Linking lineage and population observables in biological branching processes

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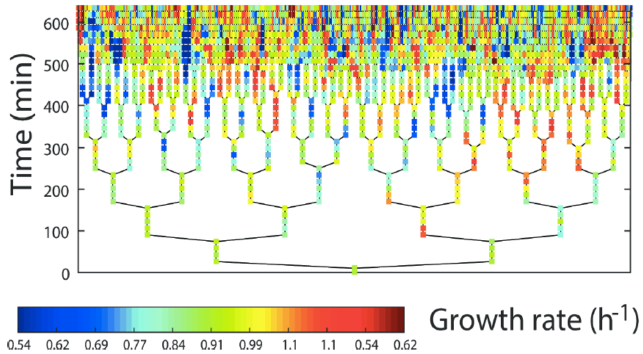
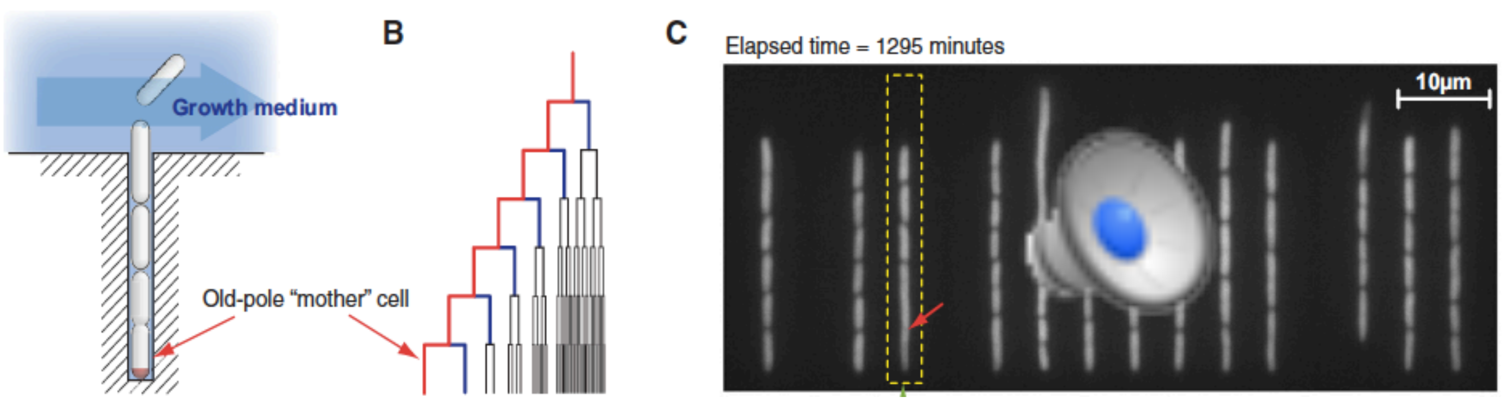
- **Time-lapse microscopy of a bacteria colony :**



S. Lahiri et al. 2017

D. J. Kiviet et al. 2014

- **Mother machine configuration :**



P. Wang et al. 2010

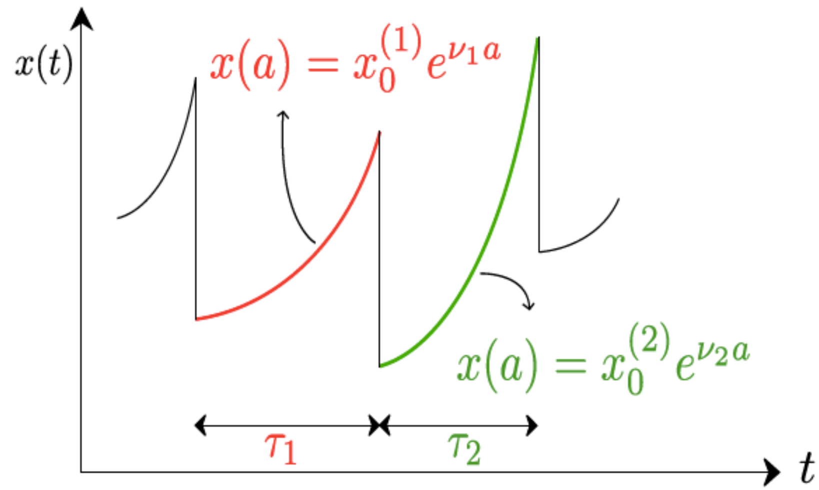
- **Parametrization of exponential growth :**

