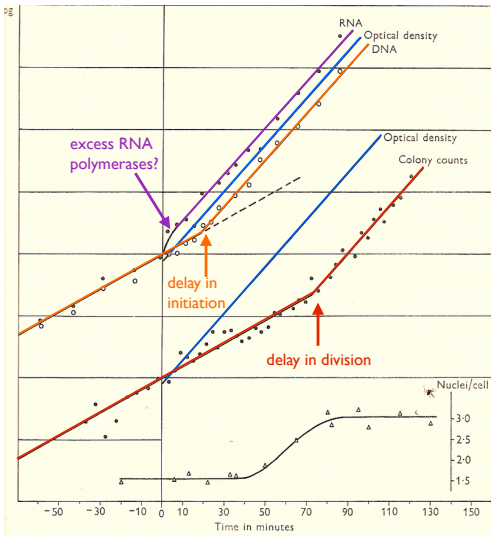
Recap

Understanding Schaechter, Maaloe, and Kjelgaard (1958)



RNA (amount of)
tells us the transcriptional activity (protein synthesis)

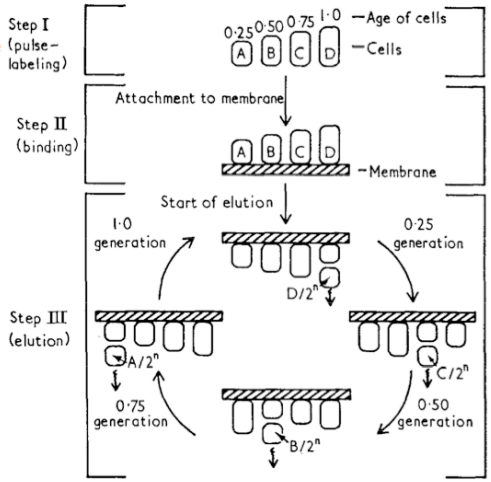
DNA (amount of)
tells us the replication initiation timing

Optical density
tells us the growth (elongation) rate

Colony counts
tells us cell number density, therefore division timing

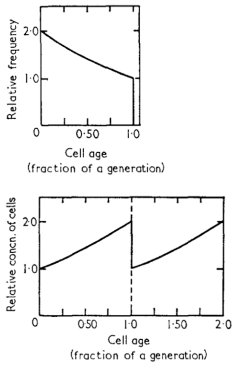
The Baby Machine and Bacterial Cell Cycle

^{14}C thymidine



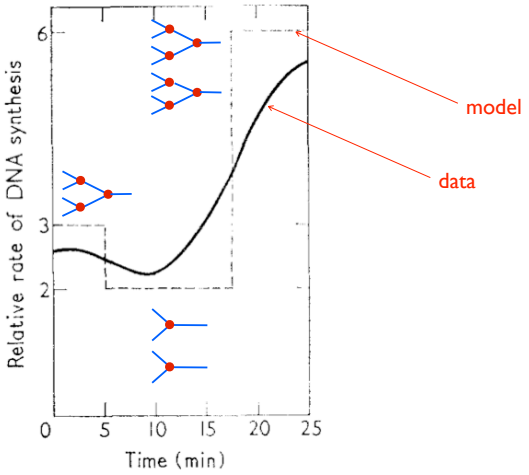
C. E. Helmstetter (1967)
C. E. Helmstetter & S. Cooper (1968)

age distribution



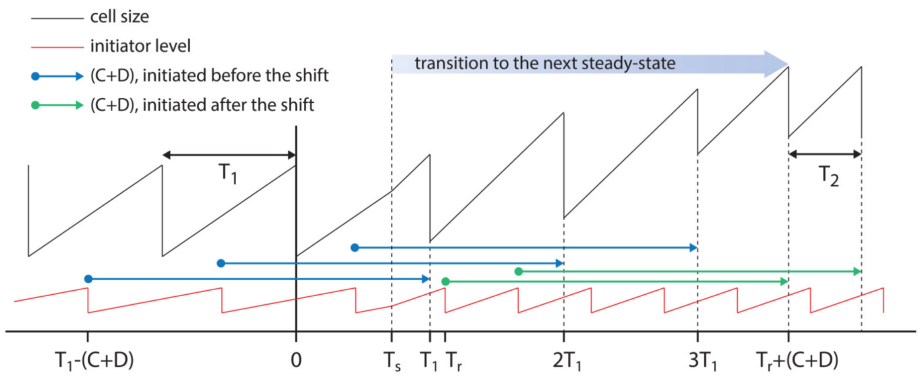
C. E. Helmstetter (1967)

E.g., mass-doubling time = 25 minutes



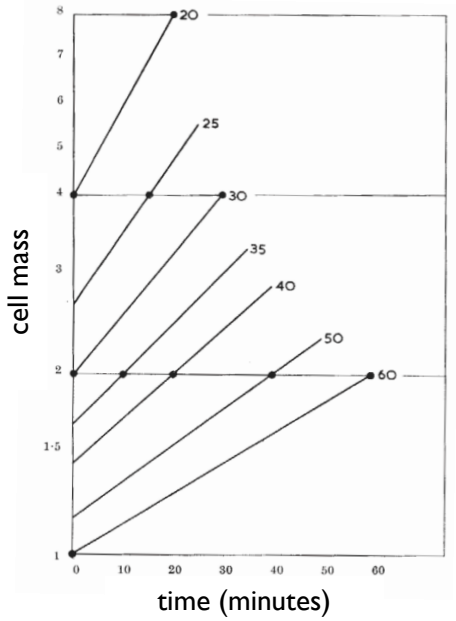
measured by ^{14}C thymidine incorporation rate

C. E. Helmstetter (1967)
C. E. Helmstetter & S. Cooper (1968)



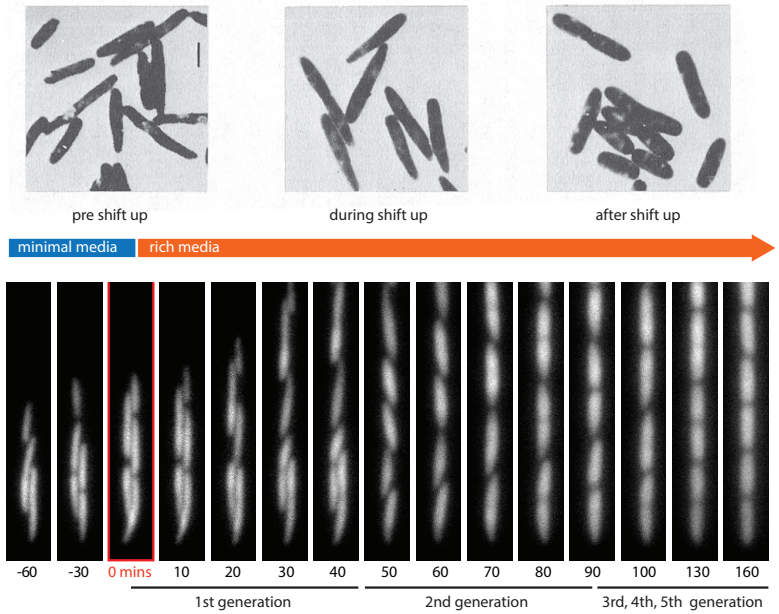
Taheri-Araghi, Frontiers in Micriobiol. 2015

