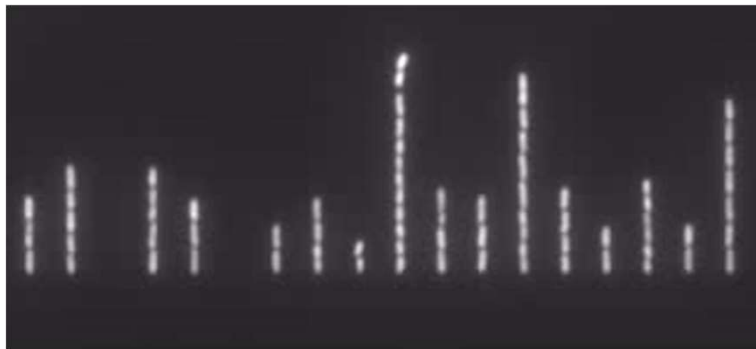


Quantitative principles in biological systems

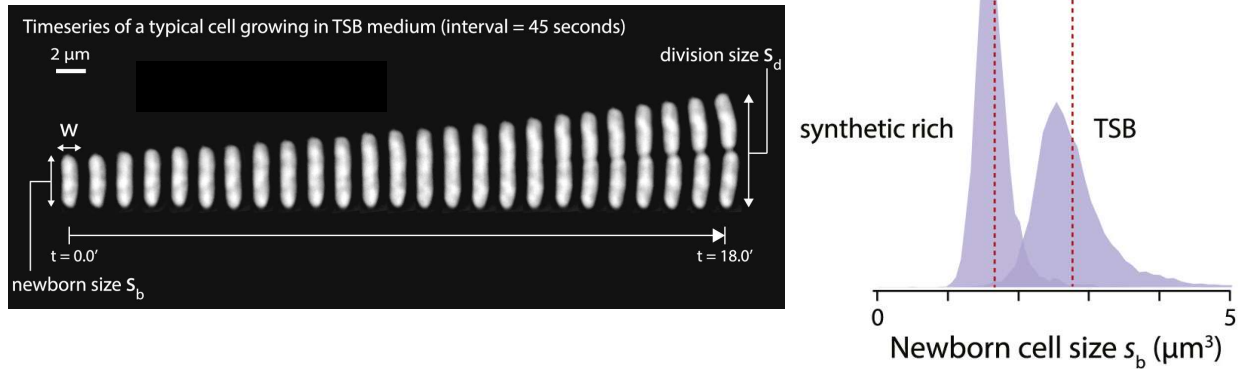
3. Cell cycle regulation

Spring 2026

Tracking single bacteria over hundreds of generations

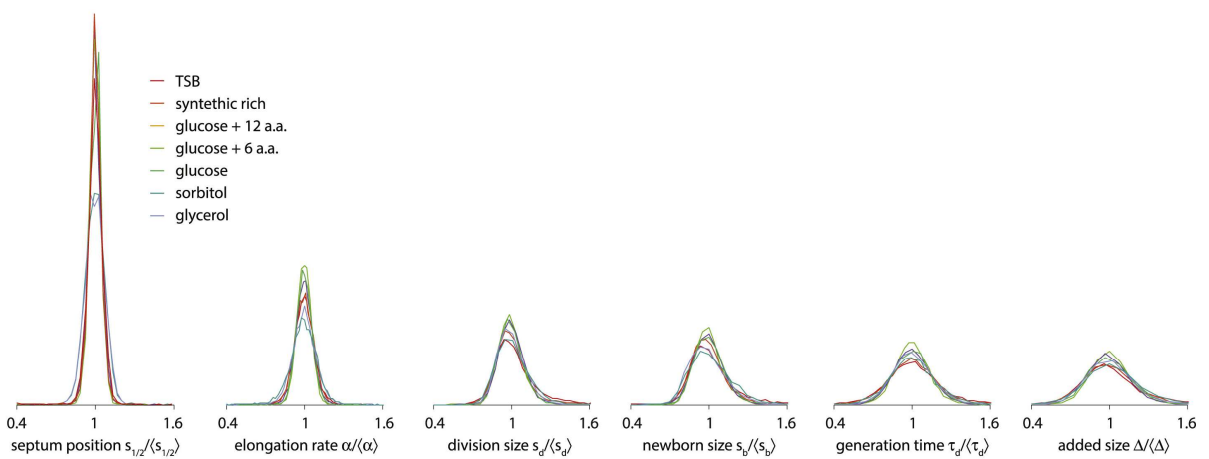


Tracking single bacteria over hundreds of generations



Taheri-Araghi et al. *Curr Biol* (2015)

