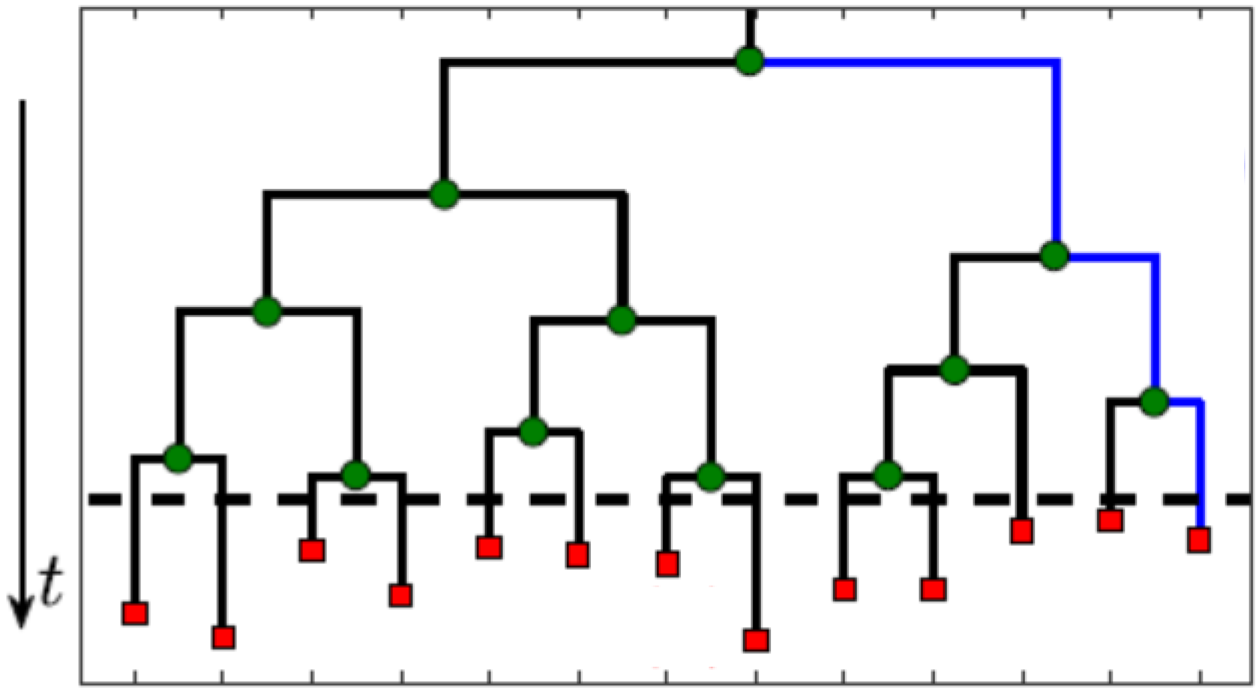
How do variability&size control affect population growth?

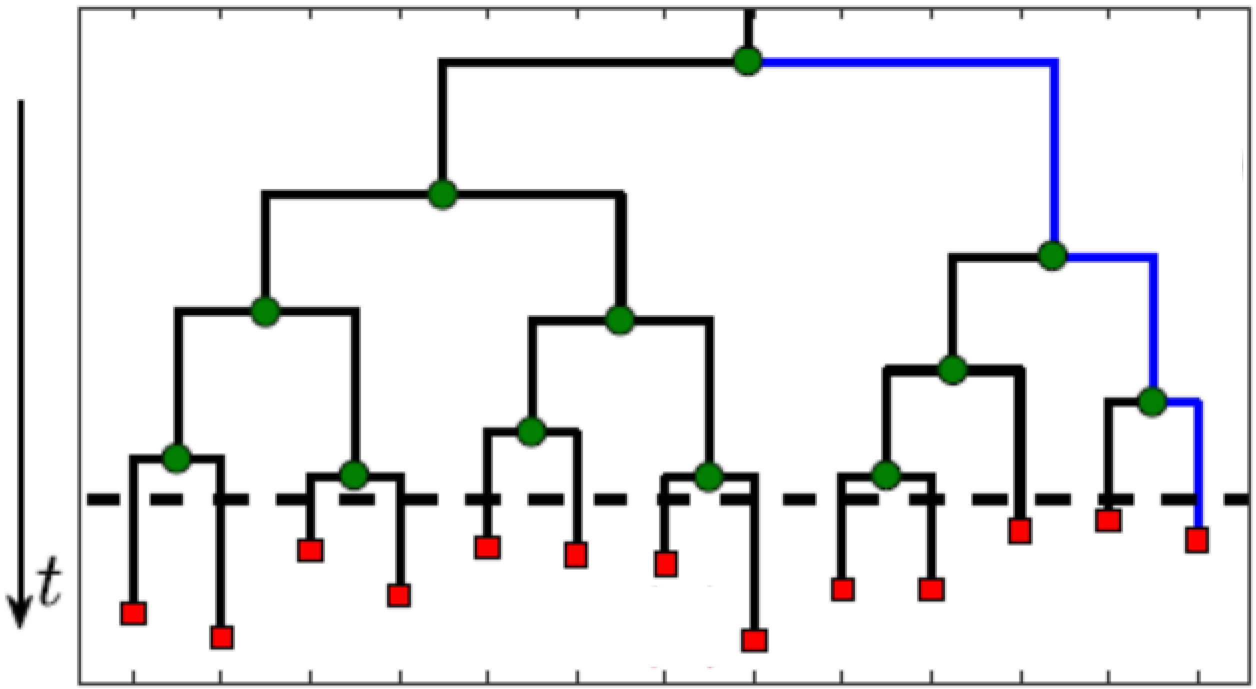


Are "adders" optimizing population growth?

$$N \propto e^{\Lambda_p t}$$

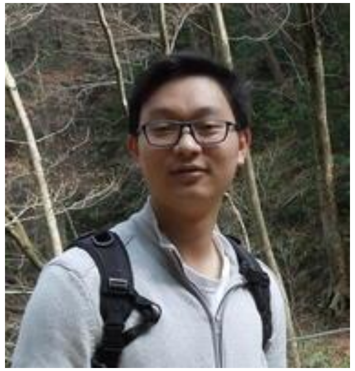
- Assume here a constant environment, and will not consider "bet-hedging" scenarios
  e.g., Balaban et al., Science (2004)

How do variability&size control affect population growth?



Are "adders" optimizing population growth?

