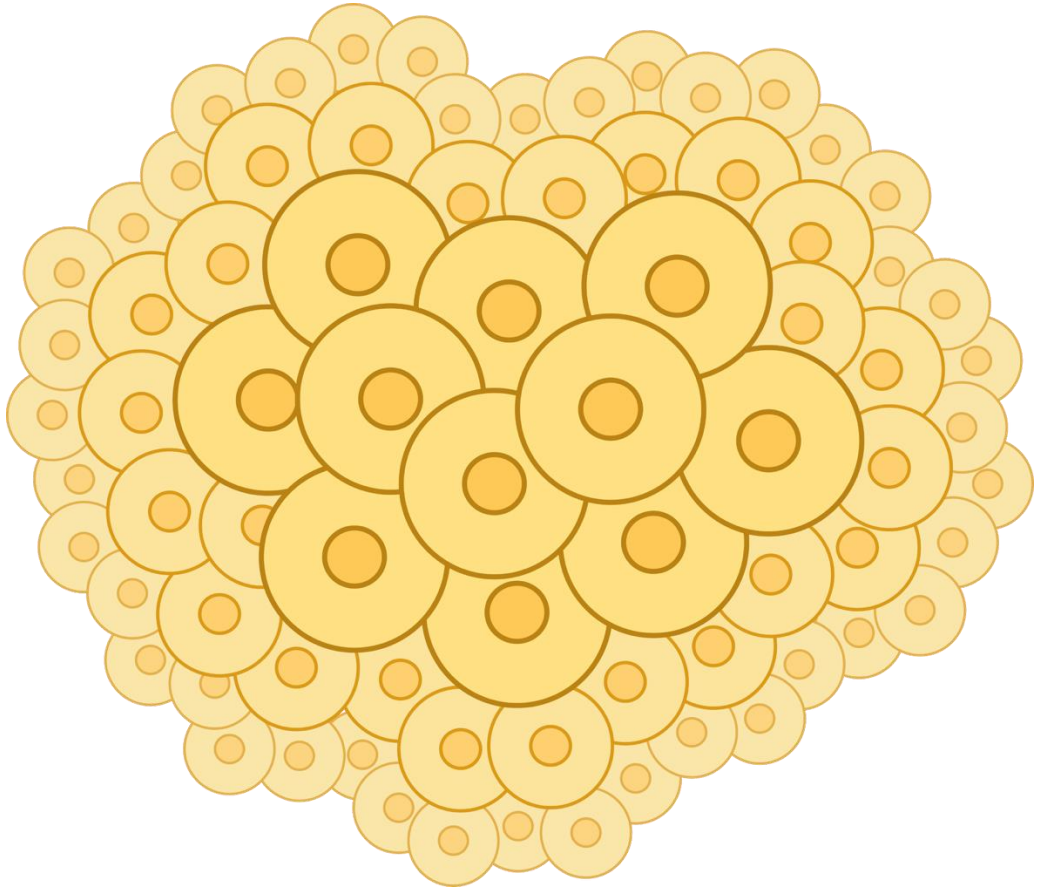
Modeling Drift and Selection in Spermatogonial Stem Cell Dynamics

Connor R. Shrader

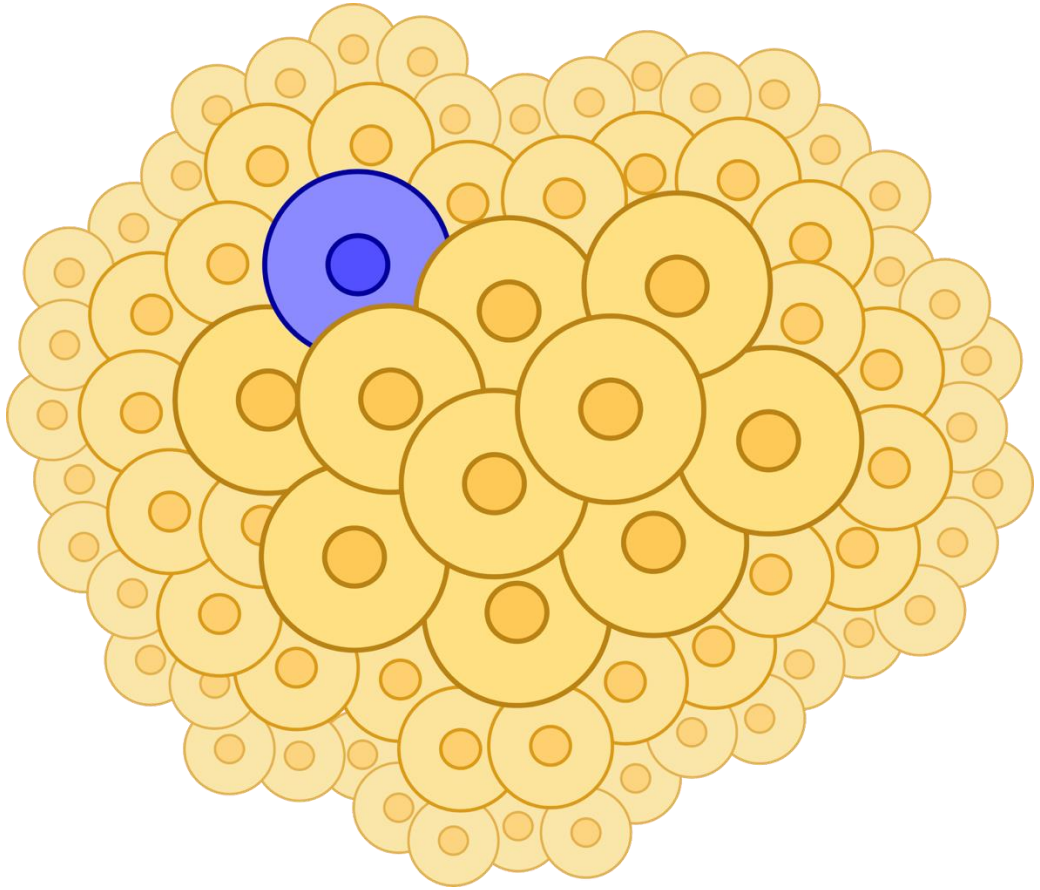
Mathematics Ph.D. Candidate

University of Utah

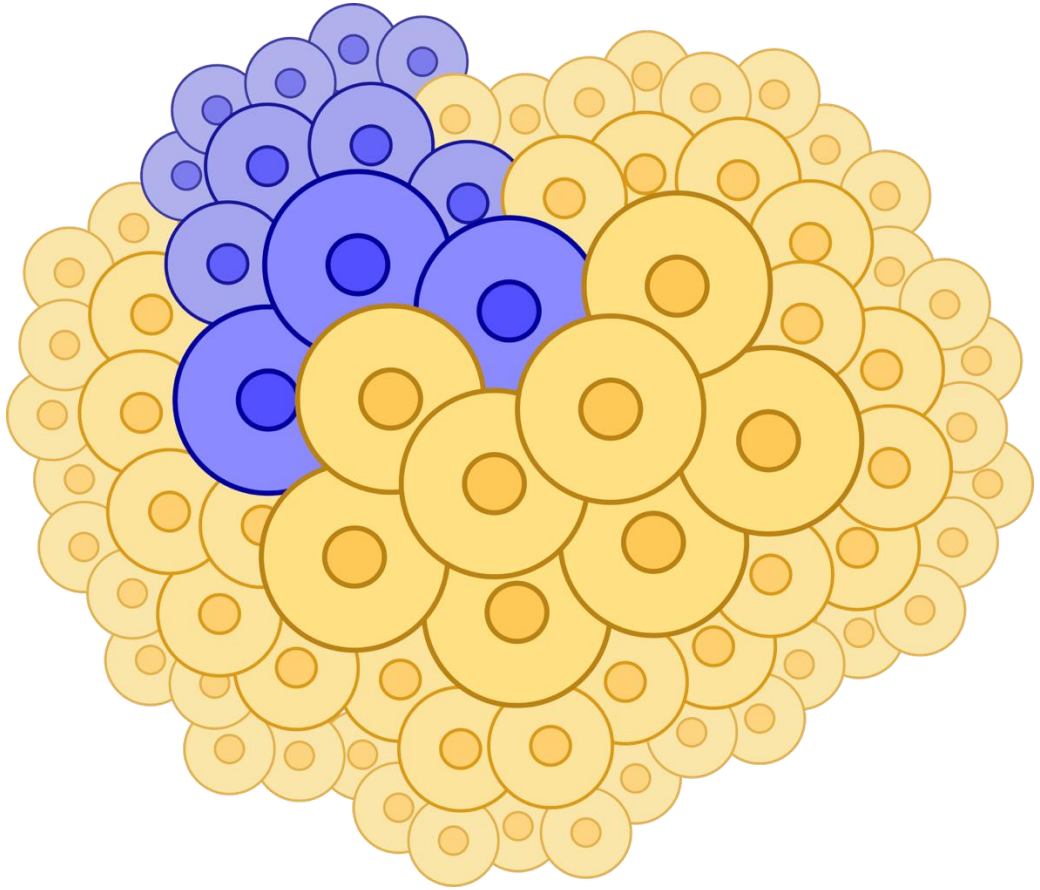
Cells in our body are constantly dividing and dying.



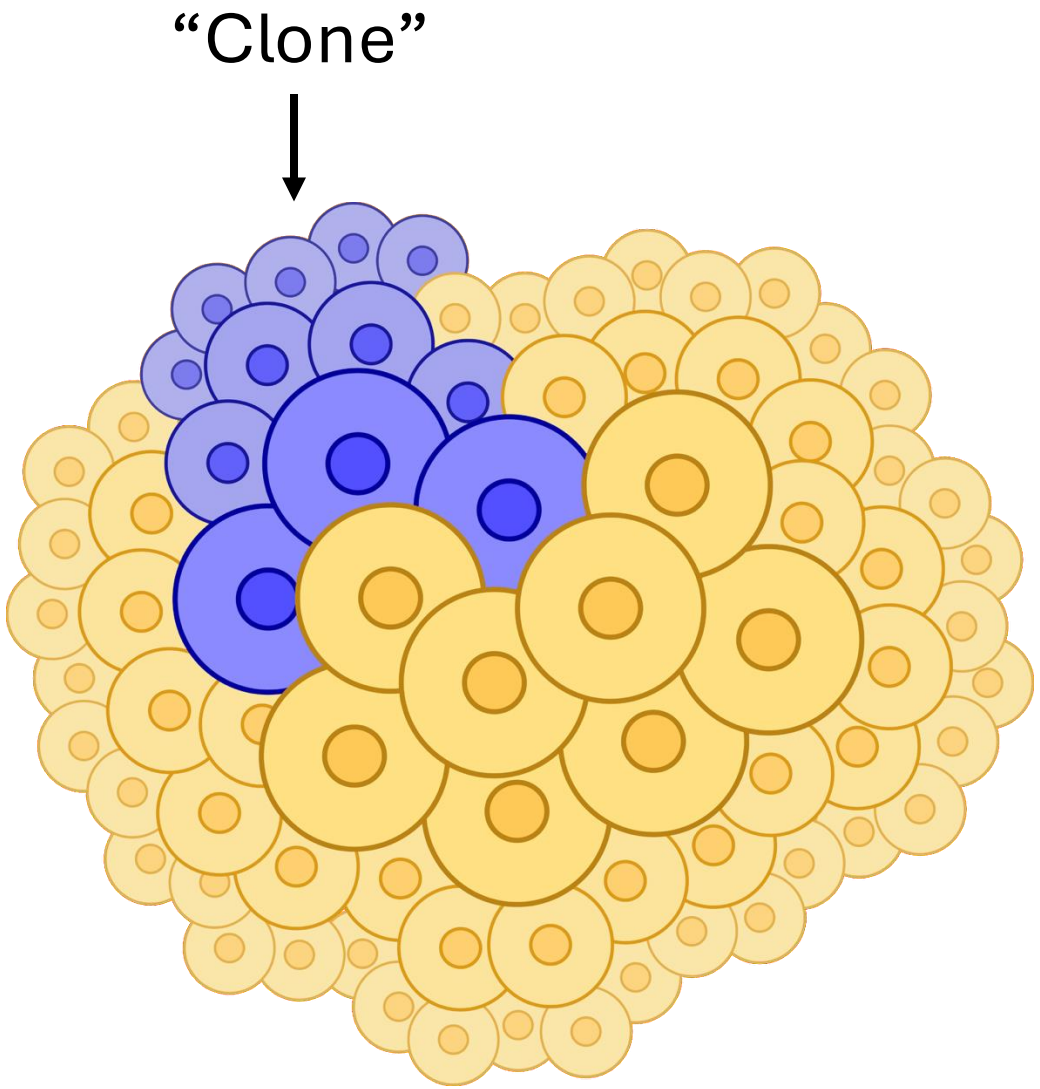
Over time, dividing cells can accumulate mutations.