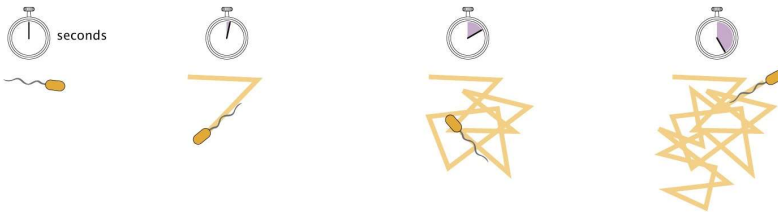
Cells achieve homeostasis despite various sources of noise.



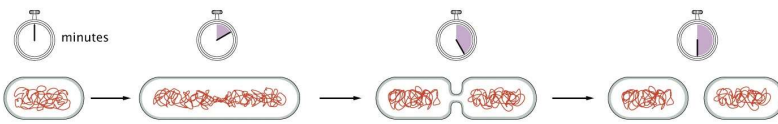
Taheri-Araghi et al. *Curr Biol* (2015)

A “timer” strategy for timing divisions

Cell movements



Bacterial cell division



$$v_d = v_b e^{\lambda t_d} + \xi$$

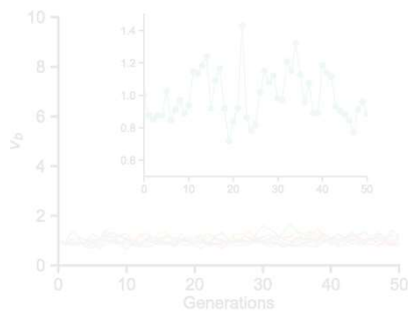
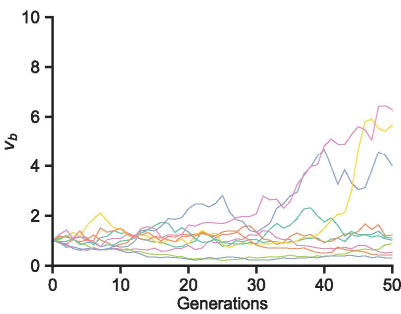
$$\text{If } t_d = \ln 2 / \lambda \dots$$

$$v_b^{\text{next}} = v_b + \xi$$

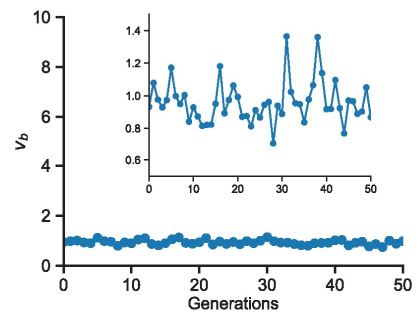
Phillips et al

A “timer” strategy fails to regulate size.

“Timer” model



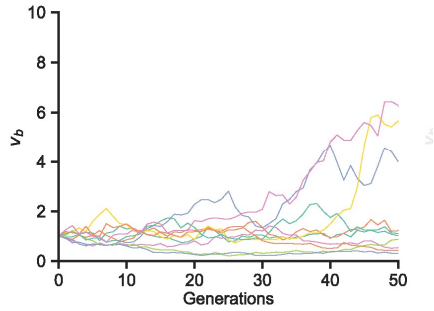
Data



Ho et al. *Annu Rev Biophys* (2018)

Consequences of "timer" ...