  A. Amir 2014   L. Robert 2014

  - Continuous stochastic map
  - Various models of control :

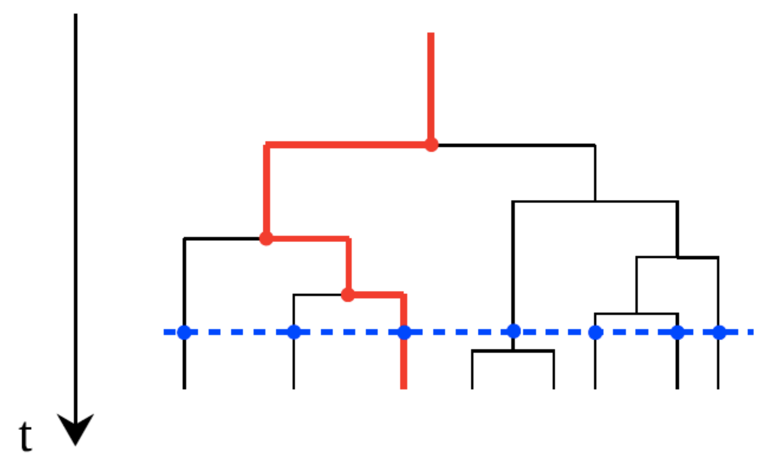
    - size models

    - age models



- **Three levels of description :**

  - Lineage
  - Snapshot
  - Tree



Cell population dynamics

- **Dynamical equation for the number density of cells**

$$\partial_t n(\mathbf{y},t) = -\nu\partial_x[xn(\mathbf{y},t)] - B(\mathbf{y})n(\mathbf{y},t) + 2\int d\mathbf{y}'\Sigma(\mathbf{y}|\mathbf{y}')B(\mathbf{y}')n(\mathbf{y}',t),$$

where

- $\mathbf{y} = (x, \nu)$ for cells of size (or *copy number*) x and single cell growth rate ν
- $B(\mathbf{y})$ division rate
- Factor 2 represents the number of progeny per cell division
- $\Sigma(\mathbf{y}|\mathbf{y}')$ probability of daughter to be in state $\mathbf{y}$ given the mother cell is in state $\mathbf{y}'$

A particular case : symmetric division at constant single cell growth rate

$$\Sigma(\mathbf{y}|\mathbf{y}') = \delta(\nu - \nu')\delta(x - x'/2)$$

- **Normalisation** $$\int d\mathbf{y}\Sigma(\mathbf{y}|\mathbf{y}') = 1$$ and $$p(\mathbf{y},t) = \frac{n(\mathbf{y},t)}{N(t)}$$

  Total population $N(t) = \int d\mathbf{y} n(\mathbf{y},t)$ and total volume $V(t) = \int d\mathbf{y} x n(\mathbf{y},t)$

- Growth rate of the population $\Lambda_p(t) = \frac{\dot{N}}{N}$ and of the volume $\Lambda_V(t) = \frac{\dot{V}}{V}$

  In general $$\Lambda_V(t) = \Lambda_P(t) + \frac{d}{dt}\ln\int \mathrm{d}\mathbf{y} x p(\mathbf{y},t)$$

- **In a steady state** $$\lim_{t\to\infty}\Lambda_P(t) = \lim_{t\to\infty}\Lambda_V(t) = \Lambda$$

- **For a lineage** similar equation for $p(\mathbf{y},t)$ as for $n(\mathbf{y},t)$ but with no factor 2

First fluctuation relation (FR) to link both levels

Cell trajectory $\{\mathbf{y}\} = \{\mathbf{y}\}_0^t$

Dynamical activity: $W_t(\{\mathbf{y}\}) = \int_0^t dt' B(\mathbf{y}(t'))$

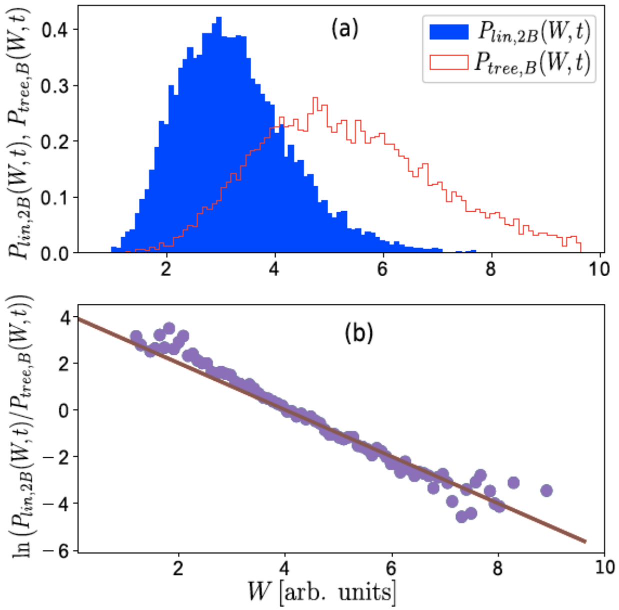
Time averaged population growth rate $\Lambda_t = \frac{1}{t} \ln \frac{N(t)}{N(0)}$