Constant initiation mass by Donachie 1968



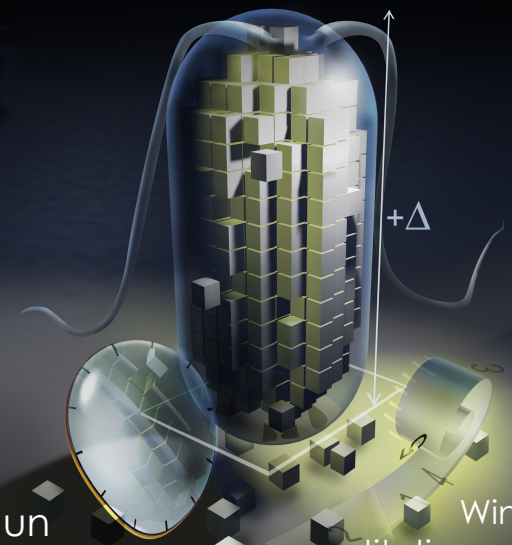
W Donachie, Relationship between cell size and time of initiation of DNA replication. *Nature 219*, 1077–1079 (1968).

Morphological changes during nutrient shift-up



Taheri-Araghi et al., Single-cell physiology, Annu. Rev. Biophys. 2015

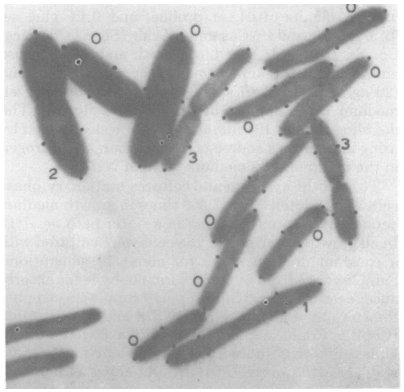
Lecture 3:
Cell size control and homeostasis in bacteria

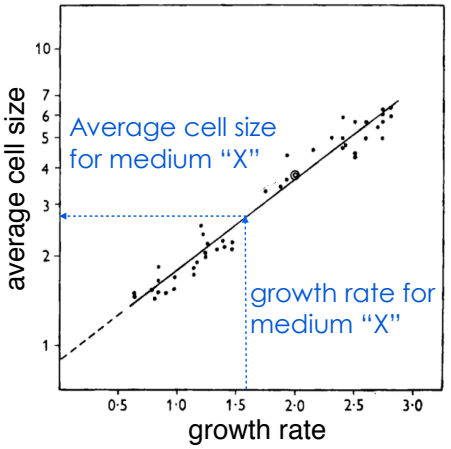


Suckjoon Jun
UCSD qBio
Physics & Molecular Biology

Winter School on quantitative systems biology
Bangalore, December 12, 2015

Growth Law links cell size and growth rate





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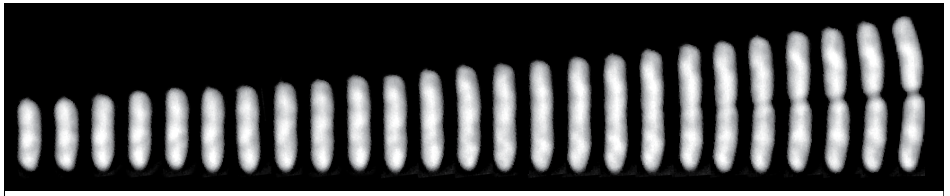
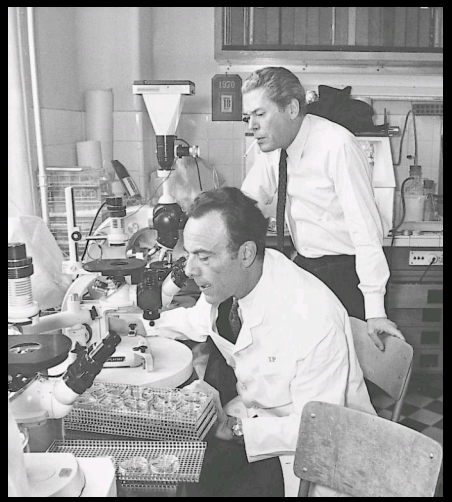


What can we predict for individual cells?

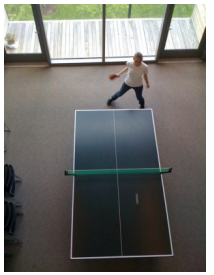
"The dream of every cell:
to become two cells.
(Le réve de toute cellule:
devenir deux cellules.)"

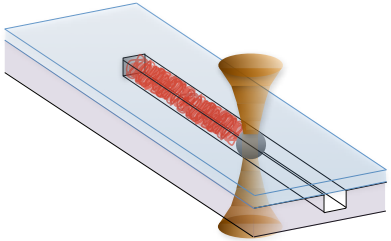
François Jacob

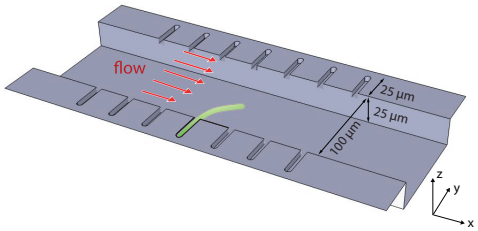


François Jacob and Jacques Monod
Institut Pasteur, 1970

Fun (and some hard) experiments we did using the mother machine



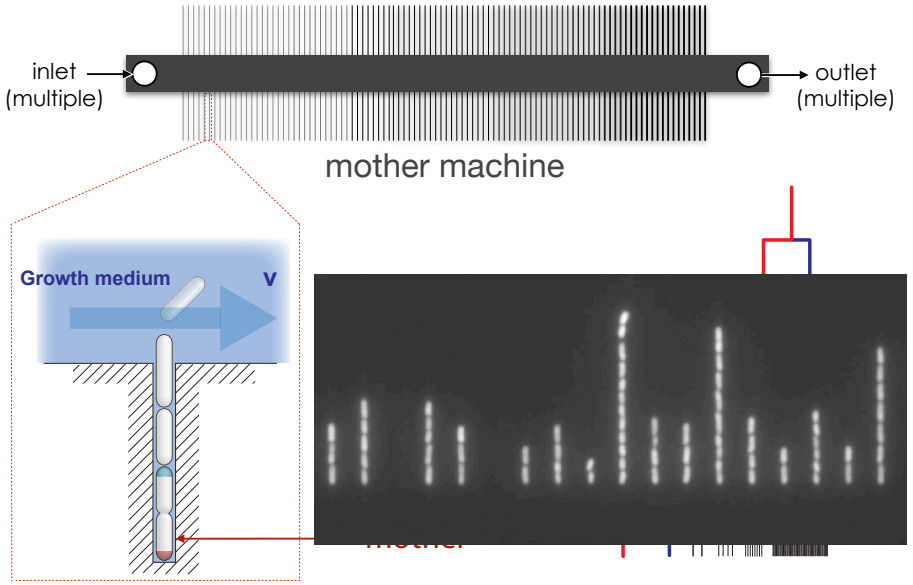




Pelletier *et al.*, *Physical manipulation of the Escherichia coli chromosome reveals its soft nature*. PNAS Plus **109**, E2649-56 (2012).

