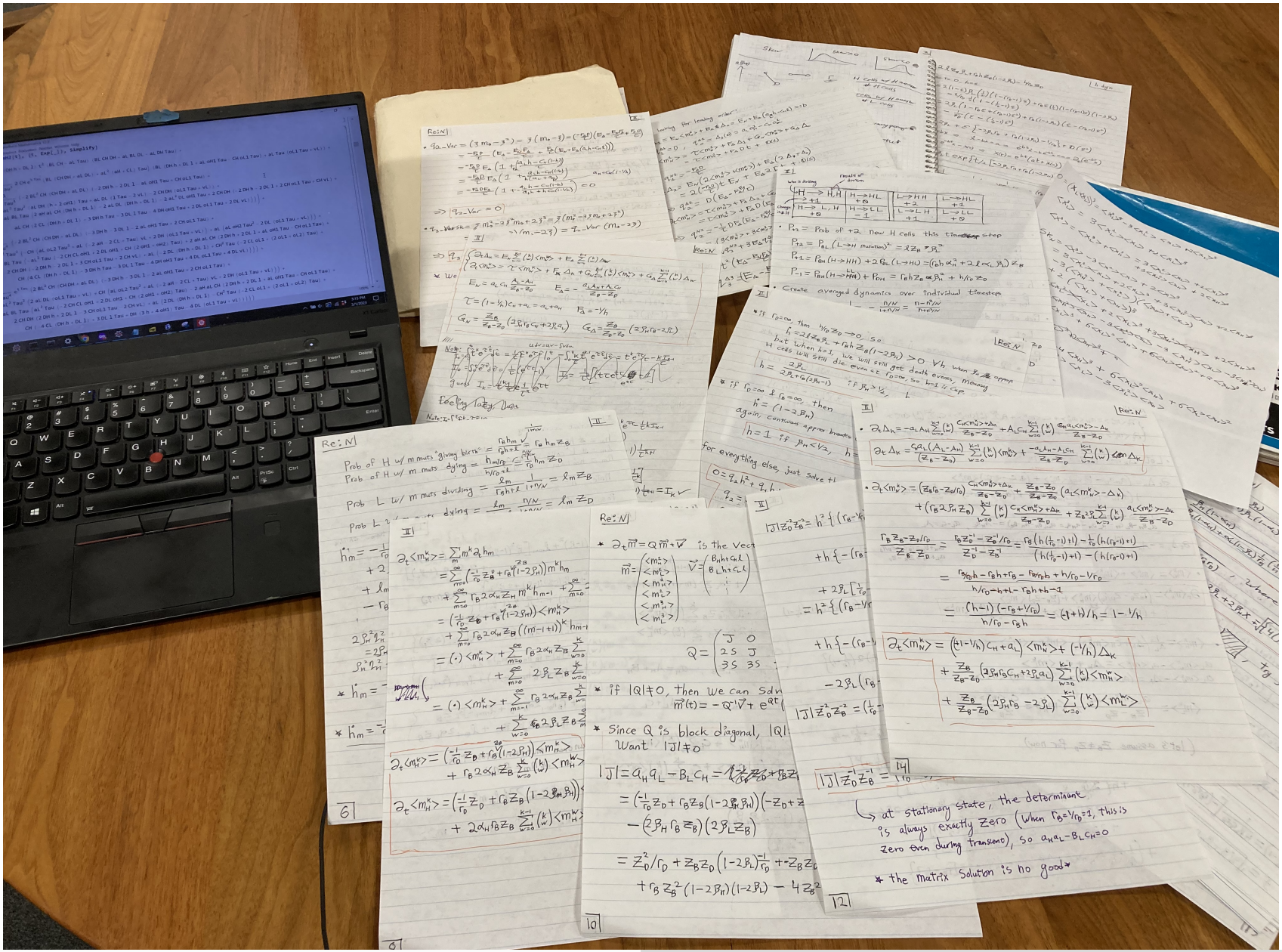
Figure: Tatsuya (2022)

Skew Hypothesis

Since L and H have different levels of mutational activity, would they seperate?