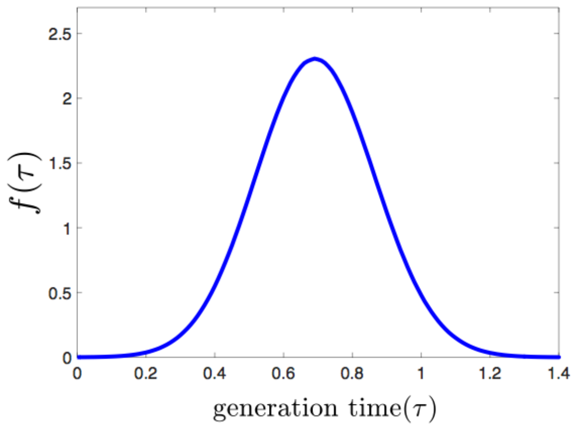
$$N \propto e^{\Lambda_p t}$$



Jie Lin

Ethan Levien

Single-cell variability: *Gaining* from noise?



independent generation time model

$$2\int_0^\infty e^{-\Lambda_p \tau} f(\tau)\,d\tau = 1$$

Powell, Microbiology, 1956

Key Assumption:
no correlation in mother-daughter generation time

Result: variability enhances the population growth

Noise-driven growth rate gain in clonal cellular populations *PNAS, 2016*

Mikihiro Hashimoto[a], Takashi Nozoe[a], Hidenori Nakaoka[a], Reiko Okura[a], Sayo Akiyoshi[a], Kunihiko Kaneko[a,b], Edo Kussell[c,d], and Yuichi Wakamoto[a,b,1]

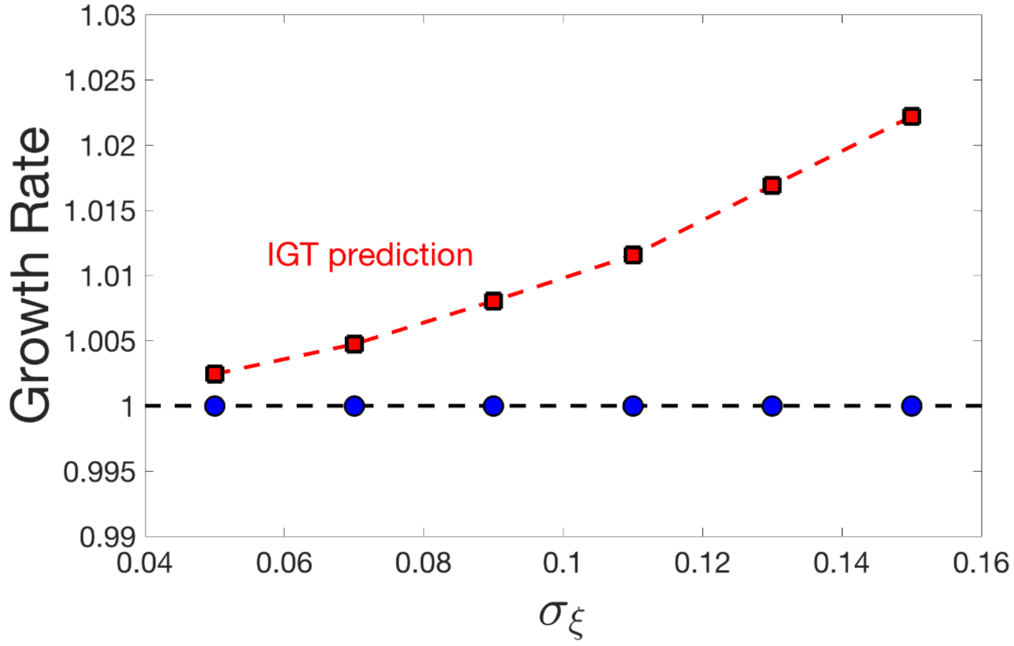
Noise and Epigenetic Inheritance of Single-Cell Division Times Influence Population Fitness *Current Biology, 2016*

Bram Cerulus, Aaron M. New,
Ksenia Pougach, Kevin J. Verstrepen

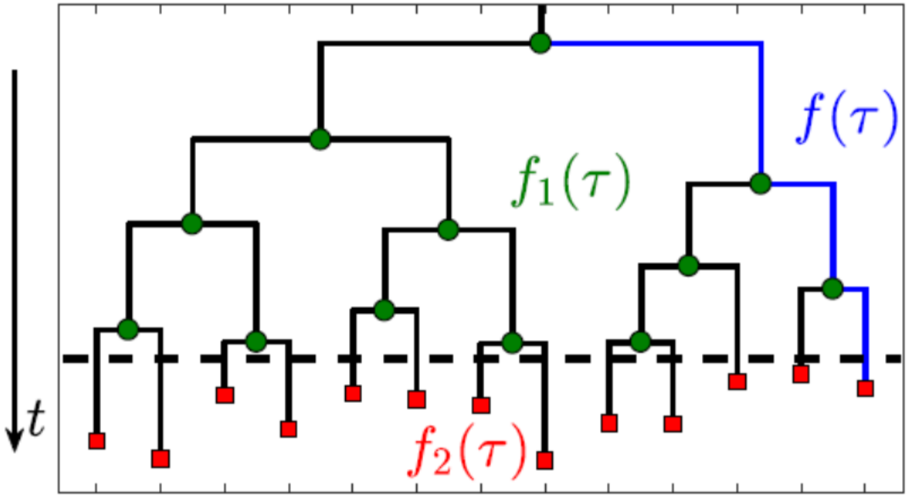
Simplified scenario: no growth rate variability

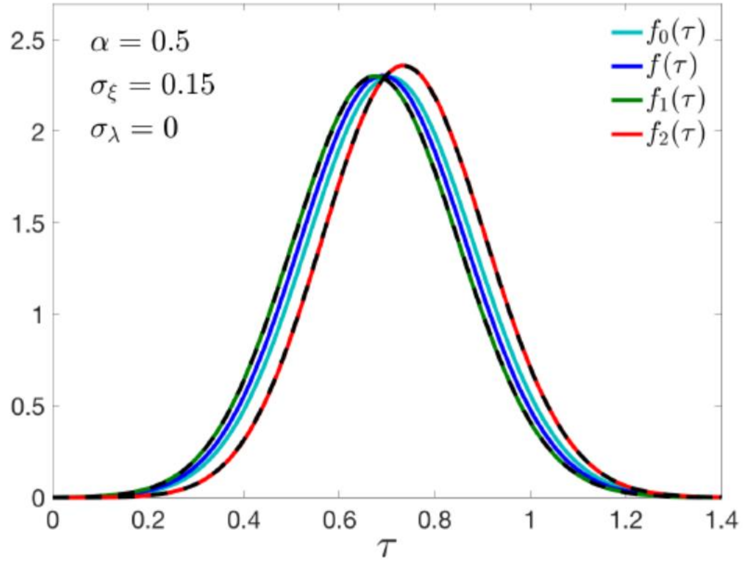
Cell size is regulated → the population growth rate = the volume growth rate

$$\frac{dV}{dt} = \sum_{i=1}^{N(t)} \frac{dv_i}{dt} = \sum_{i=1}^{N(t)} \lambda_0 v_i = \lambda_0 V \qquad \Lambda_p = \Lambda_v = \lambda_0$$