"Timer" model

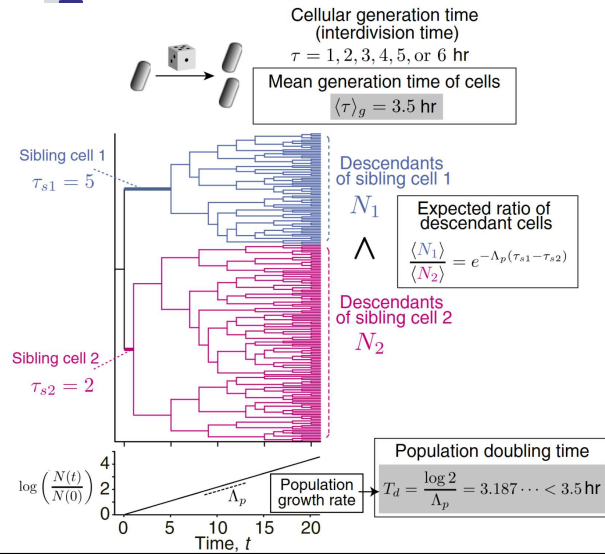


Noise-driven growth rate gain in clonal cellular populations

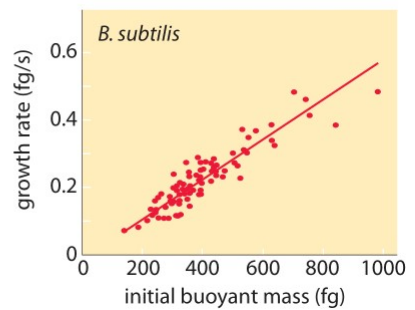
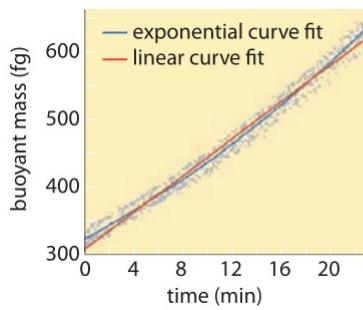
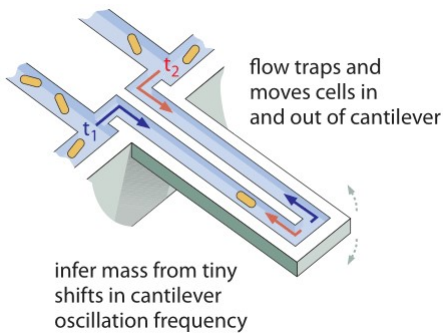
Mikihiro Hashimoto^a, Takashi Nozoe^a, Hidenori Nakaoka^a, Reiko Okura^a, Sayo Akiyoshi^a, Kunihiko Kaneko^{a,b}, Edo Kussell^{c,d}, and Yuichi Wakamoto^{a,b,1}

^aDepartment of Basic Science, Graduate School of Arts and Sciences, University of Tokyo, Tokyo 153-8902, Japan; ^bResearch Center for Complex Systems Biology, University of Tokyo, Tokyo 153-8902, Japan; ^cDepartment of Biology, Center for Genomics and Systems Biology, New York University, New York, NY 10003; and ^dDepartment of Physics, New York University, New York, NY 10003

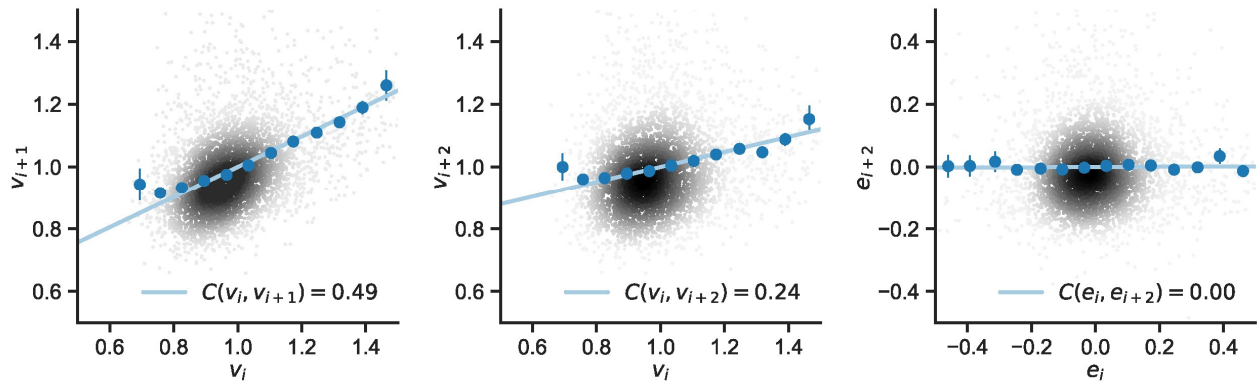
Edited by Daniel L. Hartl, Harvard University, Cambridge, MA, and approved February 5, 2016 (received for review October 19, 2015)



