More questions than answers: Relations between quantitative physiology and aging in *E. coli*

Aging in Single Celled Organisms:
From Bacteria to the Whole Tree of Life
Santa Fe Institute, February 2020

Matteo Osella
Università di Torino and INFN
Physics Department

Stat phys tools & data analysis:

- *Quantitative physiology*
- Stochastic gene expression
- Statistical physics of complex systems (genomes as collections of genes, books as collections of words...)
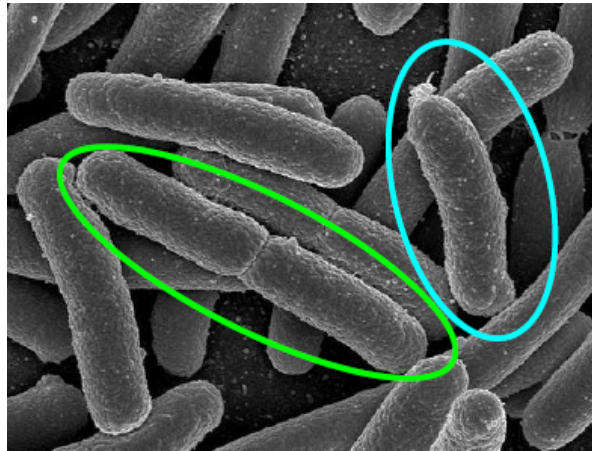
Single-cell quantitative physiology
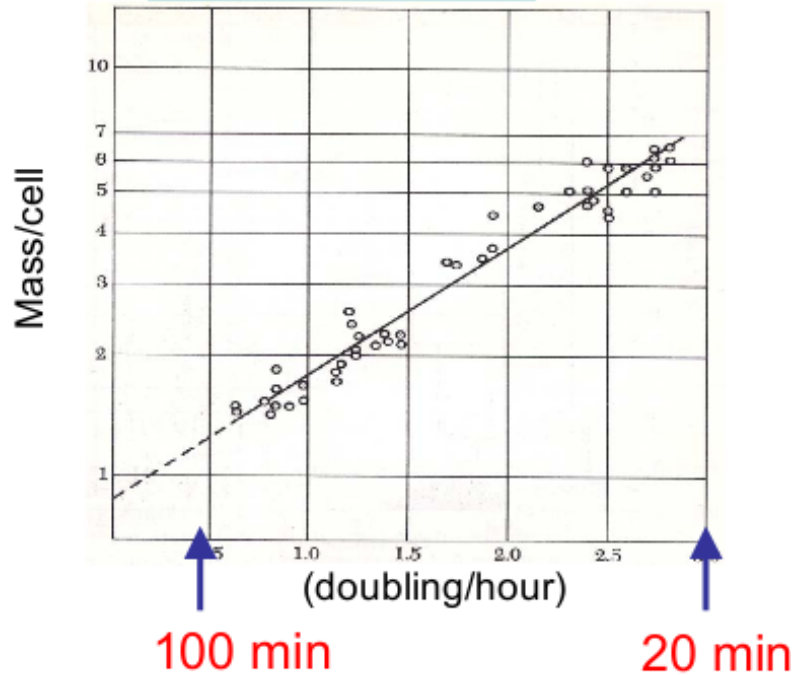
What is the single-cell growth law?
How does a cell decide it is time to divide?
How is cell-cycle progression coupled to growth?

…

(e.g. Scheacter et al. 1958, Killander-Zetterberg 1965, Donachie 1968, Nurse et al. 1976…)

# Statistical-physics-like laws in microbial physiology

SCHAECHTER, M., MAALØE, O. & KJELDGAARD, N. O. (1958). *J. gen. Microbiol.* 19,
Dependency on Medium and Temperature of Cell Size and
Chemical Composition during Balanced Growth of
Salmonella typhimurium
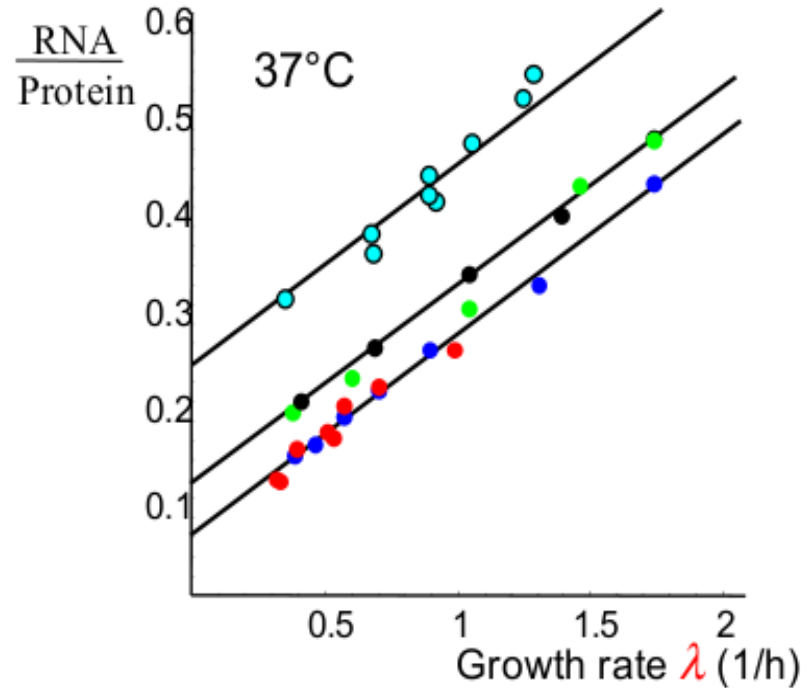
M. Scott, C. W. Gunderson, E. Mateescu, Z. Zhang and T. Hwa
"Interdependence of cell growth and gene expression:
origins and consequences",
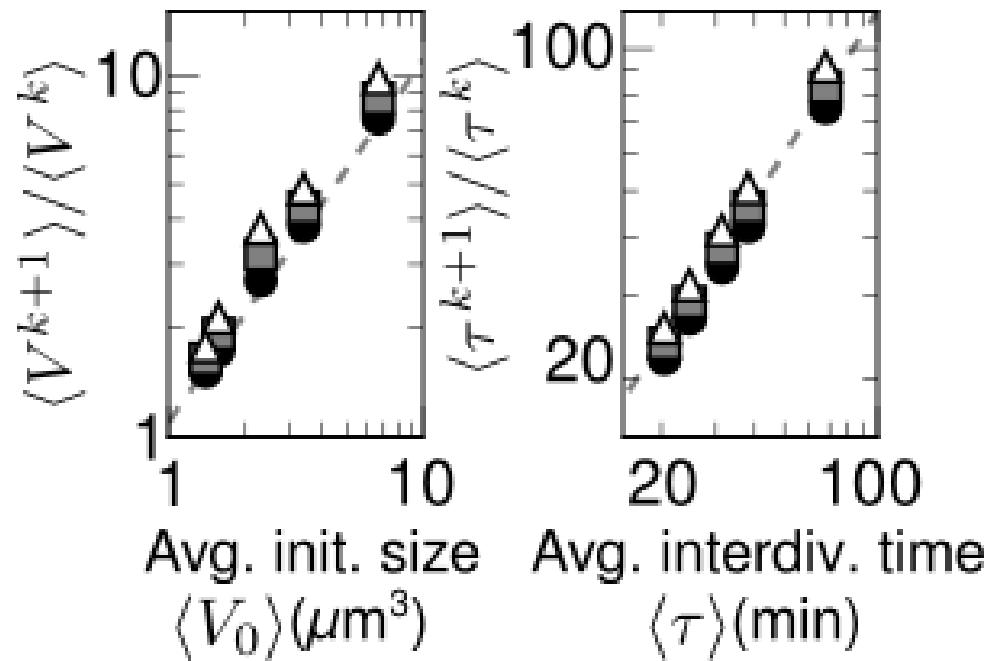Science 330: 1099-1102 (2010).