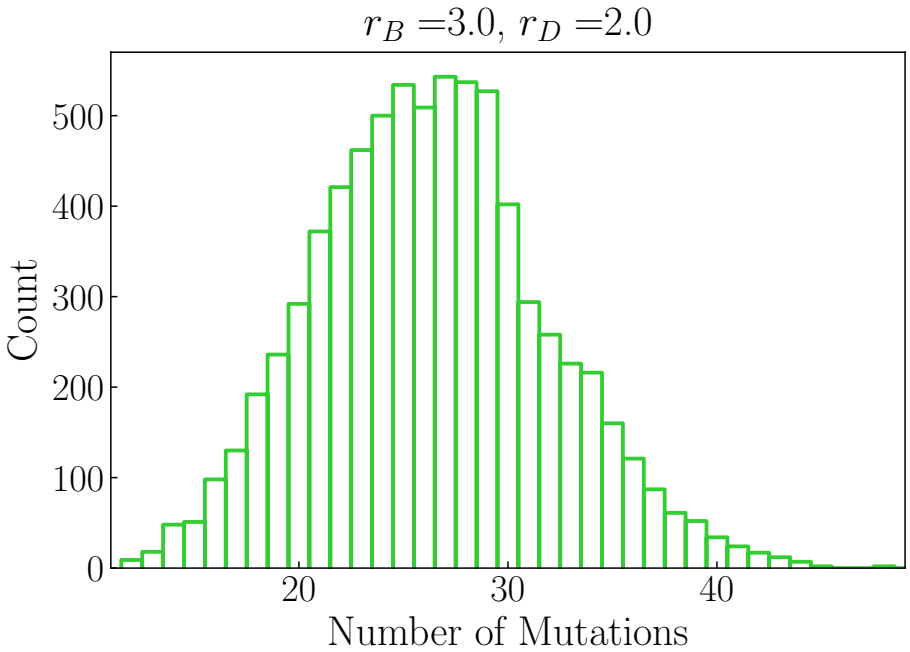
N O P E

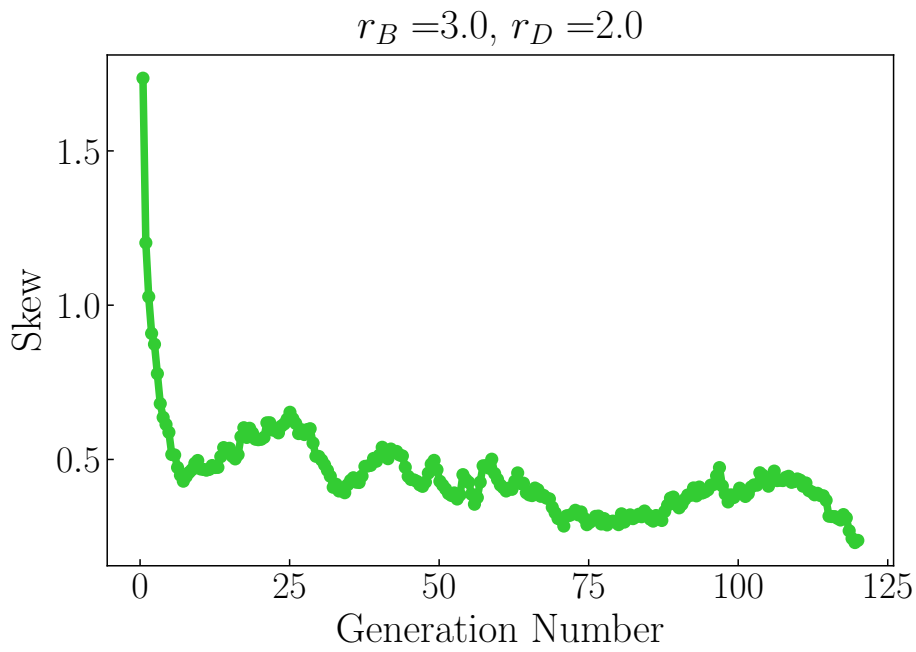

Re: N
Prob of H w/ m mates giving birth = $\frac{r_B h_m}{r_B h + 1} = r_B h_m z_B$
Prob of H w/ m mates dying = $\frac{h_m r_D}{h r_D + 1} \approx r_D h_m z_D$
Prob L w/ m mates dividing = $\frac{\lambda_m}{r_B h + 1} \frac{1}{1 + r_D N} = \lambda_m z_B$
Prob L w/ m mates dying = $\frac{l_m}{1 + r_D N} = l_m z_D$
$\dot{h}_m = -\frac{1}{r_D} h_m + \lambda_{m-1} z_B h_{m-1} - \lambda_m z_B h_m + r_B 2\alpha_{m+1} z_B h_{m+1} - r_B 2\alpha_m z_B h_m$
$\dot{h}_m = -\frac{1}{r_D} h_m + \lambda_{m-1} z_B h_{m-1} - \lambda_m z_B h_m + r_B 2\alpha_{m+1} z_B h_{m+1} - r_B 2\alpha_m z_B h_m$
$\partial_t \langle m_H^k \rangle = \sum_m m^k \partial_t h_m$
$= \sum_{m=0}^{\infty} \left(-\frac{1}{r_D} z_B^0 + r_B^0 (1-2\beta_H)\right) m^k h_m + \sum_{m=0}^{\infty} r_B 2\alpha_H z_H m^k h_{m-1} + \sum_{m=0}^{\infty} \ldots$
$= \left(\frac{1}{r_D} z_B + r_B^0 (1-2\beta_H)\right) \langle m_H^k \rangle + \sum_{m=0}^{\infty} r_B 2\alpha_H z_B \left((m-1+1)\right)^k h_{m-1}$
$= (\cdot) \langle m_H^k \rangle + \sum_{m=0}^{\infty} r_B 2\alpha_H z_B \sum_{w=0}^{k} \ldots$
$= (\cdot) \langle m_H^k \rangle + \sum_{m=-1}^{\infty} r_B 2\alpha_H z_B \sum_{w=0}^{k} \ldots + \sum_{w=0}^{k} r_B 2\beta_L z_B \ldots$
$\partial_t \langle m_H^k \rangle = \left(\frac{-1}{r_D} z_D + r_B^0 (1-2\beta_H)\right) \langle m_H^k \rangle + r_B 2\alpha_H z_B \sum_{w=0}^{k} \binom{k}{w} \langle m_H^w \rangle$