Statistics on lineage trees





Four distinct statistics:
"Leaf" cells, "Branch" cells, Lineage and Tree

$$f_0 = \frac{f_1 + f_2}{2}$$

$$f_1(\tau) = 2e^{-\Lambda_p \tau} f_0(\tau)$$

$$2\int_0^\infty e^{-\Lambda_p \tau} f_0(\tau) d\tau = 1$$

$$f_2(\tau) = 2(1 - e^{-\Lambda_p \tau}) f_0(\tau)$$

Lin and Amir, *Cell Systems* (2017); Levien, Kondev and Amir, Biorxiv:680066 (2019)
See also: Lebowitz and Rubinow, *Journal of Mathematical Biology* (1974)

Facebook of the Dead

When, if ever, will Facebook contain more profiles of dead people than of living ones?

Emily Dunham

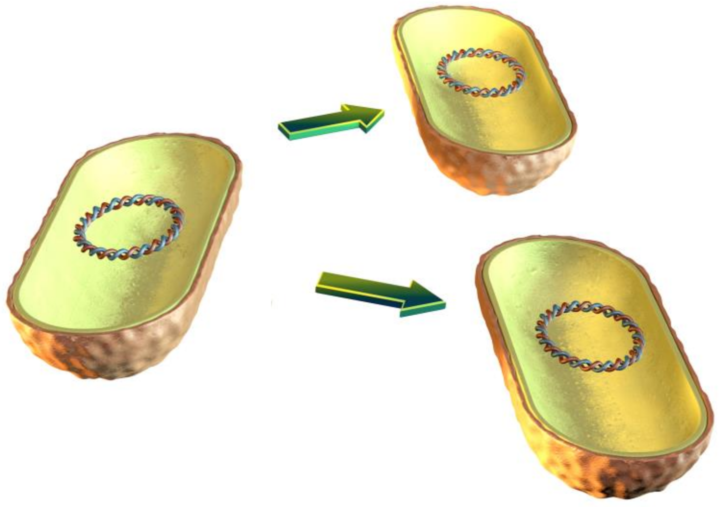
Either the 2060s or the 2130s.

Growth rate and doubling time variability

- **Two sources of noise**

σ_T = affects **generation time** noise

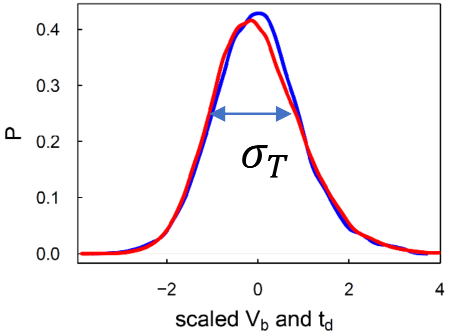
σ_λ = **growth rate** variability

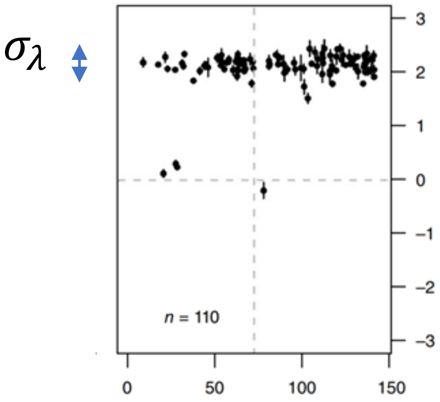


- Growth rate fluctuations are often small: CV of 6-8 %

- Generation time variability : CV of 20-30%

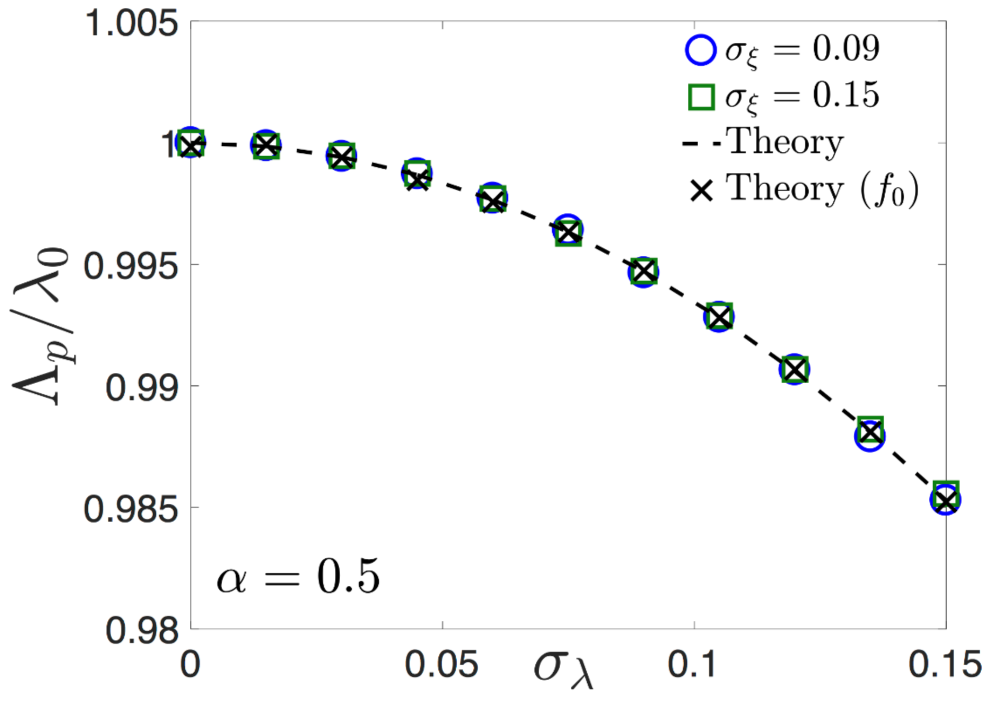
$$\Lambda_p(\sigma_t, \sigma_\lambda, \alpha) \approx \Lambda_p(\#, \sigma_\lambda, \#)$$
(as long as size is controlled!)