Exponential growth at the single cell level



Cells add a constant size from birth to division.



$$v_b^{\text{next}} = \frac{1}{2}v_b + v_0 + \xi$$

Ho et al. *Annu Rev Biophys* (2018)

Consequences of “adder”... fluctuations vs oscillations

LETTER

doi:10.1038/nature14562

A noisy linear map underlies oscillations in cell size and gene expression in bacteria

Yu Tanouchi^{1*}, Anand Pai^{1*}, Heungwon Park^{2,3*}, Shuang Huang¹, Rumen Stamatov¹, Nicolas E. Buchler^{2,3,5} & Lingchong You^{1,5}

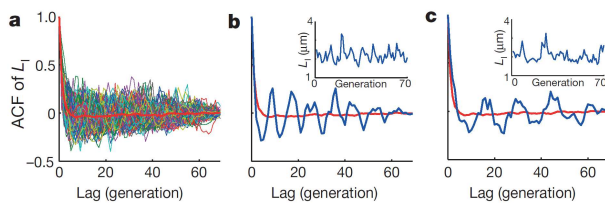
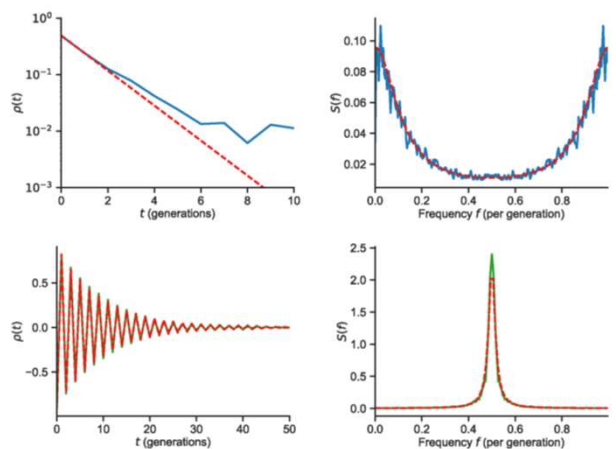


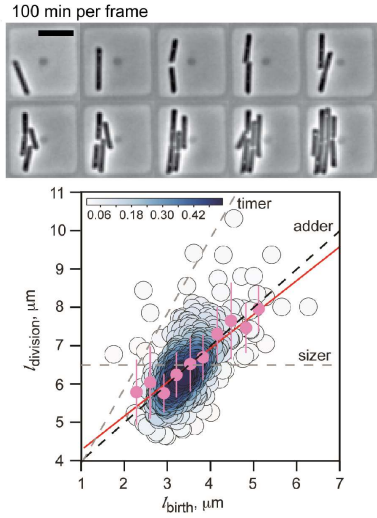
Figure 1 | Transient oscillations in cell size. **a**, ACF of all lineages ($n = 160$) and their average (thick red line). **b**, An example of L_1 oscillation with a period of ~ 8 generations. **c**, Another example of L_1 oscillation with a period of ~ 16 generations.



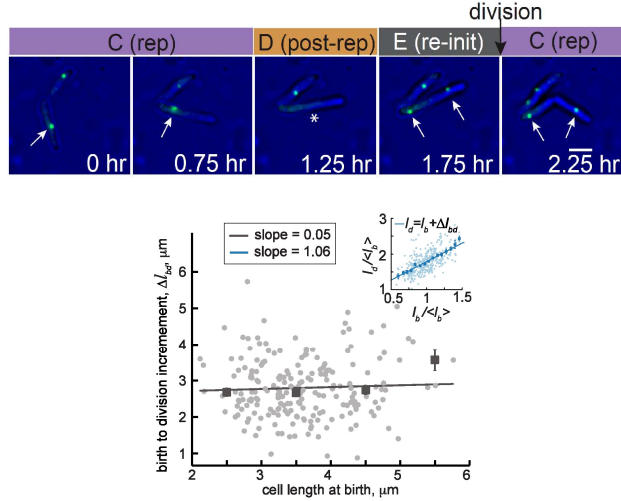
Ho et al. *Annu Rev Biophys* (2018)

Adders are common.

