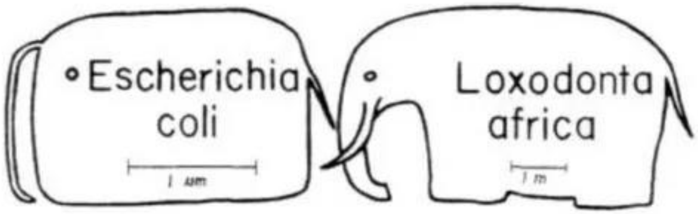
Why microbes?



- We can learn fundamental biology – applicable to higher organisms – by the quantitative study of microbes.

"Anything found to be true of *E. coli* must also be true of elephants.“
Jacques Monod, 1954

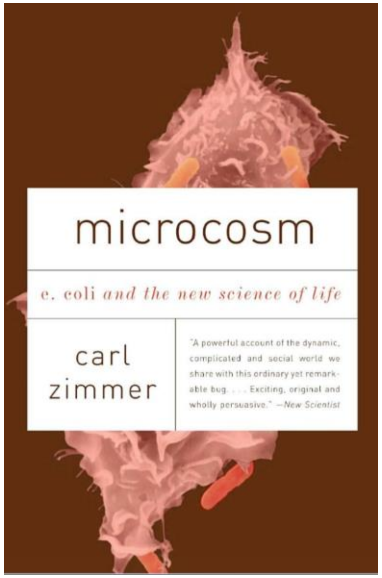
Example I: establishing the role of mutations in evolution.

Example II: Quantifying evolutionary dynamics and the processes involved in it.

- Additional lesson:

Quantitative analysis of the data can lead to novel,
qualitative insights

- So far… no physical forces etc., but a physicist's approach



Refs (for lecture I)

- **Original paper:**

  Luria and Delbruck, *Genetics* 28(6), 491 (1943)

- SI of Guo, Vucelja and AA, *Science Advances,* 5(7), eaav3842 (2019)

Yipei Guo

$p(s) \propto s$

- ***Growth, branching processes: recursion!***
- ***Details always in SI***

Jie Lin, Michael Manhart and AA:
Serial dilution with *lag times and yield*
Biorxiv:??

$s \propto \frac{\Delta\lambda}{\lambda}\log{(D)} - \lambda\Delta L$ *Proof?*

Outline

(Lecture I)

- Why study microbes? Luria-Delbruck experiment, Evolution experiments

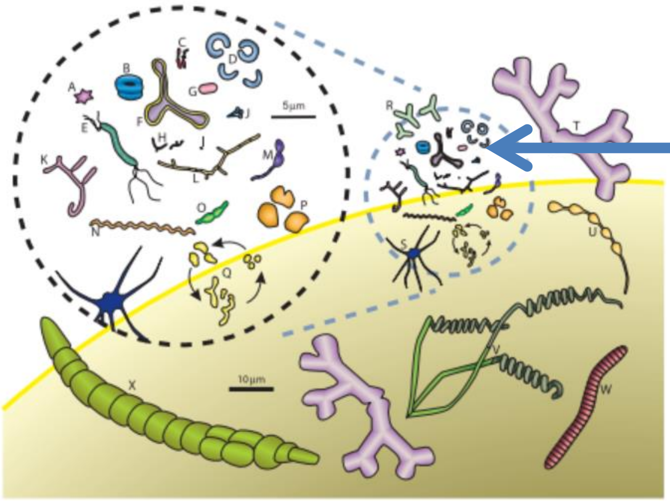
(Lecture II)

- Introduction to microbial growth, with focus on cell size regulation
- Size control and correlations across different domains of life
- Going from single-cell variability to the population growth

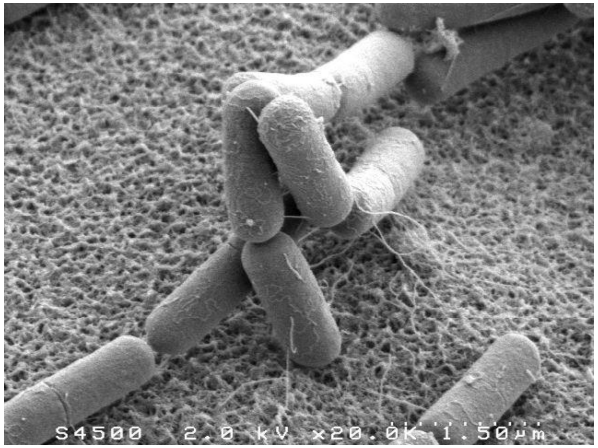
(Lecture III)

- Bet-hedging
- Optimal partitioning of cellular resources

What does a (microbial) cell need?



K. Young (2006)



B. subtilis cells

A. Chastanet et al., Front Biosci (2012)

- What determines growth at the single-cell level ?
- How do microbes maintain their shape/size?
- How are the cellular processes coordinated?

(DNA replication, transcription , protein synthesis, division…)

ASPEN
CENTER FOR PHYSICS

2020 WINTER CONFERENCE

NEW PHYSICAL MODELS FOR CELL GROWTH

January 5 through 10, 2020
Sunday evening welcome reception
Meetings Monday through Friday evening

In recent years, our quantitative understanding of cellular growth - across all domains of life - has seen a "renaissance", with a large number of both theoretical and experimental studies coming together to unravel and elucidate a plethora of novel phenomenon. Technological advances in both genetic manipulations, microscopy techniques and data acquisition and analysis have allowed us to generate datasets of unprecedented accuracy and size, providing a fertile ground for mathematical modeling.

Studying specific genes in isolation, via genetic and other types of perturbations, appears to be ill suited for understanding many growth-related problems, likely due to the strong interactions between the large number of cellular components, and interdisciplinary approaches are called for. In such an approach the theory would guide experiments in identifying the key variables, thus bridging the gap between the molecular details and the emergent behavior. Indeed, in many cases simple and universal "growth laws" are discovered, which appear to be robust and often shared across evolutionary divergent organisms.

This conference will bring together scientists pursuing the state-of-the-art in mathematical modeling of cellular growth, aspiring to find broadly applicable mechanisms and answer fundamental questions in biology through the lens of physics and mathematics, developing new and exciting models.

Application deadline is October 31, 2019

Please complete your application at:
http://www.aspenphys.org/physicists/winter/winterapps.html
Conference Website: https://amir.seas.harvard.edu/aspen

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*Ariel Amir, Harvard University
Meriem El Karoui, University of Edinburgh
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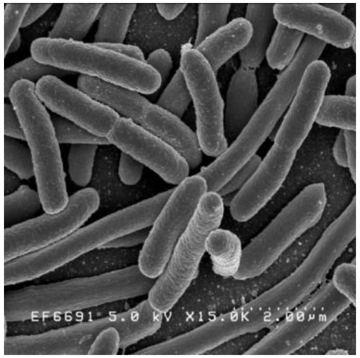
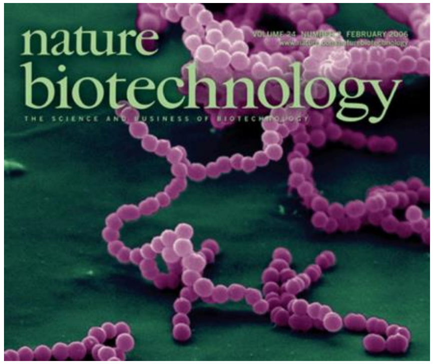
Bacterial form and growth

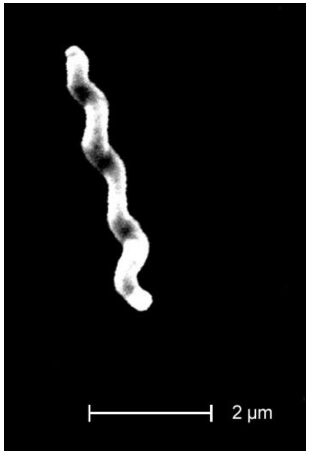
Bacteria have diverse shapes, given to them by their rigid ***cell walls***



Escherichia coli



Streptococcus pyogenes

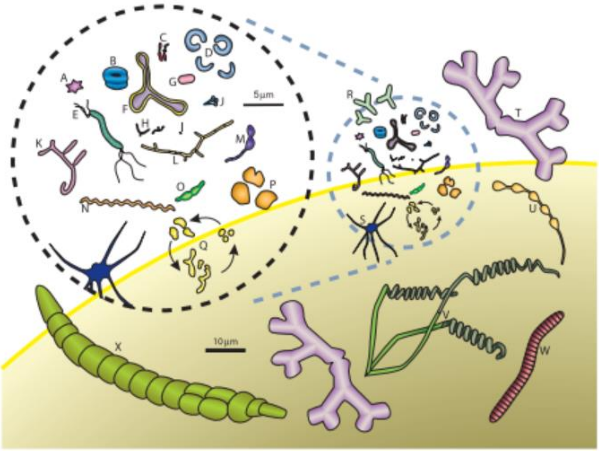


Campylobacter jejuni

"How does a bacterium construct a cell having a defined length, diameter, and overall geometry?"