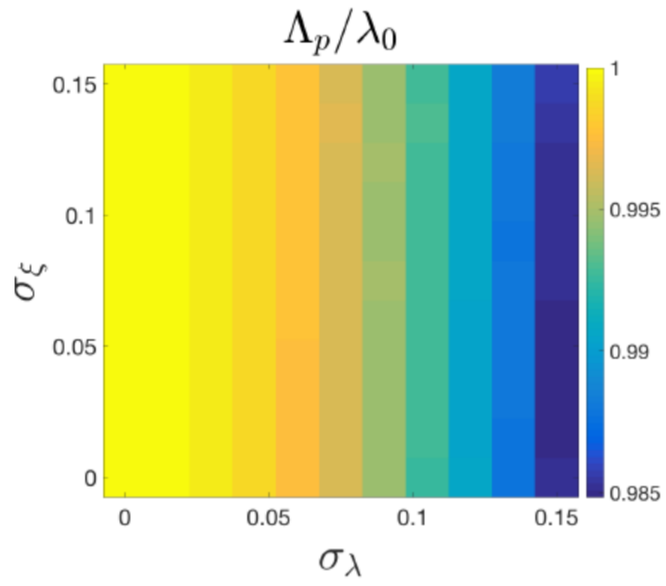


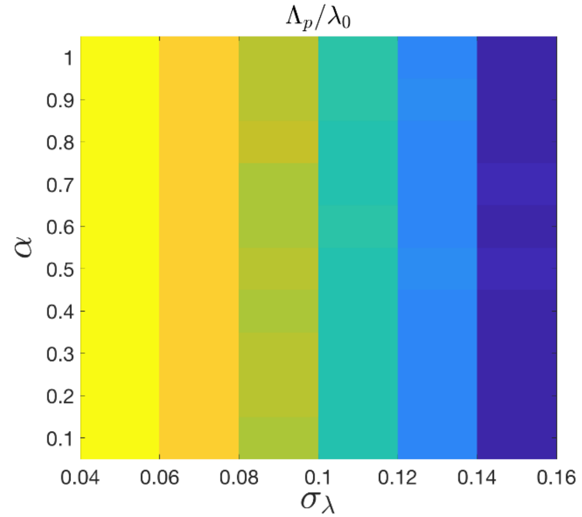


Only stochasticity in growth rate matters

$$\Lambda_p(\sigma_\lambda) = \lambda_0\{1 - (1 - \frac{\ln 2}{2})(\frac{\sigma_\lambda}{\lambda_0})^2\}$$



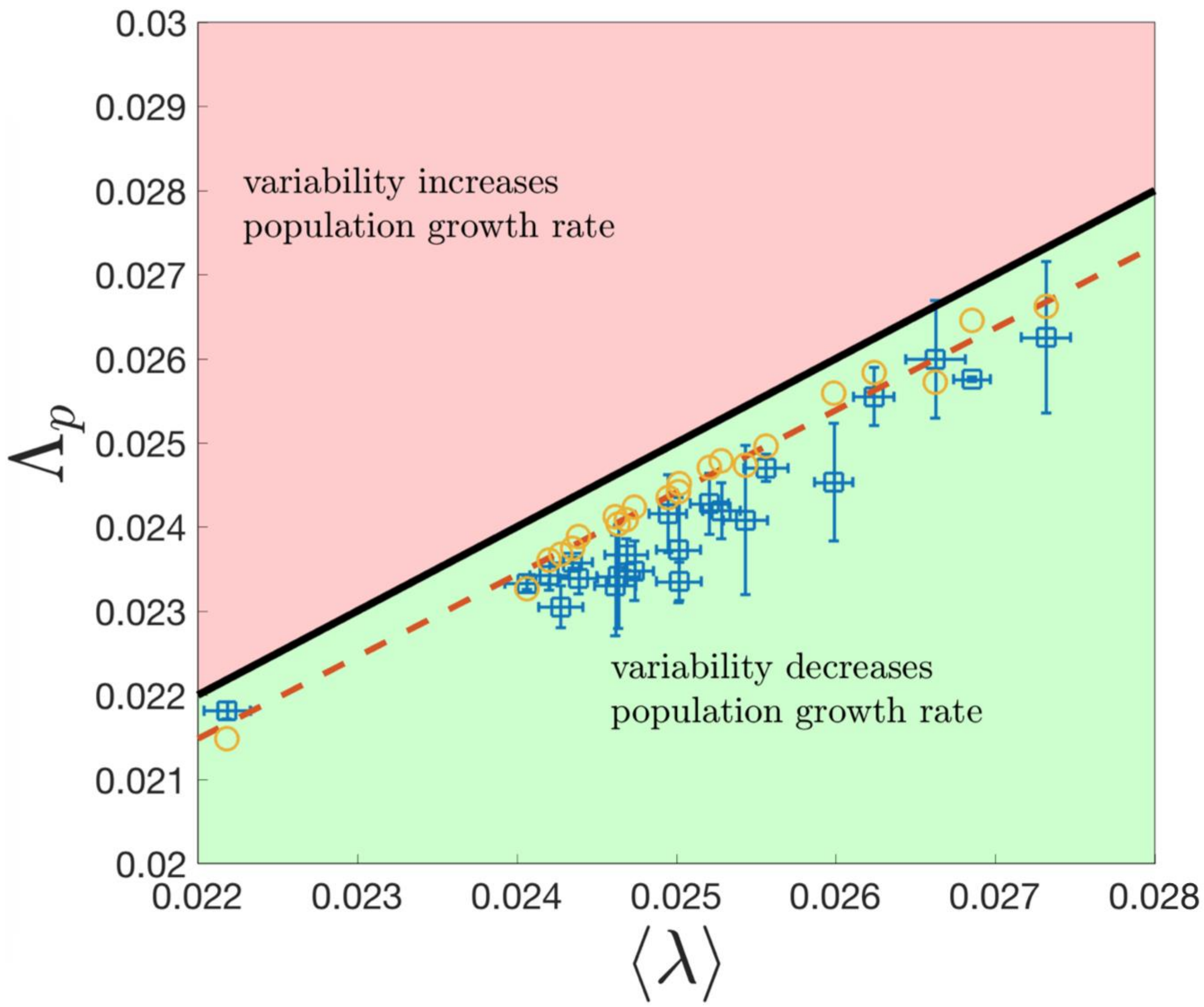




Lin and Amir, Cell Systems (2017)

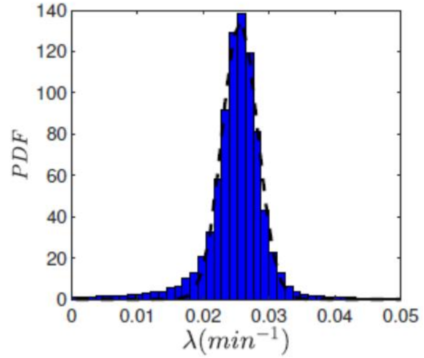
Lin and Amir, **arXiv: 1806.02818 (2018)**

Can we test this?