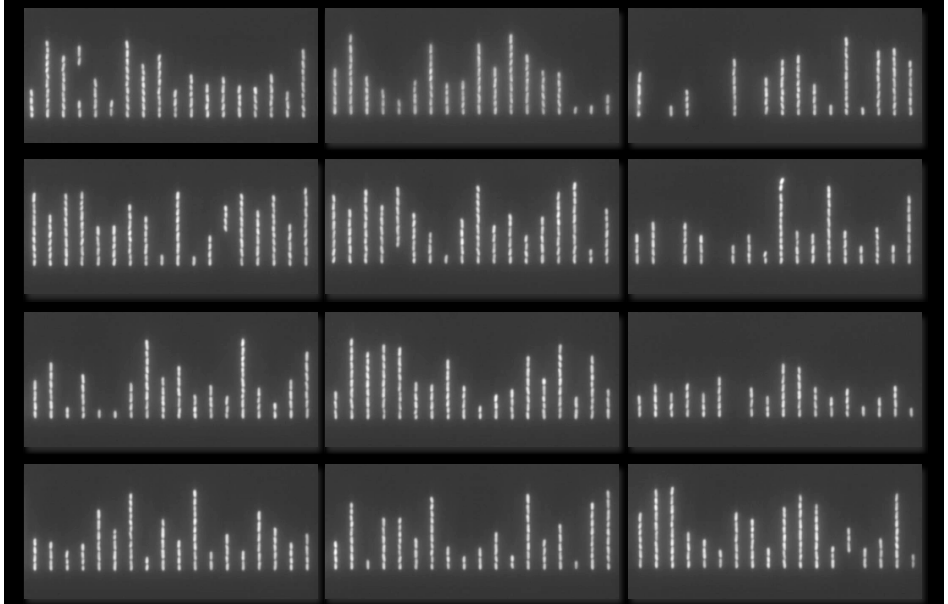
Amir, Babaeipour, McIntosh, Nelson, & Jun. *Bending forces plastically deform growing bacterial cell walls*. PNAS **111**, 5778–5783 (2014).

We study growth and cell cycle at the single-cell level

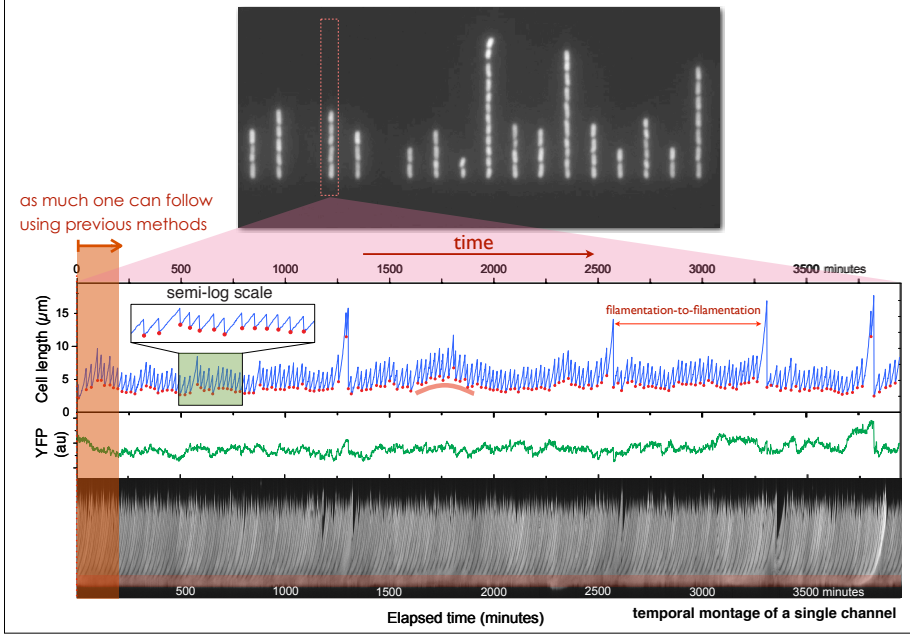


Wang et al., *Robust growth of E. coli*, Curr Biol **20**, 1099-1103 (2010)

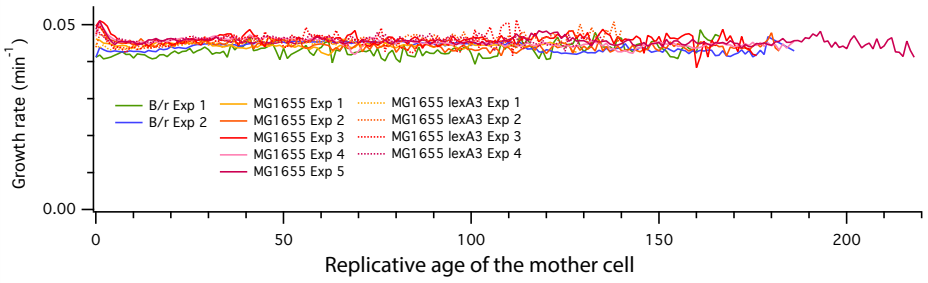
See the mother machine in high-throughput action!