Halobacterium (an archaeon)



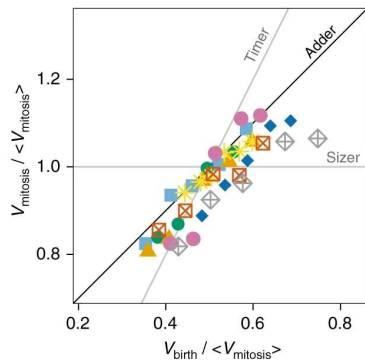
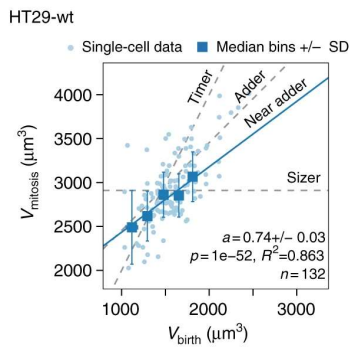
Mycobacterium (tuberculosis model)



Eun et al. *Nat Microbiol* (2017)
Logsdon et al. *Curr Biol* (2017)

Adders are common.

Mammalian cell lines

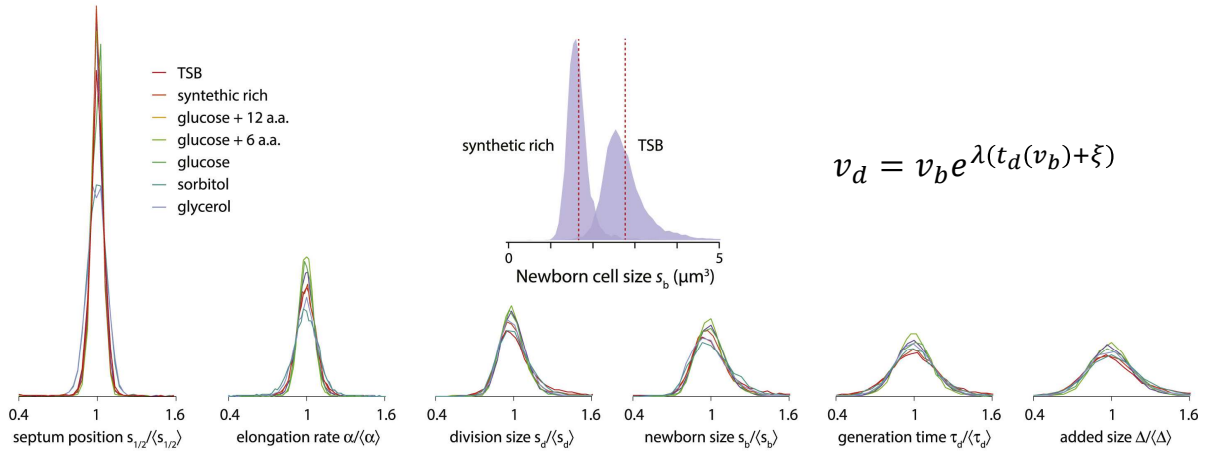


$$V_{mitosis} / \langle V_{mitosis} \rangle = a \cdot V_{birth} / \langle V_{mitosis} \rangle + b / \langle V_{mitosis} \rangle$$

	a	SE a	b	n	N
Sizer	0		1		
HT29-wt (FXm)	0.7	0.03	0.58	132	3
RPE1 (FXm)	0.8	0.02	0.52	148	3
L1210 (Son et al. 2012)	0.8	0.02	0.57	122	
HeLa-MP (channels)	0.9	0.02	0.53	137	3
Adder	1		0.5		
HT29-hgem (FXm)	1.1	0.02	0.38	141	4
MDCK-MP (channels)	1.2	0.03	0.37	87	2
HeLa-hgem (FXm)	1.2	0.01	0.31	158	2
Raji (Fxm)	1.7	0.07	0.09	108	2
Timer	2		0		