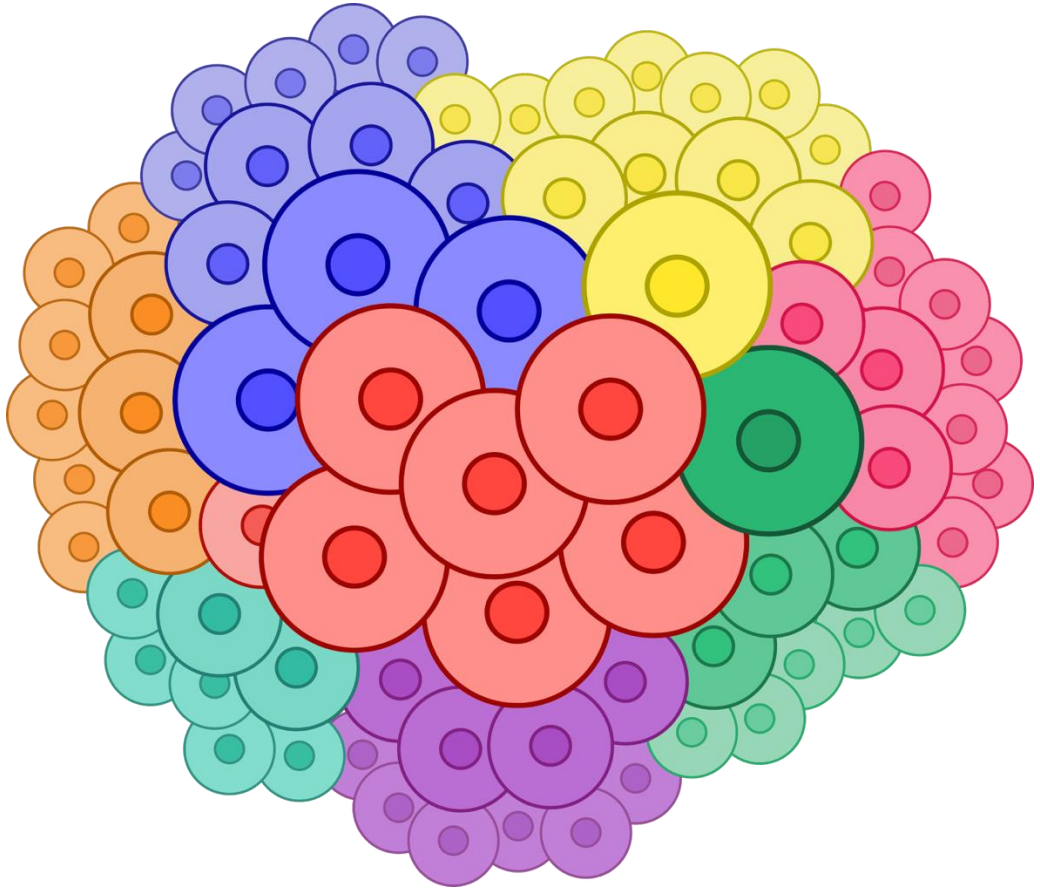
These mutations are inherited by daughter cells.



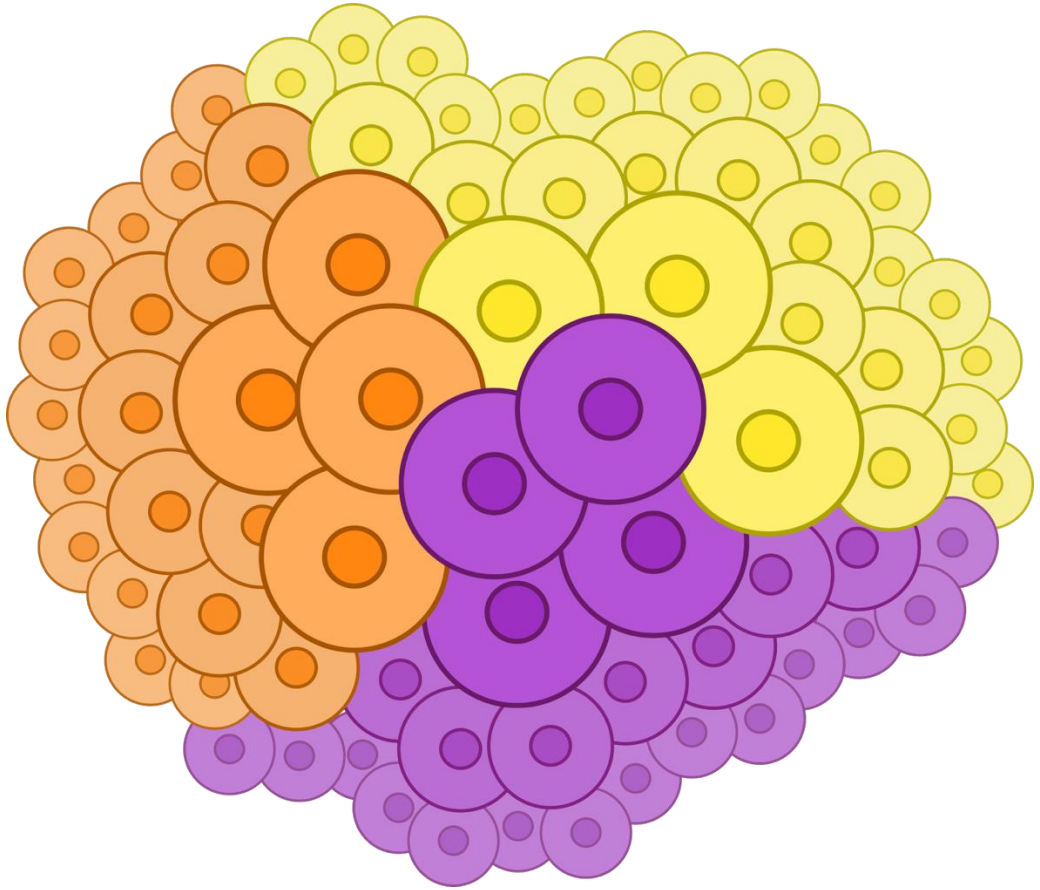
Kapadia, Chiraag D., and Margaret A. Goodell. "Tissue mosaicism following stem cell aging: blood as an exemplar." *Nature Aging* 4.3 (2024): 295-308.


“Clone”

Our tissues are full of these clones.



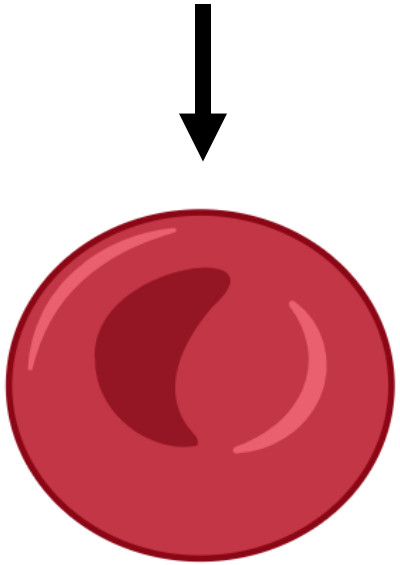
As we age, some clones begin to dominate others.



Kapadia, Chiraag D., and Margaret A. Goodell. "Tissue mosaicism following stem cell aging: blood as an exemplar." *Nature Aging* 4.3 (2024): 295-308.

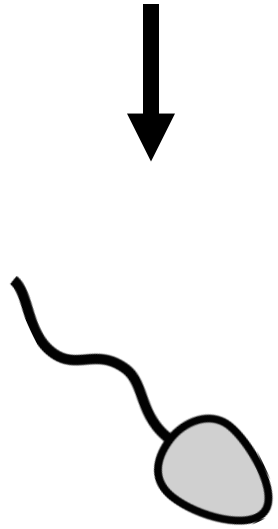
Stem cells are responsible for developing and maintaining specialized tissue.

Hematopoietic stem cells



Red Blood Cell

Spermatogonial stem cells

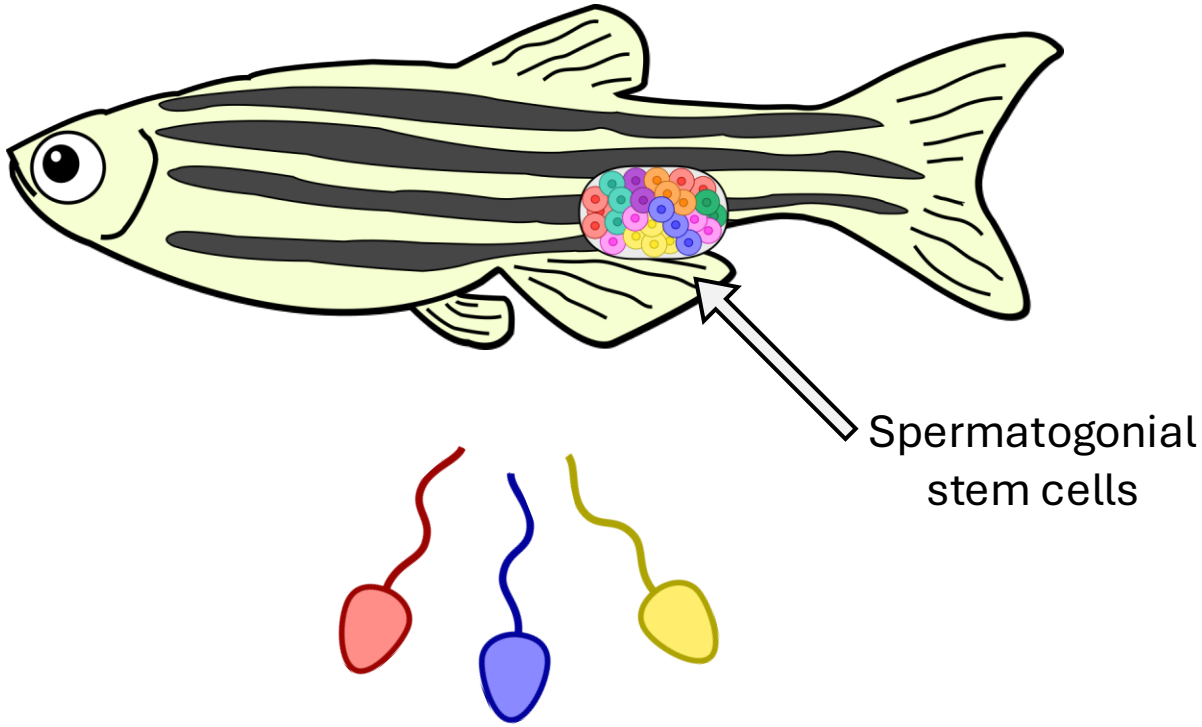


Sperm Cell

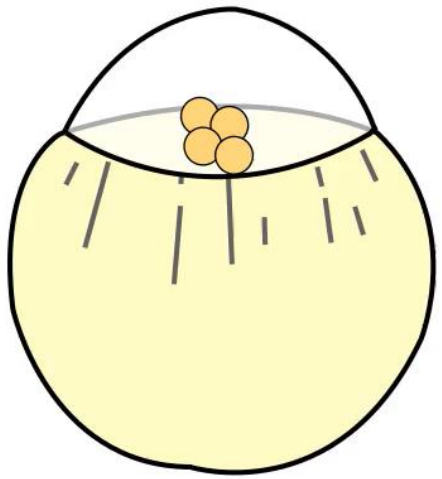
Stem cells populations are hard to directly study.

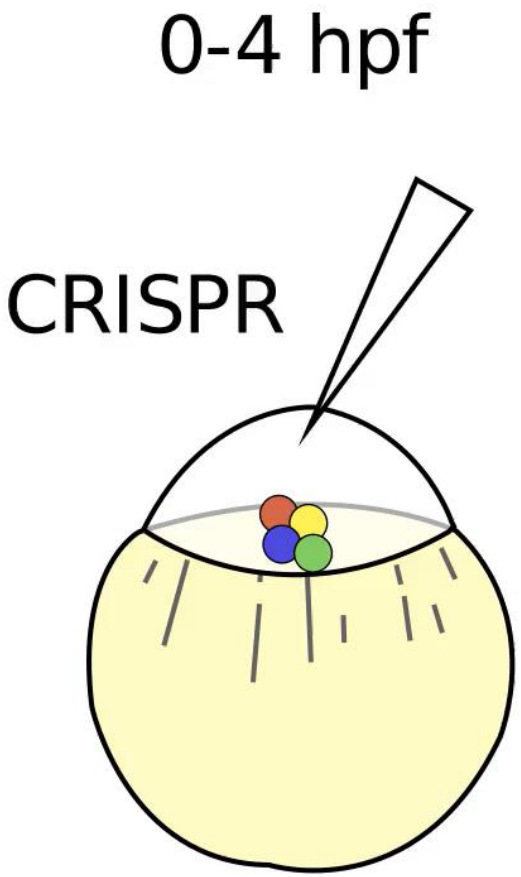
We use the **zebrafish testis** as a model system.

I combine models and experimental data to study clonal dynamics.