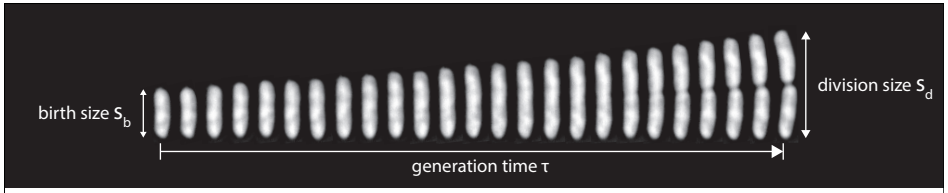
This is how we analyzed the movies back in 2009



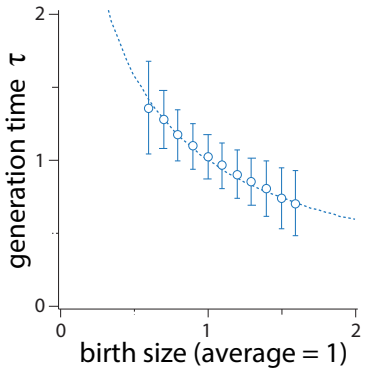
E. coli will do anything to maintain constant growth

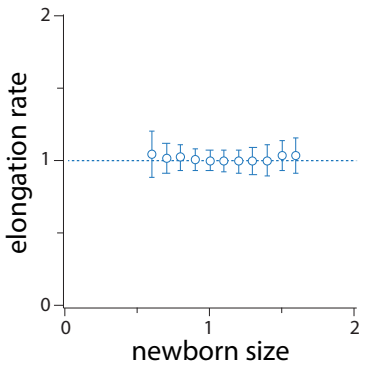


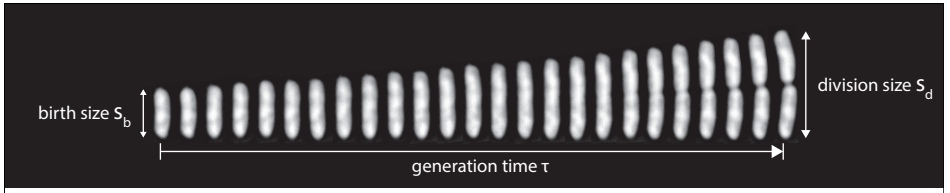
Wang et al., *Robust growth of E. coli*, Curr Biol **20**, 1099-1103 (2010)

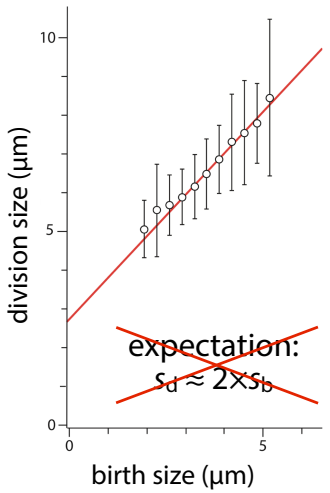


Hint of size control: the smaller the newborn cell, the longer it takes to reach division

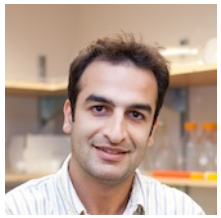








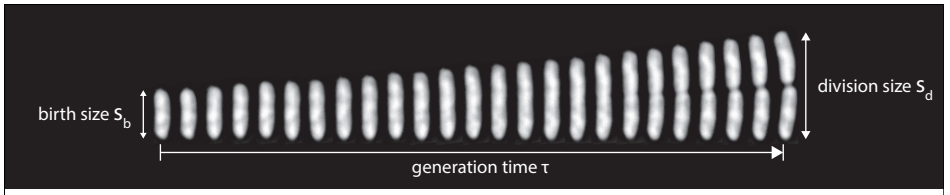
Size correlations implied an unexpected mechanism

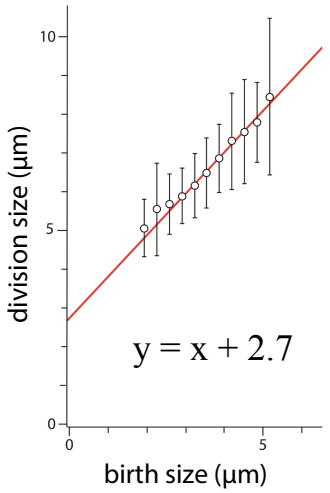


Sattar Taheri

Data from Wang et al., *Robust growth of E. coli*, Curr Biol **20**, 1099-1103 (2010)

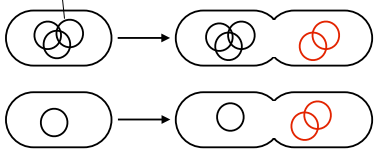
What Johan Paulsson said about Sattar's correlations back in 2012 in our last meeting...





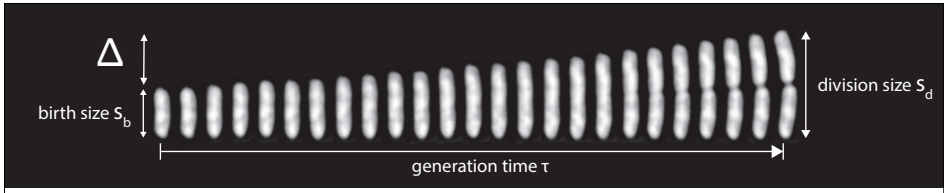
A lesson from plasmid copy-number control

plasmids: always add two

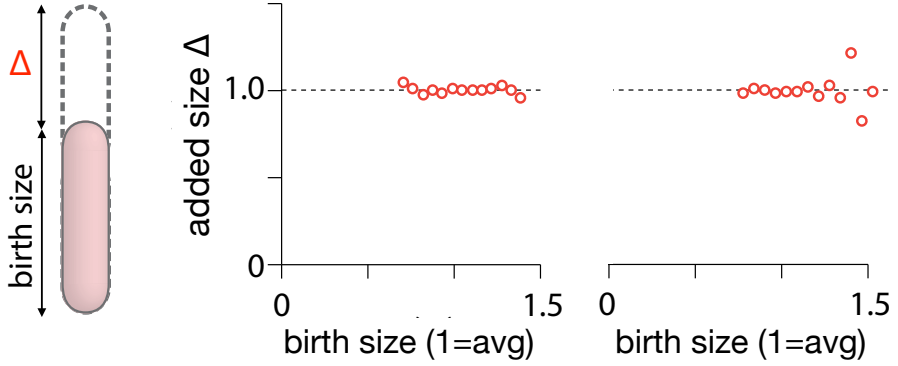


average copy number = two

Johan Paulsson



"Adder": cells grow by constant Δ irrespective of the newborn size



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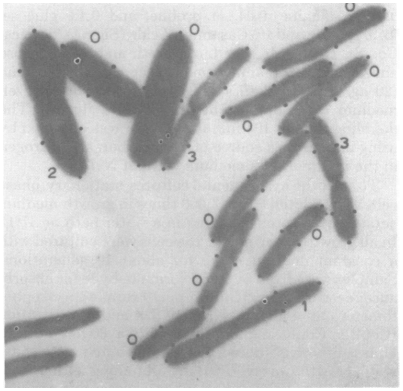
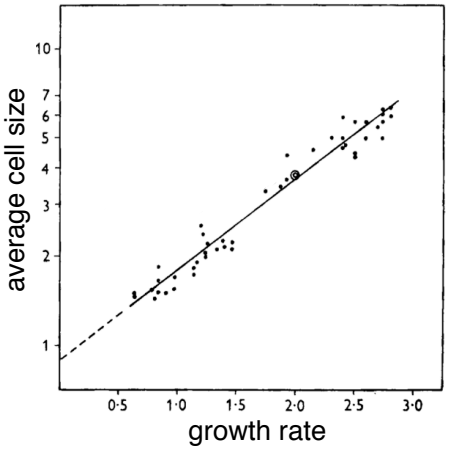
We set out to do growth experiments for a wide range of growth conditions at the single-cell level, but that was not easy.