At the single-cell level:
Universal distributions of sizes and doubling times

(Taheri-Araghi et al. Curr Biol 2015)
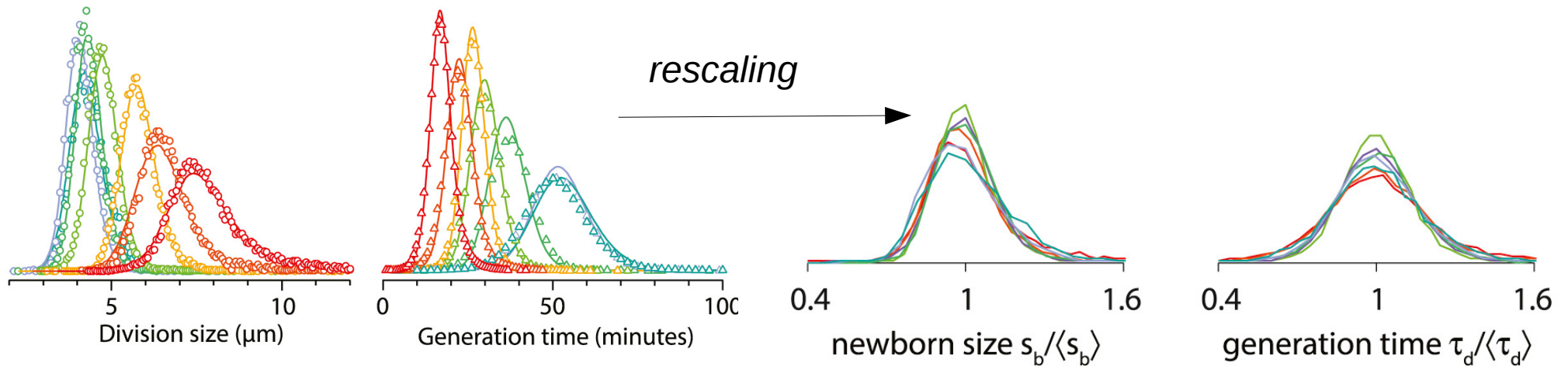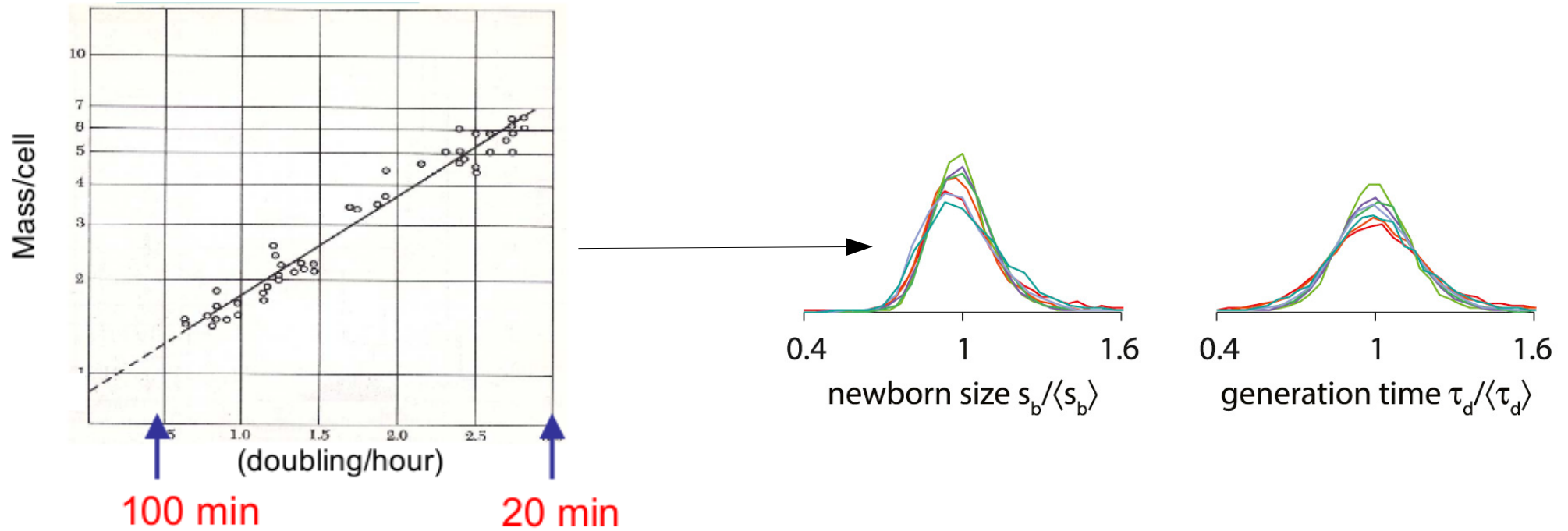

rescaling

Rescaling is equivalent to constant relative fluctuations (CV)