- How do bacteria maintain their cylindrical growth?
- How are the different processes coordinated?

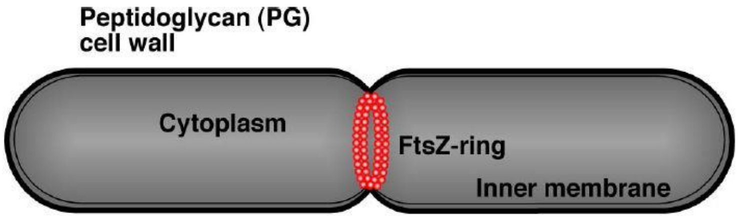
(cell wall growth, DNA replication, division *etc.*)



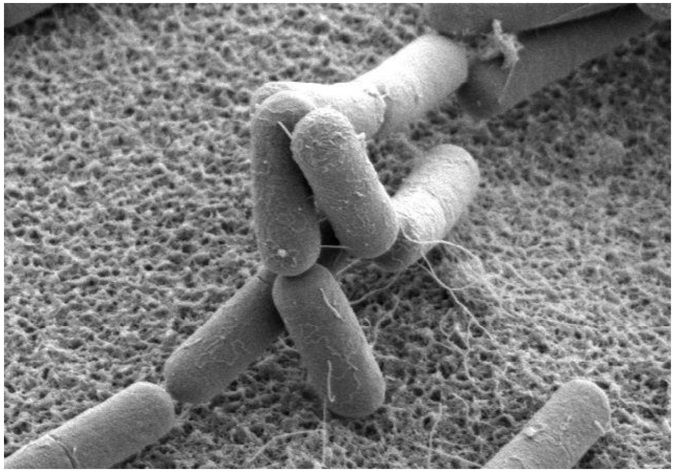
K. Young (2006)

Bacterial growth

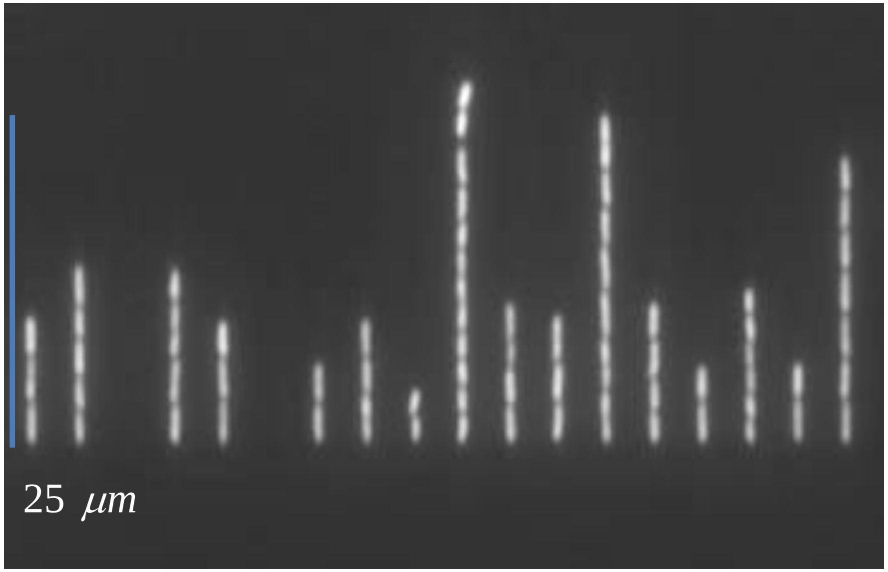
- Doubling time ~ typically tens of minutes
- Remarkable precision in growth
- All done under huge internal pressure!



Lan et al., PNAS (2007)



Bacillus subtilis
A. Chastanet et al., Front Biosci (2012)

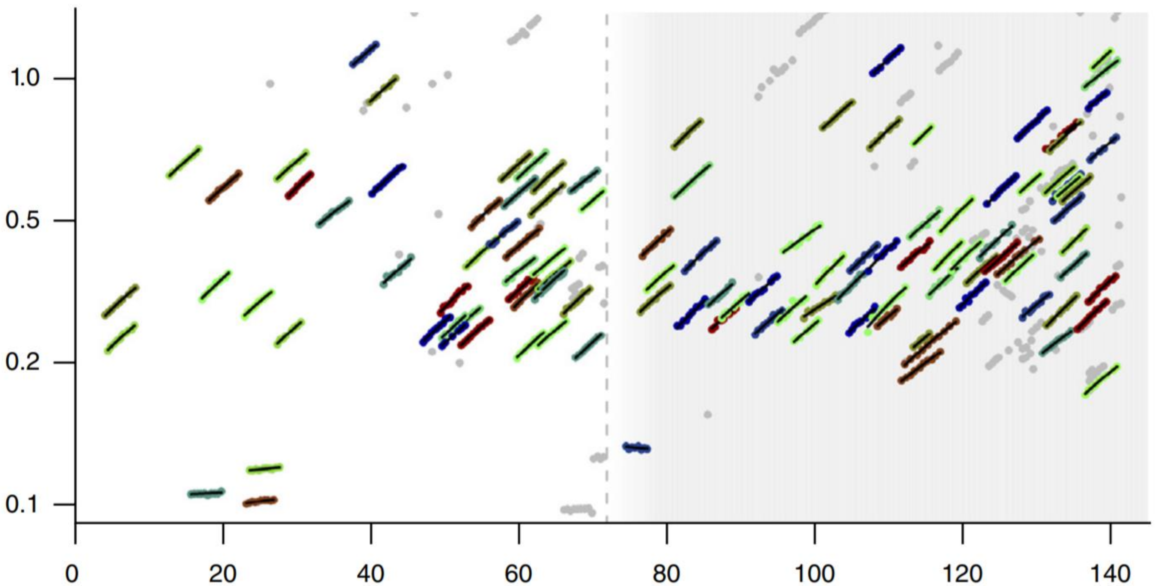


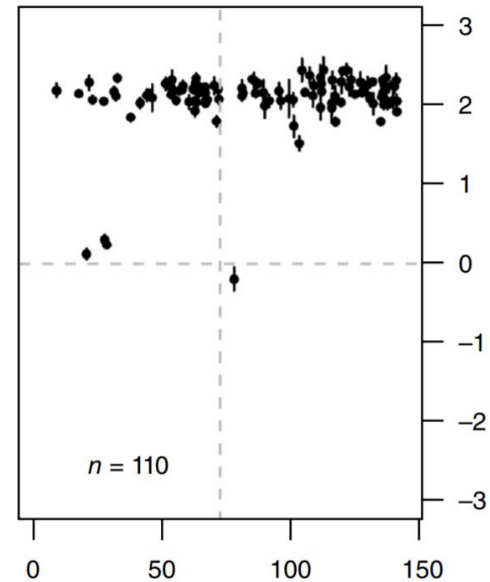
Wang et al., ***Robust Growth of Escherichia coli***
Current Biology (2010)

Exponential growth at single-cell level

Buoyant mass (pg)

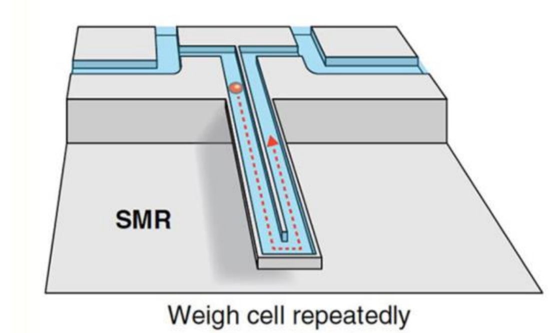
$$\frac{dm/dt}{m}$$





time (mins)