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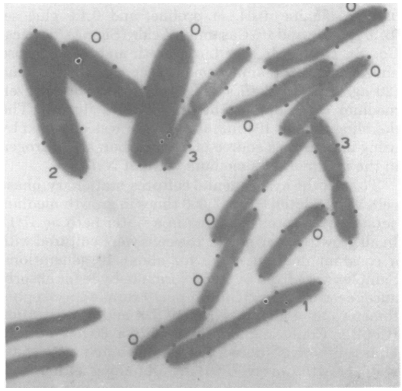
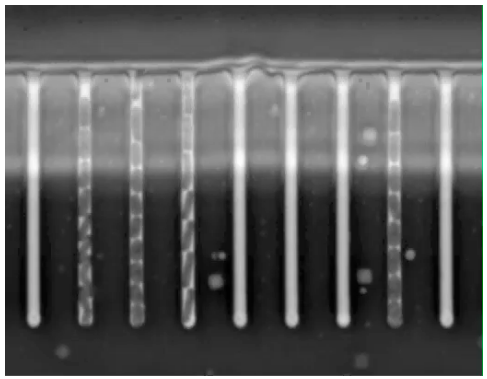
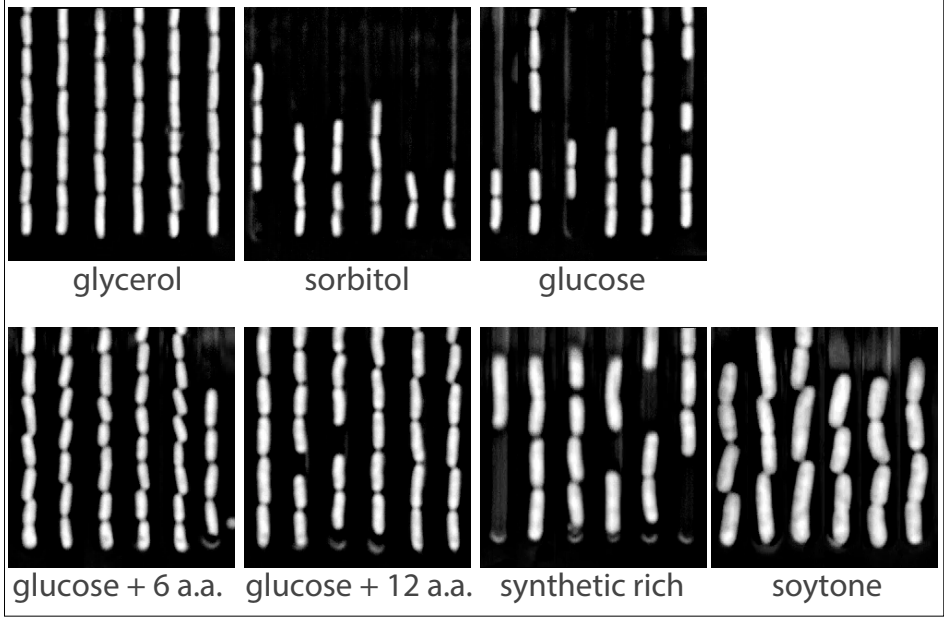




Sattar Taheri @ CSHL

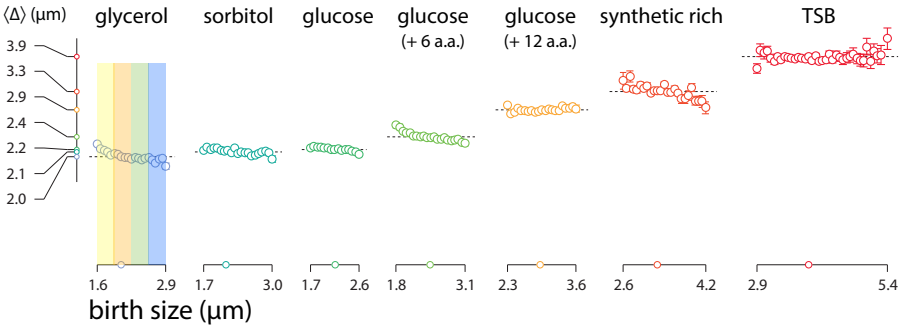
Sattar persevered for more than two years to make his experiments work.

...and he succeeded.



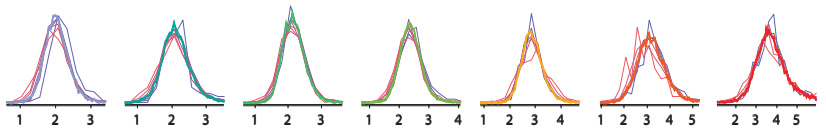
E. coli controls cell size using an "adder"

added size Δ is constant irrespective of newborn size



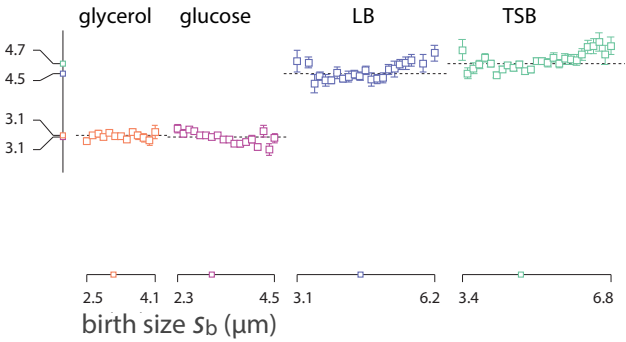
conditional distributions $p(\Delta|s_b)$ are independent of s_b

distributions $p(\Delta)$

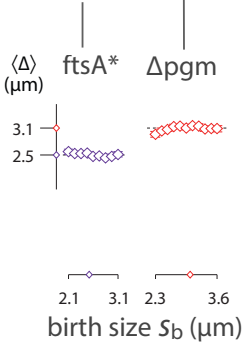


"Adder" is general

B. subtilis
(Gram positive)



E. coli size mutants
defect in cell-wall synthesis
defect in cell division



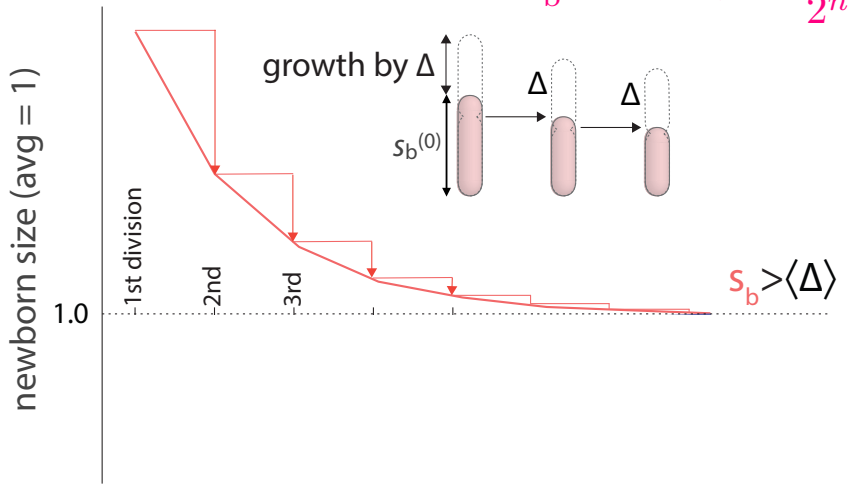

JT Sauls
(grad student)


Petra Levin
(Washington U.)