(Kennard et al Phys Rev E 2016)

A simple description of cell growth?

One timescale (doubling time) → size scale → level of cell-to-cell variability

Warnings:
balanced exponential growth; no stress or extrinsic damage; hidden
assumptions of "ergodicity", symmetry etc that could be approximately realized
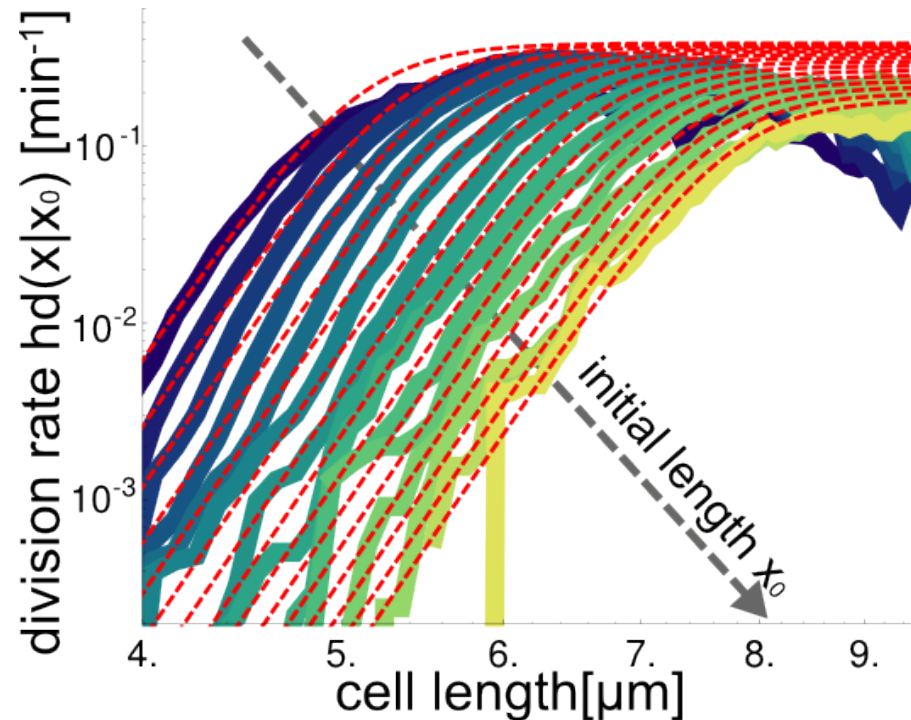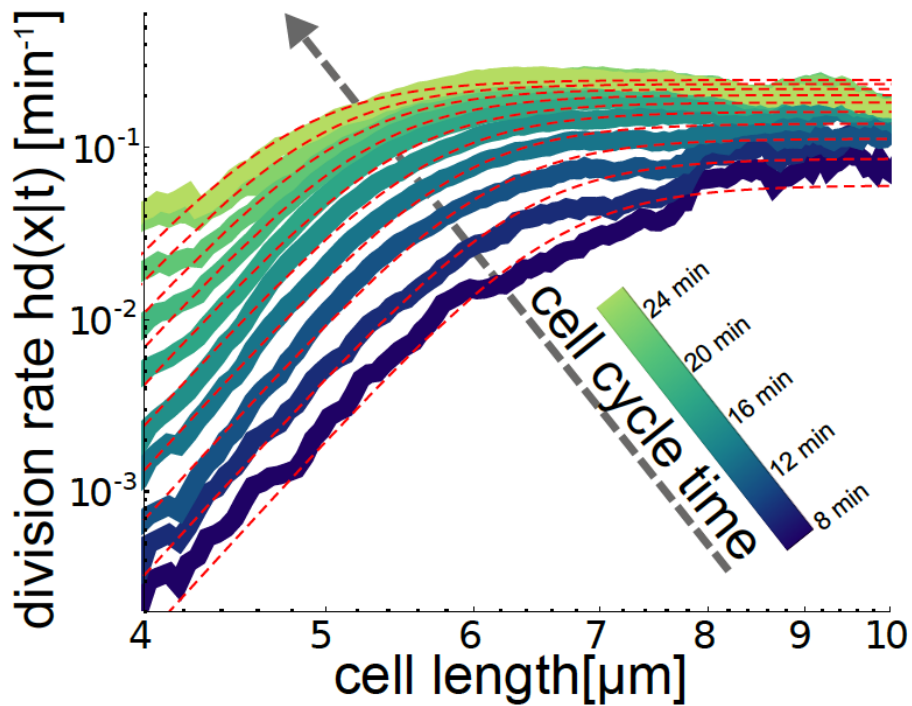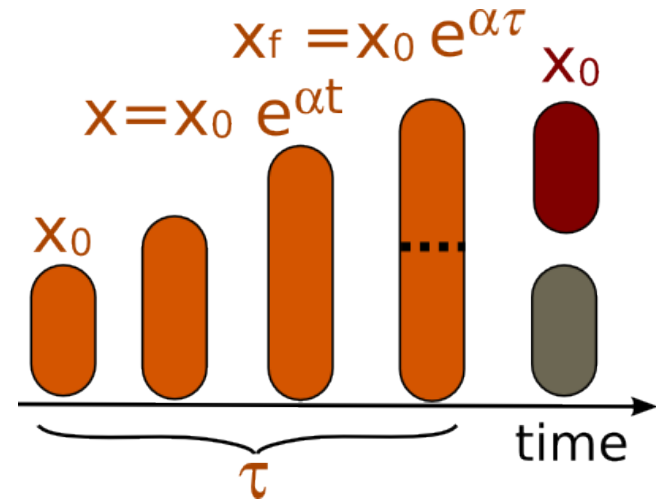only in the artificial experimental settings..
NO AGING