$\partial_t \langle m_H^k \rangle = \left(\frac{-1}{r_D} z_D + r_B z_B \left(1 - 2\beta_H r_B z_B\right)\right) + 2\alpha_H r_B z_B \sum_{w=0}^{k-1} \binom{k}{w} \langle m_H^w \rangle$
Re: N
$\partial_t \vec{m} = Q \vec{m} + \vec{V}$ is the Vec
$\vec{m} = \begin{pmatrix} \langle m_H^1 \rangle \\ \langle m_L^1 \rangle \\ \langle m_H^2 \rangle \\ \langle m_H^1 m_L^1 \rangle \\ \langle m_L^2 \rangle \\ \langle m_H^3 \rangle \\ \langle m_L^3 \rangle \end{pmatrix}$ $\vec{V} = \begin{pmatrix} B_H h_t c_H L \\ B_L h_t c_L L \\ \vdots \end{pmatrix}$
$Q = \begin{pmatrix} J & 0 & \\ 2S & J & \\ 3S & 3S & \ddots \end{pmatrix}$
* if $|Q| \neq 0$, then we can Sdv
$\vec{m}(t) = -Q^{-1}\vec{V} + e^{Qt}(\ldots)$
* Since Q is block diagonal, $|Q|$
Want $|J| \neq 0$
$|J| = a_H q_L - B_L C_H = \ldots$
$= \left(\frac{-1}{r_D} z_D + r_B z_B \left(1 - 2\beta_H r_B z_B\right)\right)\left(-z_D + z \ldots\right)$
$- \left(2\beta_H r_B z_B\right)\left(2\beta_L z_B\right)$
$= z_D^2 / r_D + z_B z_D \left(1 - 2\beta_L\right) \frac{1}{r_D} + \ldots z_B z_D$
$+ r_B z_B^2 (1 - 2\beta_H)(1 - 2\beta_L) - 4 z_B^2$
$\partial_t \Delta_k = -a_L \Delta_k \sum_{w=0}^{k-1} \binom{k}{w} \frac{C_H \langle m_H^w \rangle + \Delta_k}{z_B - z_D} + A_L C_H \sum_{w=0}^{k-1} \binom{k}{w} \frac{a_H \langle m_H^w \rangle - \Delta_k}{z_B - z_D}$
$\partial_t \Delta_k = \frac{a_H \beta_L (A_L - A_H)}{(z_B - z_D)} \sum_{w=0}^{k-1} \binom{k}{w} \langle m_H^w \rangle - \frac{a_L A_H + A_L C_H}{z_B - z_D} \sum_{w=0}^{k-1} \binom{k}{w} \Delta_k$