Bisco Hill
(Washington U.)

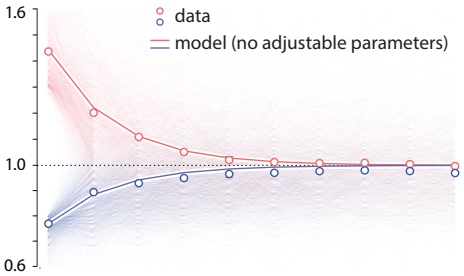
Adder ensures size homeostasis in bacteria

$$s_b^{(n)} \to \Delta \mp \frac{\Delta - s_b^{(0)}}{2^n}$$

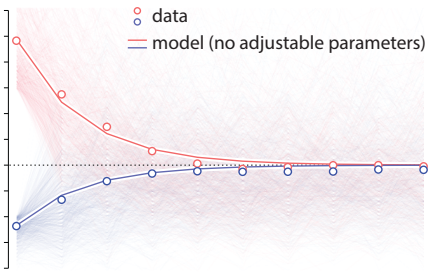


Adder ensures size homeostasis in bacteria

Confirmation: *E. coli*



Confirmation: *B. subtilis*



Sattar Taheri
(post-doc)

JT Sauls
(grad student)

Petra Levin
(Washington U.)

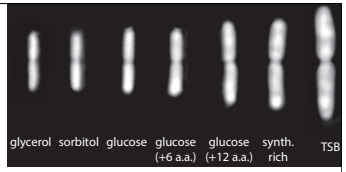
Bisco Hill
(Washington U.)

On the structure and hierarchy of basic controls underlying cellular reproduction.

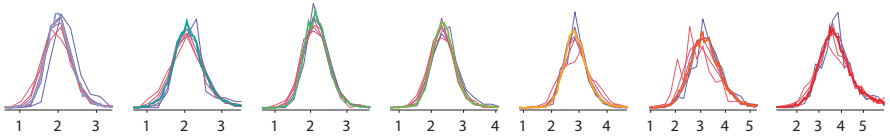
Massimo Vergassola

Serena Bradde

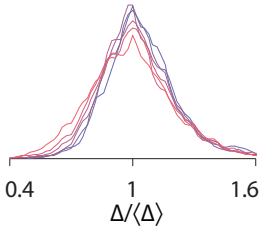
Constant Δ: Beyond correlations...



Collapse of conditional distributions $\rho(\Delta|s_b)$



added size Δ (μm)

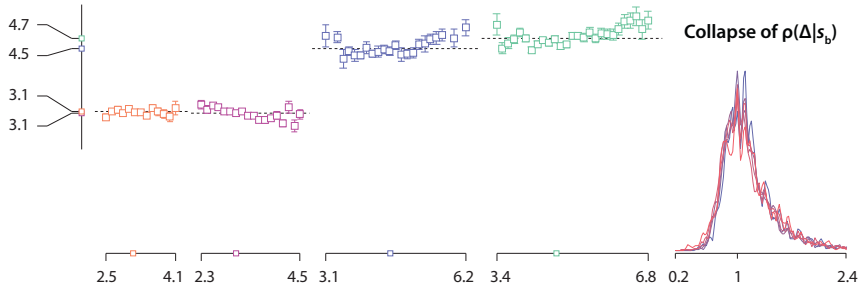


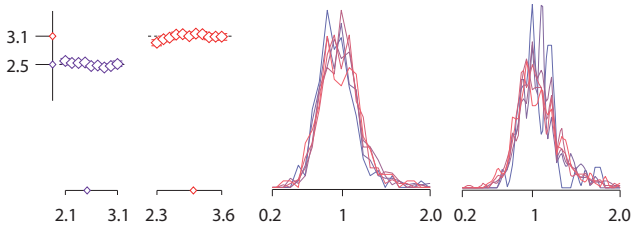
Collapse of the entire $\rho(\Delta/\langle\Delta\rangle|s_b)$ from all growth conditions

-> Δ is truly independent of s_b !!!

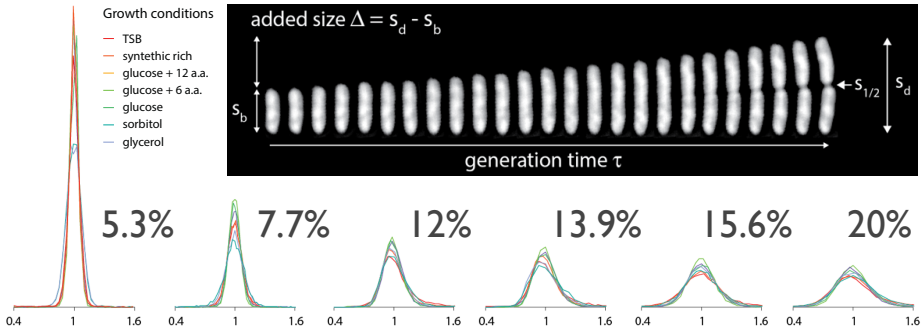
One could not conclude this from correlations.