The stochastic process of growth and division

(Osella et al PNAS 2014)

HAZARD DIVISION RATE hd

hd = probability of dividing per unit time
GIVEN the value of the measurable parameters:

How does the stochastic process of growth and division change with aging?
What is the role of cell size in aging and survival?
What is the role of cell shape and geometry in aging and cell cycle control?
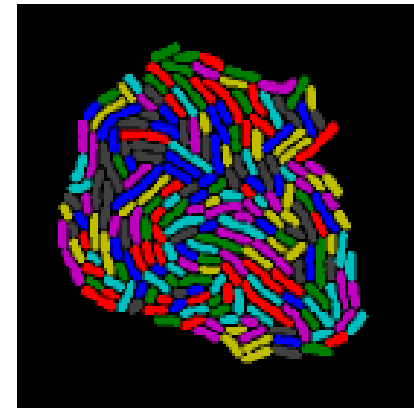
...

Which processes are actually under selection
and which ones are spandrels?
(AKA: the old question of "what is fitness?")

The hidden asymmetry in E. coli cell division

Aging and Death in an Organism That Reproduces by Morphologically Symmetric Division

Eric J. Stewart[1,2]*, Richard Madden[3¤], Gregory Paul[1,2], François Taddei[1,2]
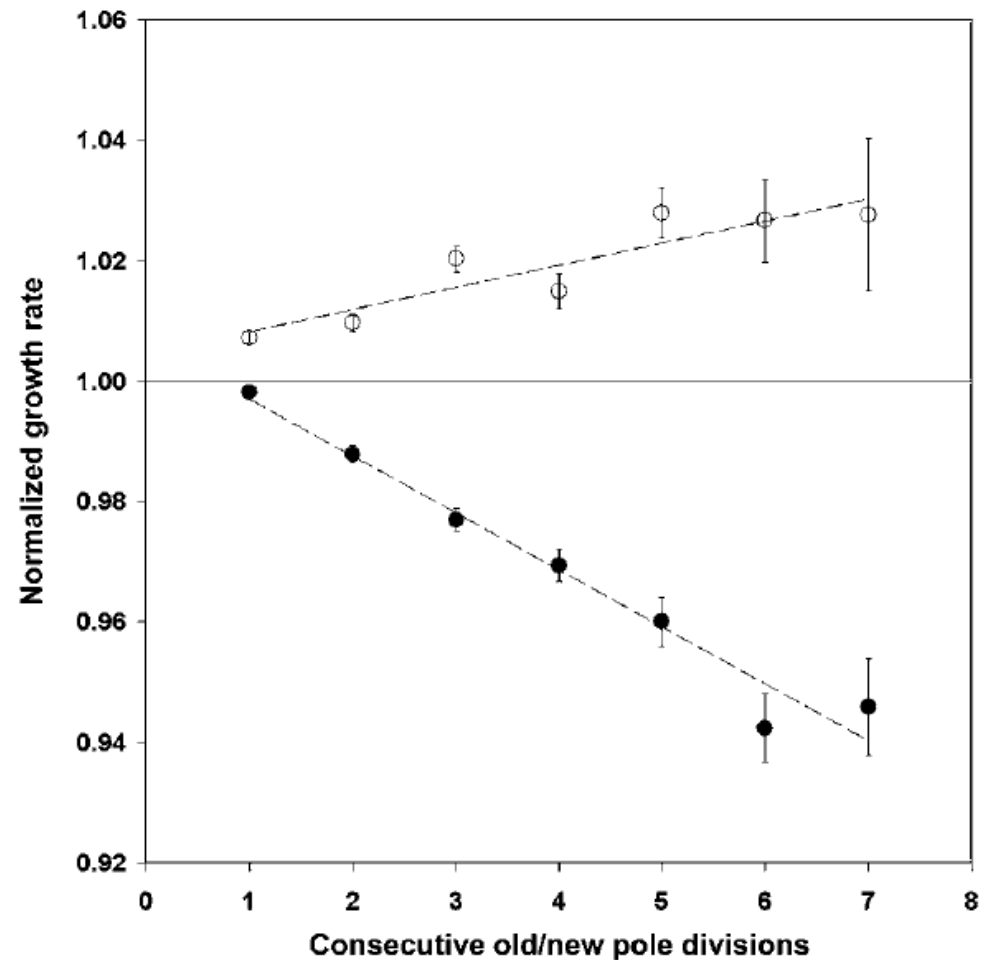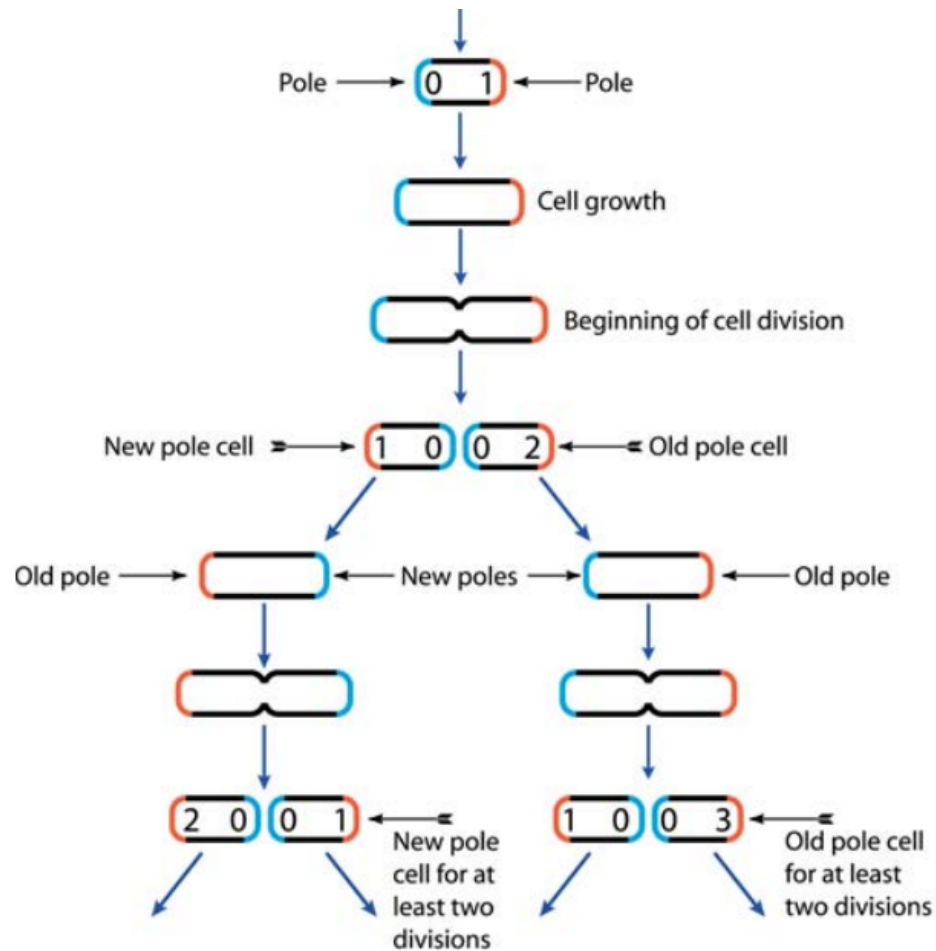
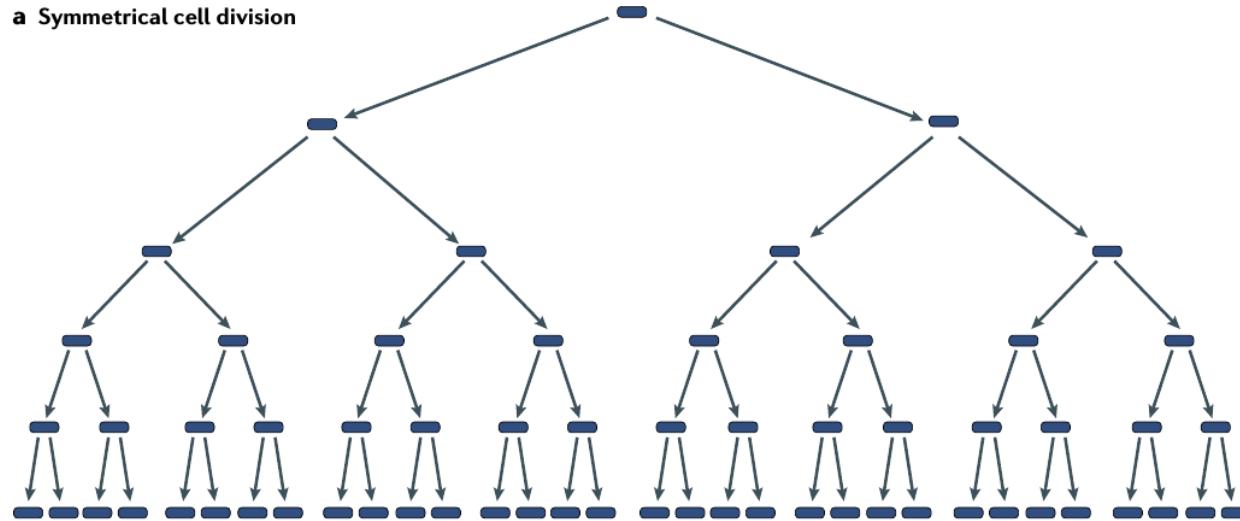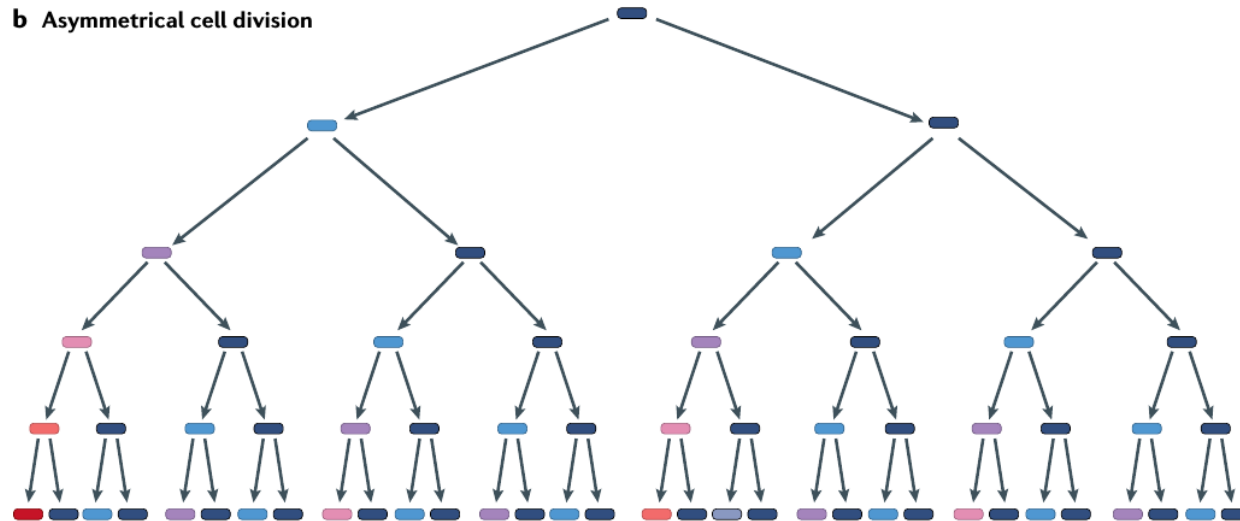# Microbial ageing and longevity