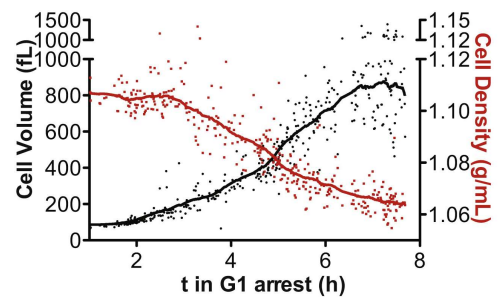
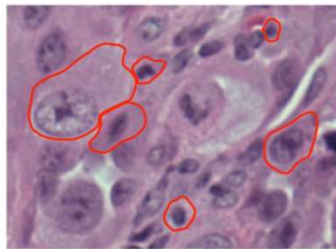
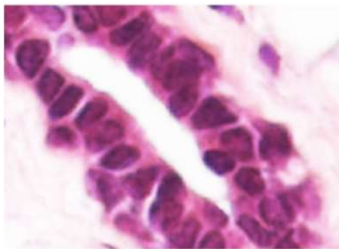
Cadart et al. *Nat Commun* (2018)

Consequences of “adder”... noise sources



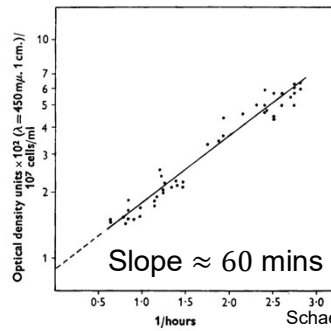
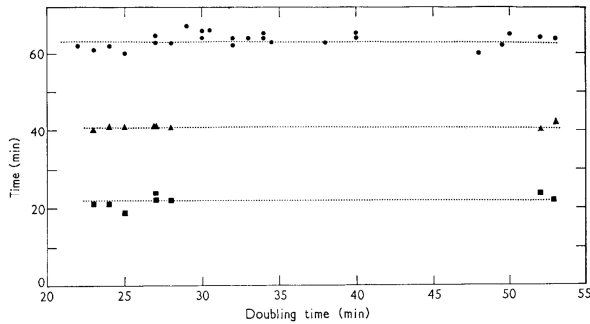
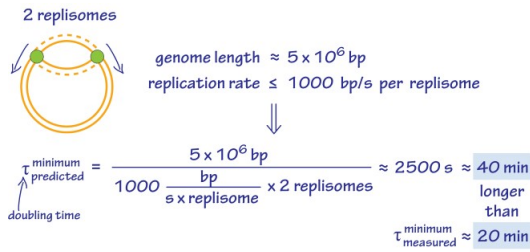
Taheri-Araghi et al. *Curr Biol* (2015)

Why care about size?



Neurohr et al. *Cell* (2019)
 Ginzberg et al. *Science* (2015)