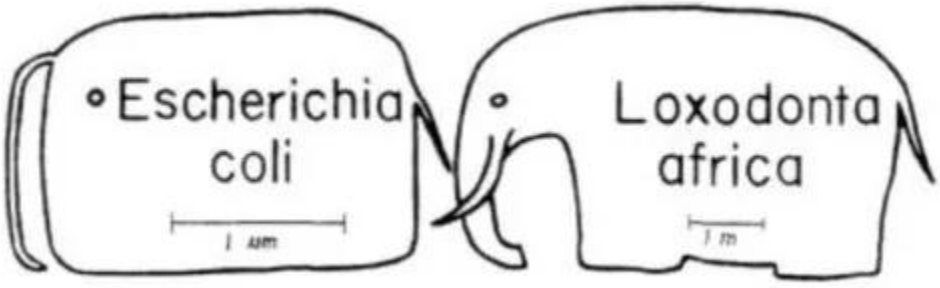
Cermak *et al.*,
Nature Biotechnology (2016)



Exponential growth (with small fluctuations) is a good approximation

Exponential growth at single-cell level

"Anything found to be true of *E. coli* must also be true of elephants.“
Jacques Monod, 1954

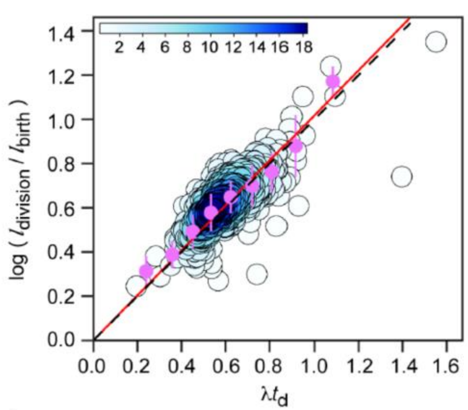


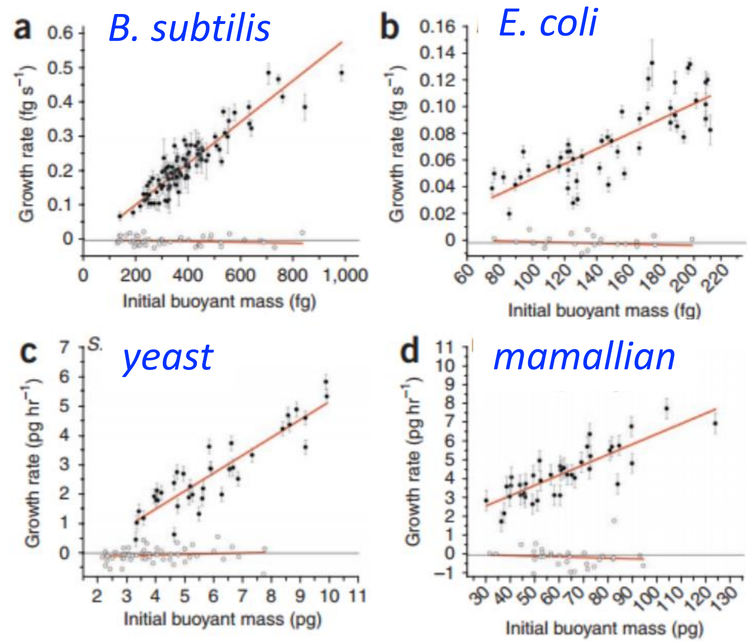
H. salinarum

Eun et al.,

Nature Microbiology

(2018)

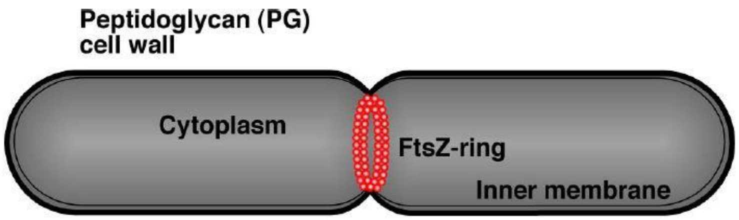




Godin *et al.*,
Nature Methods (2010)

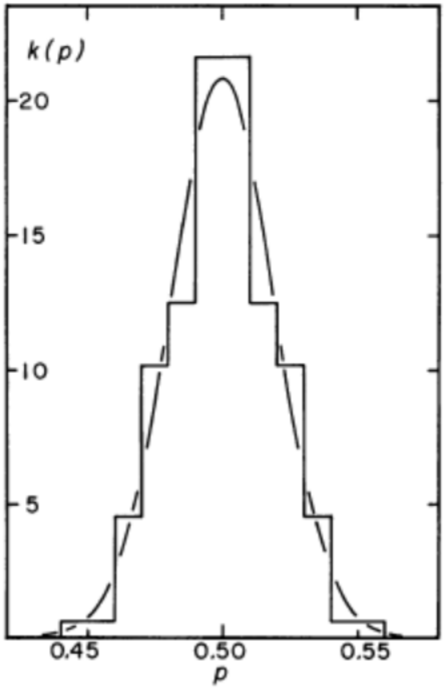
Exponential growth (with small fluctuations) is a good approximation

Symmetry of division



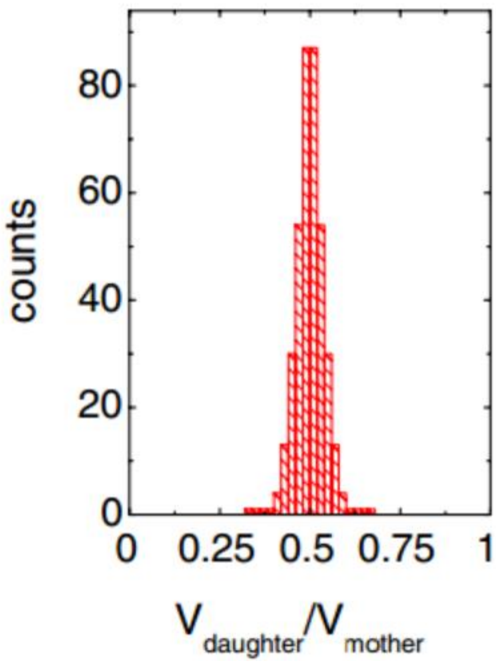
Lan et al. (2007)

- *E. coli* cells are very good in dividing symmetrically!



Marr, Harvey and Trentini (1966)

$\sigma \sim 0.018$

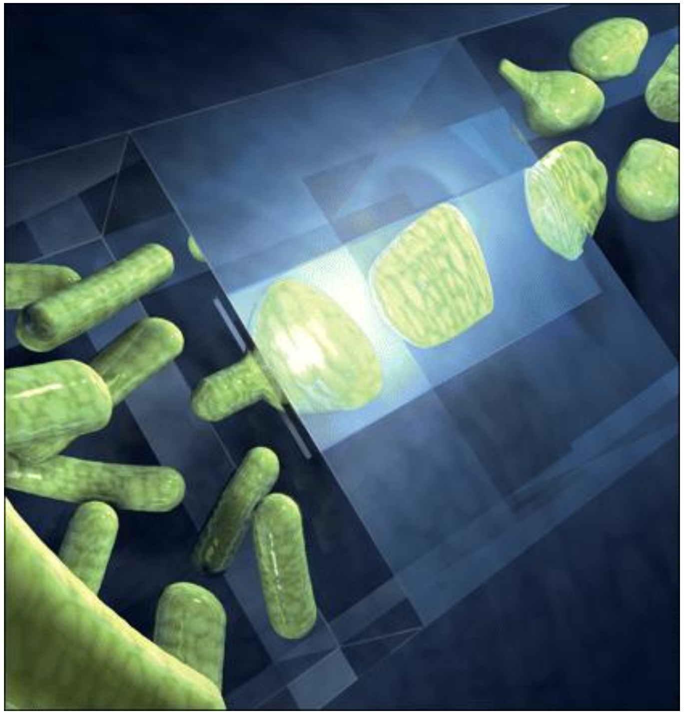


Mannik et al., PNAS (2011)