$\partial_t \langle m_H^k \rangle = \left(z_B r_B - z_D / r_D\right) \frac{C_H \langle m_H^k \rangle + \Delta_k}{z_B - z_D} + \frac{z_B - z_D}{z_B - z_D} \left(a_L \langle m_H^k \rangle - \Delta_k\right)$
$+ \left(r_B \beta_H r_B z_B\right) \sum_{w=0}^{k-1} \binom{k}{w} \frac{C_H \langle m_H^w \rangle + \Delta_k}{z_B - z_D} + z_B \beta_L \sum_{w=0}^{k-1} \binom{k}{w} \frac{a_L \langle m_H^w \rangle - \Delta_k}{z_B - z_D}$
$\frac{r_B z_B - z_D / r_D}{z_B - z_D} = \frac{r_B z_D^{-1} - z_B^{-1} / r_D}{z_D^{-1} - z_B^{-1}} = \frac{r_B \left(h\left(\frac{1}{r_D} - 1\right) + 1\right) - \frac{1}{r_D}\left(h\left(r_B - 1\right) + 1\right)}{\left(h\left(\frac{1}{r_D} - 1\right) + 1\right) - \left(h\left(r_B - 1\right) + 1\right)}$
$= \frac{r_B / r_D h - r_B h + r_B - r_B / r_D h + h / r_D - 1 / r_D}{h / r_D - h + 1 - r_B h + h - 1}$
$= \frac{(h-1)\left(-r_B + 1/r_D\right)}{h / r_D - r_B h} = \frac{-(1+h)}{h} = 1 - 1/h$
$\partial_t \langle m_H^k \rangle = \left(\left(1 - 1/h\right) C_H + a_L\right) \langle m_H^k \rangle + \left(-1/h\right) \Delta_k$
$+ \frac{z_B}{z_B - z_D} \left(a_H \beta_H r_B C_H + 2\beta_H a_L\right) \sum_{w=0}^{k-1} \binom{k}{w} \langle m_H^w \rangle$
$+ \frac{z_B}{z_B - z_D} \left(2\beta_H r_B - 2\beta_L\right) \sum_{w=0}^{k-1} \binom{k}{w} \langle m_H^w \rangle$
$|J| z_D^{-1} z_B^{-1} = \frac{1}{r_D}$
↳ at stationary state, the determinant is always exactly zero (when $r_B = 1/r_D = 1$, this is zero even during transens), so $a_H q_L - B_L C_H = 0$
* the matrix solution is no good
6
10
12
14

