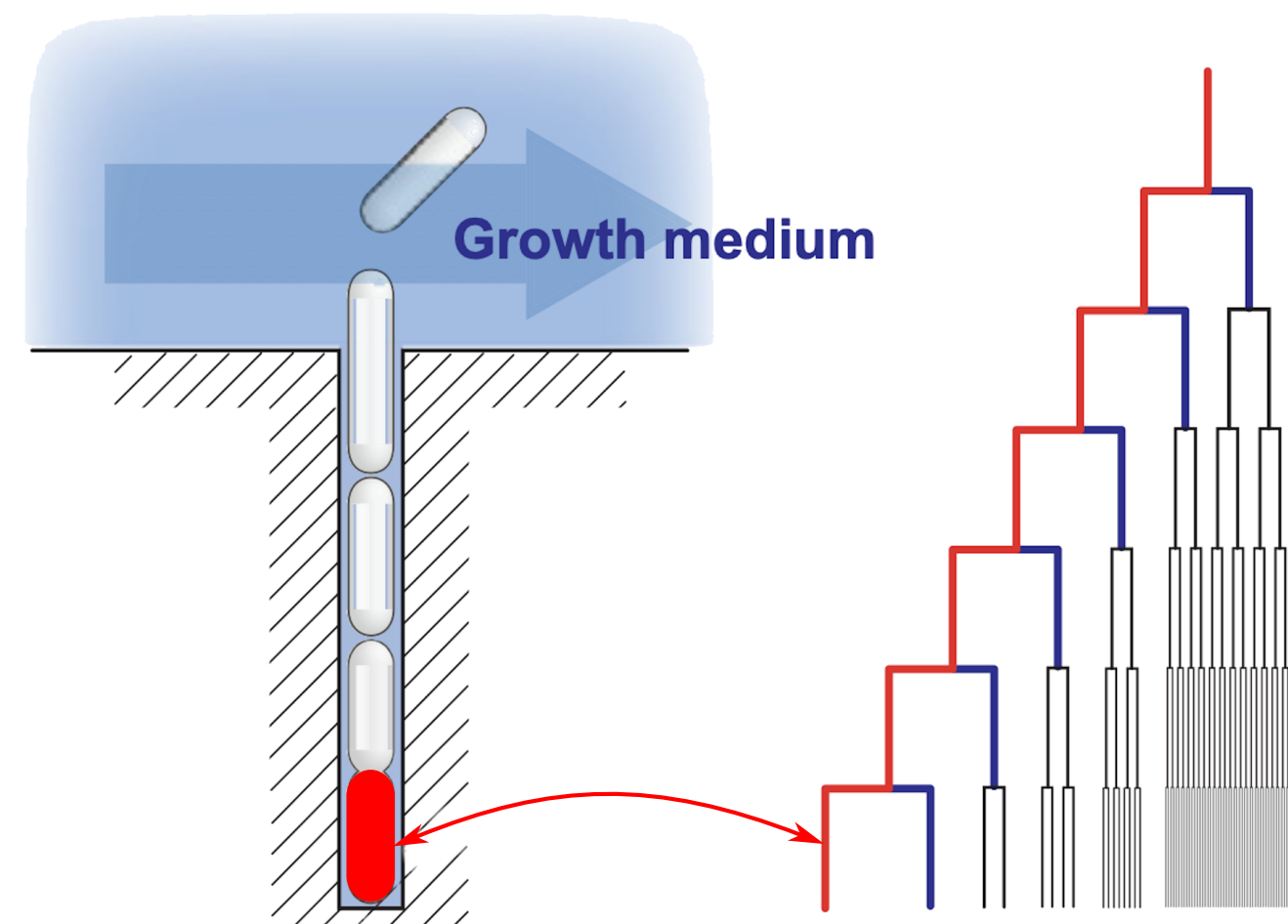


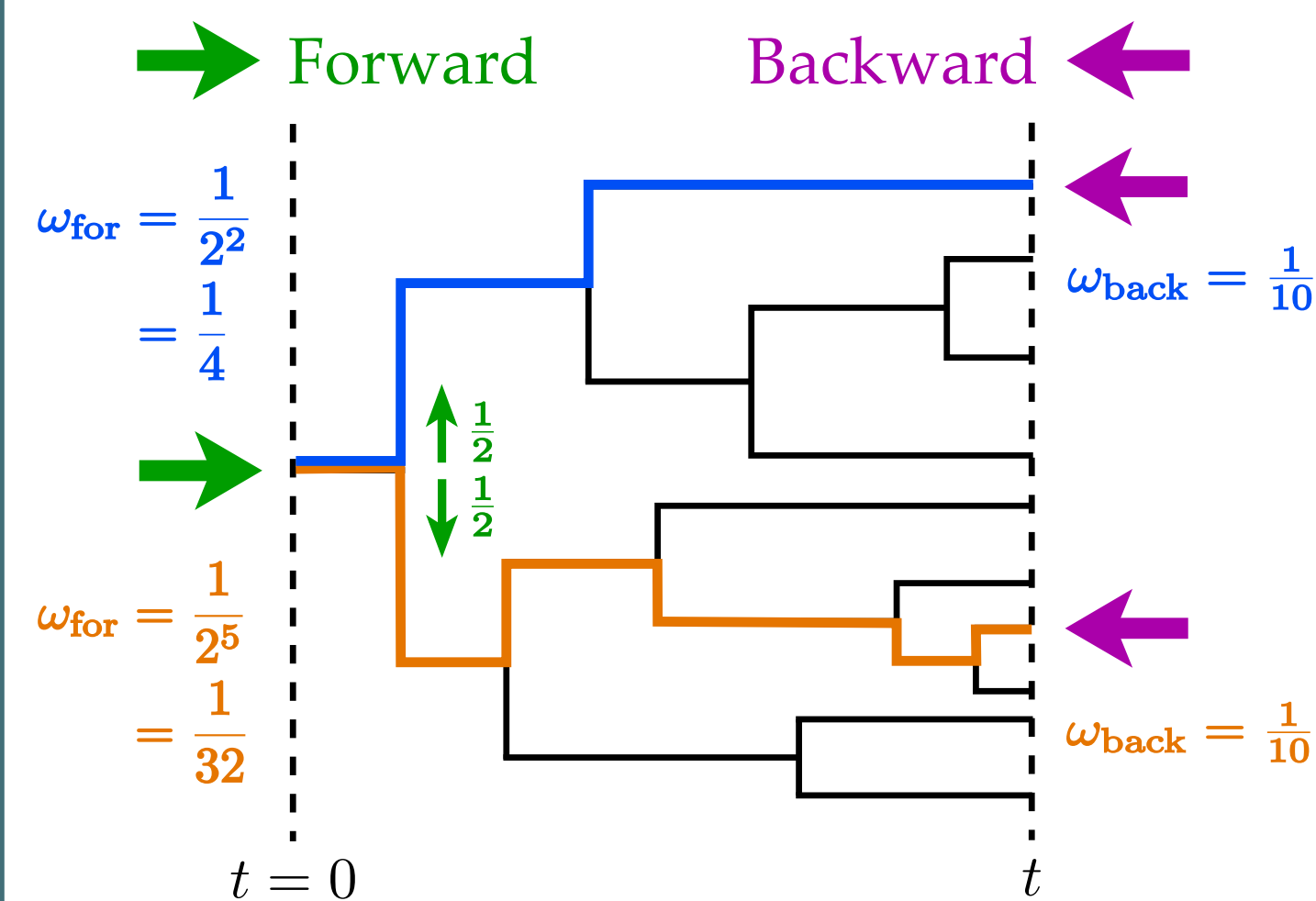
Abstract

Experiments on growing cells can be carried out either in bulk (population experiments) or in confined geometries that constrain the growth of the colony (e.g. single-lineage experiments). These two setups generate different statistics, as cells with high reproductive success are over-represented in the population, while no such effect occurs in single-lineage experiments. This bias has thus been proposed as a model-independent measure of fitness and selection [1]. We study this bias, akin to fluctuation theorems in stochastic thermodynamics, and derive a series of results analogous to Jarzynski equality, the second law, and fluctuation-dissipation theorems far from equilibrium, which establish general principles of evolution.