B. subtilis and *E. coli* size mutants are adder, too.



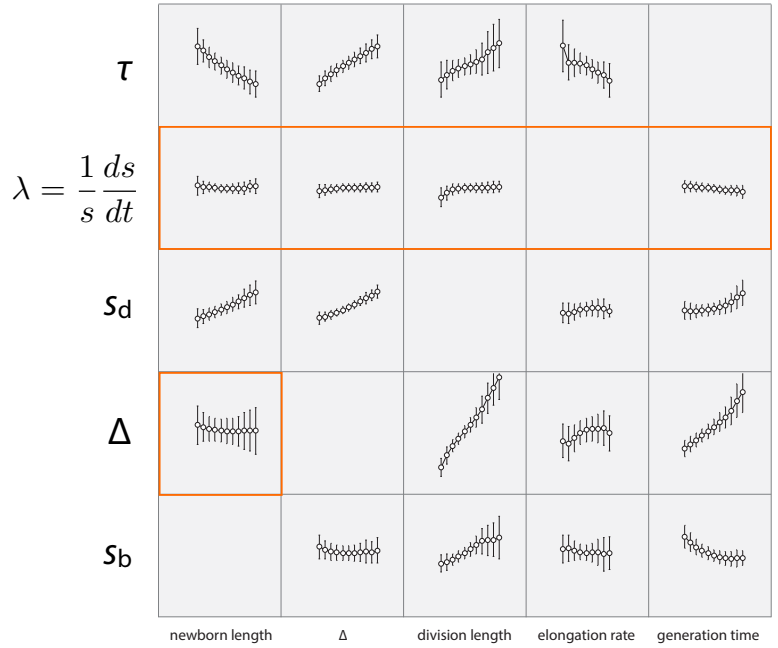


In fact, distributions of all six basic growth parameters collapse onto each other when rescaled by their respective means

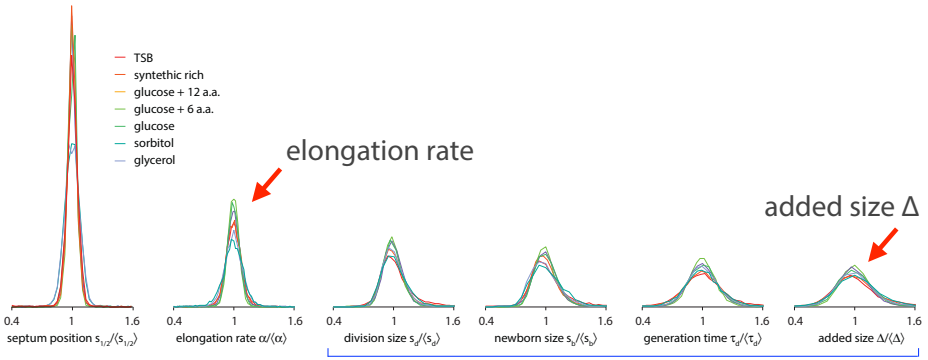


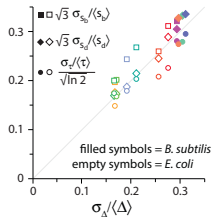
$s_{1/2}$	$\lambda = \frac{1}{s}\frac{ds}{dt}$	s_d	s_b	τ	Δ
septum position	elongation rate	division size	newborn size	generation time	added size

Only two control parameters are independent



Only two control parameters are independent

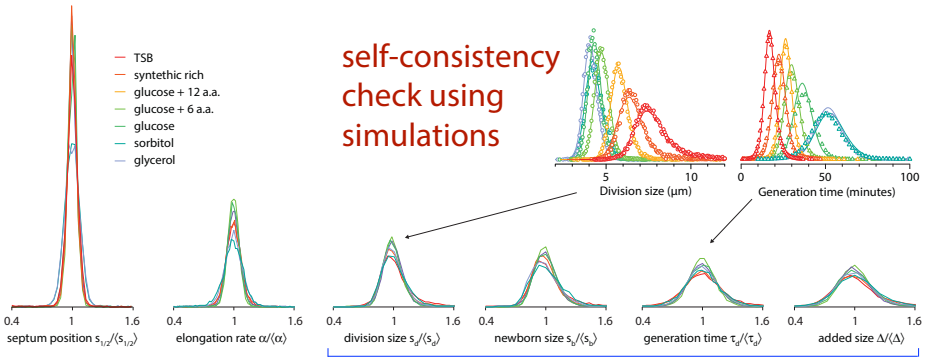


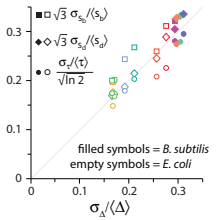


$$3\left(\frac{\sigma_d}{\langle s_d\rangle}\right)^2 \lesssim 3\left(\frac{\sigma_b}{\langle s_b\rangle}\right)^2 \approx \frac{1}{\ln 2}\left(\frac{\sigma_\tau}{\langle\tau\rangle}\right)^2 \approx \left(\frac{\sigma_\Delta}{\langle\Delta\rangle}\right)^2$$

We can also show analytically that s_b, s_d, τ inherit the scaling form of Δ; if Δ distributions collapse, so do those for s_b, s_d, τ.

Only two control parameters are independent





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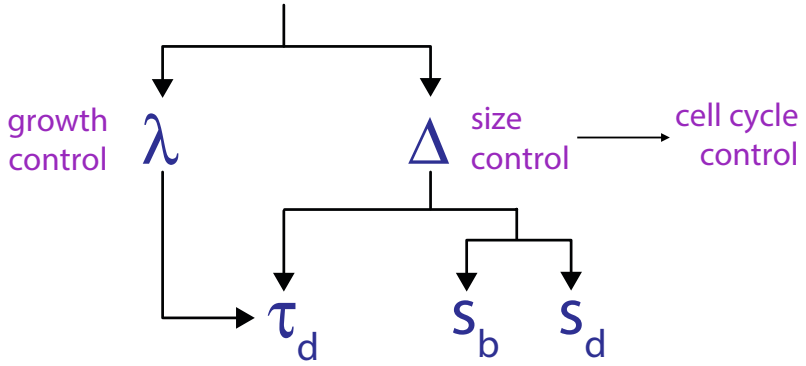
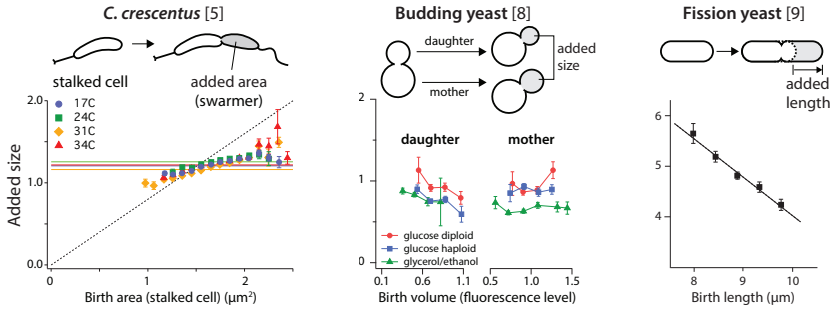
Our proposed hierarchy of cellular reproduction controls

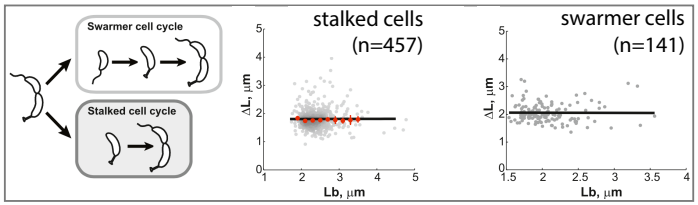


To what extent is adder general?