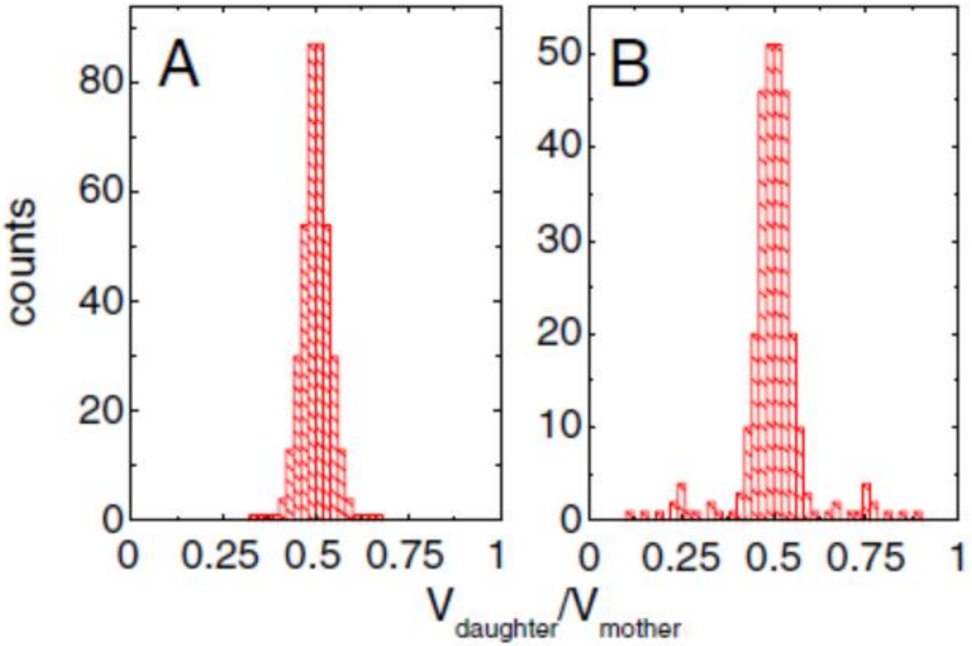
$\sigma \sim 0.037$

→ Small effect on size distribution

Symmetry of division



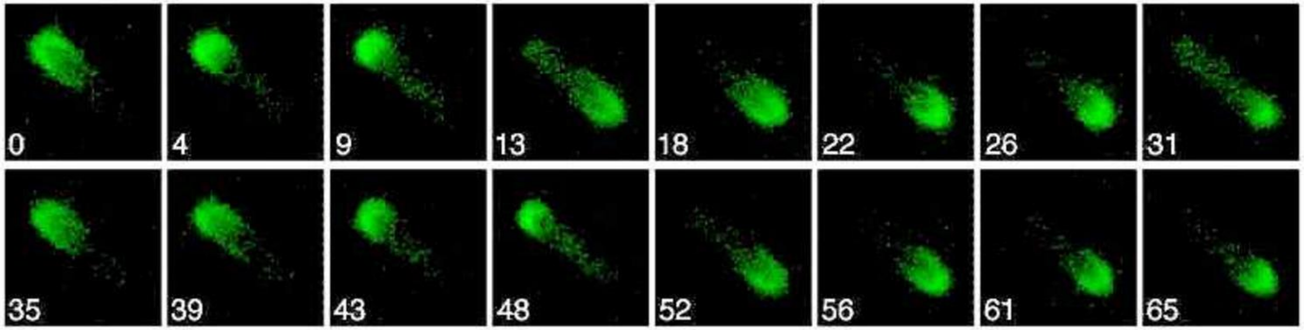
From: PNAS cover, Mannik et al. (2009)

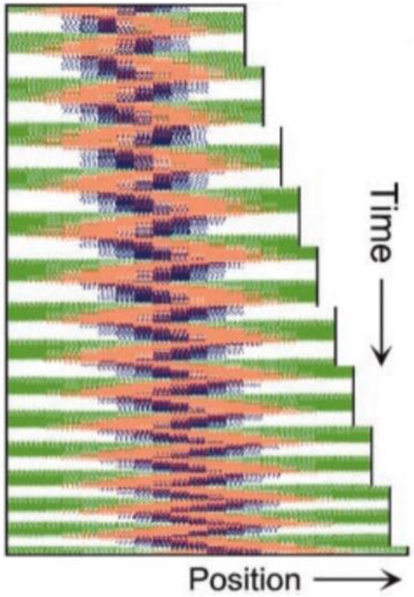


Mannik et al., PNAS (2012)

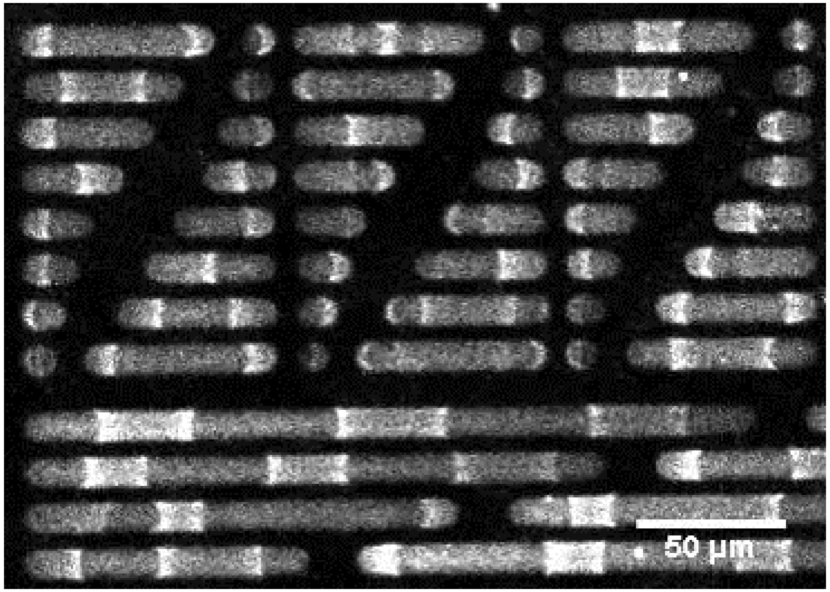
- Remarkably, cells divide symmetrically even when severely deformed mechanically

Min oscillations





Meinhardt and de Boer, PNAS (2001)

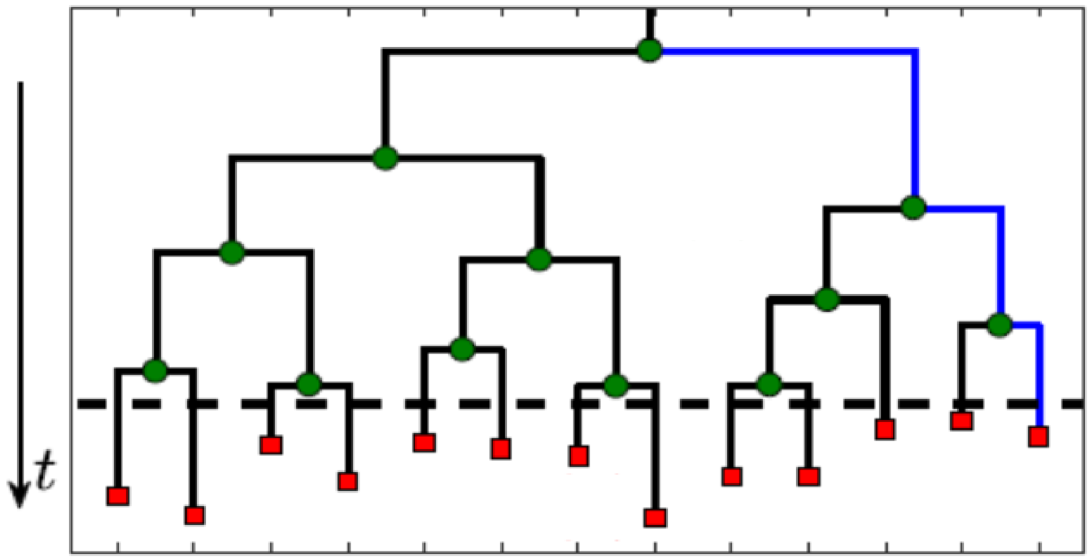


Zieske and Schwille, eLife (2014)

“What I cannot create, I do not understand”
R. Feynman

For recent modeling work:
Jonas et al. PNAS (2018)

Dealing with noise: single-cell **size** variability:



Focus now on control of ***Division timing,***

e.g., Following size at birth across lineage

- If generation time is stochastic (and assuming symmetric division):

$v_{n+1} = \frac{1}{2} v_n e^{\lambda t}$ → *log(v)* does a random walk [**no** size control]

→ *Generation times must be correlated ("timer" doesn't work in regulating size)*

Generic model for cell size control **AA, PRL (2014)**

$v_d = f(v_{nb})$ *Determinstic "strategy" which the cell will attempt to implement*

Definitions:
v_0=average newborn size
τ= mass doubling time
λ=ln(2)/ τ

$v_d = 2v_0$

"Perfect" size control

$v_d = 2v_{nb}$

No size control *("timer" model)*

- If the noise is small: only $\mathbf{f'(v_0) = 2(1-\alpha)}$ matters,

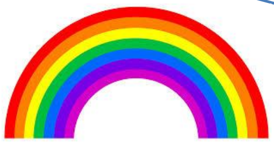
(Taylor expand around typical size)

→ Two models with the same derivative are equivalent!