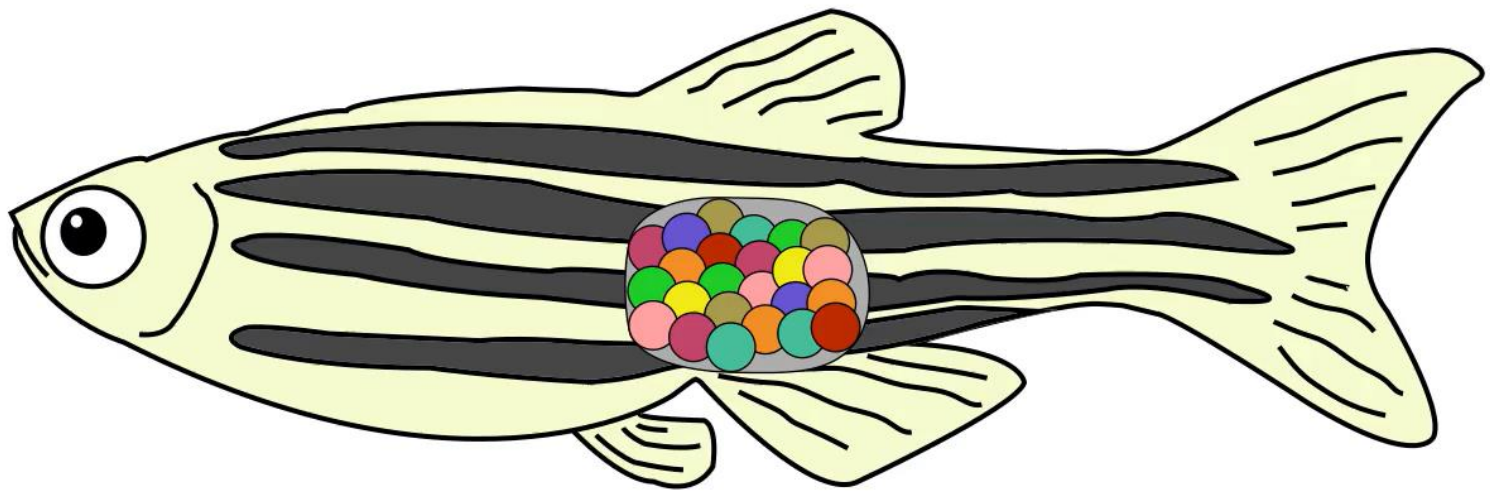
0-4 hpf



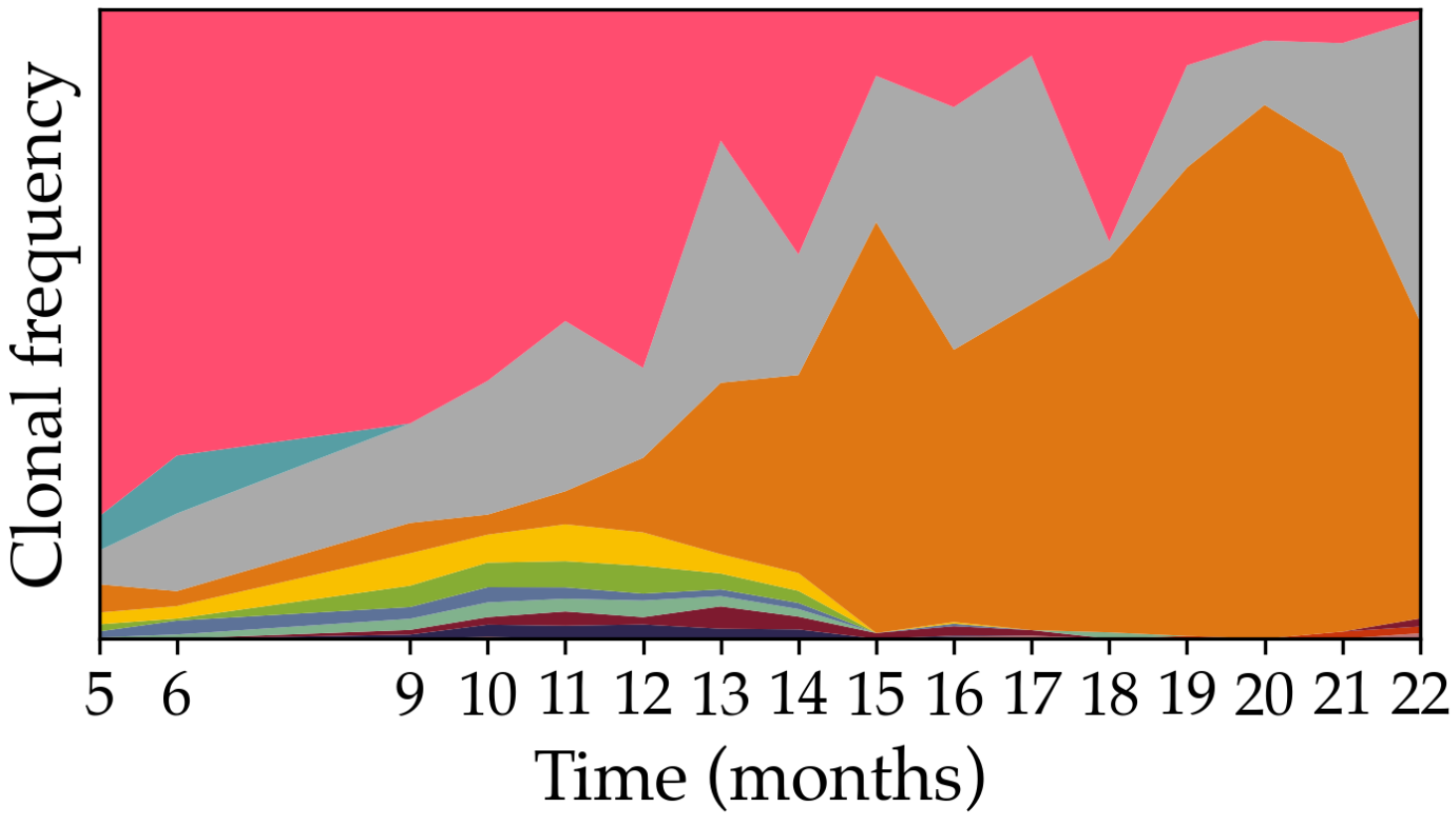


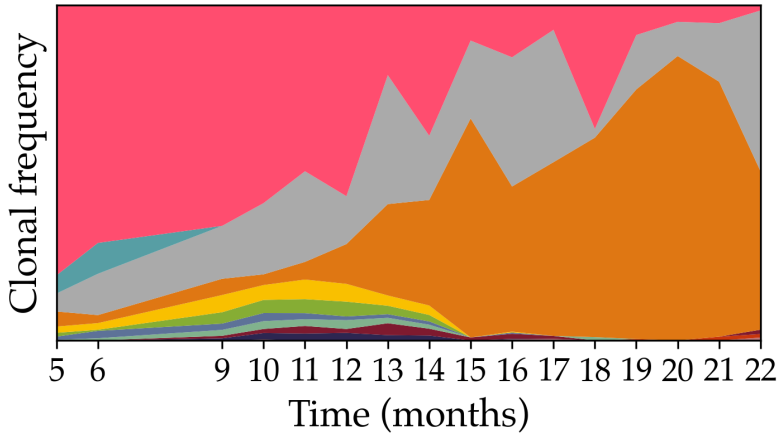
McKenna, Aaron, et al. "Whole-organism lineage tracing by combinatorial and cumulative genome editing." *Science* 353.6298 (2016): aaf7907.

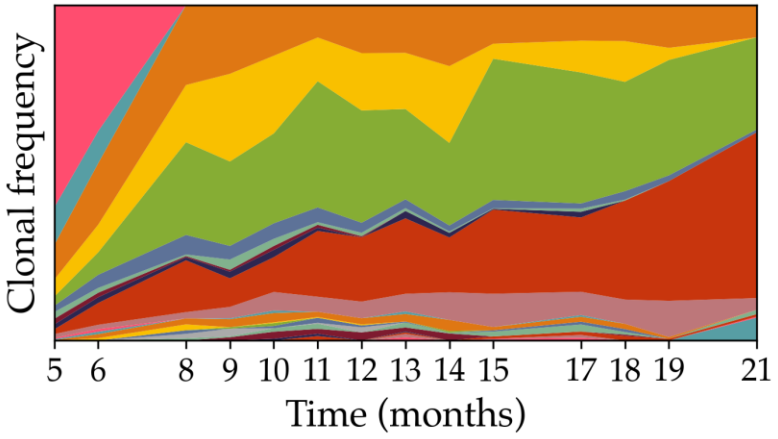
adulthood

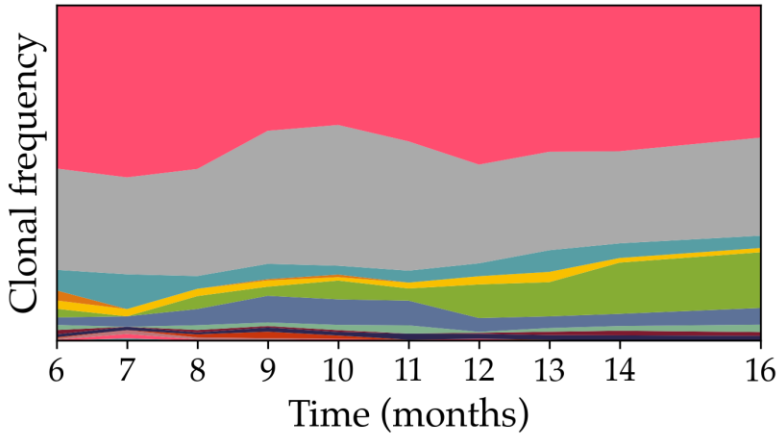


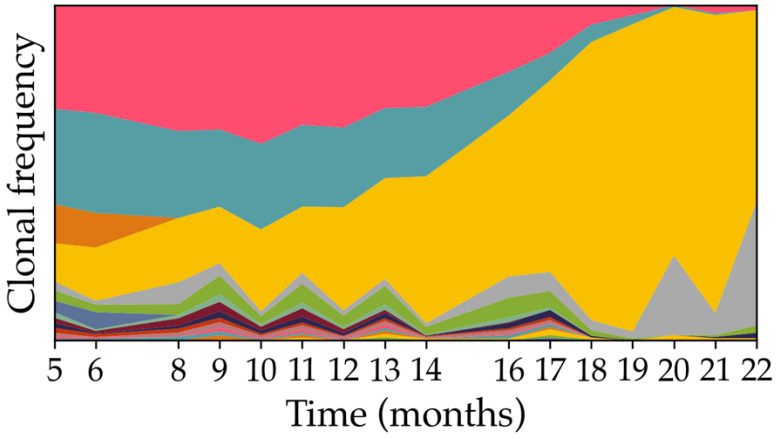
McKenna, Aaron, et al. "Whole-organism lineage tracing by combinatorial and cumulative genome editing." *Science* 353.6298 (2016): aaf7907.


Clonal frequency
5 6 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time (months)





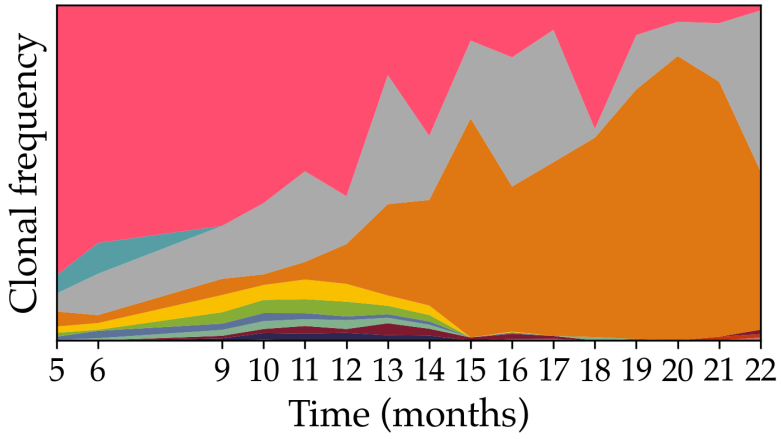


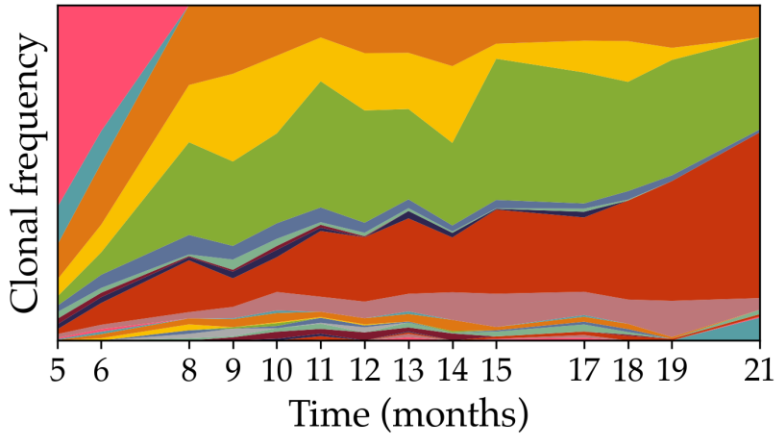


A few clones dominate the sperm pool.

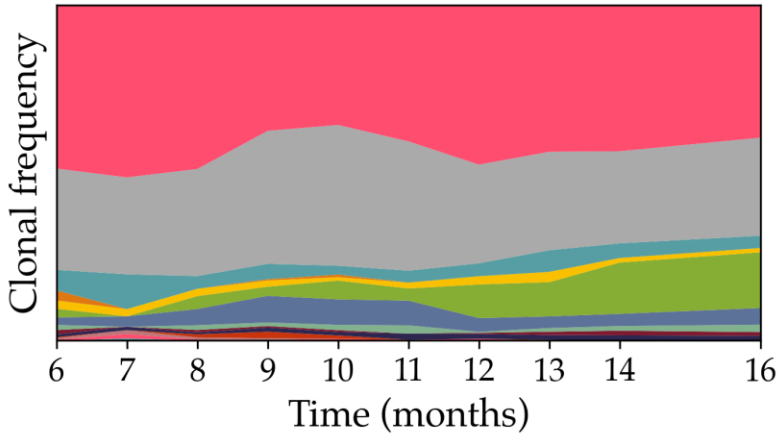
Small clones persist.

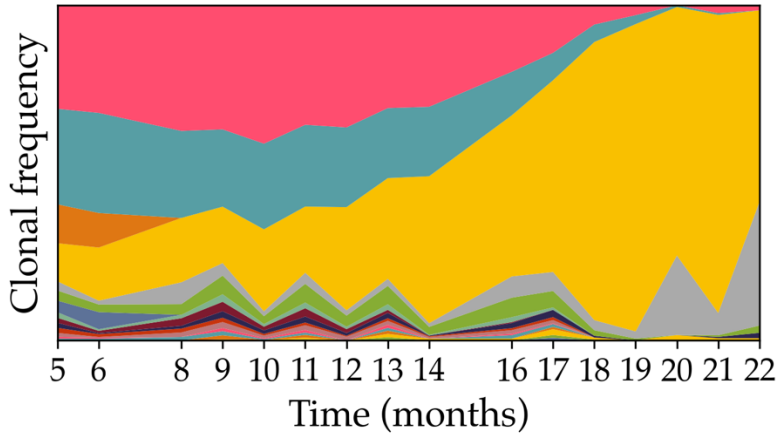
Consistent trends emerge.