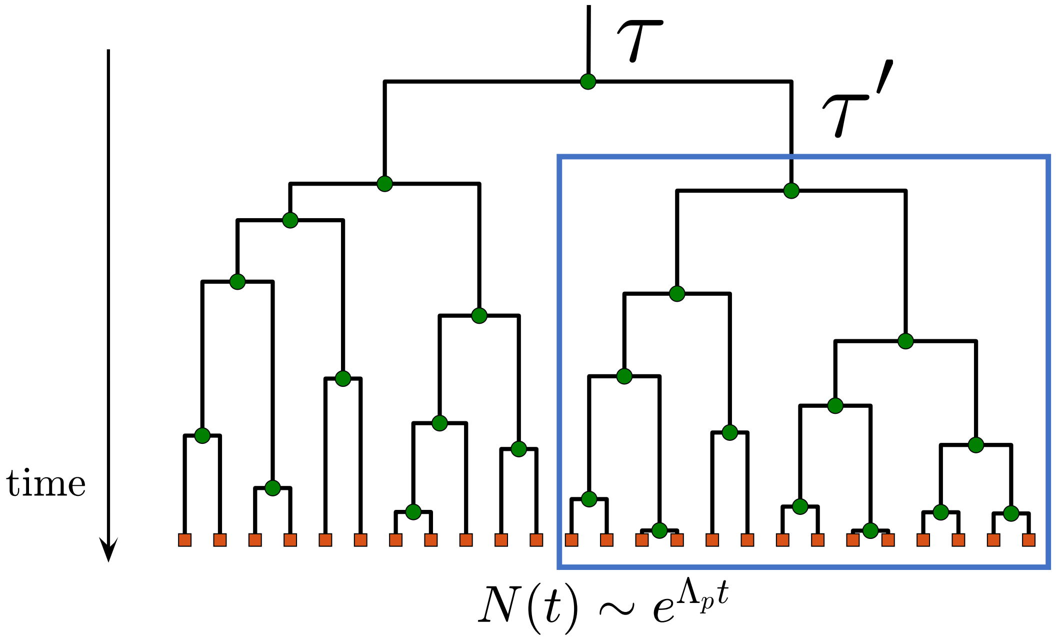


Lin and Amir, Cell Systems (2017)

Stewart et al.,
Plos Biology (2005).



Generalizations: growth rate correlations



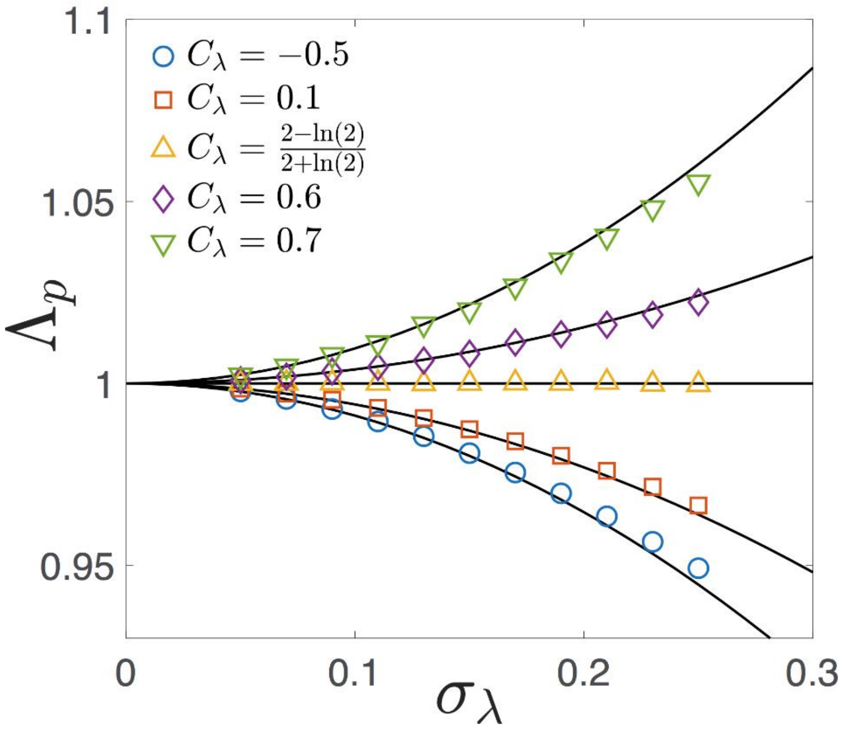
Conditional probability distribution

$$h(\tau'|\tau)$$

$$N(t) = A(\tau)e^{\Lambda_p t} \Longrightarrow A(\tau)e^{\Lambda_p t} = 2\int_0^\infty A(\tau')e^{\Lambda_p (t-\tau)} h(\tau'|\tau)d\tau'$$