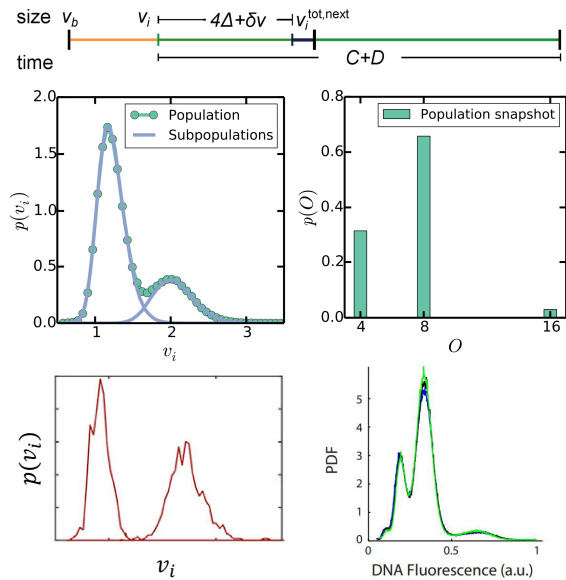
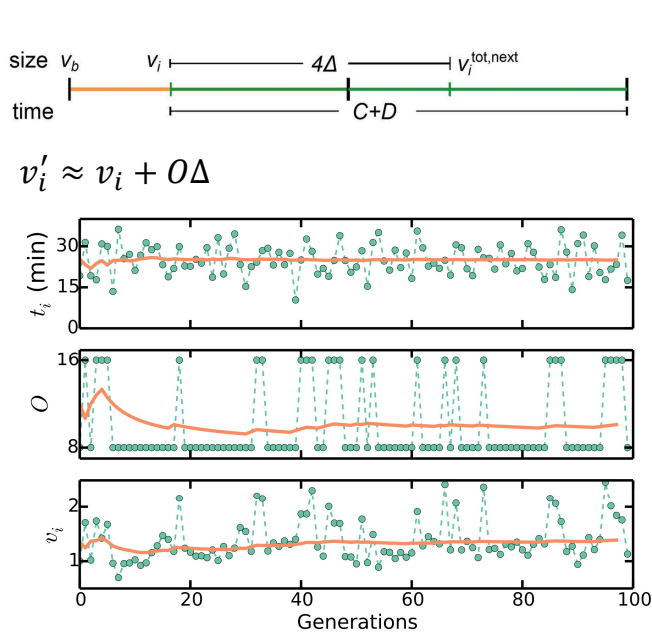
DNA replication and cell division are tightly linked.



$$v_b = v_i 2^{(C+D)/\tau}$$

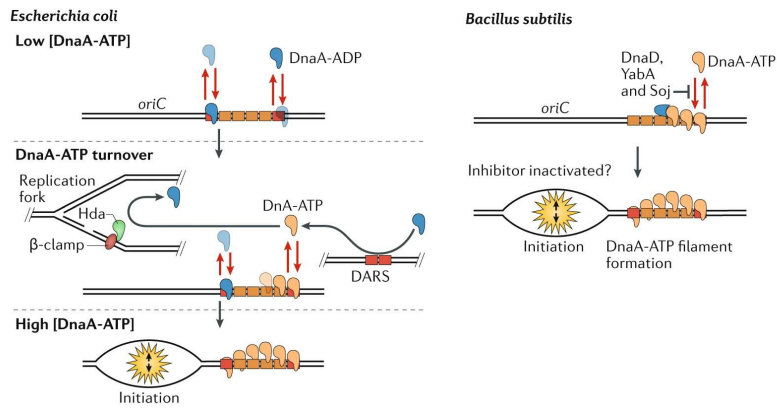
Phillips et al
 Schaechter et al. *J Gen Microbiol* (1958)
 Cooper and Helmstetter. *J Mol Biol* (1968)

Consequences of “adder per origin”... feature not bug



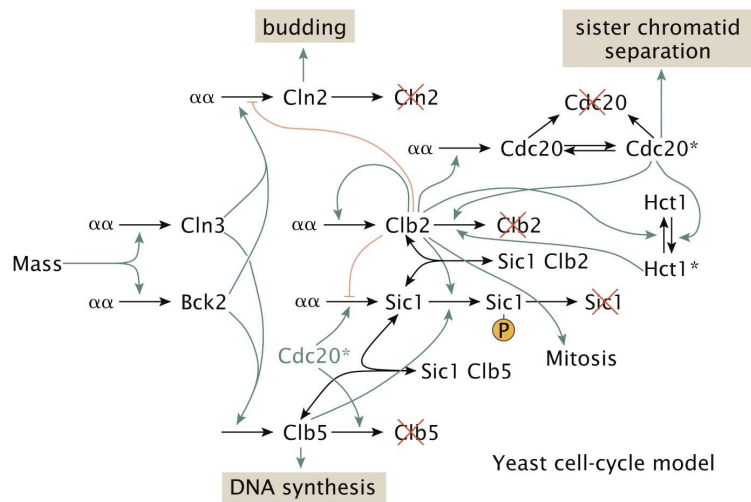
Wallden et al. *Cell* (2016)
 Ho and Amir. *Front Microbiol* (2015)

So what is the molecular mechanism?