- A convenient choice: $f(v_{nb})=2v_0^{\alpha} v_{nb}^{1-\alpha}$

$\alpha = 1$ ***"Perfect" size control***

$\alpha = 0$ ***No size control***



See also: Brenner, Newman, Osmanović, Rabin, Salman, and Stein, PRE 2015

Generic model for cell size control

α=1/2

$f(v_{nb})=2v_0^{\alpha} v_{nb}^{1-\alpha}$ ⇒ $f(v_{nb}) \approx v_{nb}+v_0$

(***Incremental Model*** **,** Sompayrac and Maaløe, 1973)

Within this model, a cell attempts to add a (constant) volume before division.

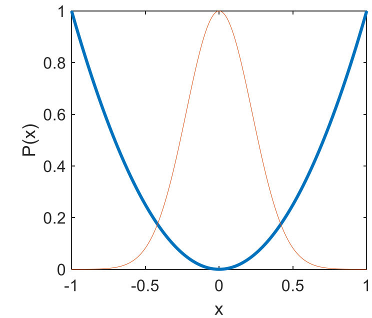
Adding noise…

Generically we will assume: $t = t_a + t_n$

$$t_a = \tau + \frac{\alpha}{\lambda} \ln[v_0/v_{nb}]$$

t_n = *Noise (random variable with standard deviation* σ_T *)*

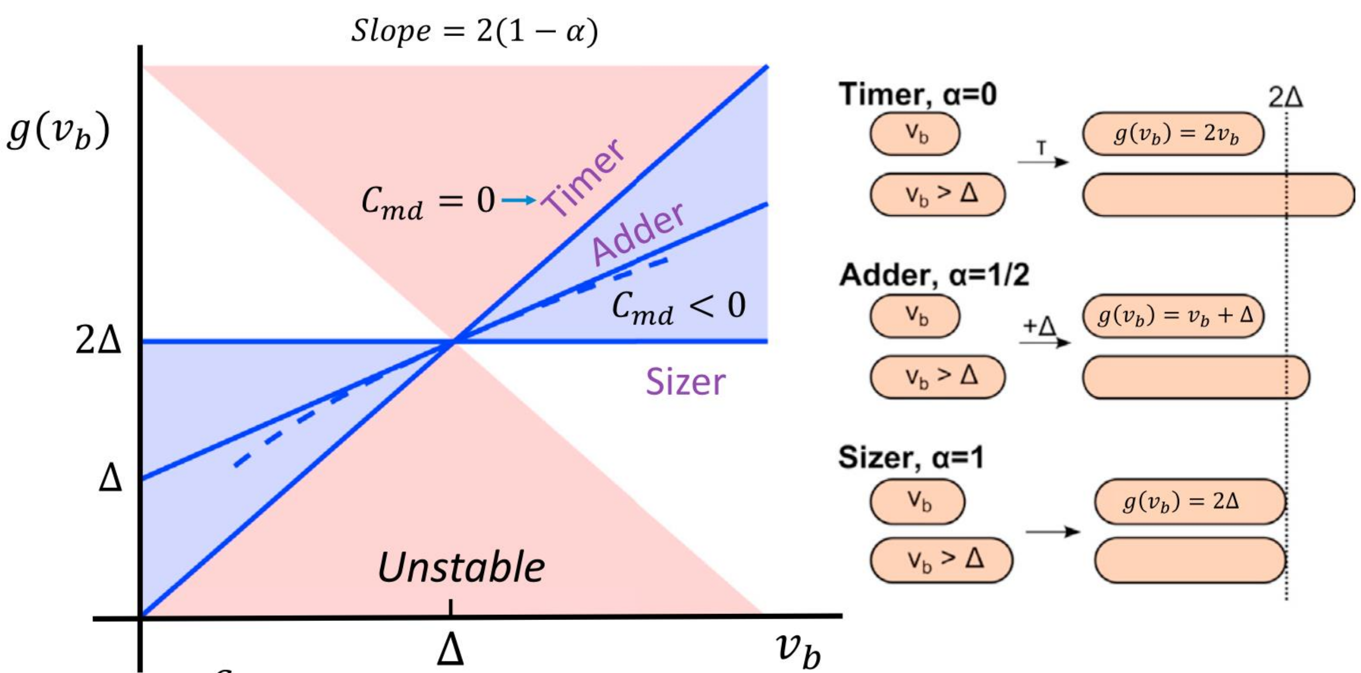
Generic model for cell size control



$$\frac{dx}{dt} = -\frac{k}{\gamma}x + \sigma\xi$$ (Ornstein-Uhlenbeck process)

$$x_{n+1} = (1-\alpha)x_n + \lambda\xi$$ (Discrete stochastic map/ autoregressive process)

x_n: $\log_2$ (Size at n'th birth)



C_{md}: Pearson correlation coefficient between the mother and daughter cells' generation times

AA, eLife (2017)
Ho, Lin and Amir, Annual Reviews of Biophysics (2018)

Po-Yi Ho (Harvard→ Stanford)

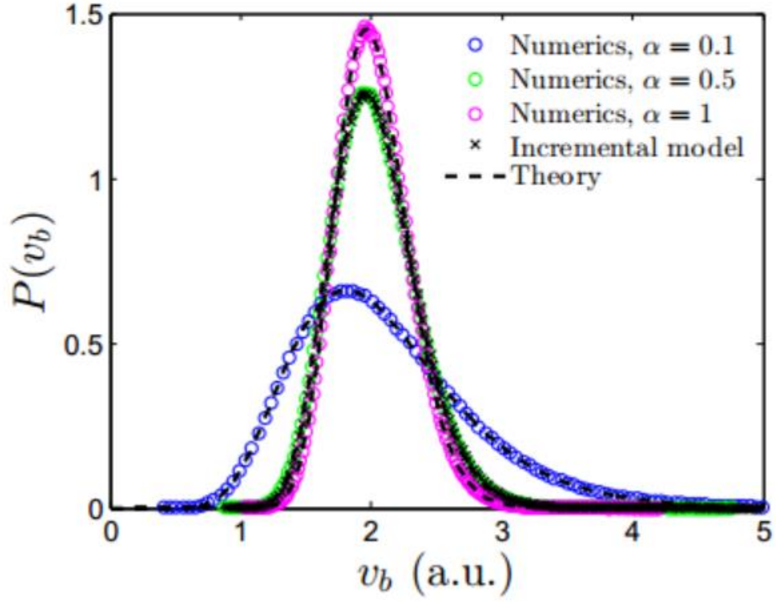
Solving the model

$$\log_2[V_d/V_0] = (1-\alpha)\log_2[V_m/V_0] + \lambda t_n$$

But V_d and V_m must have the same distribution!

→ *Size distribution is log-normal (right skewed),*

and we can find its variance.



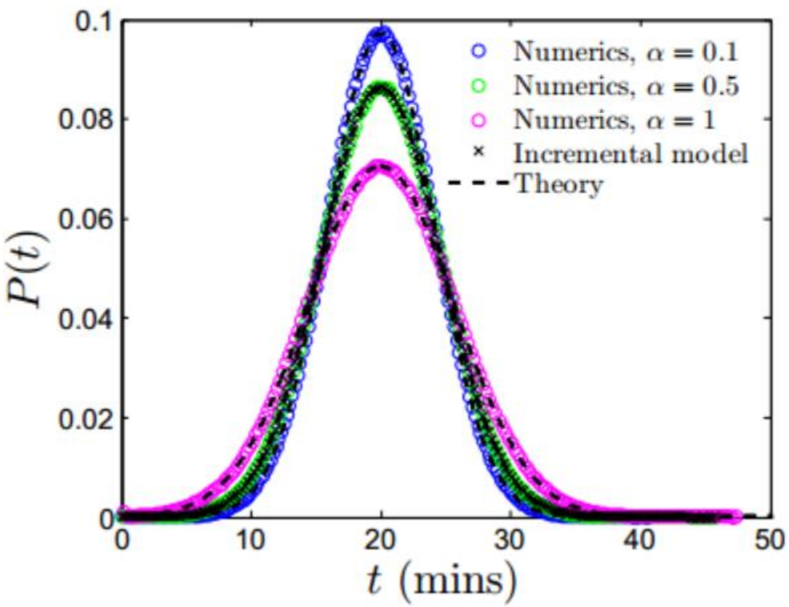
$$\rightarrow P(V_{nb}) = \frac{1}{\sqrt{2\pi}\ln[2]\sigma_v}\frac{e^{-log^2{}_2\left[\frac{V_{nb}}{V_0}\right]/2\sigma_v{}^2}}{V_{nb}},\ \sigma_v = \sqrt{\frac{\sigma_T}{\tau(2-\alpha)\alpha}},\text{CV}\approx \ln(2)\,\sigma_v$$