Roy Z. Moger-Reischer and Jay T. Lennon *

a Symmetrical cell division

b Asymmetrical cell division

Young ▮▮▮▮▮ Old
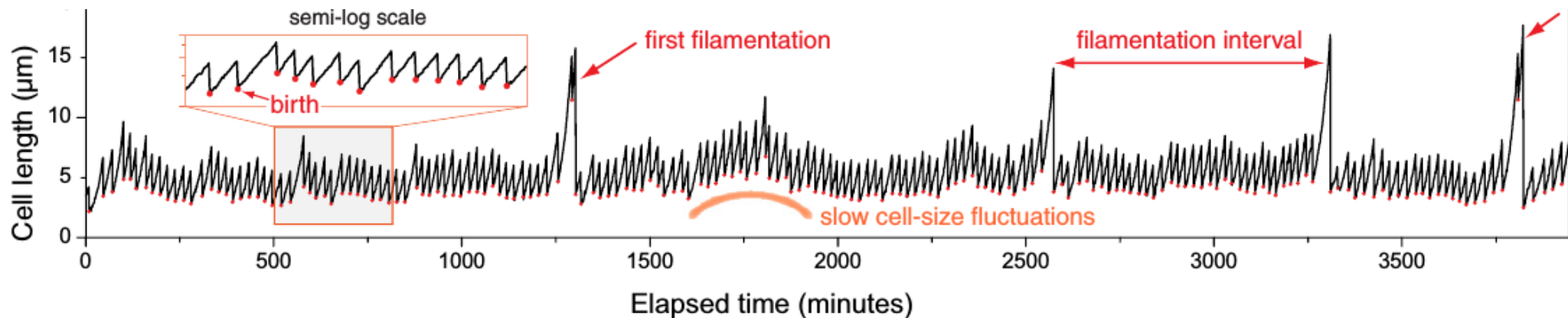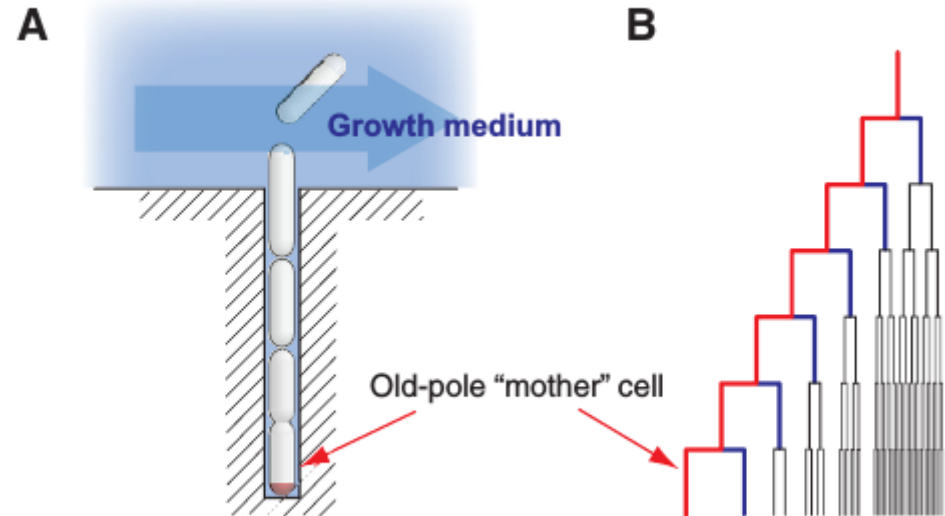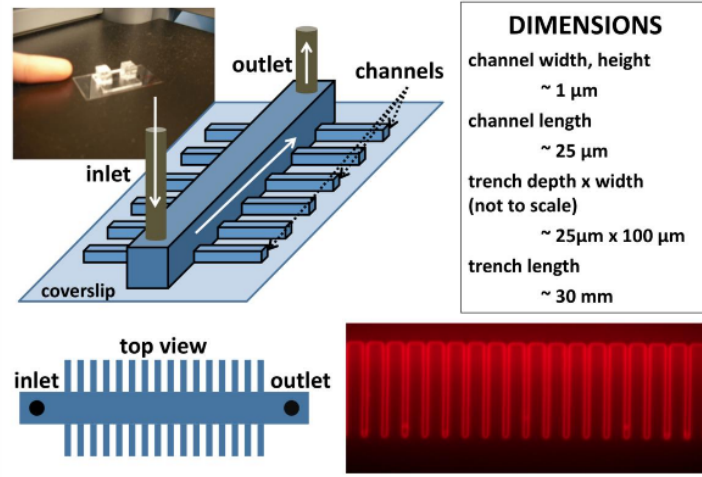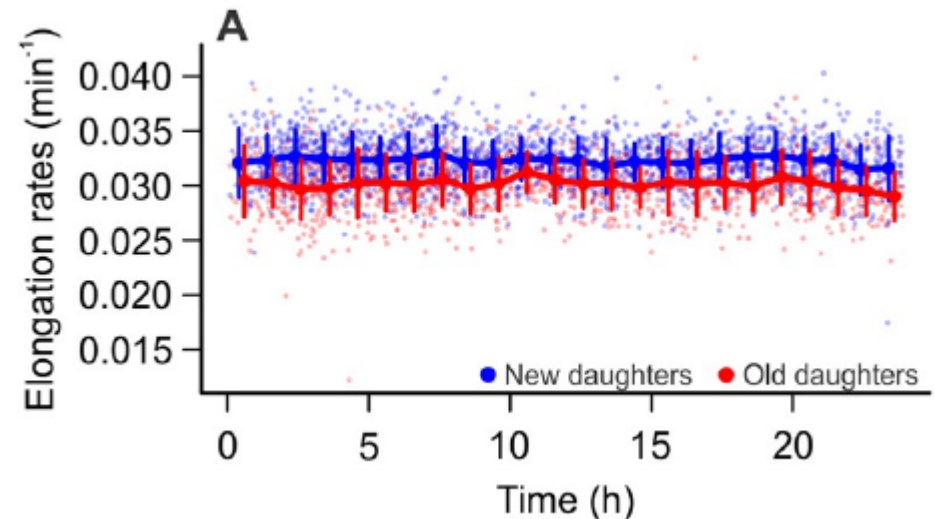
Microfluidic devices for aging and cell-size control studies