- First FR :

$$\langle A(\{\mathbf{y}\})\rangle_{tree,B} = \langle A(\{\mathbf{y}\}) e^{W_t(\{\mathbf{y}\}) - t\Lambda_t}\rangle_{lin,2B}$$

- Crooks like relation G. Crooks 2000

$$P_{tree,B}(W,t) = P_{lin,2B}(W,t) e^{W - t\Lambda_t}$$

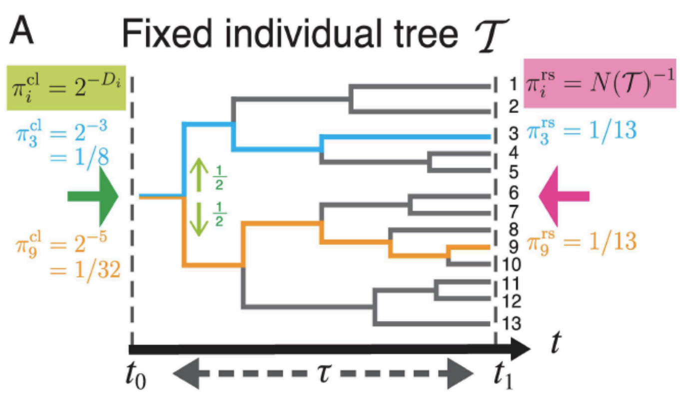


A second FR holds at the same division rate

$$P^{tree}(\{\mathbf{y}\}) = P^{lin}(\{\mathbf{y}\}) e^{K \ln 2 - t\Lambda_t}$$

Here $K = K(\{\mathbf{y}\})$ counts the number of divisions, related to fitness

There is a statistical bias present in choosing one individual uniformly in a population as opposed to following a lineage



Chronological probability distribution

forward in time = $P^{tree}(\{\mathbf{y}\})$

Retrospective probability distribution

backward in time = $P^{lin}(\{\mathbf{y}\})$

T. Nozoe et al. 2017
T. J. Kobayashi et al. 2015

Consequences for mean generation times

- In the long time limit $t/\langle K\rangle \to \langle\tau\rangle$ and $\Lambda_t \to \Lambda$