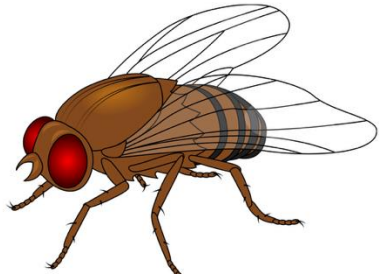
How strong is genetic **drift**?

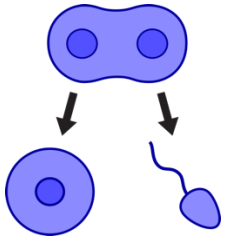


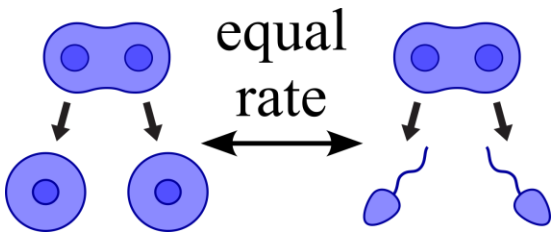


Is there evidence of **selection**?

Clonal drift is *sometimes* seen in some other organisms.

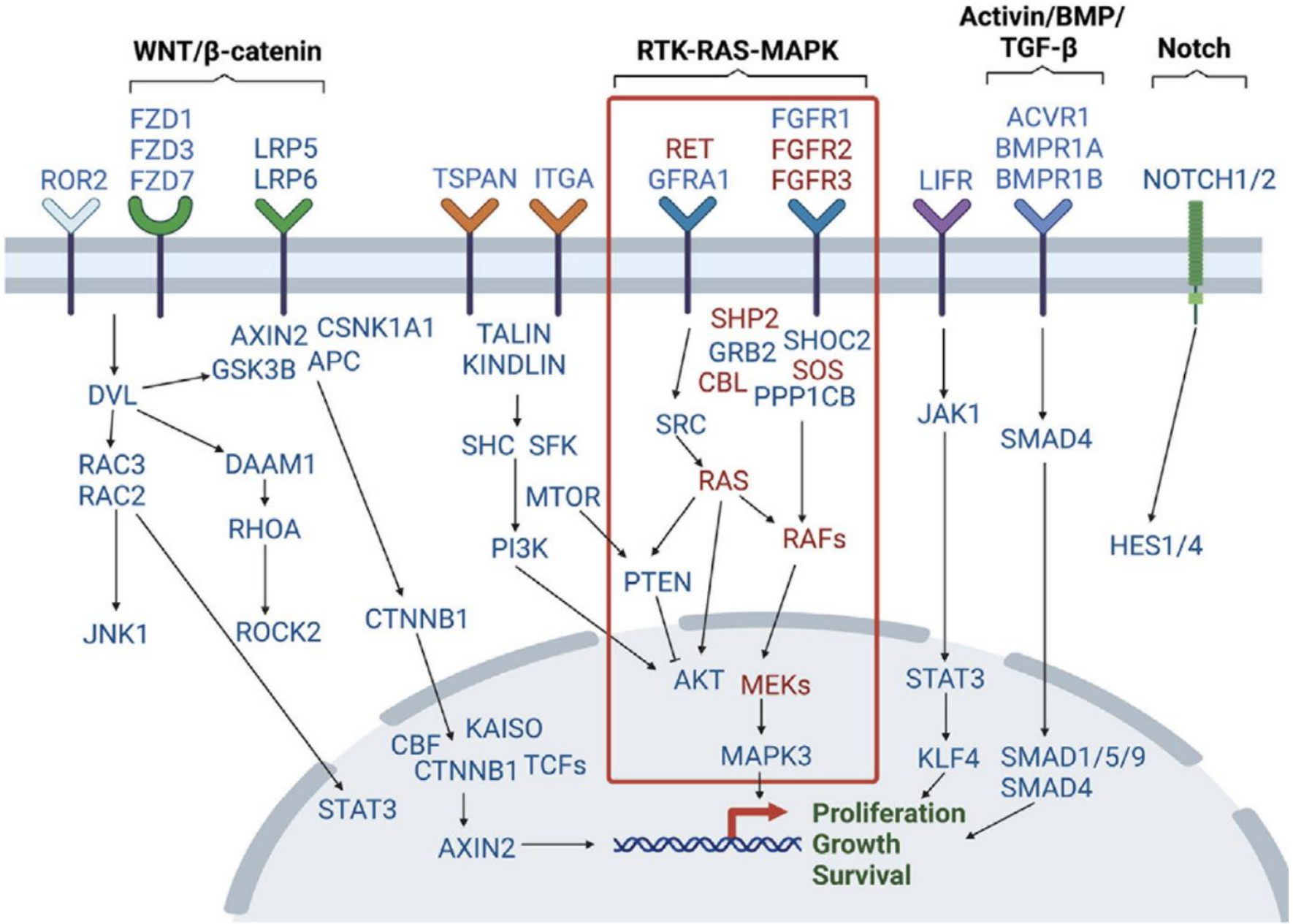




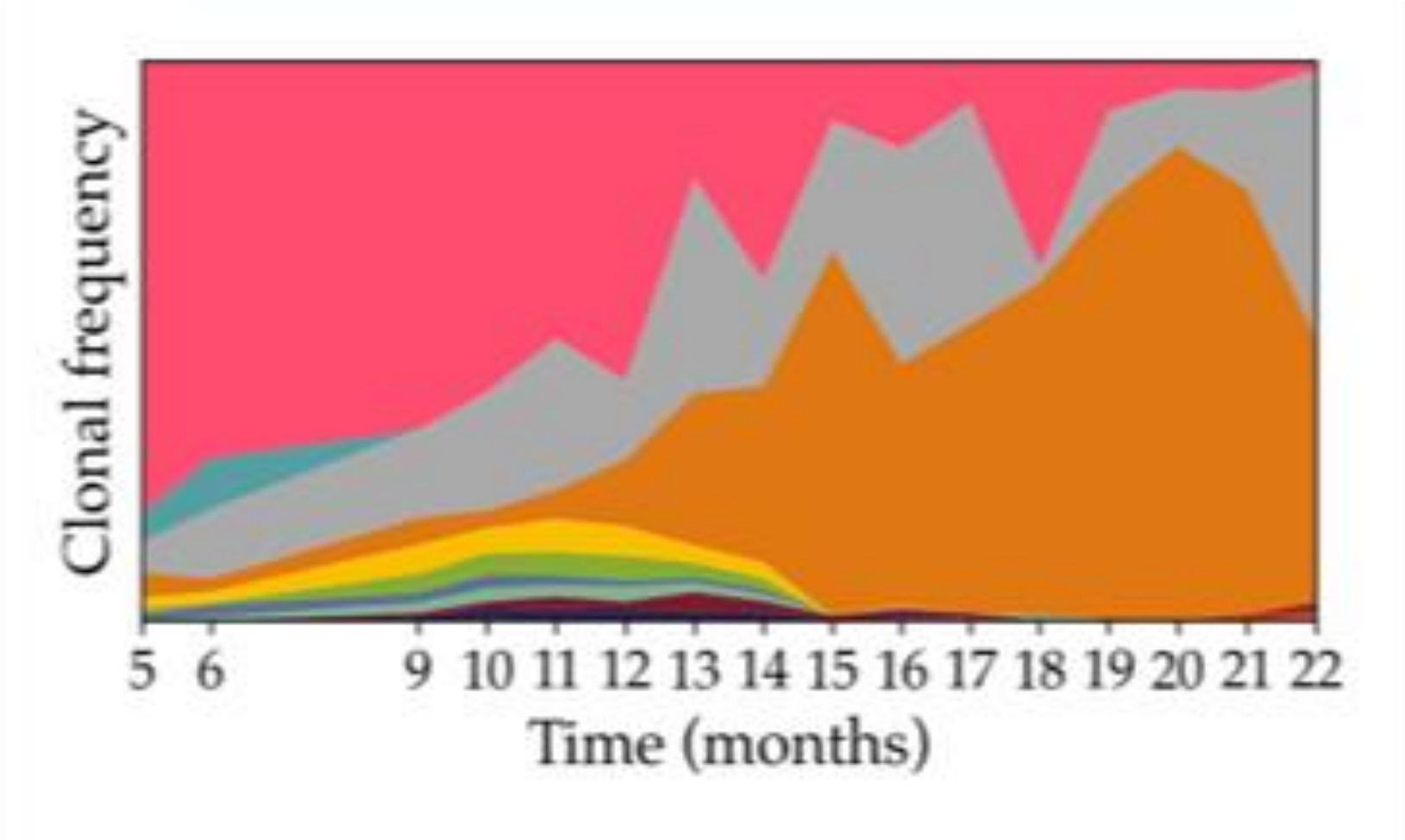


Positive selection is seen in humans through **paternal age effect** mutations.

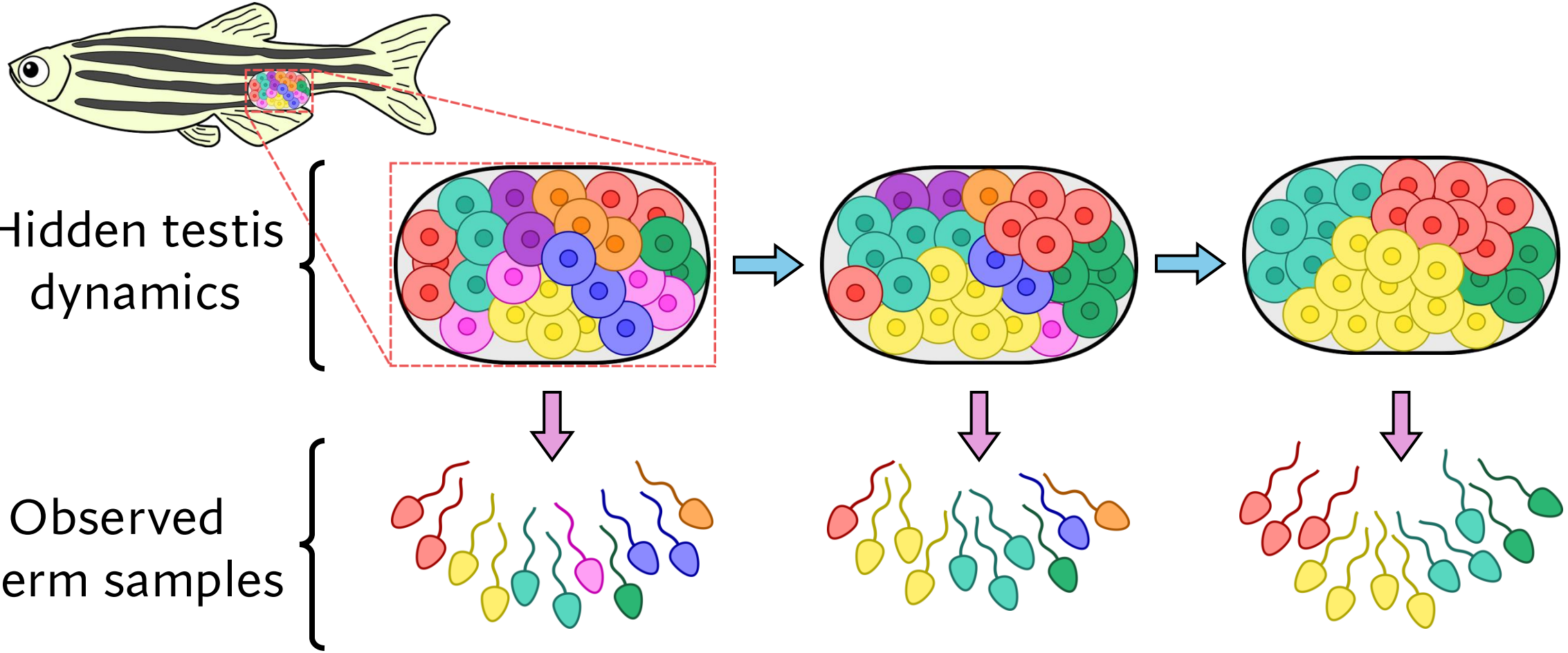
Klein, A. M., Nakagawa, T., Ichikawa, R., Yoshida, S., & Simons, B. D. (2010). Mouse germ line stem cells undergo rapid and stochastic turnover. *Cell stem cell*, *7*(2), 214-224.



Wood, K. A., & Goriely, A. (2022). The impact of paternal age on new mutations and disease in the next generation. *Fertility and Sterility*, *118*(6), 1001-1012.