Single-lineage experiments [2]



Population experiments [1]



Backward sampling: $\omega_{\text{back}}(l) = 1/N(t)$.

→ Over-represents lineages that divided more than average

Forward sampling: $\omega_{\text{for}}(l) = 2^{-K(l)}/N_0$.

→ Cancels the effect of selection of successful lineages

→ Reproduces statistics from single lineage experiments

Fluctuation theorem and consequences [4]

The forward-backward (or lineage-population) bias is expressed as a **fluctuation theorem**:

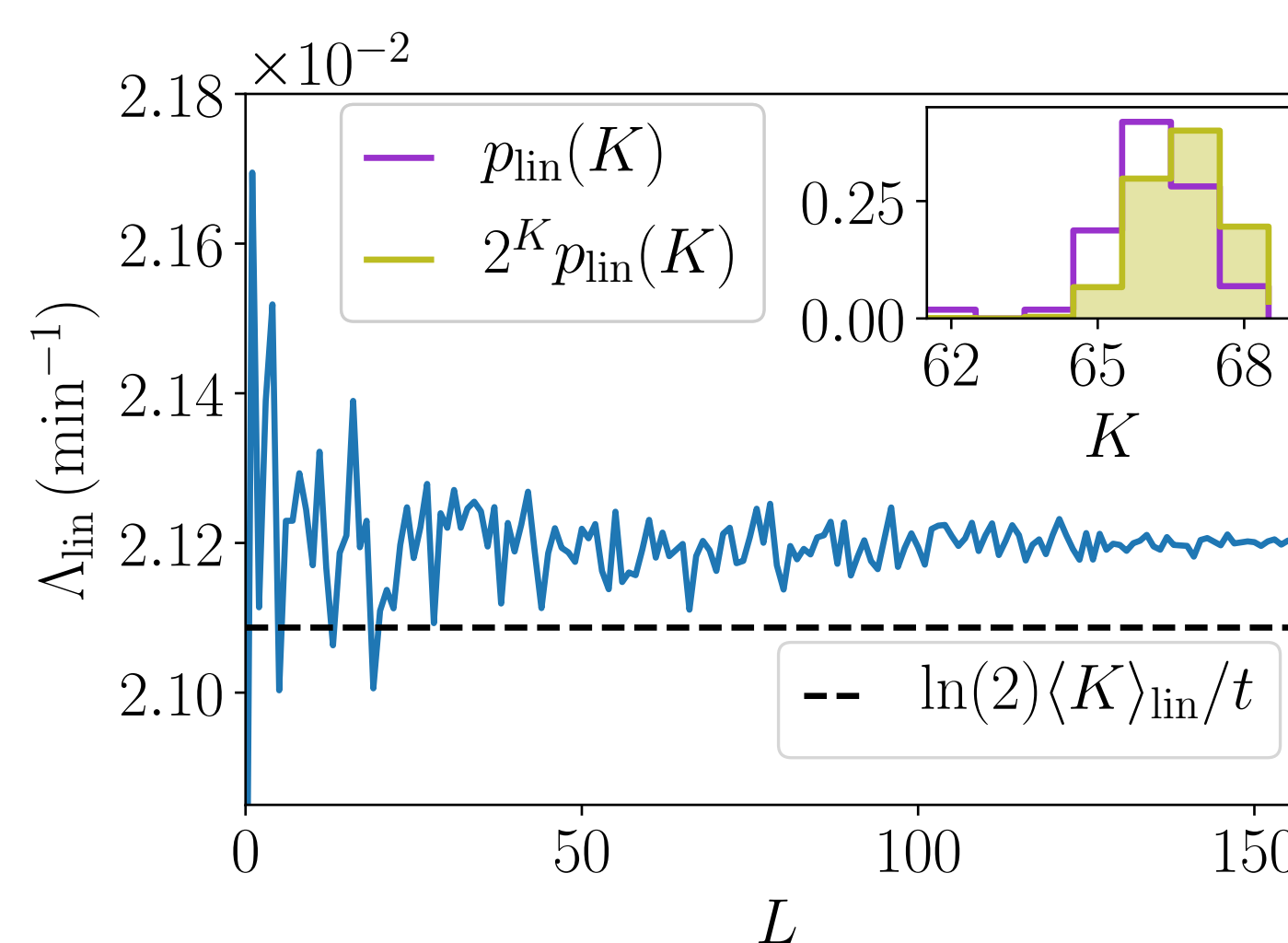
$$p_{\text{back}}(K, t) = p_{\text{for}}(K, t) e^{K \ln 2 - t \Lambda_t} \quad \text{with} \quad \Lambda_t = \frac{1}{t} \ln \frac{N(t)}{N_0} : \text{population growth rate}$$