Solving the model

$$t = \tau + \alpha \ln[V_0/V_m] + \lambda t_n$$

→ *Time distribution is Gaussian, we can calculate its variance in the same way*

$$P(t) = \frac{1}{\sqrt{2\pi}\sigma_t} e^{-\frac{(t-\tau)^2}{2\sigma_t{}^2}}, \sigma_t = \sigma_T \sqrt{\frac{2}{2-\alpha}}$$



- Both size and time distributions controlled by the same noise!
- For extended discussion of the mathematical problem (including asymmetric division):

Stochastic modeling of cell growth with symmetric or asymmetric division
Marantan and Amir, Phys. Rev. E. (2016)

Correlation between mother and daughter size

For a narrow size distribution, we can expand:

$$\ln[V_{nb}/V_0] \approx \frac{V_{nb}-V_0}{V_0}$$

→Therefore it is equivalent to calculate the correlation coefficient of log(size)

$$C_{md} = \frac{\mathrm{E}[\ln[V_{mother}/V_0]\ln[V_{daughter}/V_0]]}{\sigma^2{}_v}$$

Using: $\ln[V_d/V_0] = (1-\alpha)\ln[V_m/V_0] + \lambda t_n$

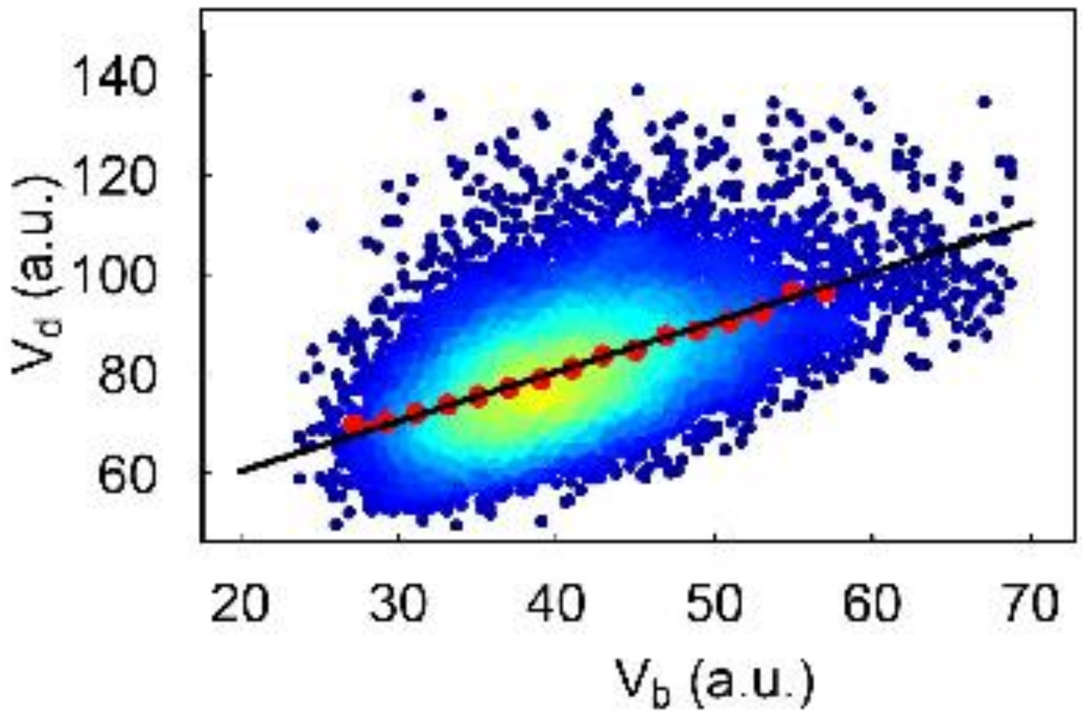
→ C_{md}=(1-α)

A robust way of finding the size control strategy!

Measured value of 0.55 → suggests the incremental model

$$\alpha = \frac{1}{2} \iff f(v_{nb}) \approx v_{nb} + v_0$$

Correlations!



Soifer, Robert and Amir, Current Biology (2016)

Stewart et al., Plos Biology (2005).

See also: Campos et al, Cell (2014)

Taheri-Araghi et al, Current Biology (2014)

Slope of best fit very close to 1 → Incremental Model

Correlations!

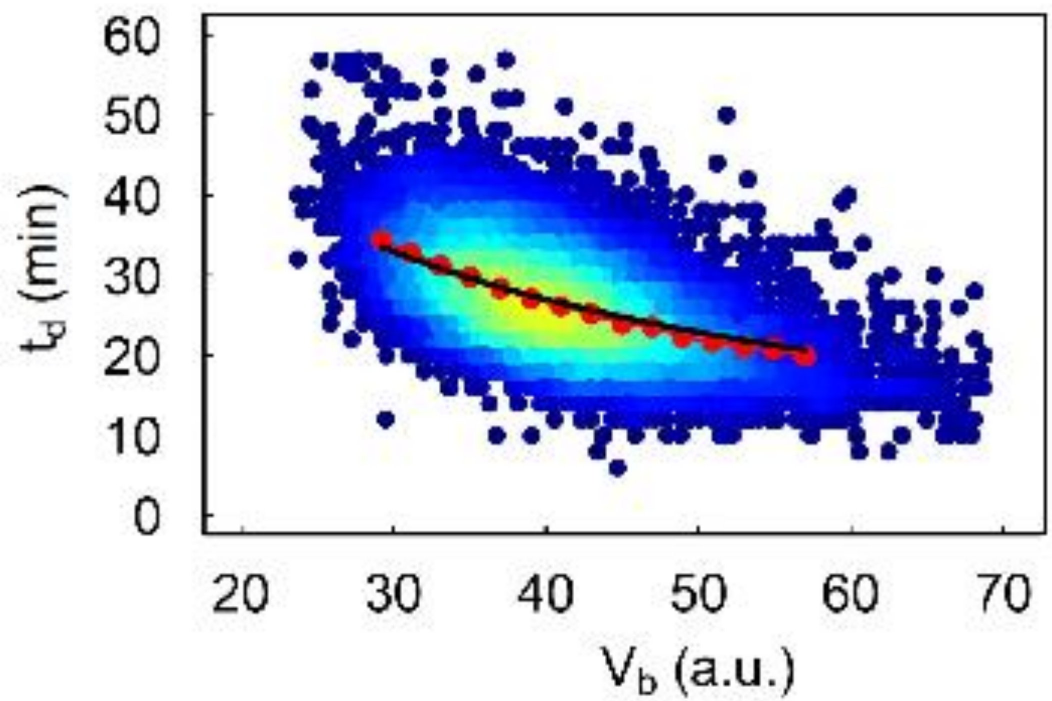
Similarly, there will be a negative correlation of size and time:

- Similarly: $C_{xt} = -\sqrt{\frac{\alpha}{2}}$
- Size-time correlation coefficient measured recently found to be -½:
  Robert et al., BMC (2014) → **Consistent with incremental model!**

For the incremental model:

$$V_d = V_b + \Delta \;\rightarrow$$

$$\boldsymbol{\lambda t_a = \log[1 + v_0/v_{nb}]}$$

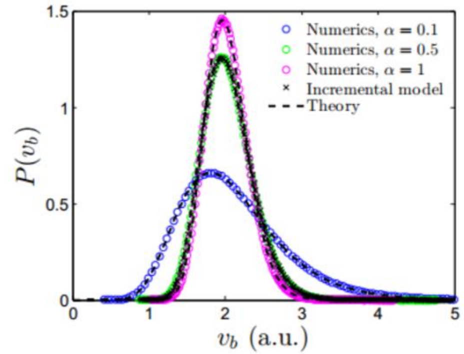


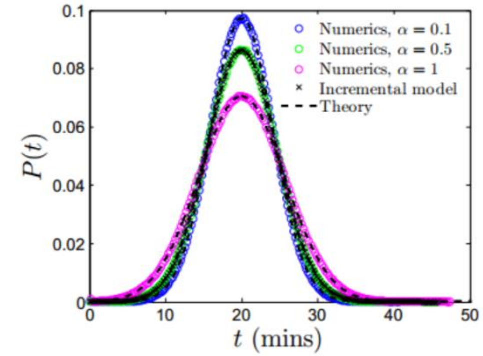
Soifer, Robert and Amir, Current Biology (2016)
see also: Osella et al, PNAS 2014