BJOL

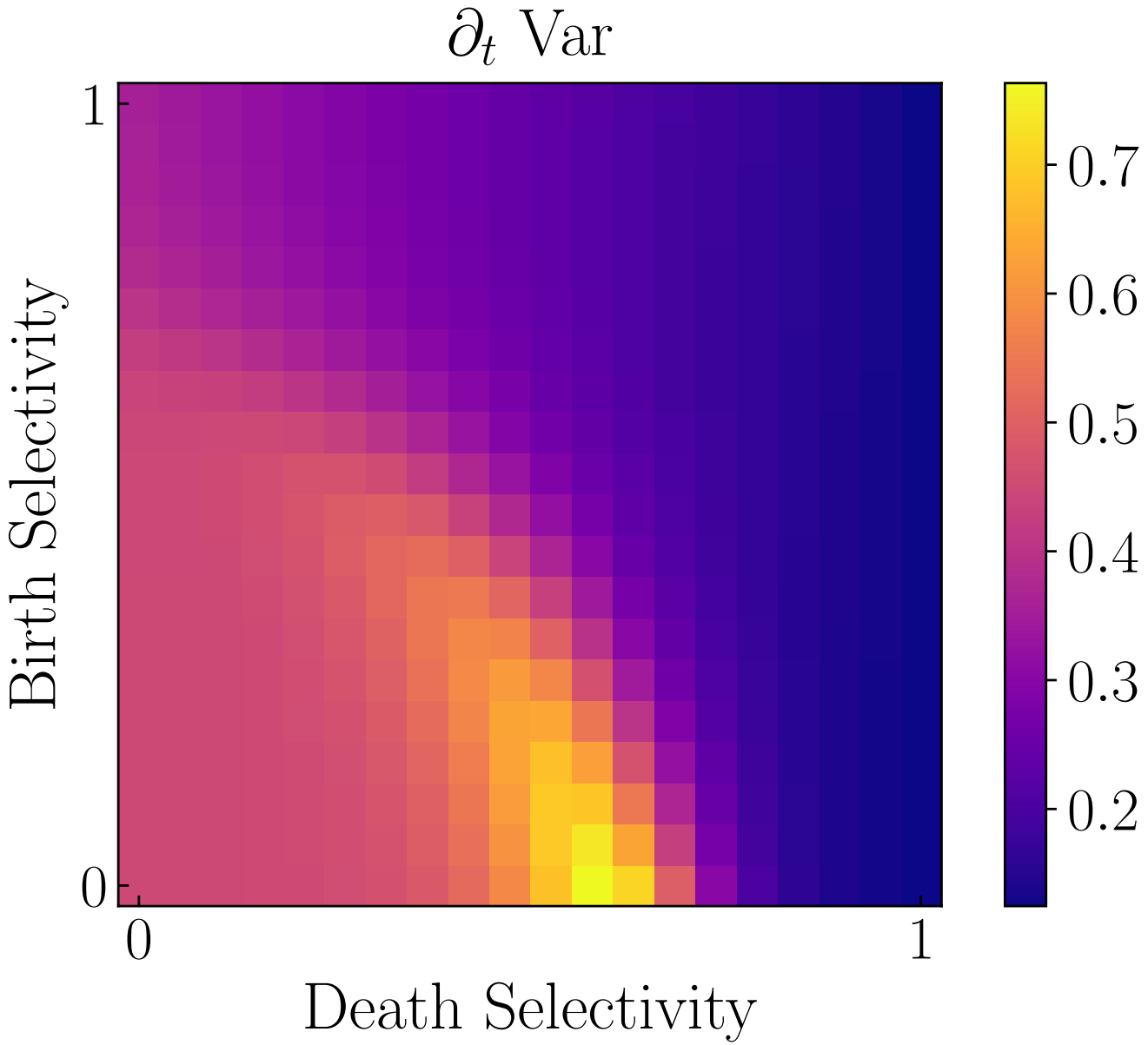
Calculation Outline: The Truth

$$\text{Skew} = \mathbb{O}(t^{-1/2}) \to 0$$





Dynamical Footprint of Selection



Ancestry Hypothesis

Ancestry Hypothesis

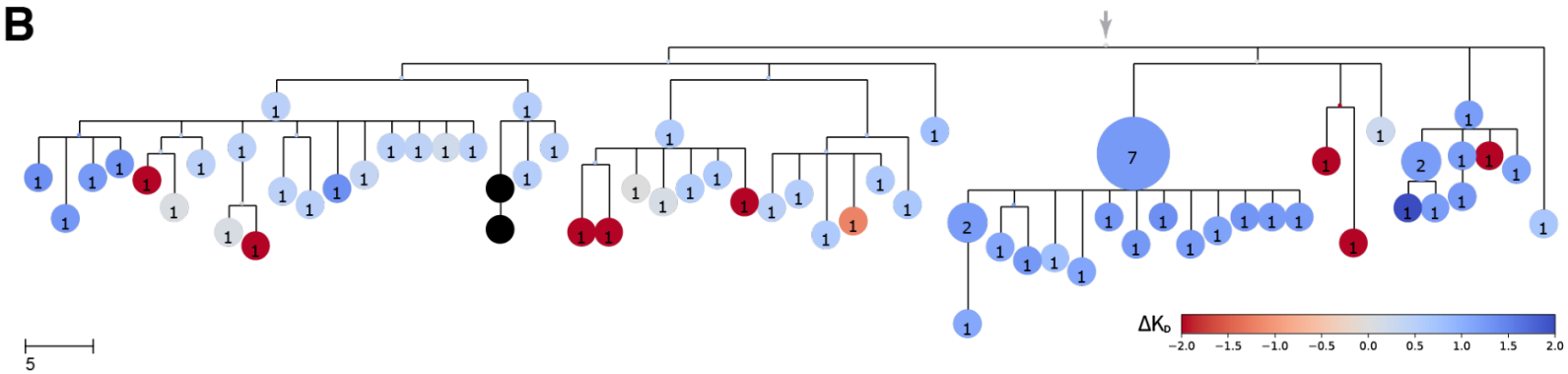


Figure: Tatsuya (2022)