Clonal frequency
5 6 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time (months)

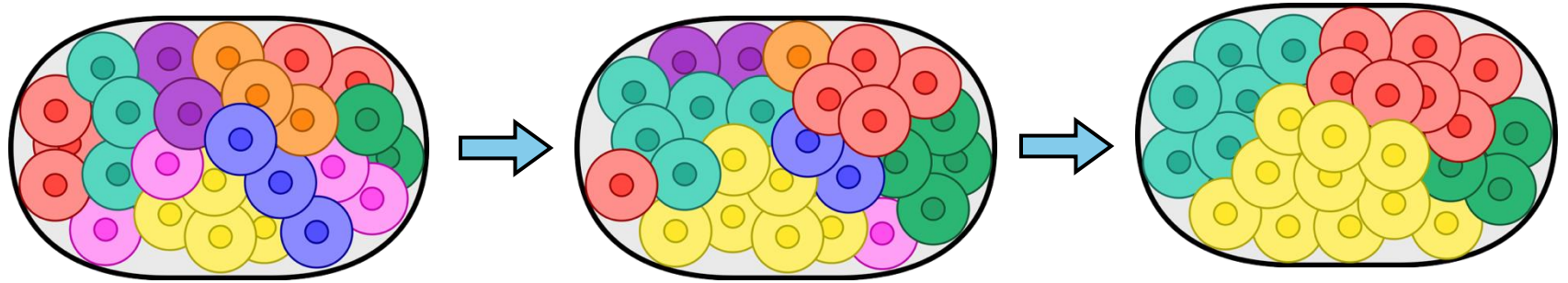
Hidden Markov modeling setup



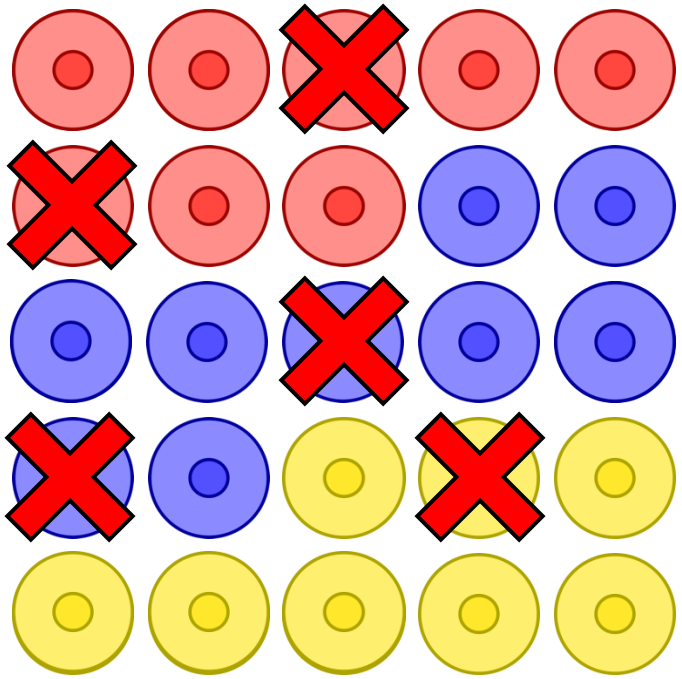
Hidden Markov modeling setup

Use the **Moran process** for the hidden dynamics.

Hidden testis dynamics



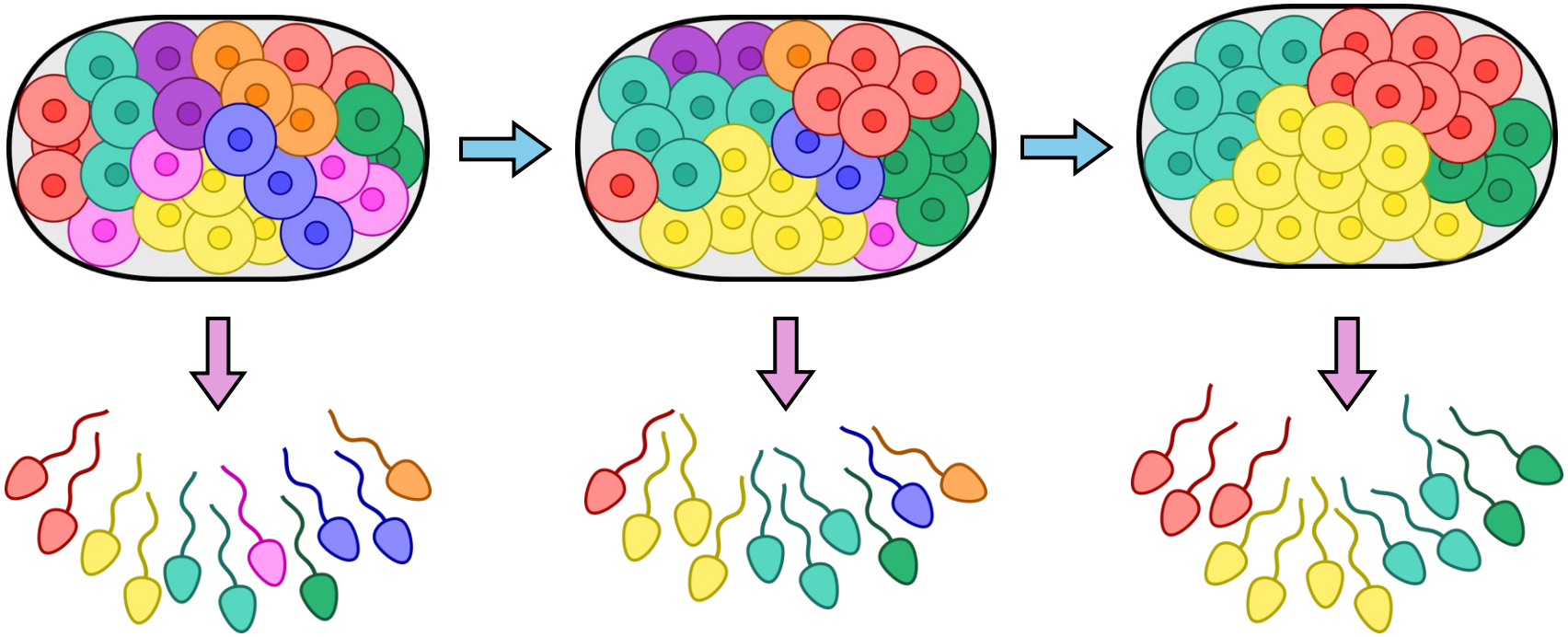
Moran process



Stem cells differentiate at rate r.

Measures strength of **genetic drift**.

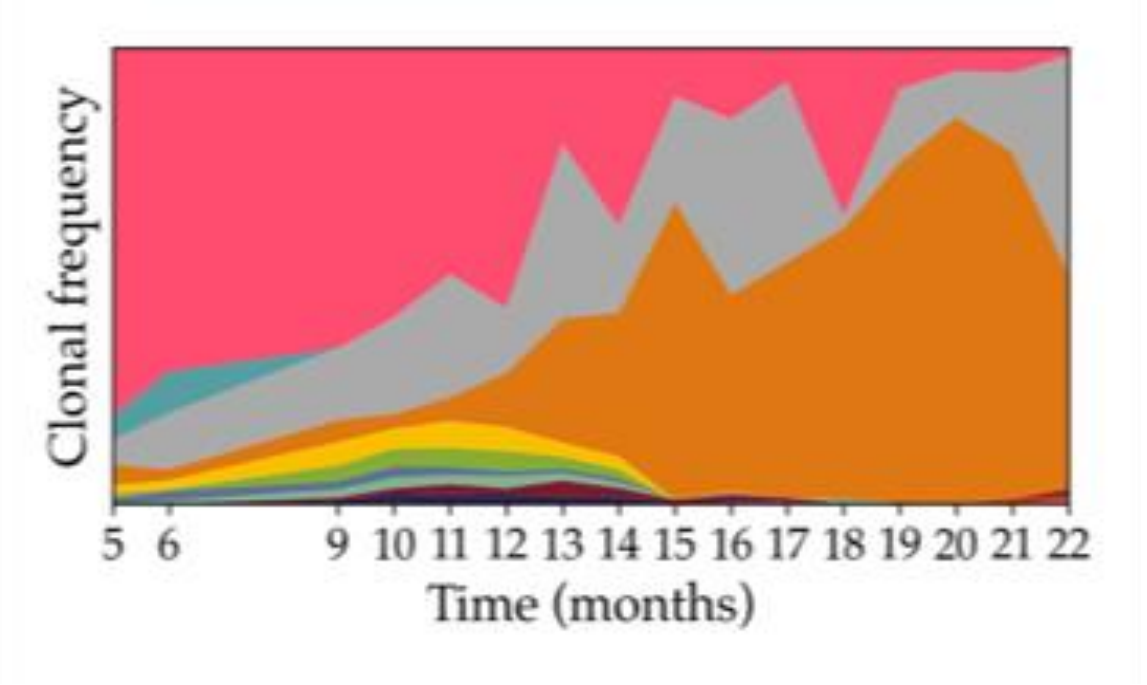
Observed sperm data



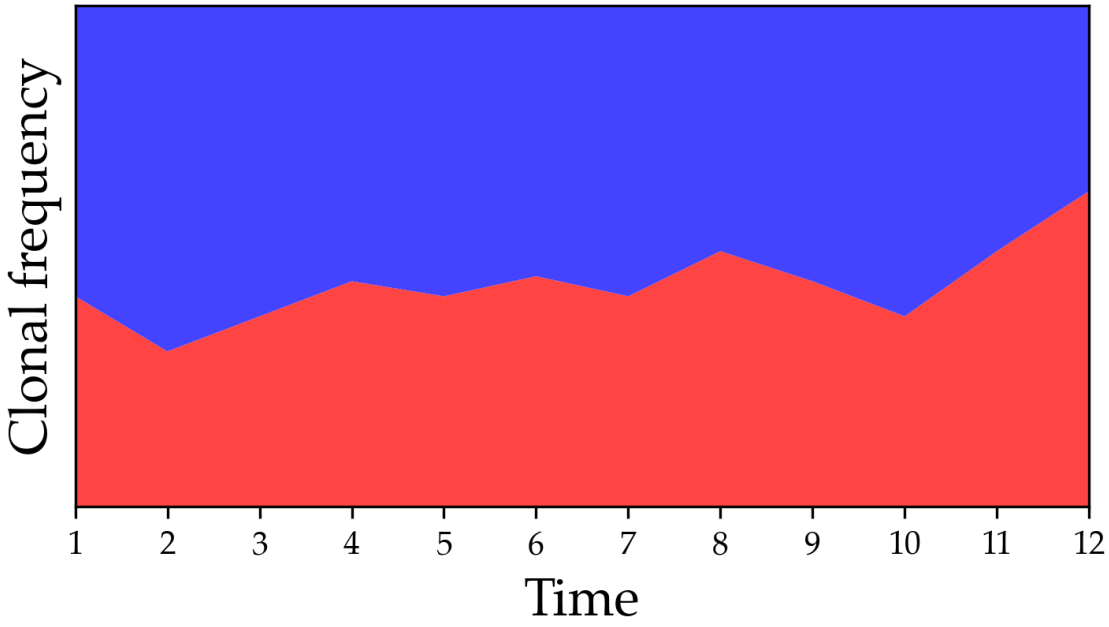
Sample stem cells with replacement!

Are clones undergoing drift?

Is the differentiation rate r non-zero?



A simple example

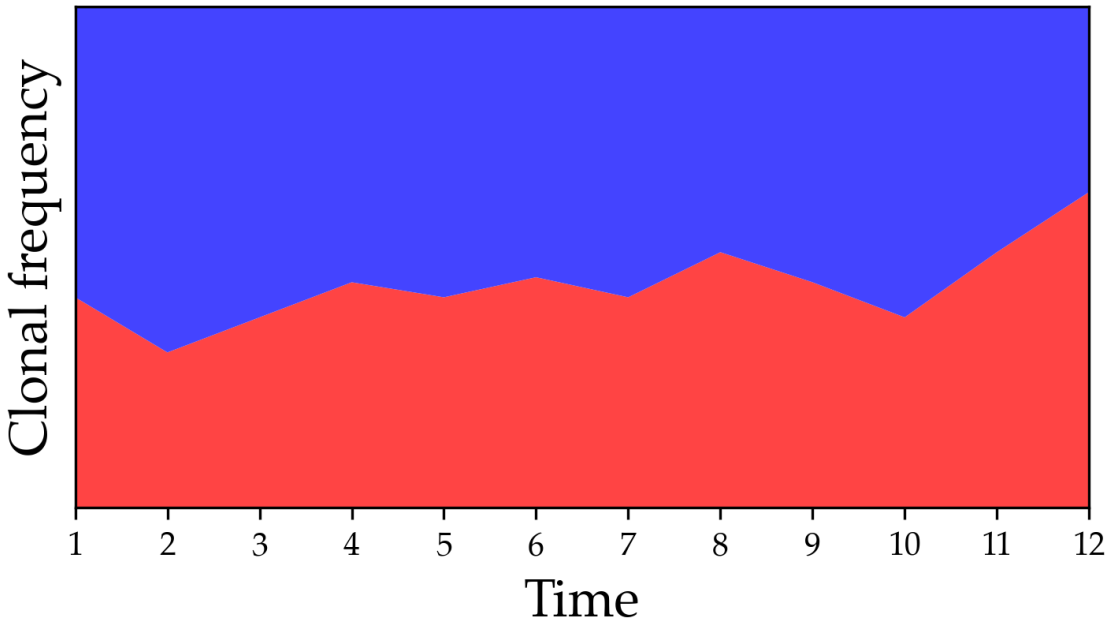


200 stem cells
100 sperm per sample

??? differentiation rate

Estimate parameters using ML (maximum likelihood)

$$\mathcal{L}(r) = \ln(\Pr(\text{observed data} : \text{differentiation rate } r)).$$