Connecting time and size distributions

Using the previous formulas:

$$\sigma_t = \sigma_T \sqrt{\frac{2}{2-\alpha}}, \qquad \sigma_v = \sqrt{\frac{{\sigma_T}^2}{\tau^2 \alpha (2-\alpha)}}$$



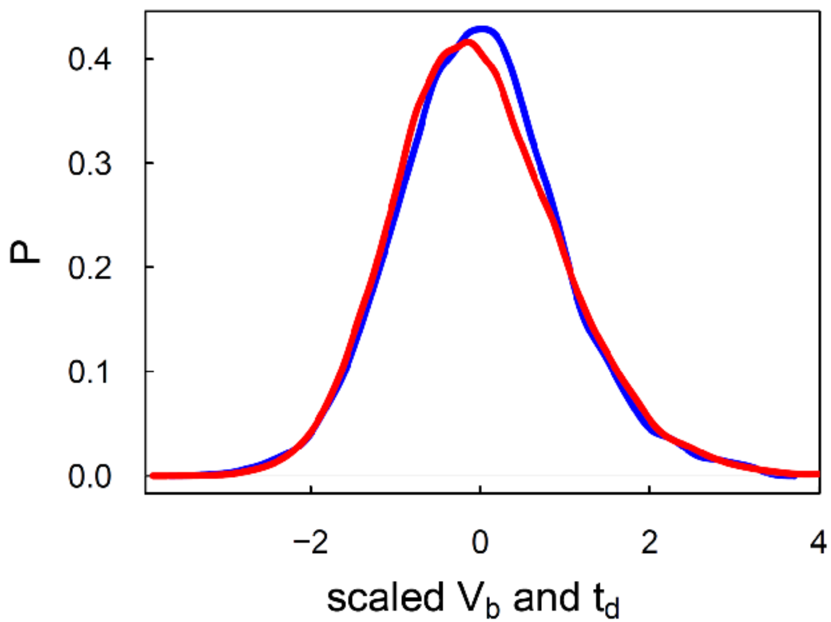


$$\gamma = CV_{size} / CV_{time} = \ln(2) / \sqrt{2\alpha} \approx 0.69$$

Data from three different experiments

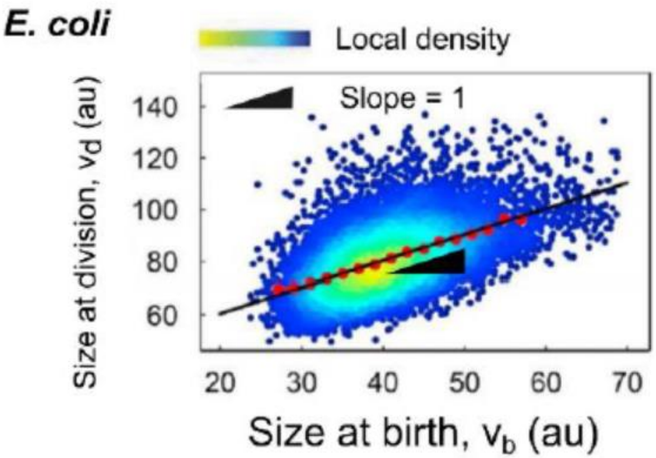
on agarose gels:

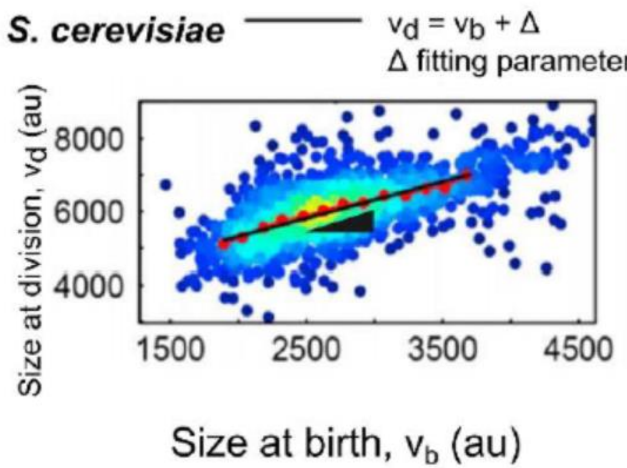
$\gamma = 0.72, 0.67, 0.63$ (average 0.67)

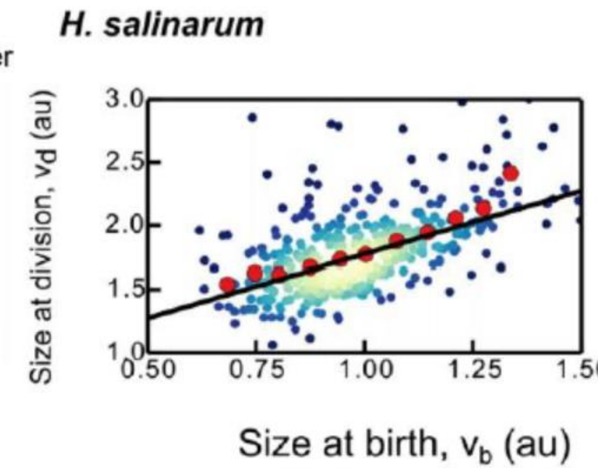


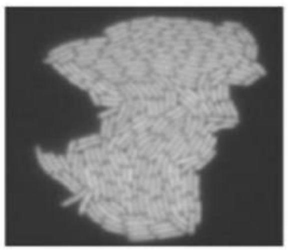
Soifer, Robert and Amir, Current Biology (2016)

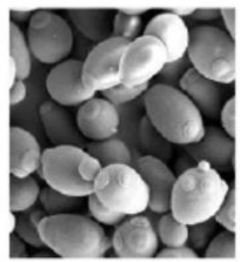
“Adders” in Nature

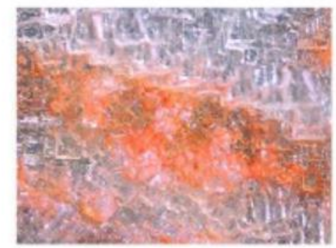






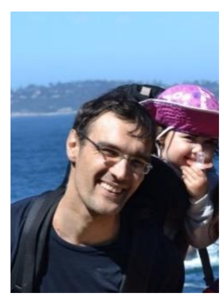




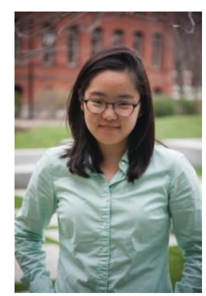


Soifer et al., Current Biology (2016)
Eun et al., Nature Microbiology (2018)
Logsdon et al., Current Biology (2017)

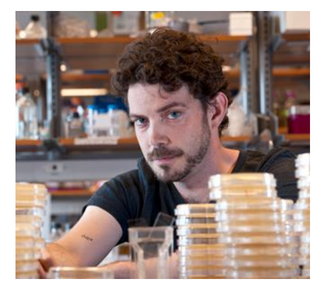
Bree Aldridge
(Tufts)



Ilya Soifer
(CalicoLabs)

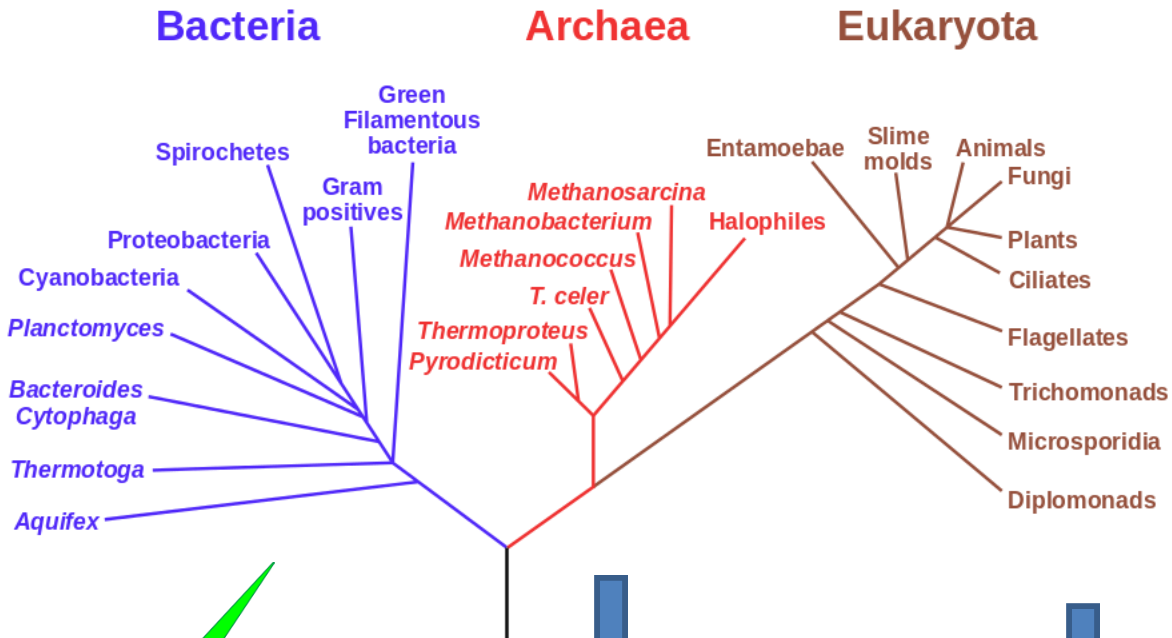


Yejin Eun
(Harvard)