Ping Wang,[1,5] Lydia Robert,[2,3,5] James Pelletier,[1]
Wei Lien Dang,[1] Francois Taddei,[2] Andrew Wright,[4]
and Suckjoon Jun[1,*]

The mother machine

Aging increases filamentation (and death rate); no growth rate decline in steady exp growth
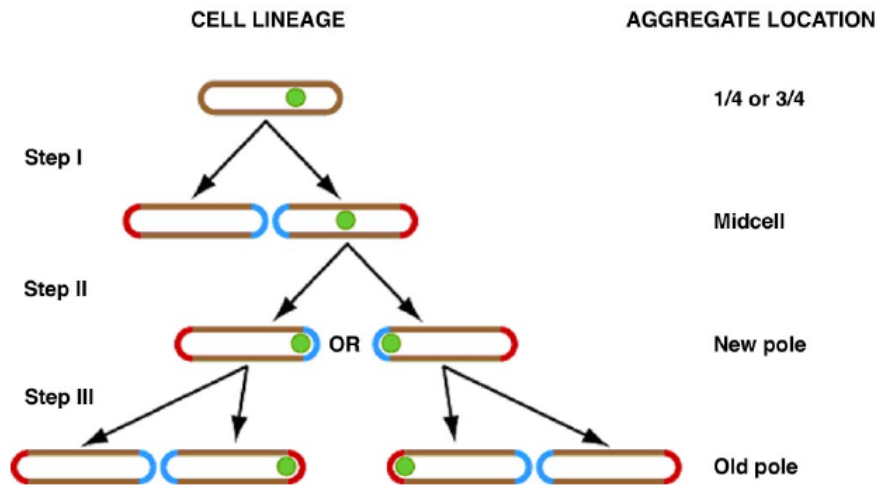
Audrey Menegaz Proenca[1,2]*, Camilla Ulla Rang[1], Andrew Qiu[1], Chao Shi[1],
Lin Chao[1]*

Asymmetric damage accumulation and the trade-off between repair and segregation

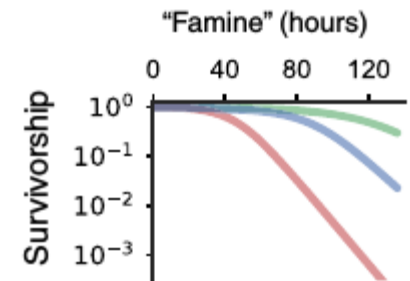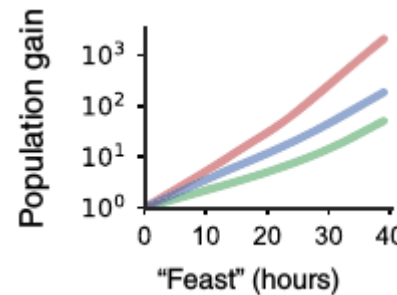*Aggregation of misfolded proteins leads to asymmetric accumulation*

CELL LINEAGE   AGGREGATE LOCATION

Step I   1/4 or 3/4

Step II   Midcell

OR   New pole

Step III   Old pole

Lindner *et al.*   PNAS | February 26, 2008

Trade off between stress response and growth
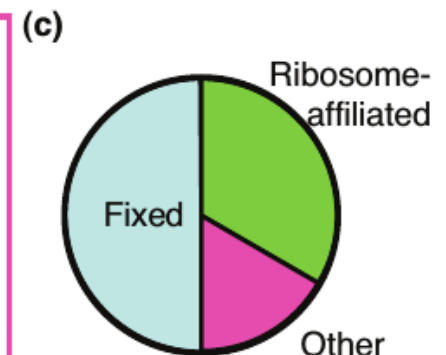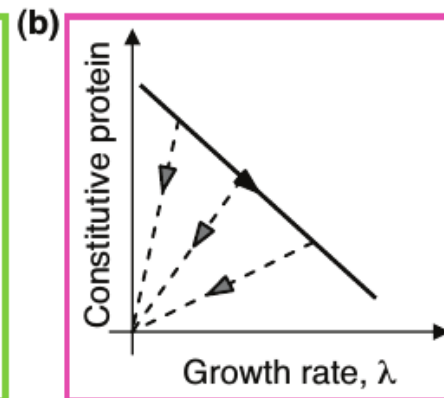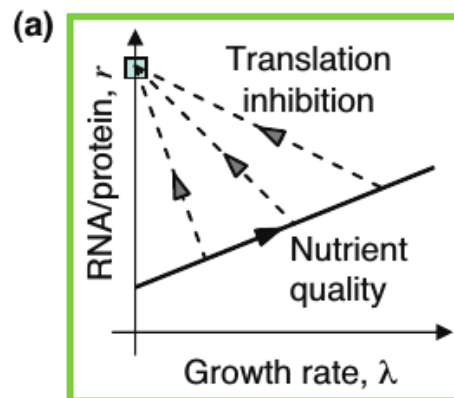
■ Δ*rpoS*   ■ *wt*   ■ Δ*rssB*

