A somatic genetic clock for clonal organisms

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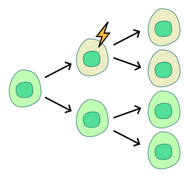
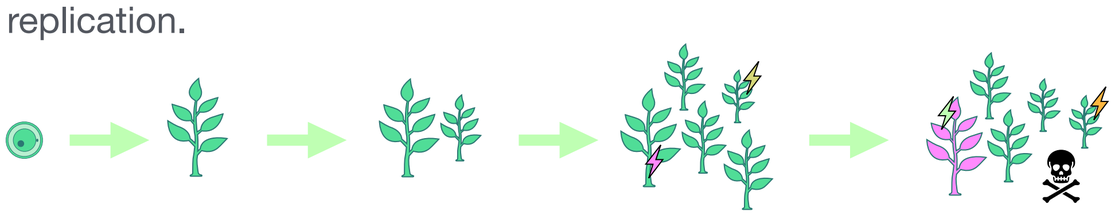
1. Somatic genetic clock

Cells accumulate somatic mutations when they divide, leading to somatic genetic variation within multicellular organisms.

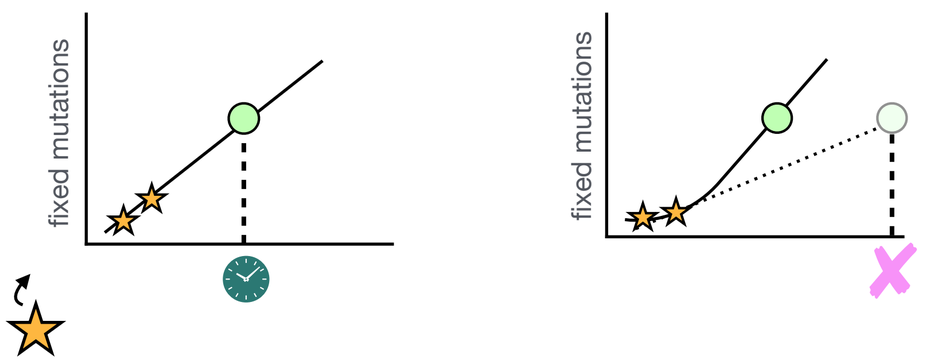


Clonal organisms grow from a single zygote by module replication.



Somatic mutations become fixed in modules by neutral drift [1].

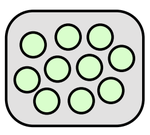
Fixed mutations accumulate linearly [2] and could provide a somatic genetic clock to estimate the age of clonal organisms.



We can calibrate the clock with clones of known age…

…but mutations do not fixate instantaneously, thus it takes time to reach linearity.

2. Model of a clonal organism

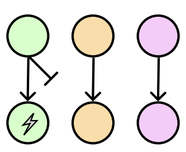


The clonal organism is represented as a collection of *modules* that consist of *cells*.

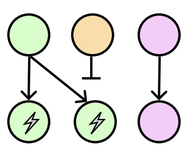
Modules grow to *N* cells by symmetric cell division at rate *b*.

Cells in homeostatic modules continue to proliferate by:

asymmetric division



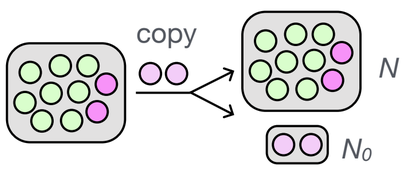
or **symmetric division.**



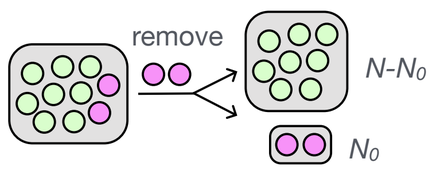
At division cells obtain μ new mutations on average.

Homeostatic modules produce new modules at rate *r* by:

branching



or **splitting.**



The module population grows exponentially to a fixed size, and then module death is implemented to keep population constant.