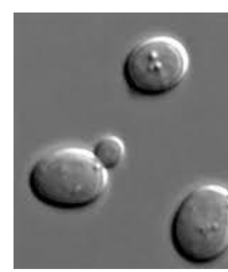
Ethan Garner
(Harvard)

Phylogenetic Tree of Life

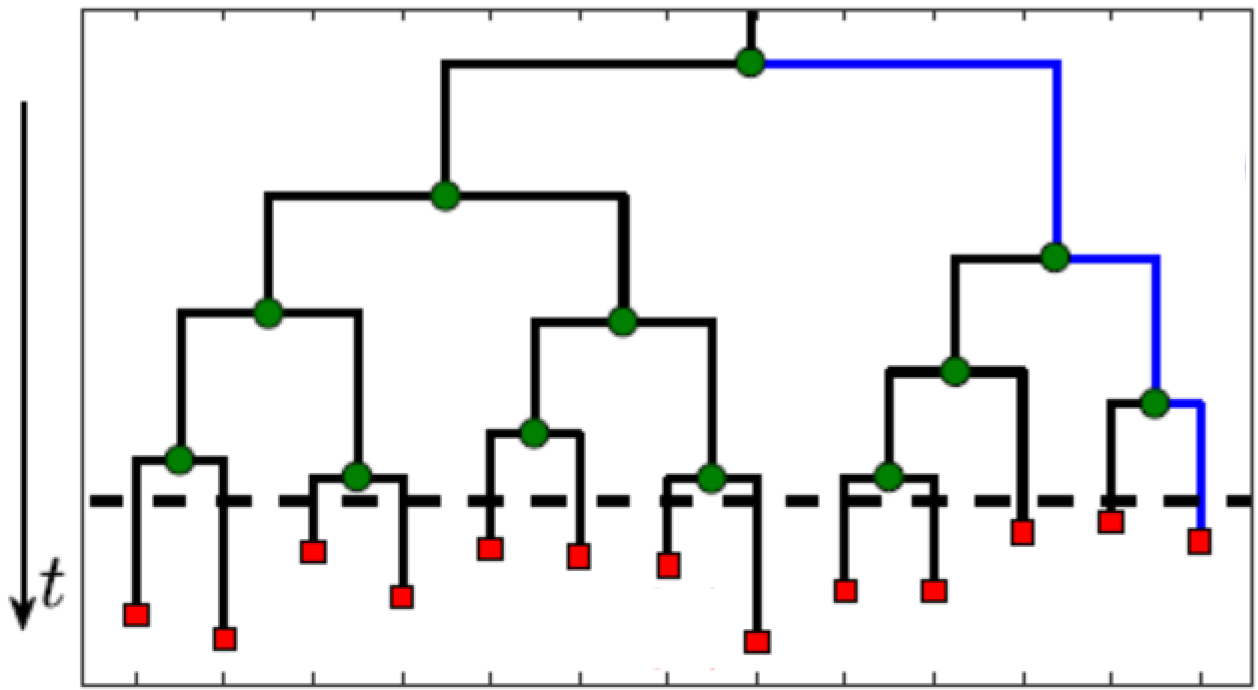


Are "adders" optimizing population growth?

By now 6 species of bacteria



How do variability&size control affect population growth?

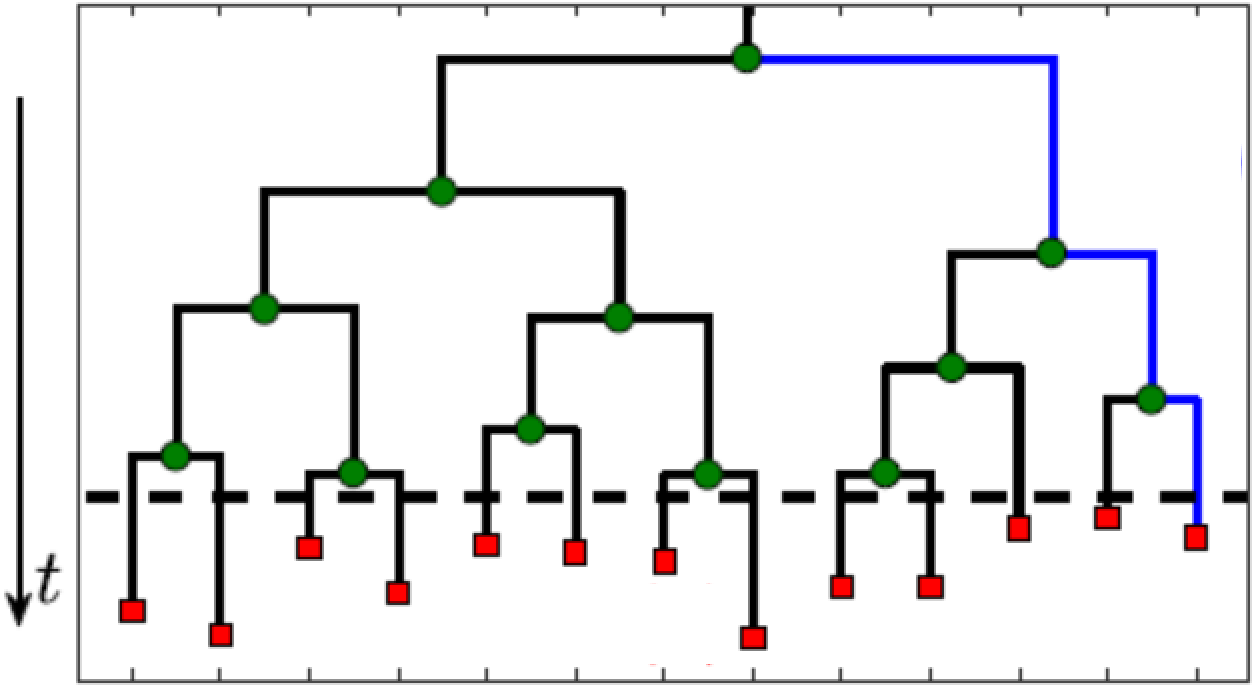


Are "adders" optimizing population growth?

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

- 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?

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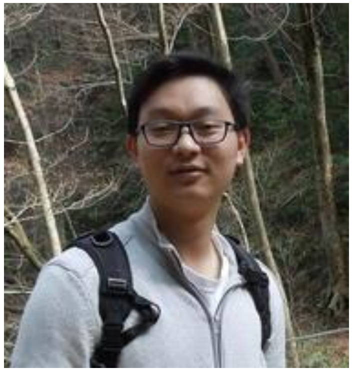
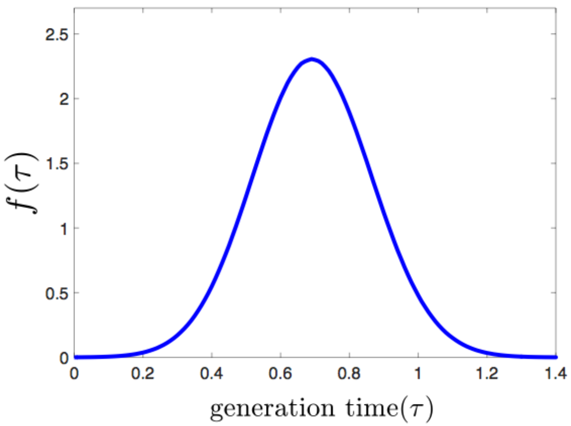


Jie Lin

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