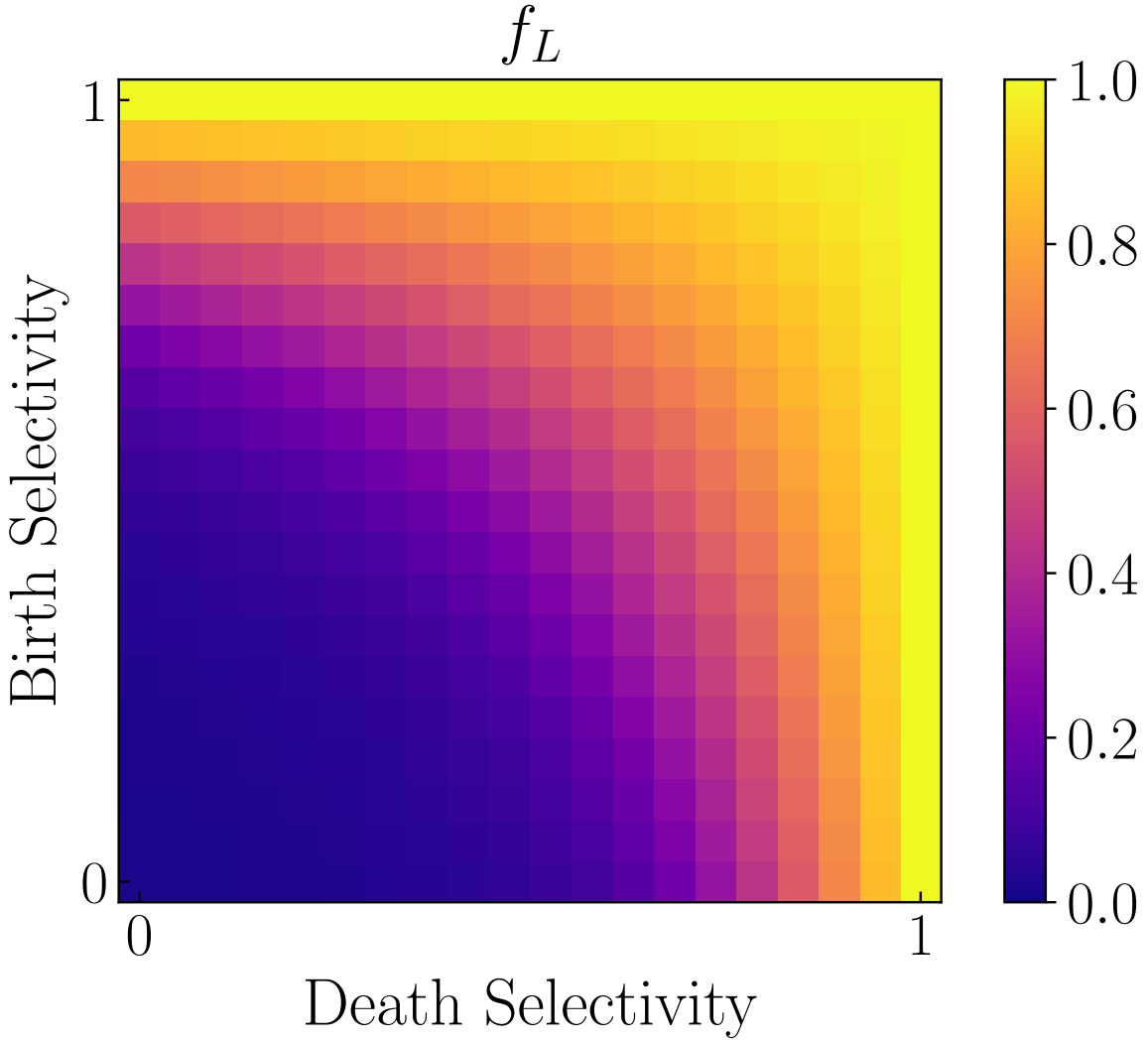
Ancestry Hypothesis

$$f_H = \frac{\text{number of H cells with H ancestors}}{\text{number of H cells}}$$

$$f_L = \frac{\text{number of L cells with H ancestors}}{\text{number of L cells}}$$

Ancestry Hypothesis: False

Notably, f_H and f_L **only** depend on the combined $r_B r_D$.