3. Delay to linearity

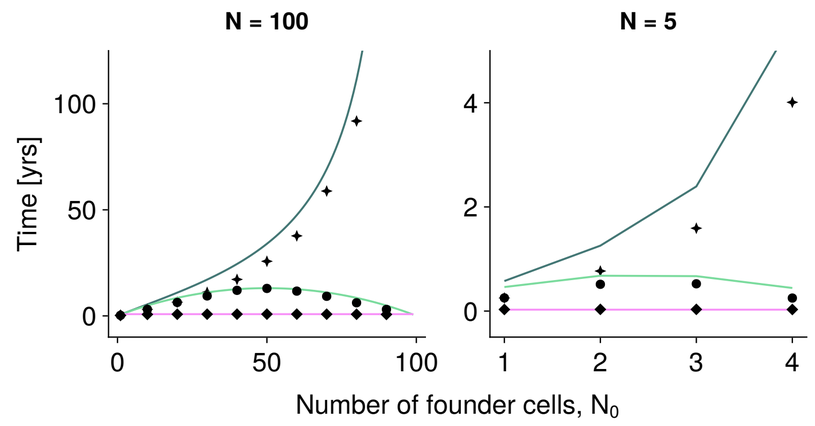
The time to reach linear accumulation is related to the conditional fixation times T.

Fixation by **symmetric cell division** in homeostatic modules is a Moran process: $T \approx b/N$ [3].

Repeated formation of new modules is approximated as a modified Wright-Fisher process. We calculate T using a diffusion approximation:

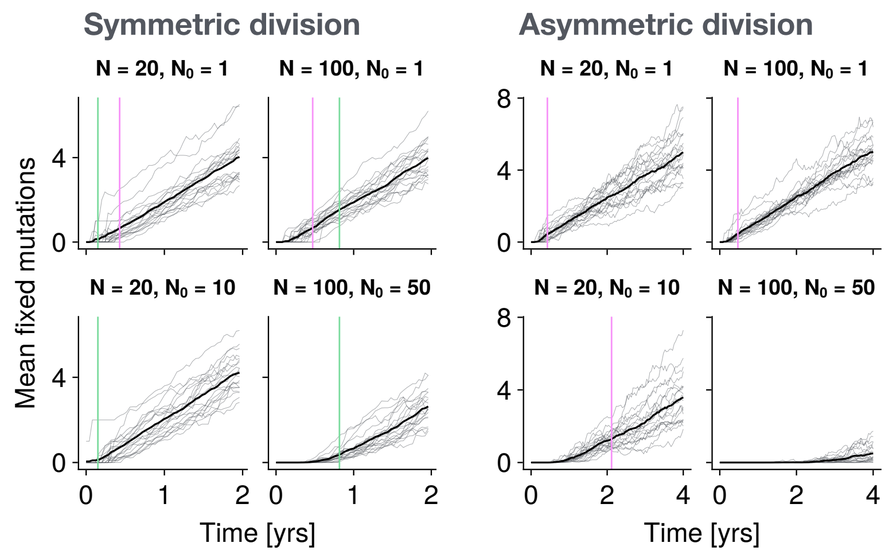
branching: $T \approx \dfrac{4N_0}{r\left(1-(N_0/N)^2\right)}$ **splitting:** $T \approx \dfrac{4N_0}{r}\left(1-N_0/N\right).$

Comparing theory and simulation:



✦ asymmetric division & **branching**
● asymmetric division & **splitting**
◆ **symmetric division** & **splitting**

Longer fixation times correspond to a longer delay to linearity:



4. Conclusions

The **somatic genetic clock can be applied when linearity is reached quickly**, e.g. if modules consist of a small number of cells (*N*), there are a small number of founder cells (N_0), and/or homeostasis is maintained by symmetric cell division.

REFS:
[1] TBH Reusch et al. (2021) *Trends in Ecology and Evolution,* 36(12).
[2] M Kimura & T Ohta (1971) *Journal of Molecular Evolution,* 1.
[3] T Antal & I Scheuring (2006) *Bulletin of Mathematical Biology,* 68(8).

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