Other organisms also show a linear relationship between added size and birth size.

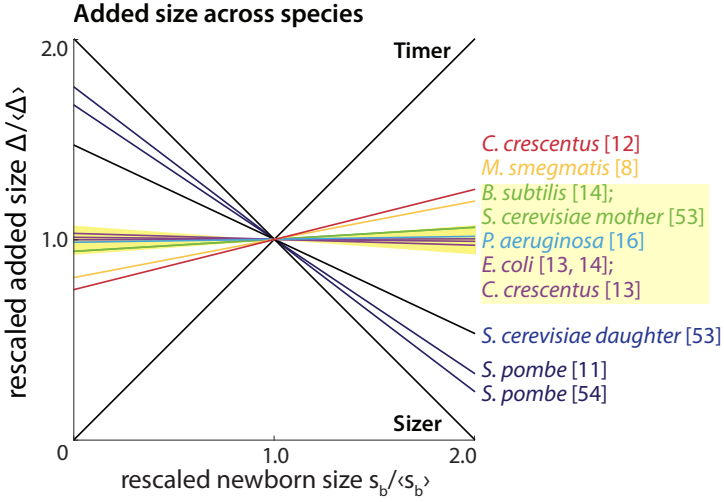


Scherer/Dinner labs (2014) | Fred Cross lab (2007, 2009) | Fantes (1977)



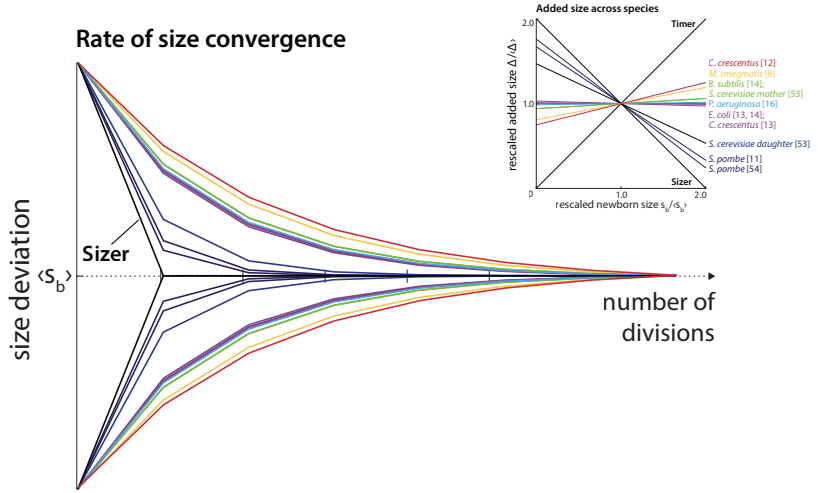
Jacobs-Wagner lab (2014)

The linear relationship ensures size homeostasis



Jun and Taheri-Araghi, TRENDS in Microbiology (2015)
JT Sauls, D. Li, and S. Jun, Current Opinion in Cell Biology (2016)

The linear relationship ensures size homeostasis



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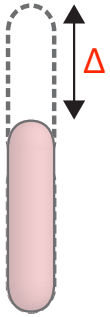
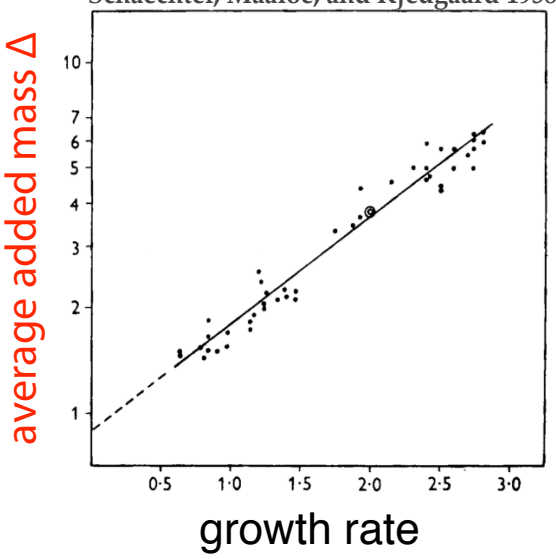
JT Sauls, D. Li, and S. Jun, Current Opinion in Cell Biology (2016)

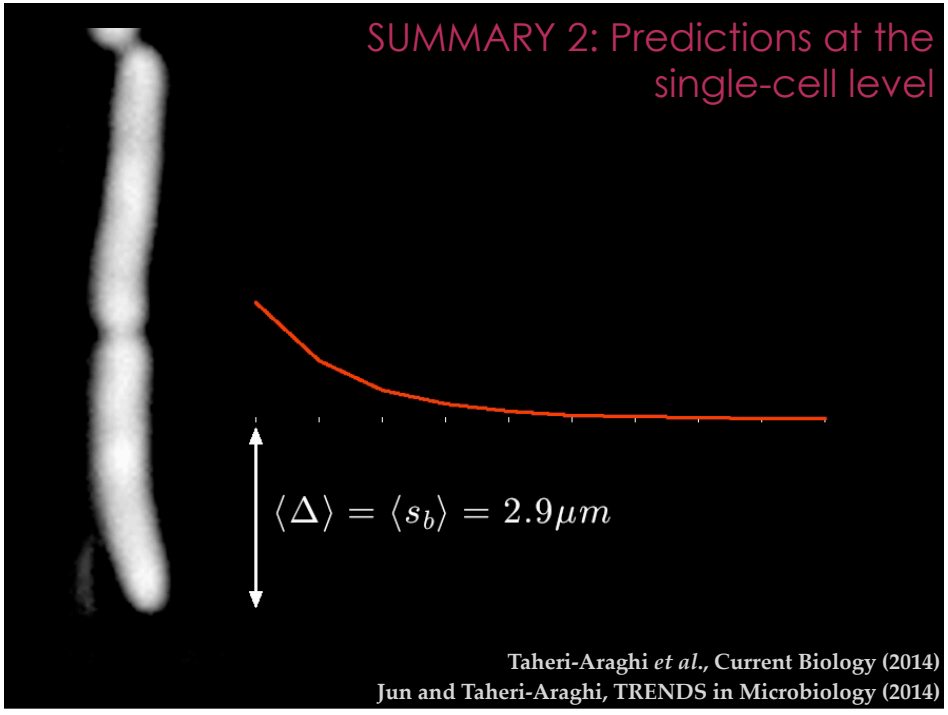
SUMMARY 1: The Growth Law and Adder



Schaechter, Maaloe, and Kjedgaard 1958



SUMMARY 2: Predictions at the single-cell level



Taheri-Araghi *et al.*, Current Biology (2014)
Jun and Taheri-Araghi, TRENDS in Microbiology (2014)

Snippet appeared in a local Indian newspaper's science section...