No repair vs wt vs costly maintenance

Yang *et al., Sci. Adv.* 2019;**5**:eaaw2069   29 May 2019
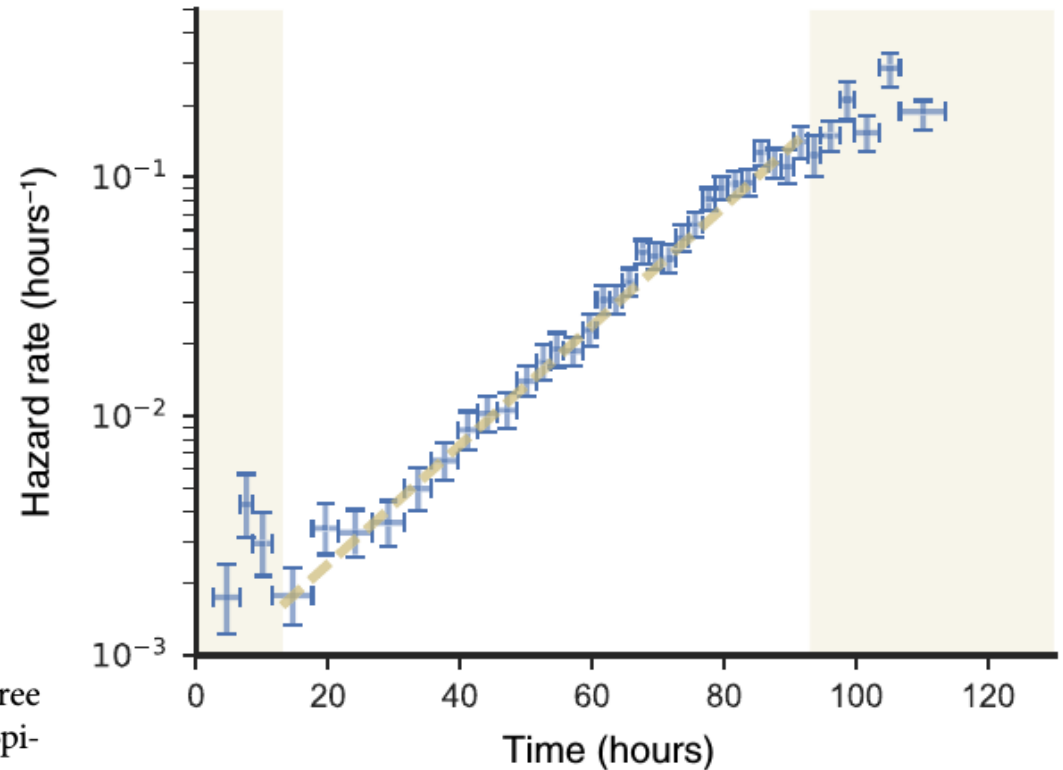
Theory of resource partioning in presence of aging?

Terence Hwa Lab
A simple phenomenological theory of resource partitioning for balanced exp growth

(a) Translation inhibition / Nutrient quality — RNA/protein, *r* vs Growth rate, λ

(b) Constitutive protein vs Growth rate, λ

(c) Ribosome-affiliated / Fixed / Other

Current Opinion in Biotechnology

Temporal scaling of aging as an adaptive strategy of
Escherichia coli

To observe cell mortality, we included in the carbon source–free medium a red-fluorescent, DNA-binding, bacterial viability dye propidium iodide (PI), which penetrates the cells only when cellular membrane potentials are disrupted.
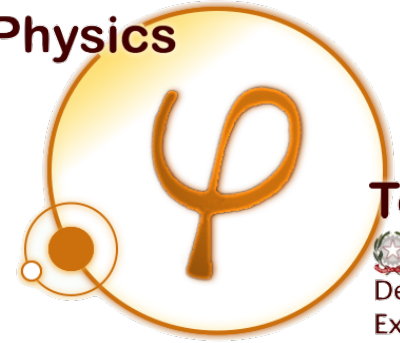
Thank You !

People involved

Experiments
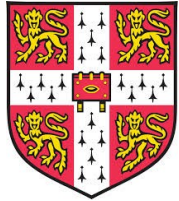
Pietro Cicuta Lab
Cavendish Lab, Cambridge

Sander Tans Lab
AMOLF, Amsterdam

Theory & Data Analysis

Marco Cosentino Lagomarsino
IFOM & Univ. of Milan)

Jacopo Grilli
(Santa Fe Institute,
Now ICTP Trieste)

Gabriele Micali
(Eawag, Zurich)
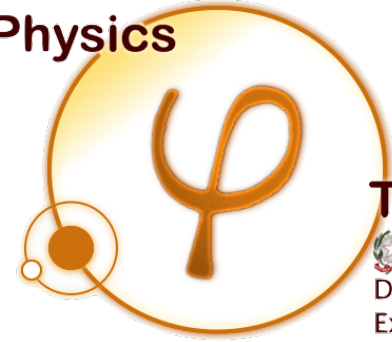
References:

i) *Concerted control of Escherichia coli cell division*
M Osella, E Nugent, M Cosentino Lagomarsino. PNAS 2014

ii) *Stochasticity and homeostasis in the E. coli replication and division cycle*
A Adiciptaningrum, M Osella, M Cosentino Lagomarsino, SJ Tans. Sci Rep 2015

iii) *Individuality and universality in the growth-division laws of single E. coli cells*
AS Kennard, M Osella, A Javer, J Grilli, P Nghe, S Tans, P Cicuta, M Cosentino Lagomarsino. PRE 2016

iv) *Relevant parameters in models of cell division control*
J Grilli, M Osella, AS Kennard, M Cosentino Lagomarsino. PRE 2017

v) *Step by step, cell by cell: quantification of the bacterial cell cycle*
M Osella, S Tans, M Cosentino Lagomarsino. Trends in Microbiology 2017

vi) *Concurrent processes set E. coli cell division*
G Micali, J Grilli, M Osella, M Cosentino Lagomarsino. Science Advances, 2018

vii) *Dissecting the control mechanisms for DNA replication and cell division in E. coli*
G Micali ,J Grilli, J Marchi, M Osella, M Cosentino Lagomarsino. Cell Reports, 2018

Role of aging in size control