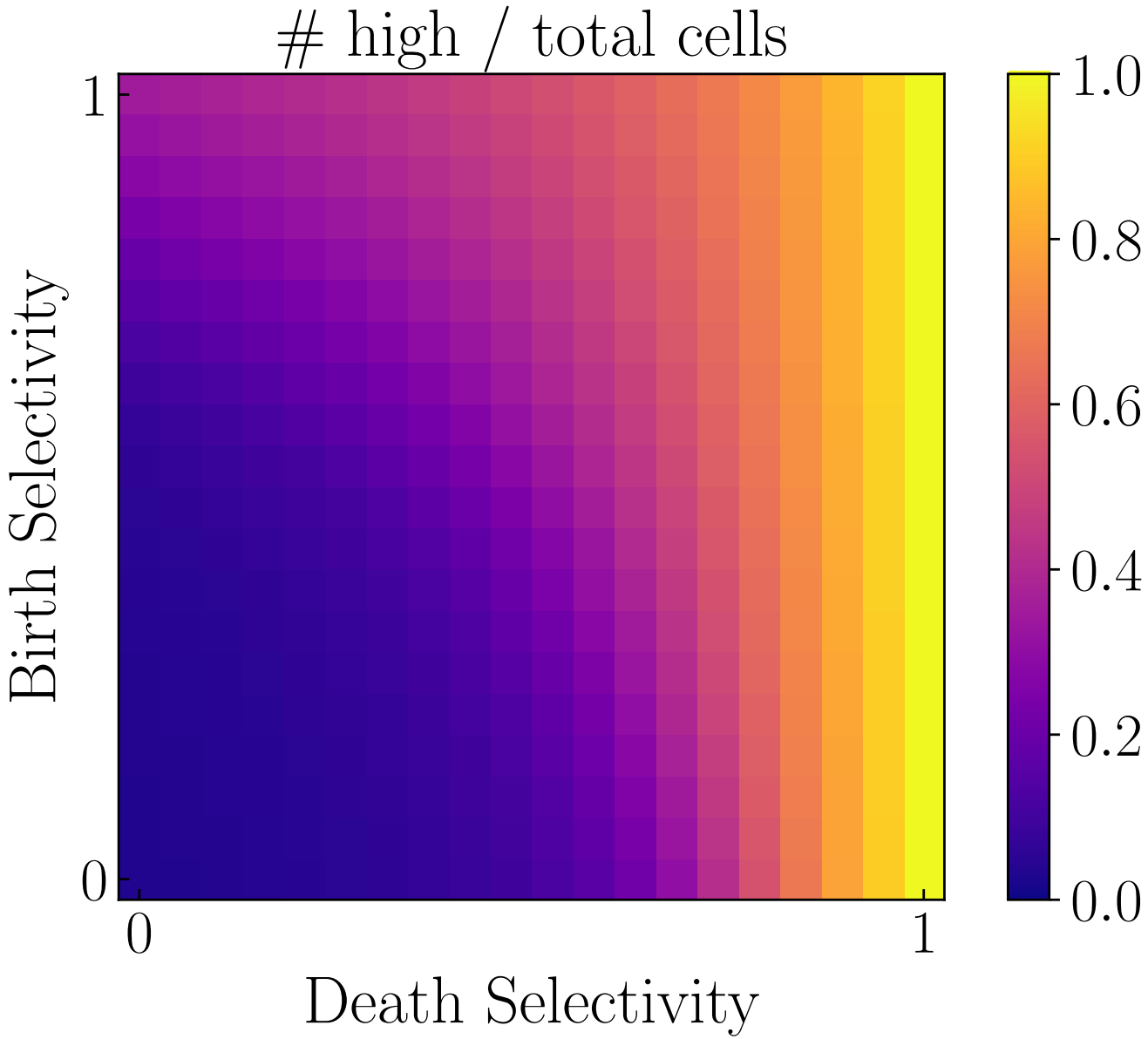


Is there anything static that distiguishes r_D and r_B?