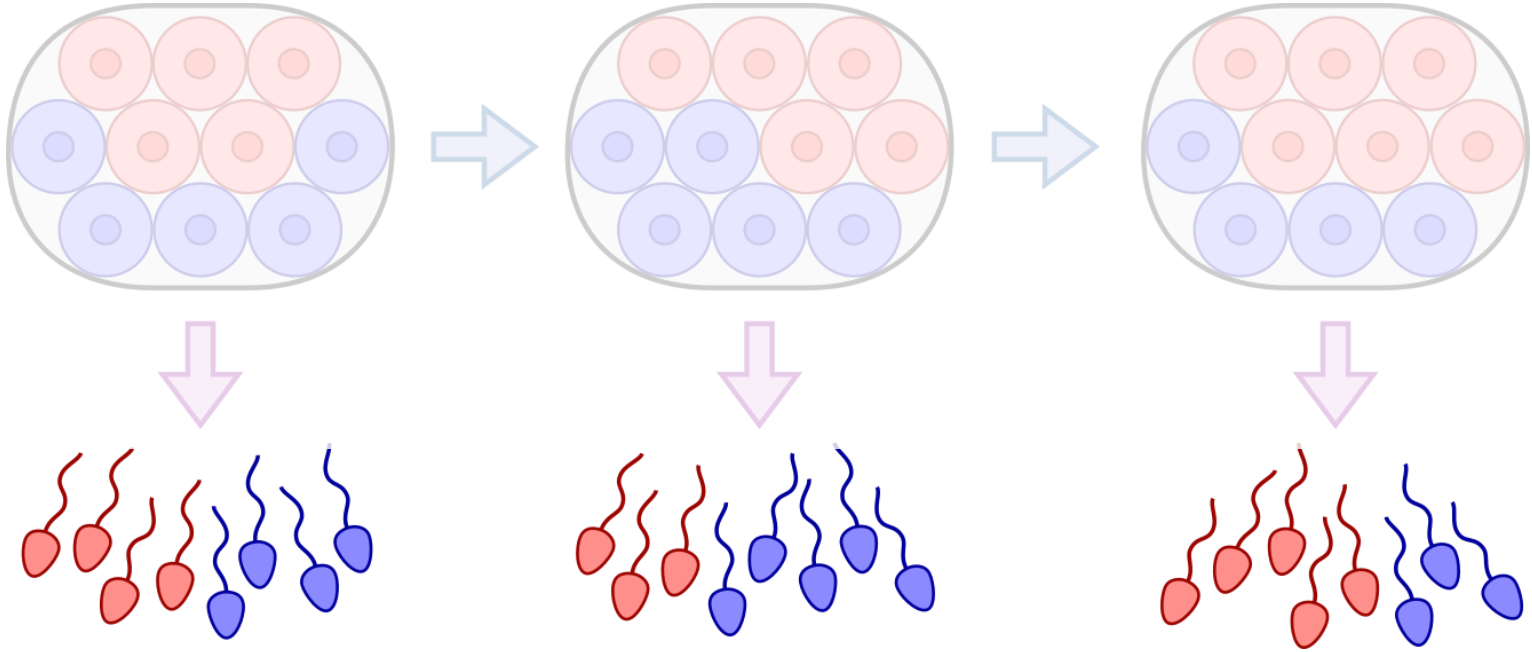
Null hypothesis: $r = 0$.

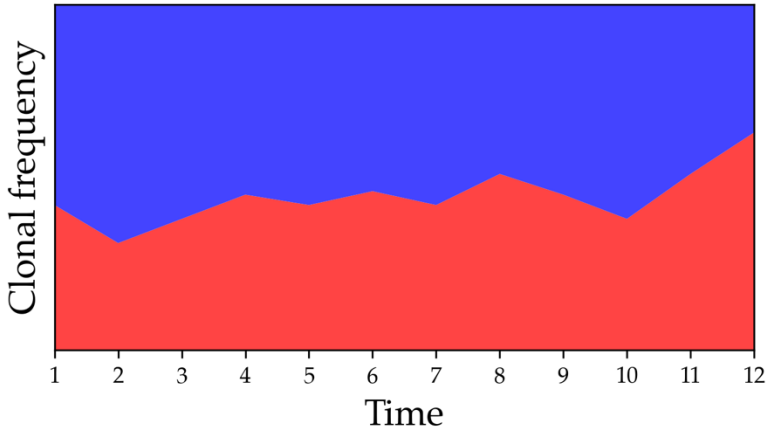
Use the log likelihood ratio test statistic,

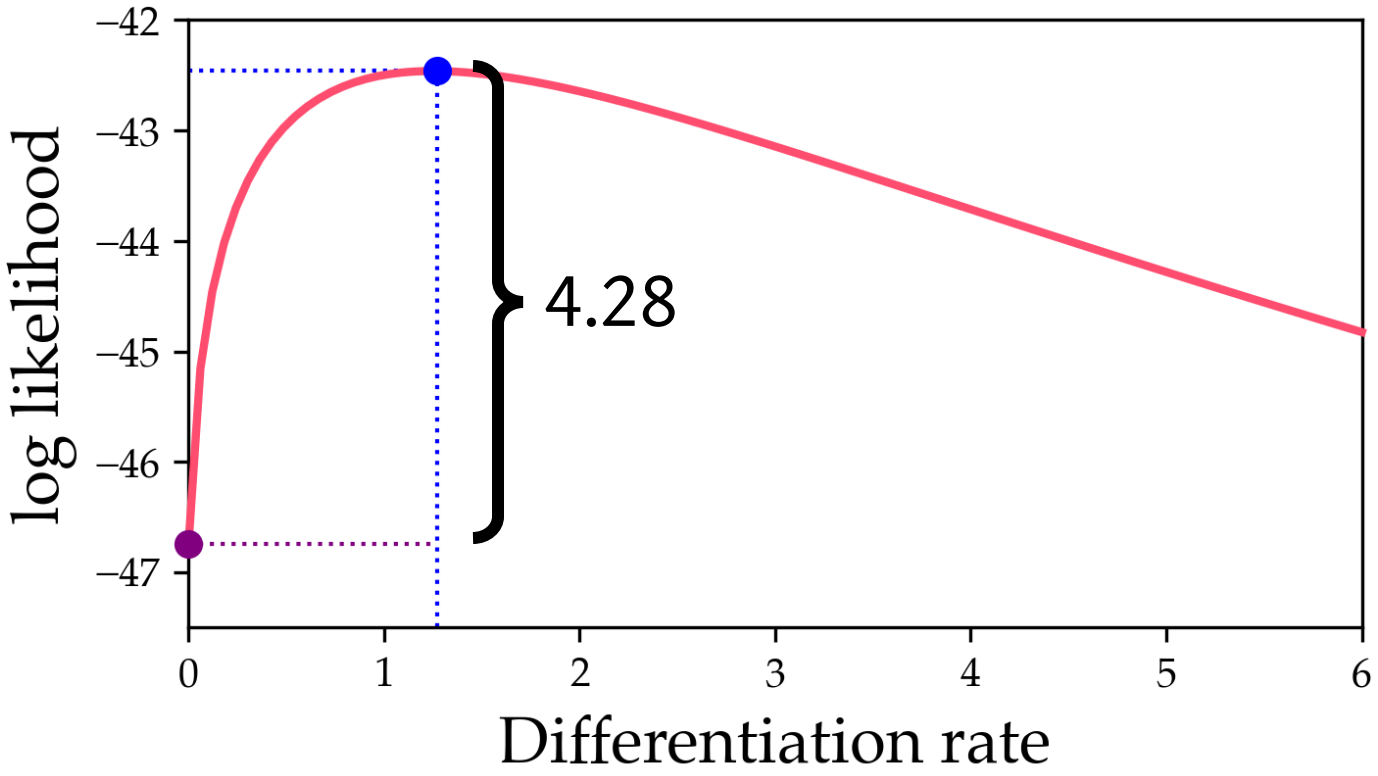
$$\lambda = 2(\max(\mathcal{L}) - \mathcal{L}(0))$$

We'll accept that $r \neq 0$ if $\lambda > 6$.

Likelihood calculations are made using the **forward algorithm**.



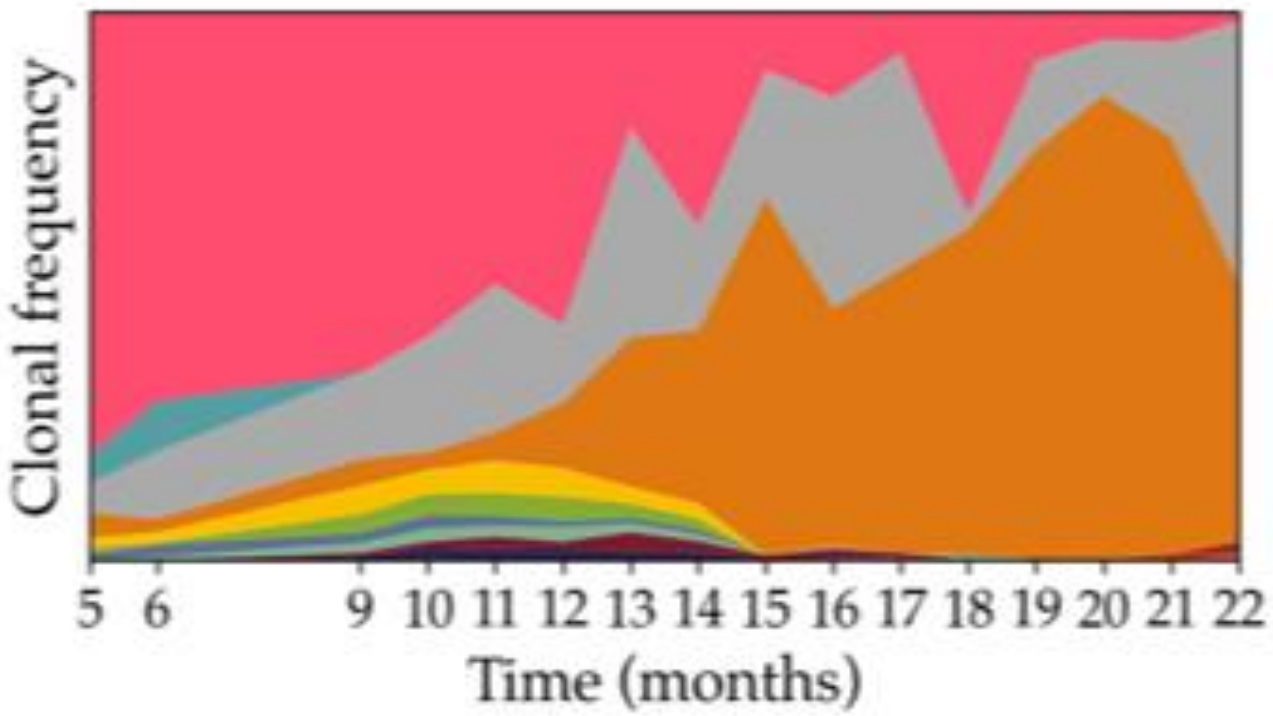




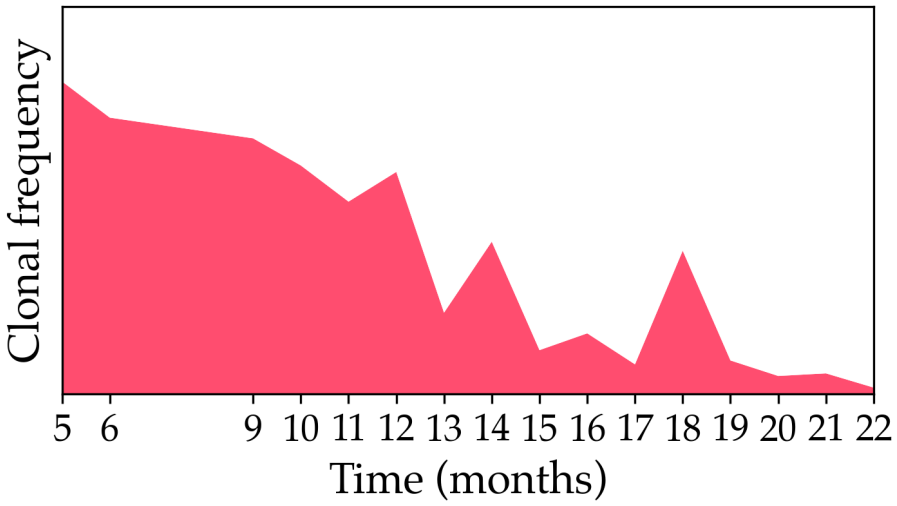
The likelihood is maximized at $r = 1.25$.

The test statistic λ is 8.57.