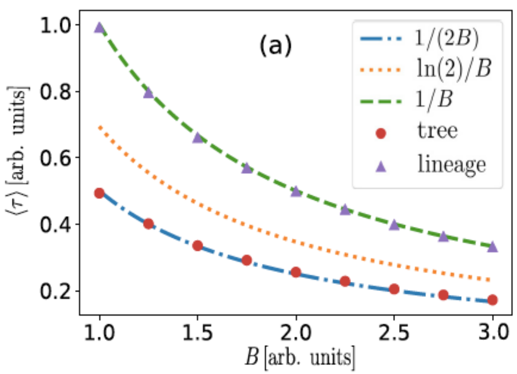
then

$$\langle\tau\rangle_{tree} \leq T_d \leq \langle\tau\rangle_{lin}$$

with $T_d = \ln 2/\Lambda$ the population doubling time

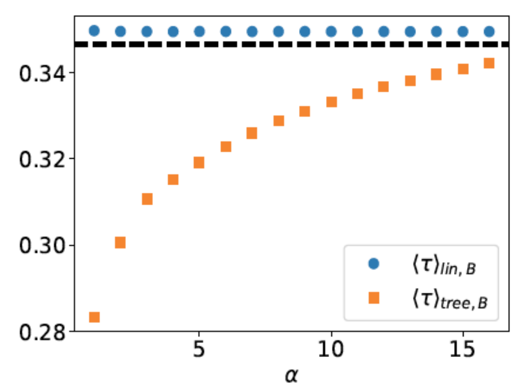
For constant division rate

$$B = \Lambda$$



For non-constant division rate

$$B(x,\nu) = \nu x^{\alpha}$$

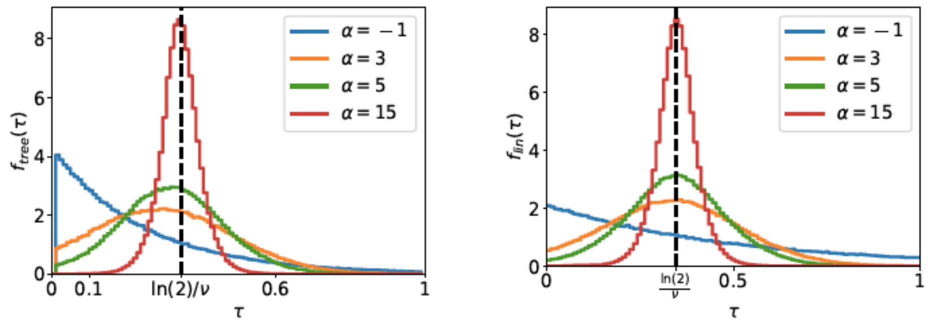


Generation times distributions

- **For constant division rate** $f_{lin,B}(\tau) = B \cdot e^{-B\tau}$

$$f_{\text{tree},B}(\tau) = f_{\text{lin},2B}(\tau)$$

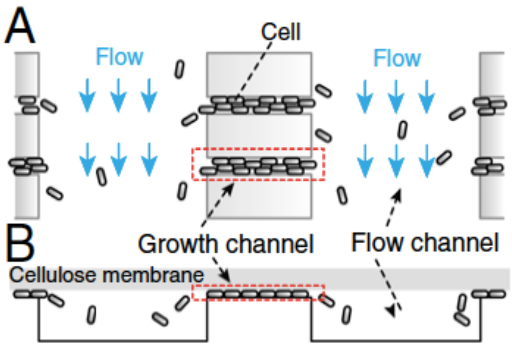
- **For non-constant division rate** $B(x,\nu) = \nu x^{\alpha+1}$

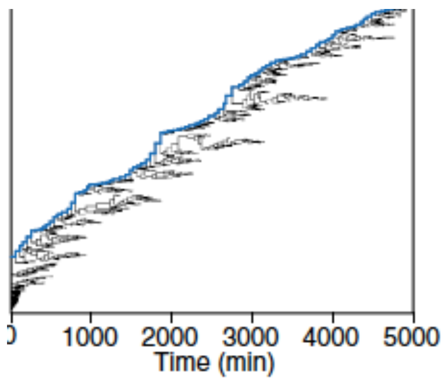


Distributions become peaked near T_d as α increases

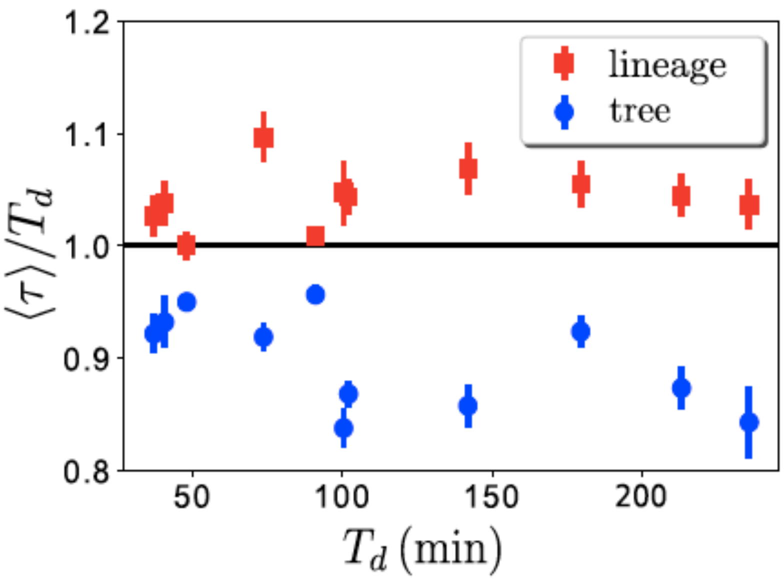
For the tree distribution, the mean is always less than T_d

Experimental tests





M. Hashimoto et al. 2015



- Both inequalities are verified in this experiment
- Interpretation used in the paper : an age model with negligible mother-daughter correlations

Conclusions

- **A fluctuation relation captures a statistical bias present in the statistics of the branched tree when compared to lineage statistics**

- **Inequalities for generation times are satisfied by age models without mother-daughter correlations *and* by size models.**

- **Fluctuations of single cell growth rate have an impact on the population growth rate**

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