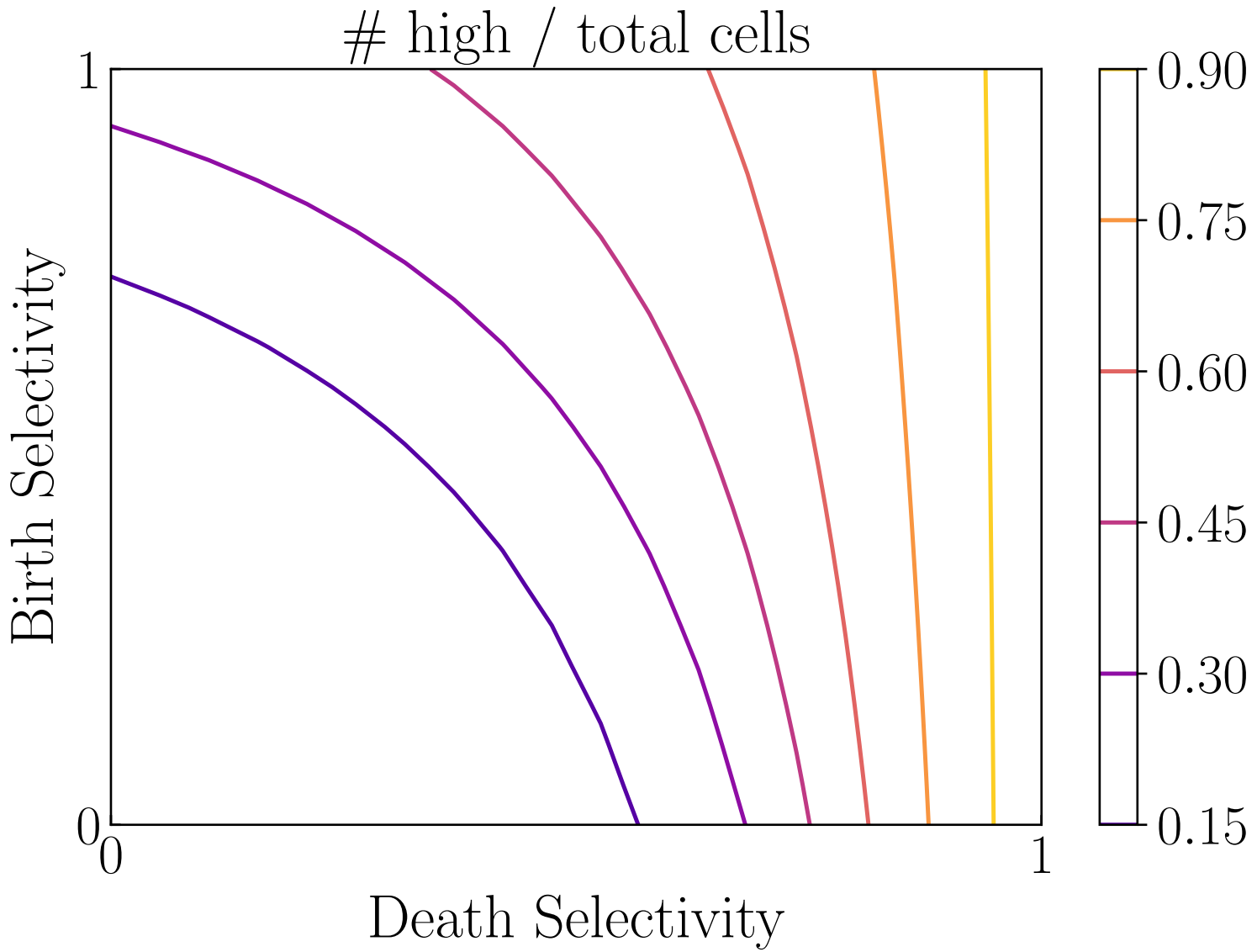
Overall selectivity

$$\boxed{\text{Fraction of cells which are High affinity} = \frac{1}{1 + r_B g(r_B r_D)}}$$

Overall selectivity



Overall selectivity



Static Signals of Selection Scheme?

Mutation Distribution Shape	Nope
Preferential Ancestry	Not Really
Overall Selection Strength	Yep
Extinction and Exit Times	Yep

Thanks to Gabriel Victora, Tatsuya Araki, & Arup Chakraborty for the comments.

Selected References & Image Sources


Tatsuya Araki, Replaying Life's Tape With Intraclonal Germinal Center Evolution, Rockefeller University (2022).


Gordon L. Ada and Sir Gustav Nossal, The Clonal-Selection Theory, Scientific American (1987).


Bertrand Ottino-Loffler, Jacob Scott, and Steven Strogatz, Evolutionary Dynamics of Incubation Periods, eLife (2017).


Alexander Gitlin, Ziv Shulman, and Michel Nussenzweig, Clonal Selection in the Germinal Centere by Regulated Proliferation and Hypermutation, Nature (2014).


James Murray, Mathematica Biology, Springer (1993).


Clara Young and Robert Brink, The Unique Biology of Germinal Center B Cells, Immunity (2021).

Talk available at: ottinoloffler.com