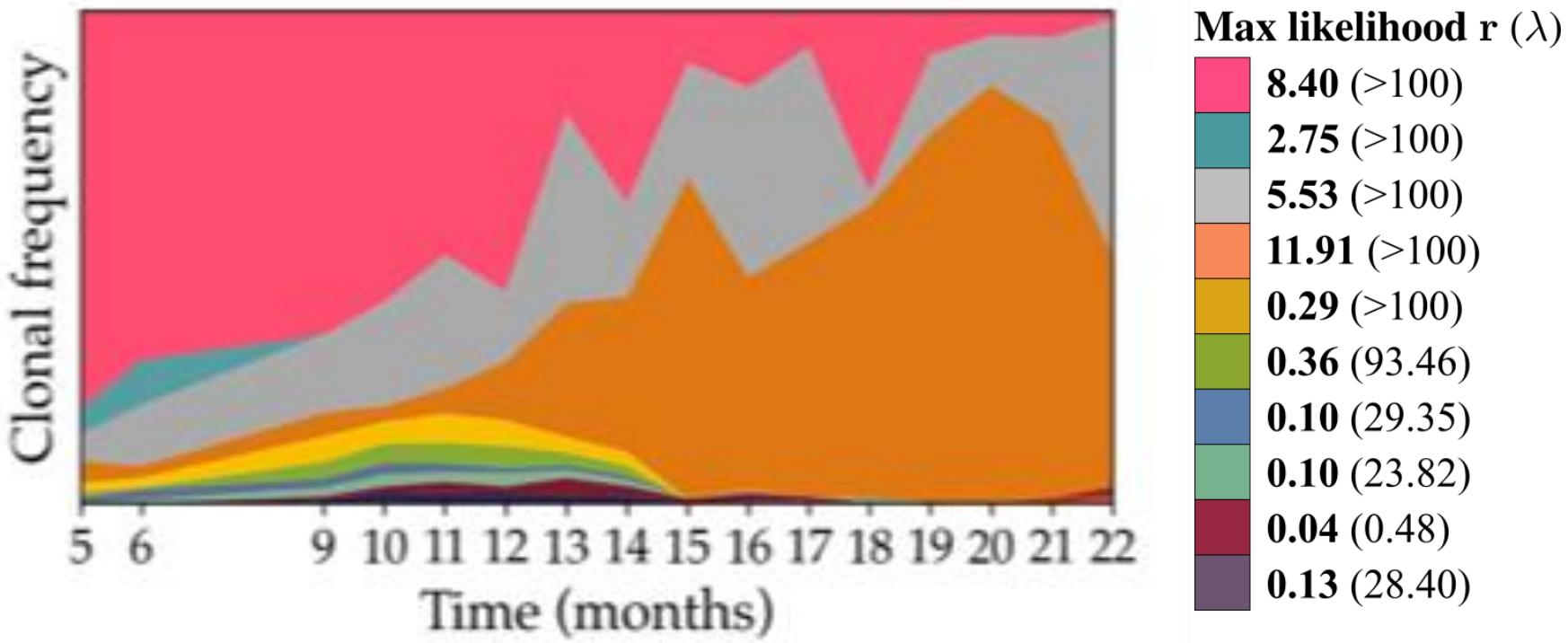
Measuring genetic drift in experimental data

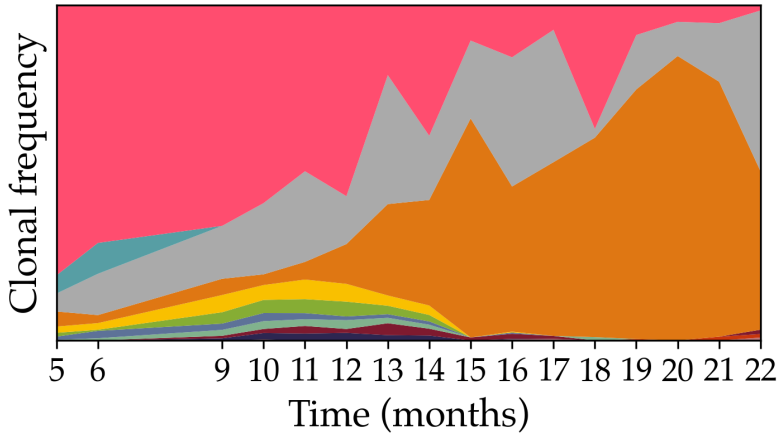


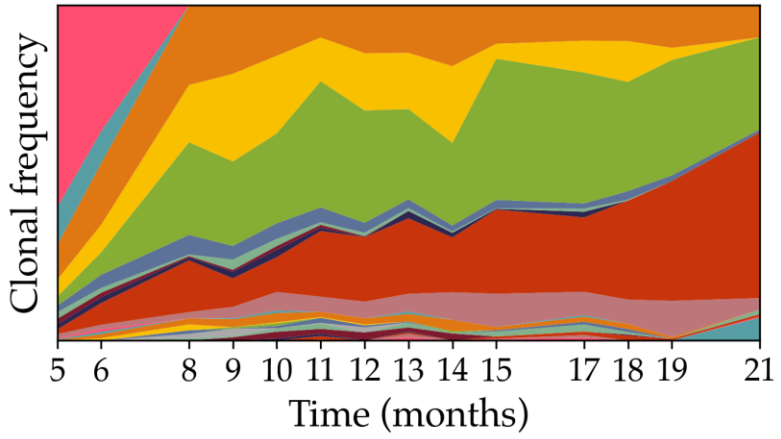
Estimate drift of each clone individually.



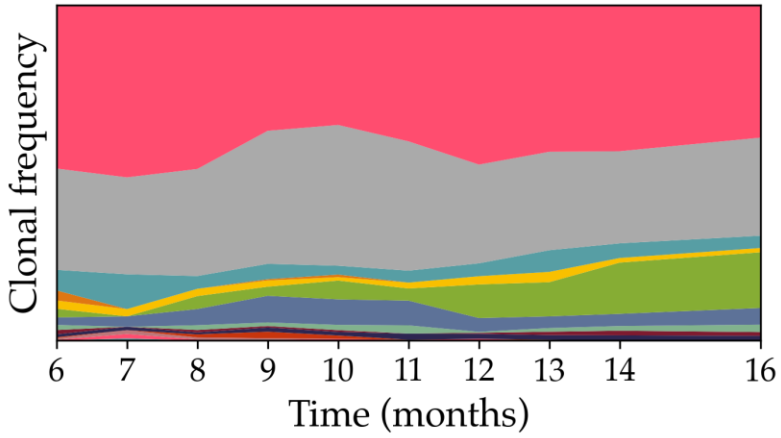
Measuring genetic drift in experimental data

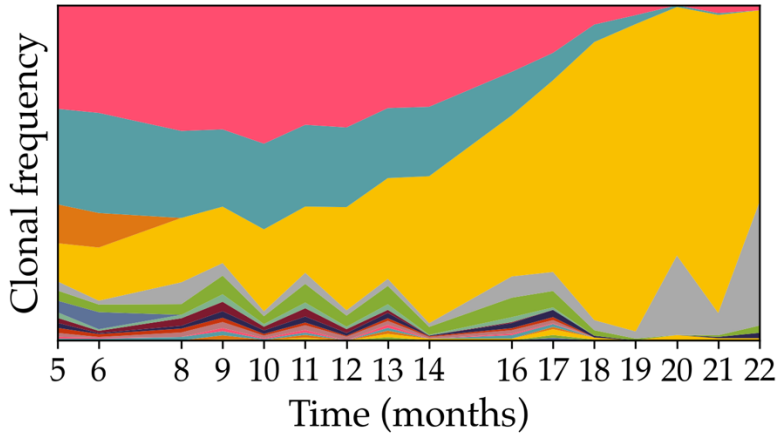






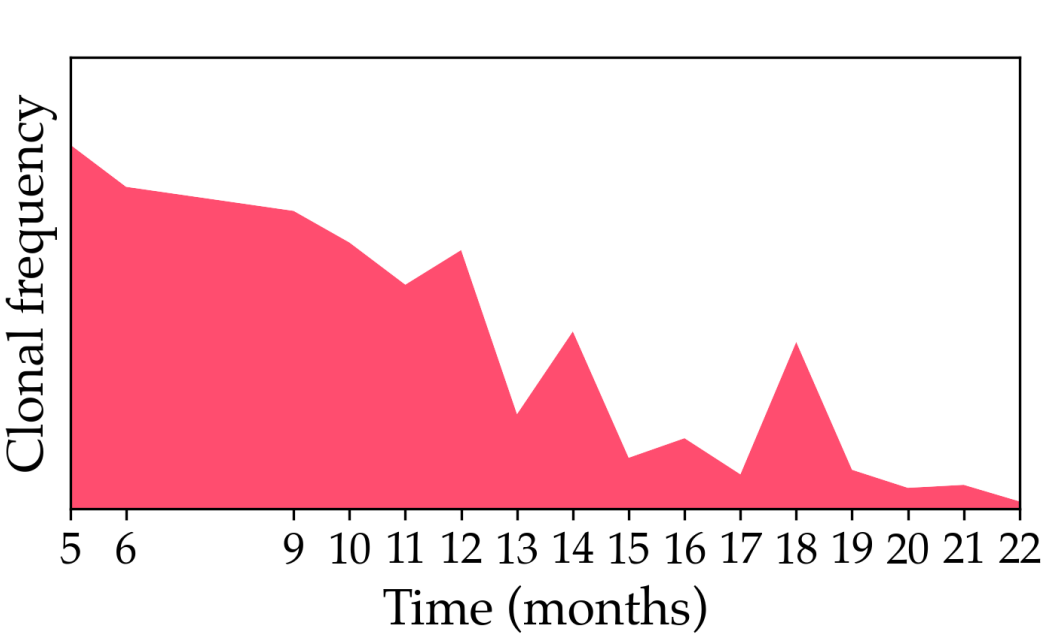
Large clones experience more drift than small clones.

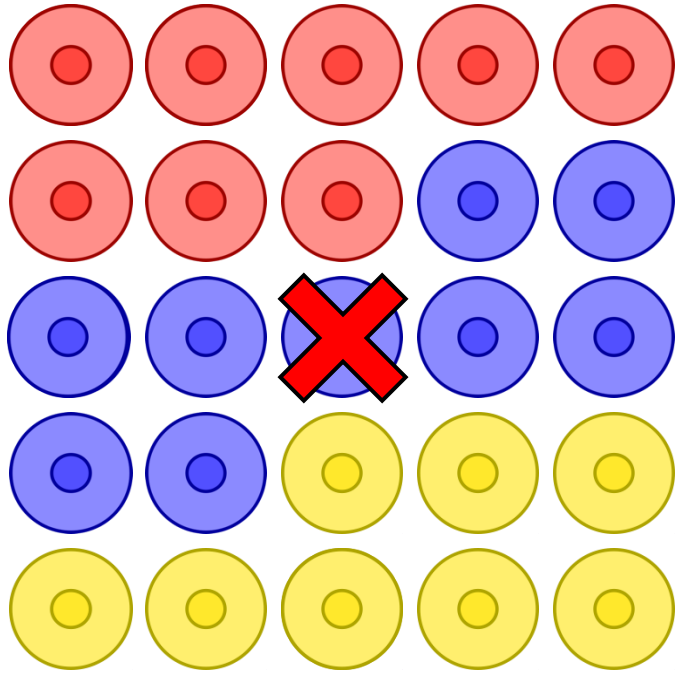




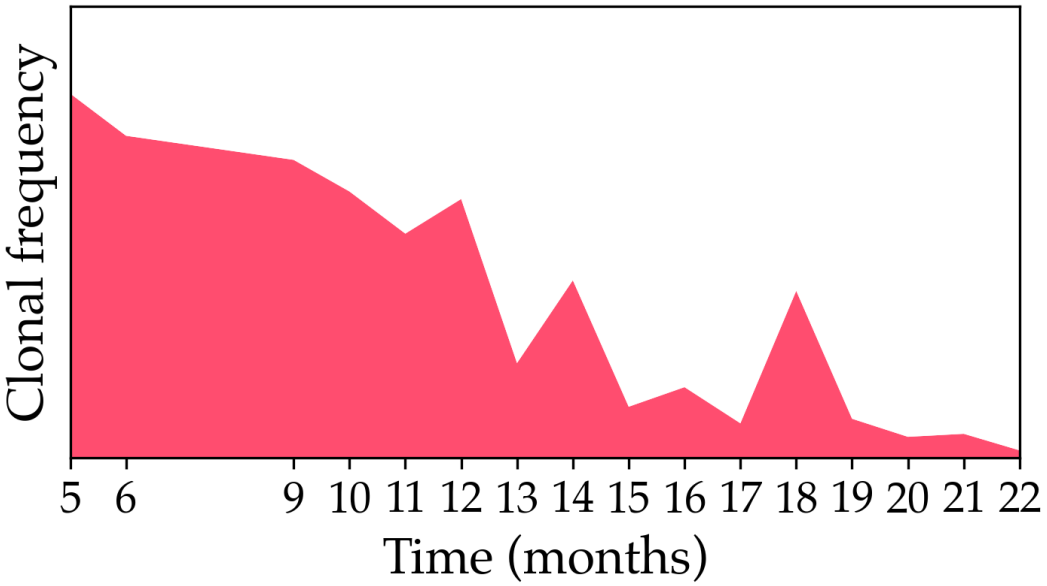
Clones that begin large tend to decrease in size.

Is there evidence of selection?





Weigh probability of a target clone dividing by $1 + s$.



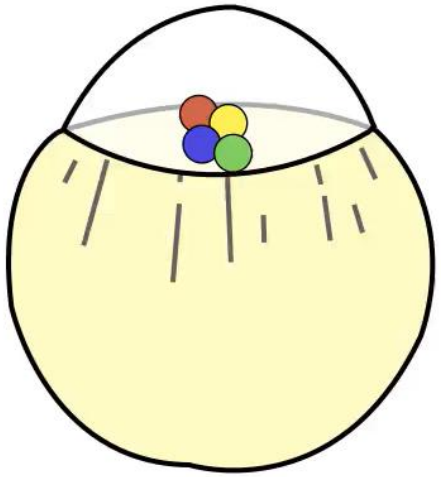
Null hypothesis: $s = 0$.