Jarzynski equality

$$\Lambda_t = \frac{1}{t} \ln \langle 2^K \rangle_{\text{for}}$$

Population growth rate estimator from the statistics of L independent single lineages [3]:

$$\Lambda_{\text{lin}} = \frac{1}{t} \ln \left[\frac{1}{L} \sum_{i=1}^L 2^{K_i} \right]$$



Second law

$$\frac{t}{\langle K \rangle_{\text{back}}} \leq \frac{\ln 2}{\Lambda_t} \leq \frac{t}{\langle K \rangle_{\text{for}}}$$

When $t \rightarrow \infty$ (+ dynamical conditions), inequality between mean generation times and population doubling time :

$$\langle \tau \rangle_{\text{back}} \leq T_d \leq \langle \tau \rangle_{\text{for}}$$

Cells divide faster in populations!

Fitness and selection [1]

Fitness landscape: captures correlations between a cell trait s and the number of divisions:

$$h_t(s) = \Lambda_t + \frac{1}{t} \ln \left[\frac{p_{\text{back}}(s, t)}{p_{\text{for}}(s, t)} \right]$$

Strength of selection: change in mean fitness between the ensembles with (backward) and without (forward) selection:

$$\Pi_S = \langle h_t(s) \rangle_{\text{back}} - \langle h_t(s) \rangle_{\text{for}}$$

Fluctuation-response relations for the selection strength [5]

The strength of selection is bounded by the fluctuations in fitness ($\sigma(h_t)$) and by the χ^2 distance:

$$\Pi_S \leq \min \left[\sigma_{\text{for}}(h_t) \chi^2(p_{\text{back}}; p_{\text{for}}), \sigma_{\text{back}}(h_t) \chi^2(p_{\text{for}}; p_{\text{back}}) \right]$$

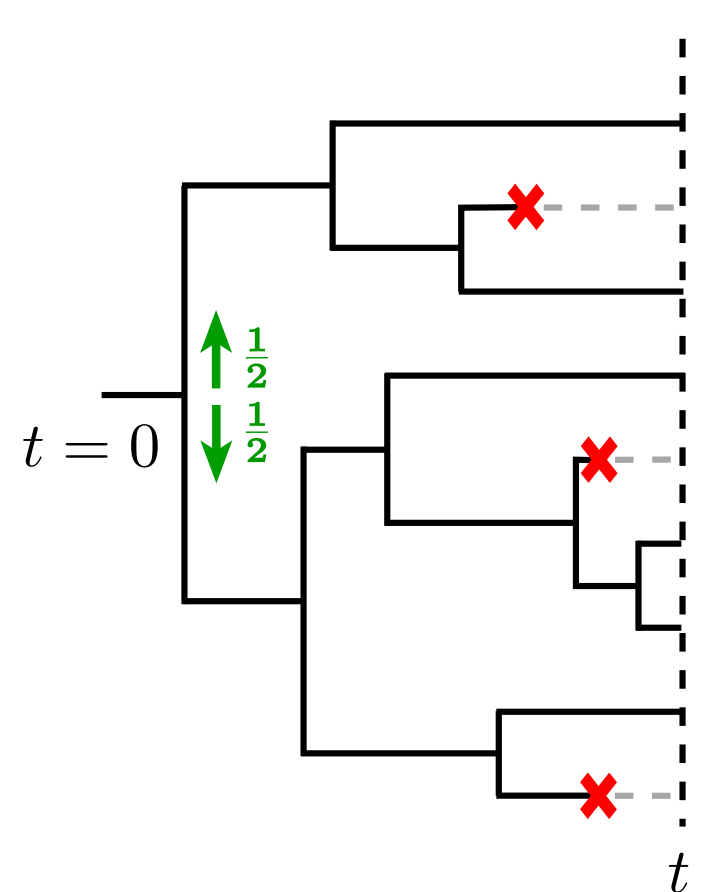
Case of equality in the limit of small selection:

$$\Pi_S \sim t \sigma^2(h_t) \quad (// \text{ Fisher's theorem of natural selection})$$