Lin and Amir, **arXiv: 1806.02818**

Single-cell variability: *Gaining/Losing* from noise

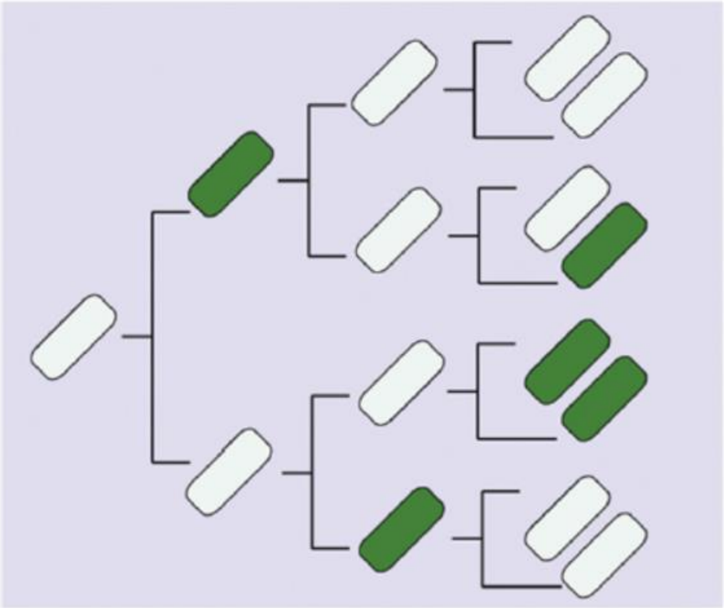


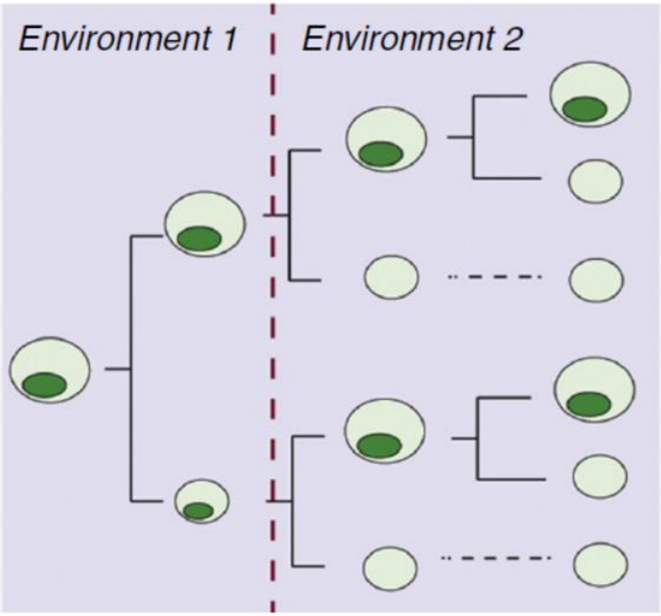
$$\Lambda_p = 1 - \left(1 - \frac{\ln(2)}{2}\frac{1+a}{1-a}\right)\sigma_\lambda^2$$

$$a_c = \frac{2-\ln(2)}{2+\ln(2)} \approx 0.5$$

Lin and Amir, **arXiv: 1806.02818**

Single-cell variability: origins and fitness advantage





Stochastic

e.g. bacterial persistence
Gene expression patterns
Plasmids

<u>Generation time and cell size</u>

Deterministic

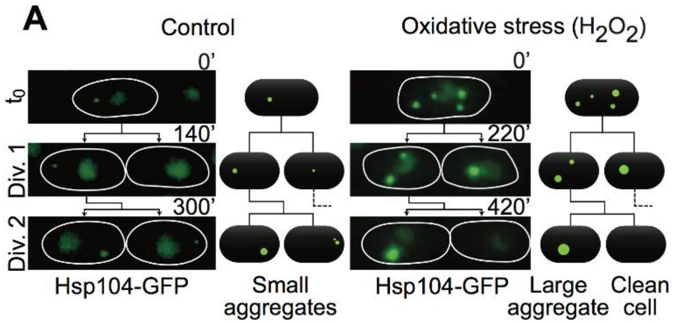
e.g. aging in yeast
Partitioning of efflux pumps in bacteria
Growth of *M. tuberculosis*

Lin, Min and Amir, *Physical Review Letters* (2019)

Martins and Locke, Current Opinion in Microbiology (2015)

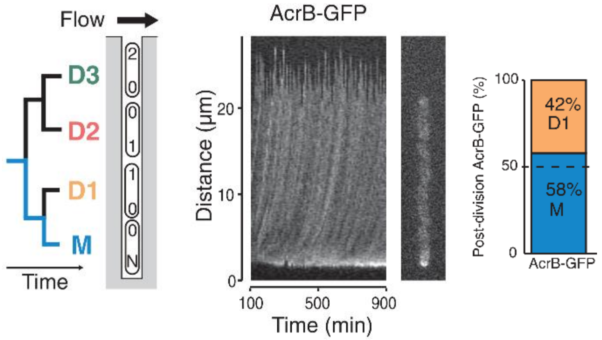
Another mechanism of phenotypic heterogeneity: Asymmetric protein segregation

Deleterious proteins



Coelho et al., Current Biology 2013

Beneficial proteins



Bergmiller et al., Science 2017

Cell Systems
Article

CellPress

Asymmetric Damage Segregation Constitutes an Emergent Population-Level Stress Response

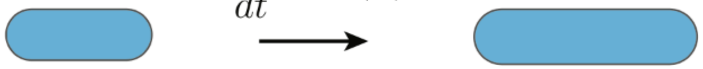
Søren Vedel,[1,2,*] Harry Nunns,[1,3] Andrej Košmrlj,[4] Szabolcs Semsey,[1] and Ala Trusina[1,*]

Under what conditions does asymmetric protein segregation enhance the population fitness?