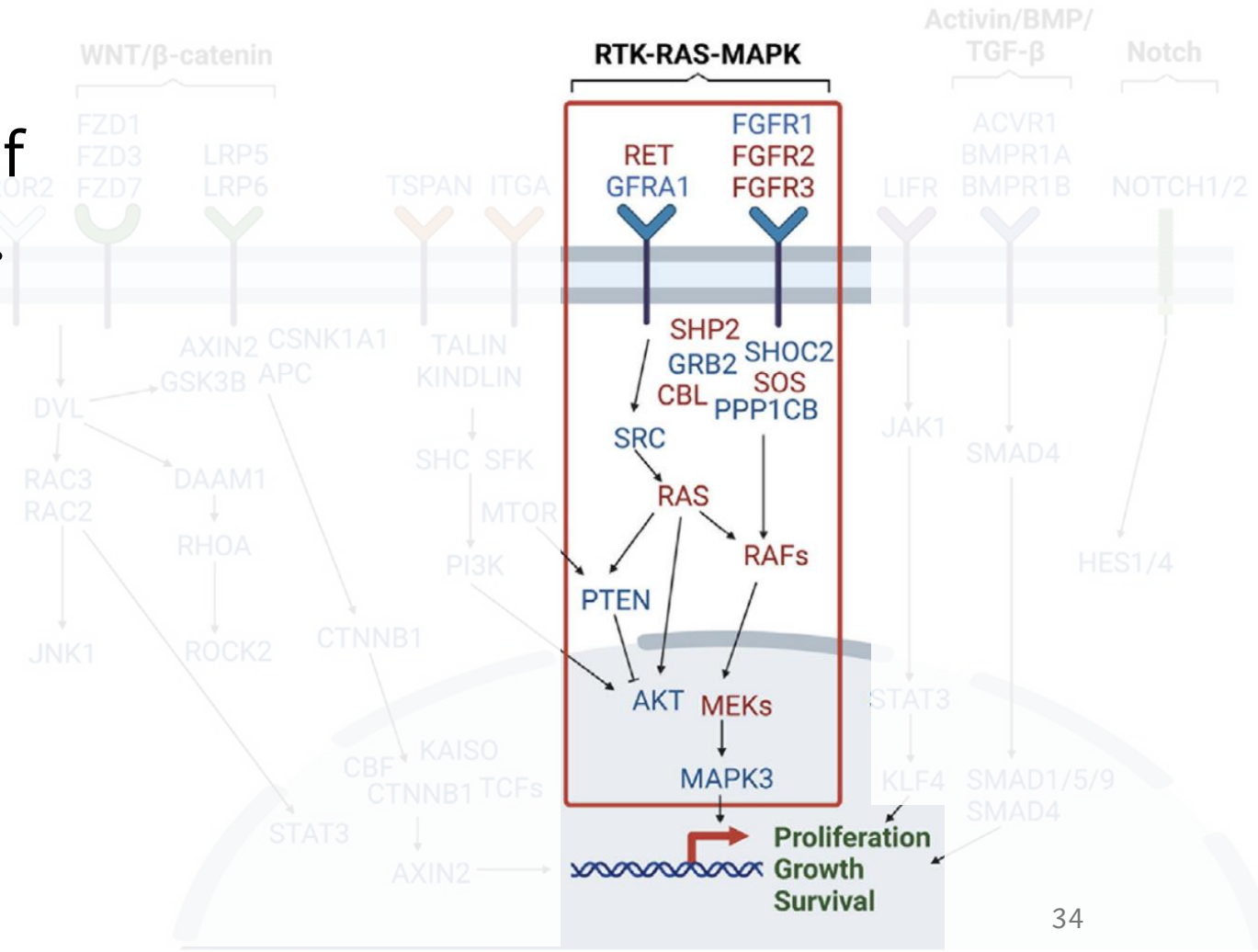
The likelihood is maximized at $s = -0.19$.

The test statistic λ is 8.36.

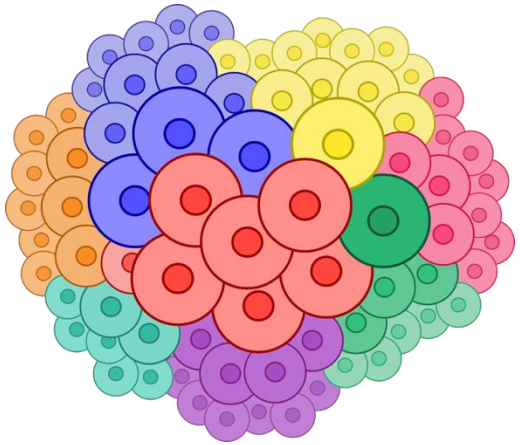
Introducing selection experimentally

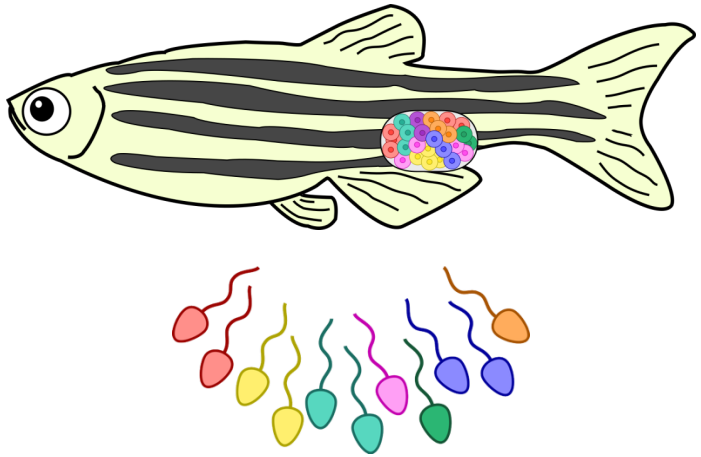
Insert a mutation in one of the primordial germ cells.

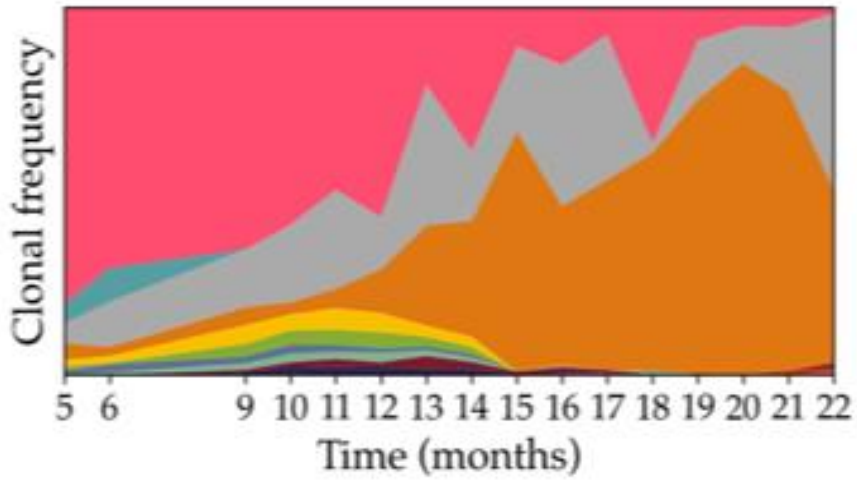


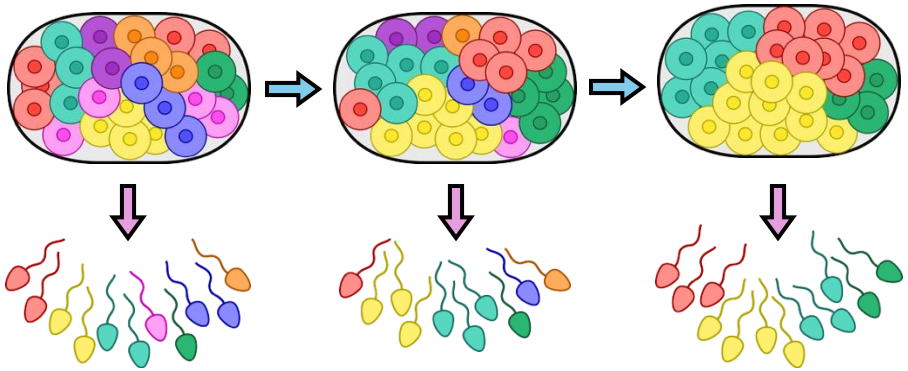


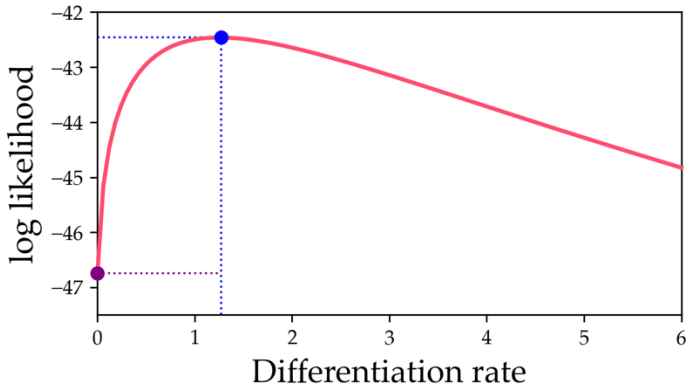
Summary






Clonal frequency
5 6 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time (months)




log likelihood
−42
−43
−44
−45
−46
−47
0 1 2 3 4 5 6
Differentiation rate

Acknowledgements

Fred Adler
(advisor)

Jamie Gagnon
(lab PI)

Jenna Weber

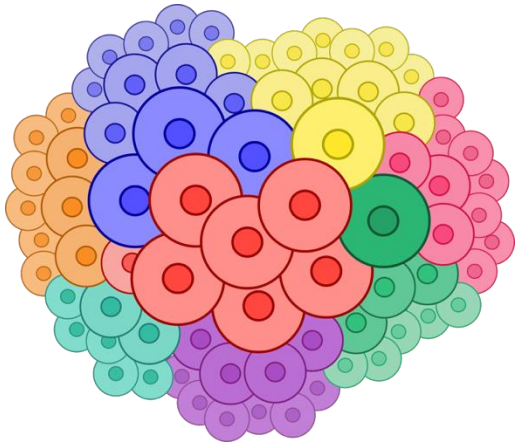
Andy Sposato

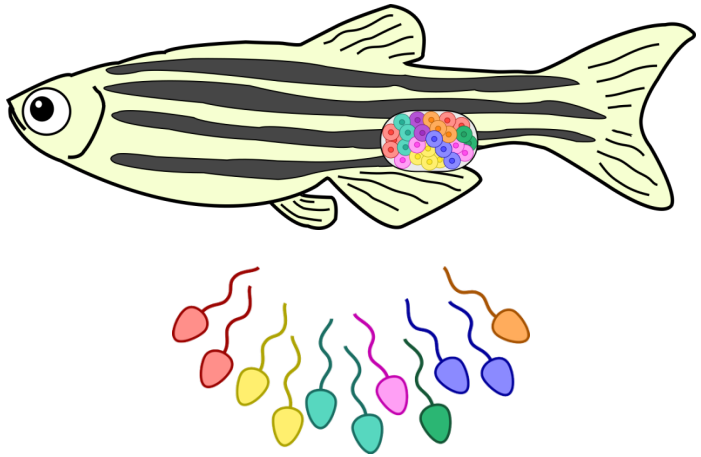
Utah Genetics Training Program
(T32-GM141848)

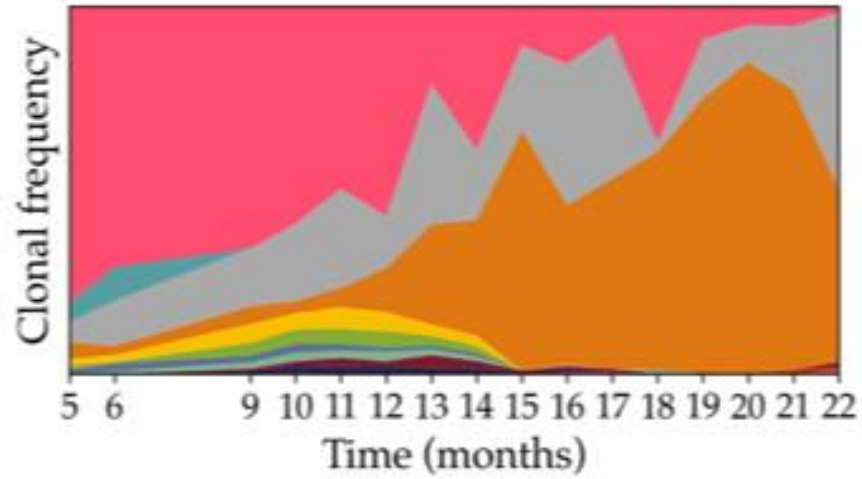
NSF Graduate Research Fellowship

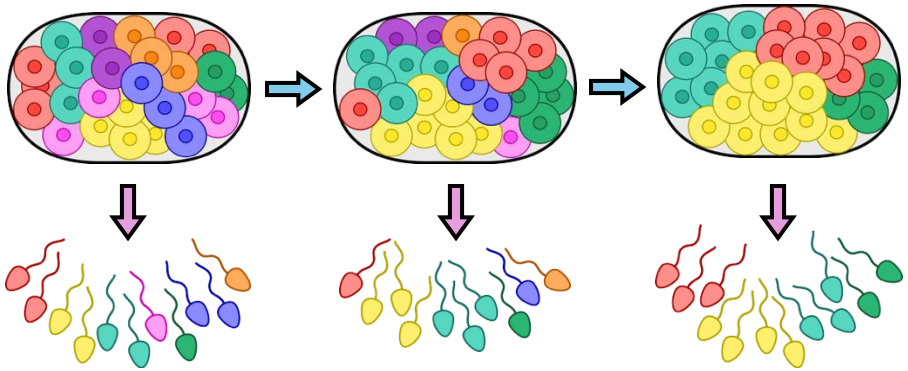
Let's collaborate!
connor.shrader@utah.edu
math.utah.edu/~shrader/

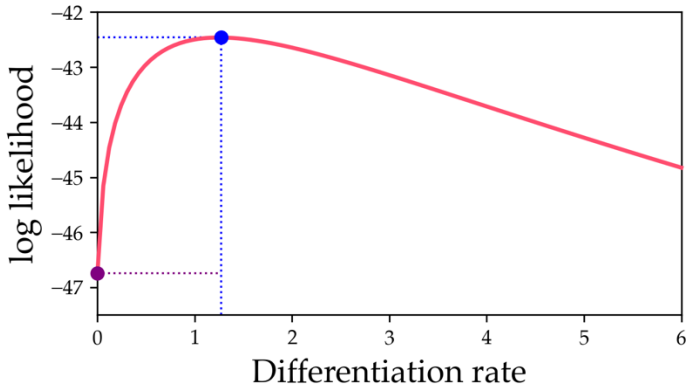
Thank you!






Clonal frequency
5 6 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time (months)




log likelihood
−42
−43
−44
−45
−46
−47
0 1 2 3 4 5 6
Differentiation rate