A lower bound depending on the fluctuations in fitness landscape is also derived:

$$\Pi_S \geq \mathcal{L}_S(\sigma_{\text{for}}(h_t), \sigma_{\text{back}}(h_t))$$

Lineage statistics in presence of cell death [7]



If some lineages die before time t :

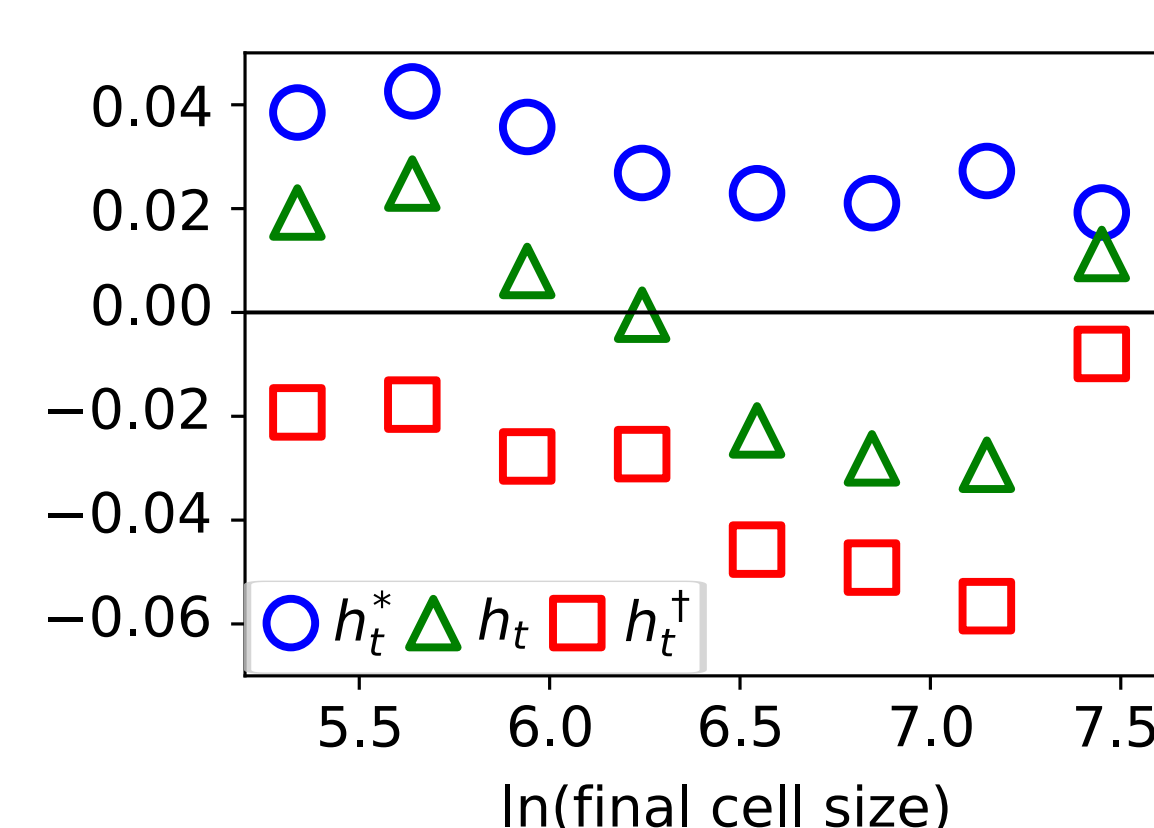
$$p_{\text{for}}^*(s, t) = p_{\text{for}}(s, t | \text{survival})$$

we separate the effects:

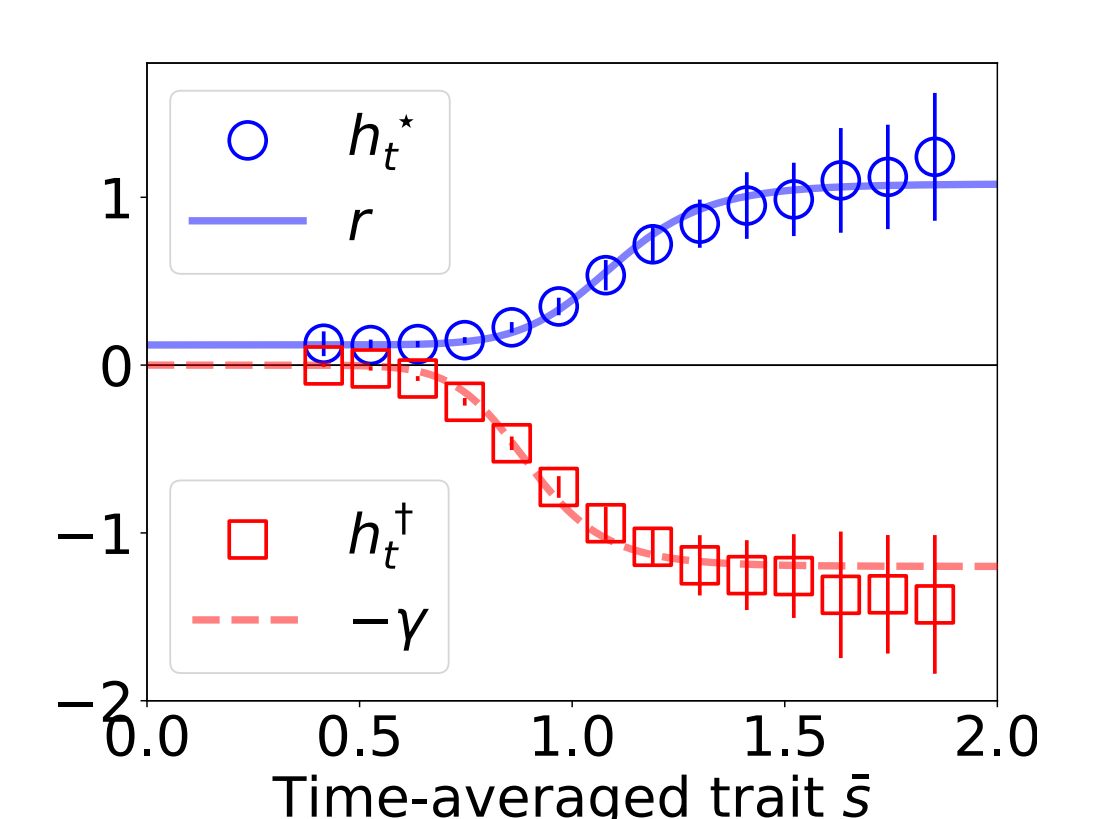
$$h_t^*(s) = \frac{1}{t} \ln \left[\frac{p_{\text{back}}(s, t)}{p_{\text{for}}^*(s, t)} \right] : \text{Fitness landscape}$$

$$h_t^\dagger(s) = \frac{1}{t} \ln \left[\frac{p_{\text{for}}^*(s, t)}{p_{\text{for}}(s, t)} \right] : \text{Survivor bias}$$

Disentangling fitness and survival in antibiotics data [6]:



Inferring the division rate $r(s)$ and death rate $\gamma(s)$ (for slowly fluctuating traits):



References

- [1] T. Nozoe et al. *PLoS Genet.* (2017). [2] P. Wang et al. *Curr. Biol.* (2010). [3] Y. Tanouchi et al. *Sci. Data* (2017). [4] A. Genthon et al. *Sci. Rep.* (2020). [5] A. Genthon et al. *Phys. Rev. Research* (2021). [6] Y. Wakamoto et al. *Science* (2013). [7] A. Genthon et al. *arXiv:2305.05406* (2023).