Reyes-Lamothe and Sherratt. *Nat Rev Microbiol* (2019)

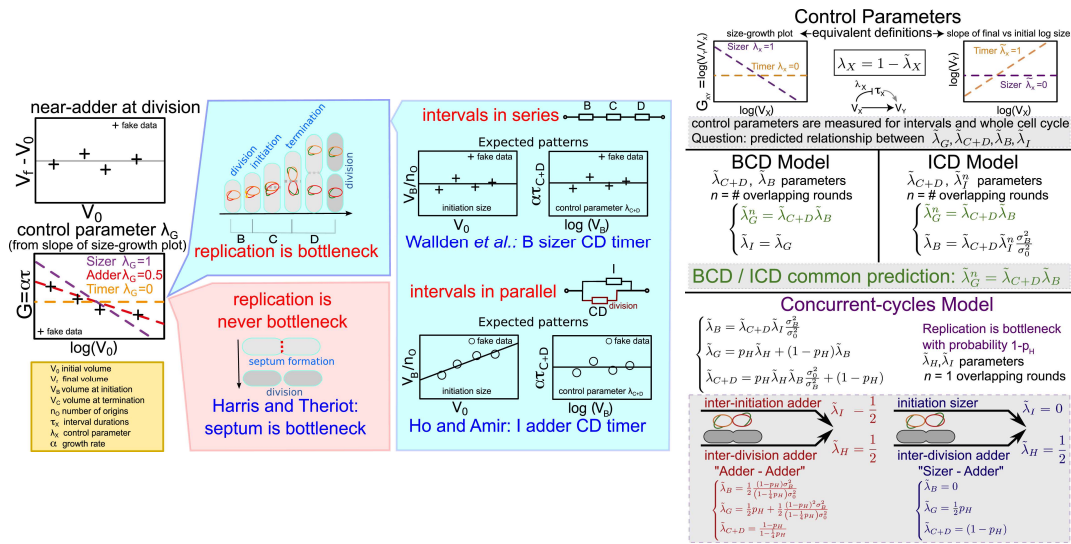
So what is the molecular mechanism?



Yeast cell-cycle model

Phillips et al

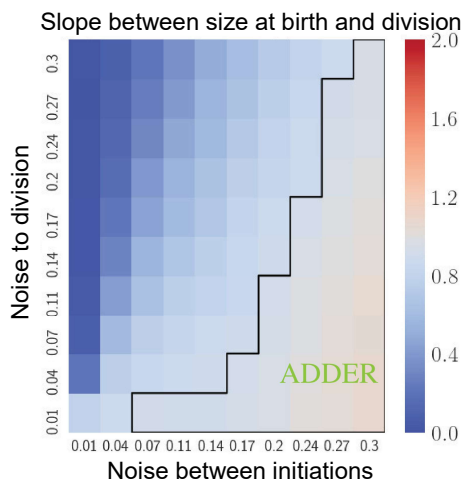
Consequences of "adder per origin"... zoo of models?



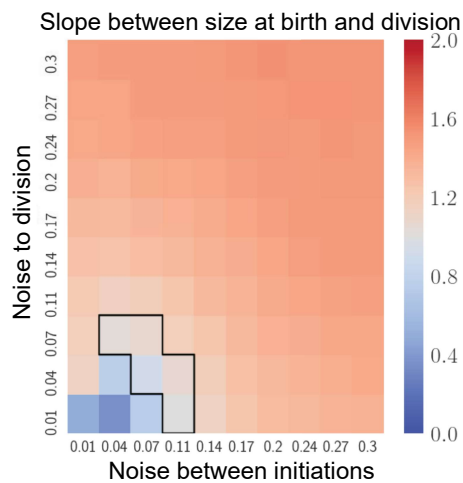
Micali *et al.* *Cell Rep* (2018)

Adder correlations can emerge robustly depending on model structure.

Initiator accumulation



Inhibitor dilution



Ho. *PhD thesis* (2019)

Summary

- Random walks are everywhere, and noise is not negligible.
- The devil is in the details (but sometimes the details vanish).