Mathematical model

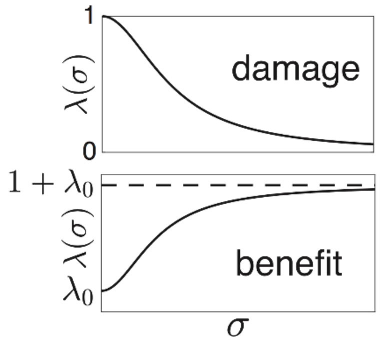
(i) Exponential growth of cell volume

$V_b = 1$ $\qquad \frac{dV}{dt} = \lambda(\sigma)V \qquad$ $V_d = 2$

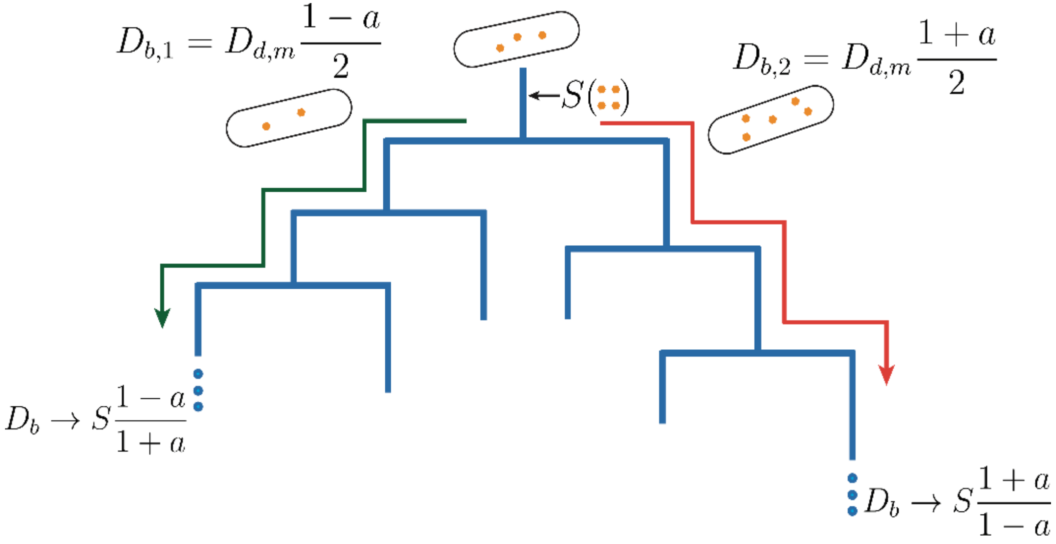


$$\sigma = \frac{D}{V} \qquad D(V) = D_b + S(V - V_b)$$

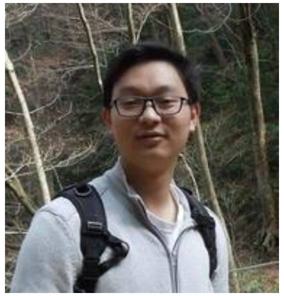
(ii) Protein concentration determines the single-cell growth rate



(iii) Asymmetric segregation of protein



Jiseon Min



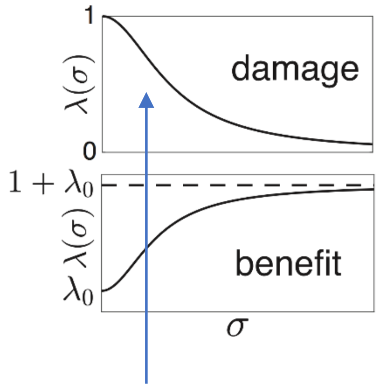
Jie Lin

Lin, Min and Amir, *PRL* (2019)

Solution for small asymmetry:

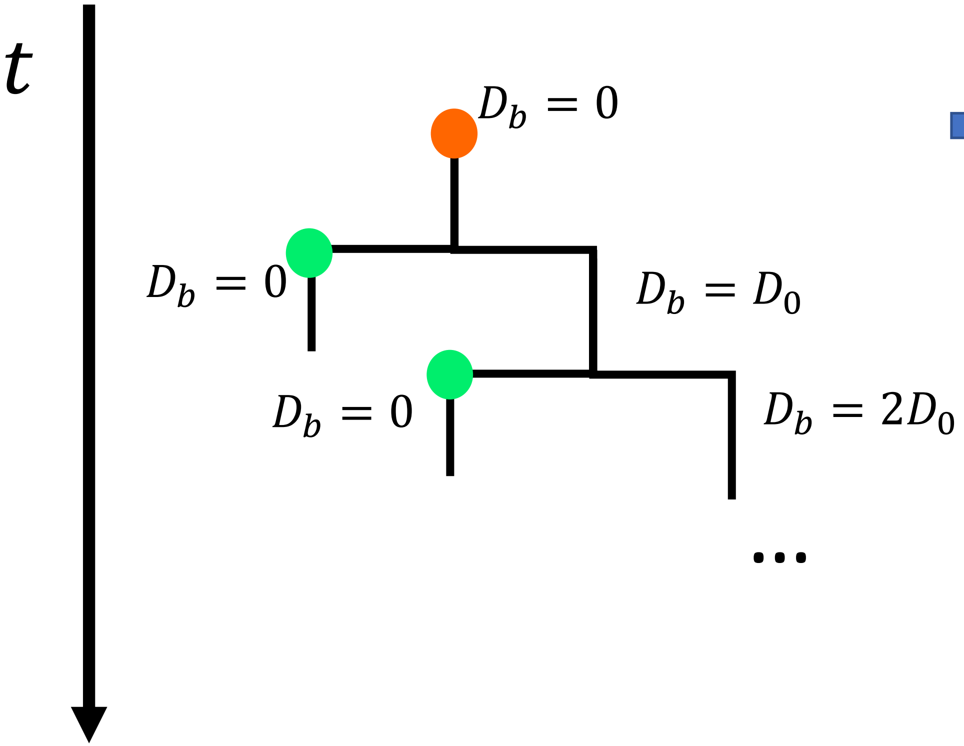
Fitness function:

$$\Lambda_p(a) - \Lambda_p(0) \approx A\,S^2 \frac{\partial\lambda}{\partial\sigma^2}^2\Big|_S a^2 + C_4 a^4$$



Leading term changes sign at the inflection point S_c

Solution for total asymmetry:



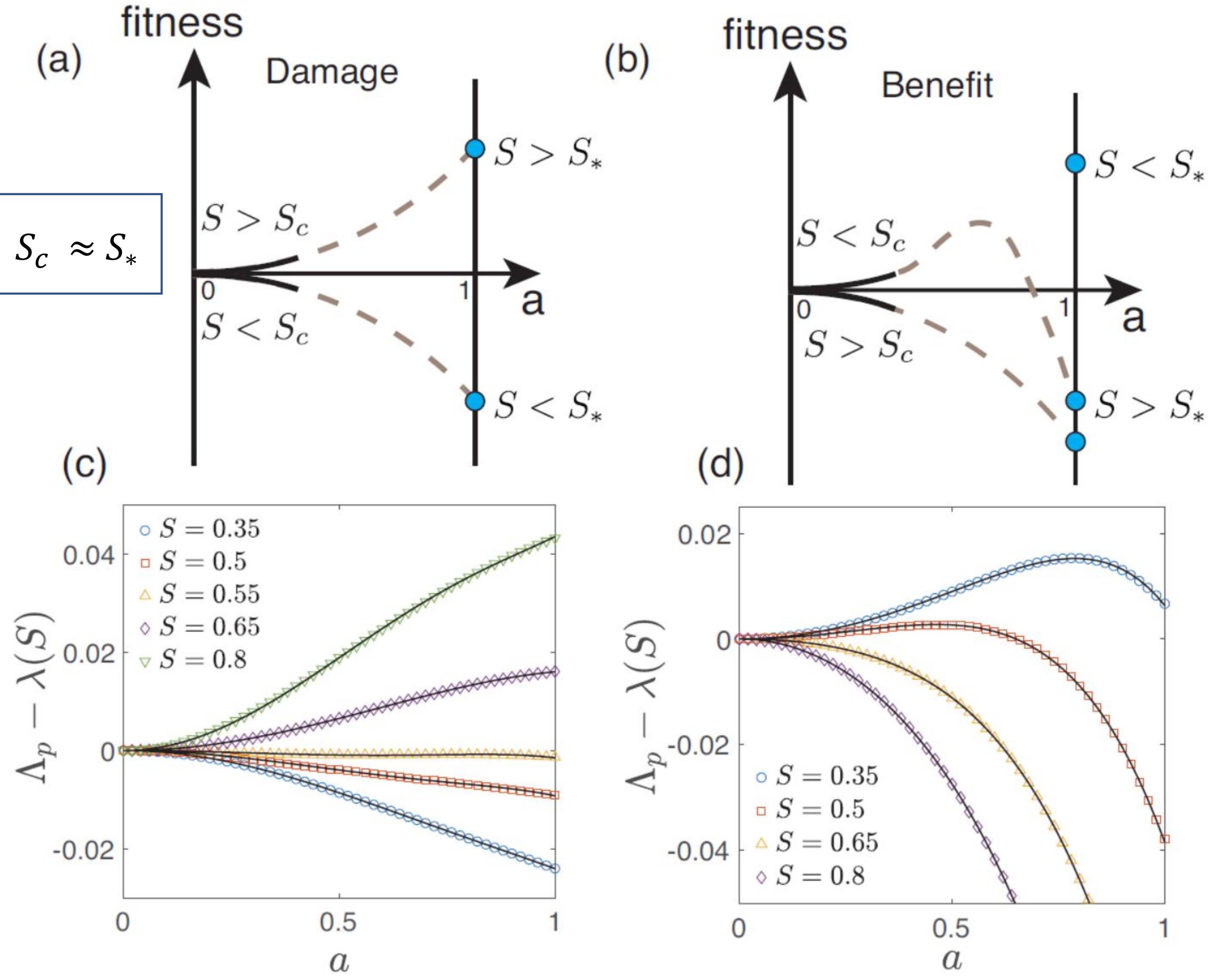
$$\sum_{i=0}^{\infty} \exp\Big(-\Lambda_p \sum_{j=0}^{i} \tau_j\Big) = 1.$$

Totally asymmetric wins over Totally symmetric division at S_*

Damage	*Benefit*
$S_c \approx S_*$	$S_c > S_*$

Graphical interpolation

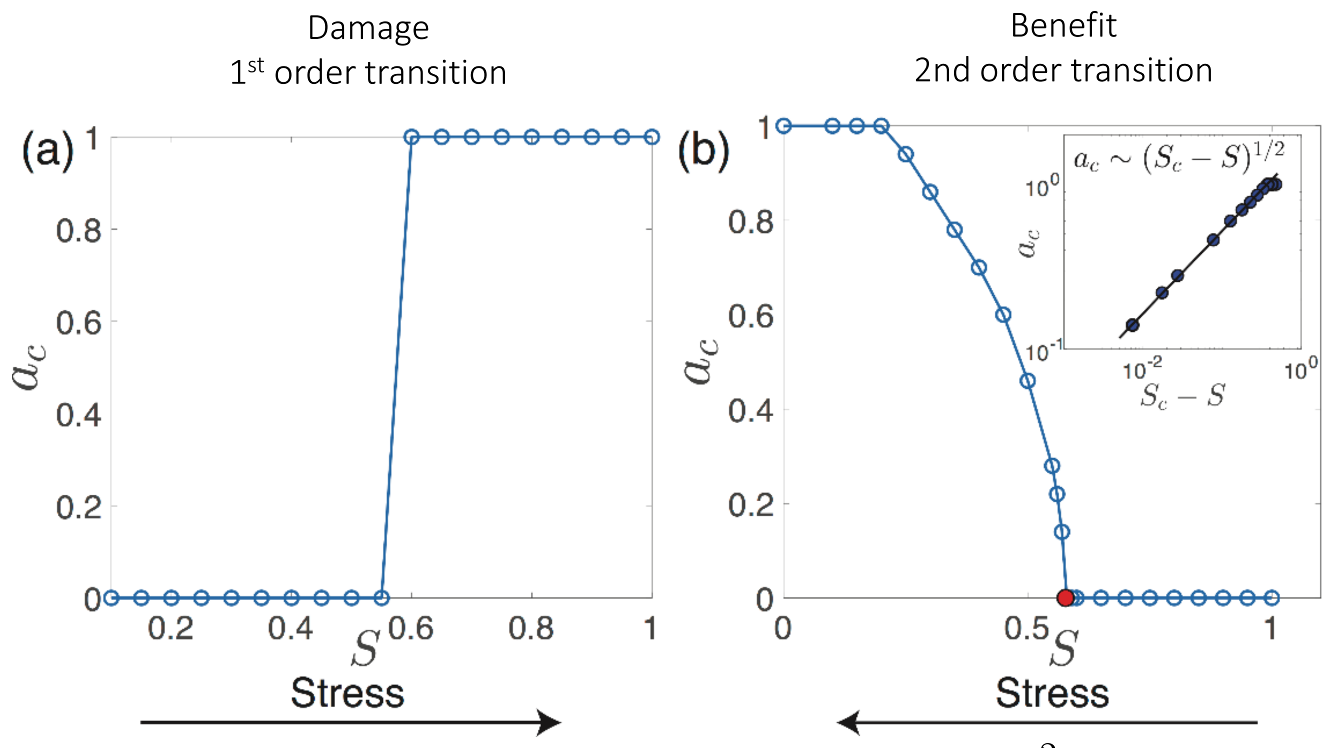
$S_c \approx S_*$



$S_c > S_*$

Result of graphical interpolation: Phase transitions!

- Control parameter: the protein accumulation rate, S
- Order parameter: the optimal asymmetry degree, a_c



Critical point: S_c (the Inflection point of the growth rate function $\left.\frac{d^2\lambda}{d\sigma^2}\right|_{S_c} = 0$)

Acknowledgments

Felix Barber (yeast size control)
Yipei Guo (bacterial evolution)
Felix Wong (bacterial mechanics)
Po-Yi Ho (cell cycle regulation)
Dr. Ethan Levien (bet hedging)
Dr. Jie Lin (population growth)
Jiseon Min (damage partitioning)
Paul Dieterle (collective dynamics)

David Nelson, Ethan Garner, Andrew Murray, Nancy Kleckner (Harvard)
Bree Aldridge and Michelle Logsdon (Tufts)
Lars Renner (Dresden)
Sven van Teefelen (Pasteur)
Ilya Soifer (Calico)
Naama Barkai (Weizmann)
Nathalie Balaban (Hebrew University)