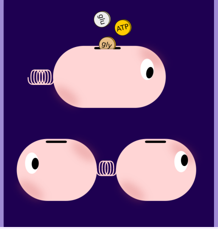


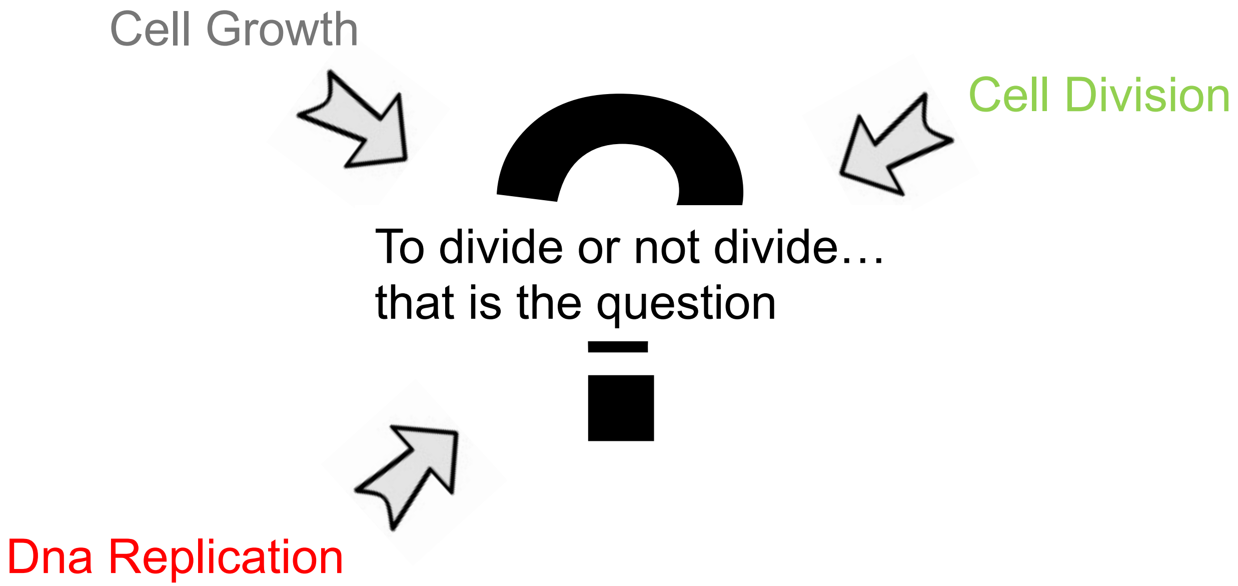
Cell division coordination

Mattia Corigliano, SPCG Group @ IFOM

Book chapter authors:

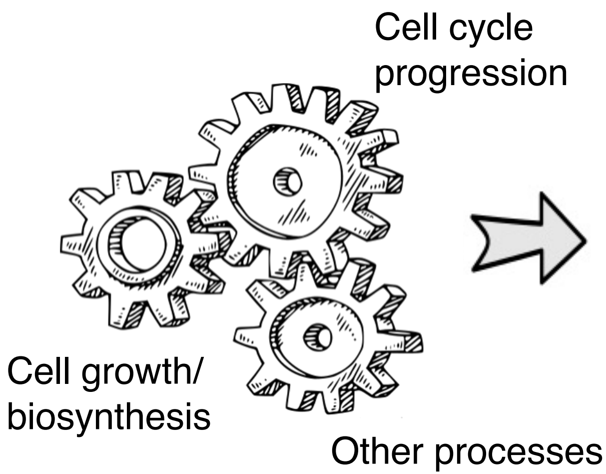
Mattia Corigliano, IFOM
Jacopo Grilli, ICTP
Gabriele Micali, Humanitas
Marco Cosentino-Lagomarsino, IFOM & University of Milan

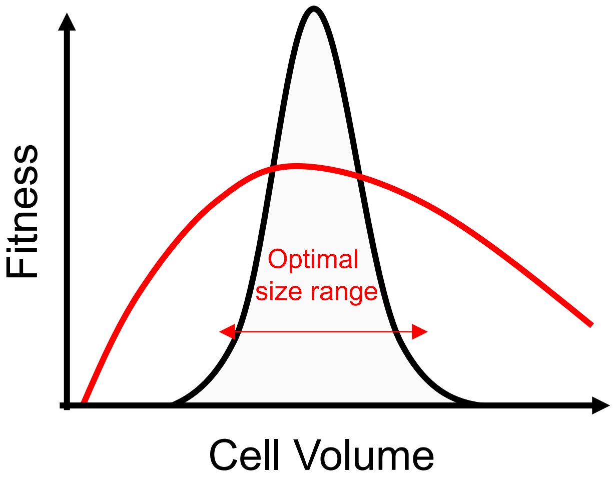
Cell division control/coordination



Why cell division control/coordination?

Because coordination of cell division, growth and other processes allow for cellular homeostasis and optimal functioning



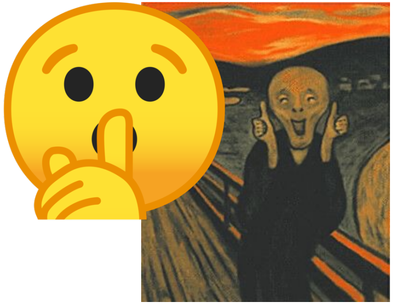


Zatulovskiy, E and Skotheim, JM, Trends in Genetics, May 2020, Vol. 36, No. 5

Neurohr , GE and Amon, A, Trends in Cell Biology, March 2020, Vol. 30, No. 3

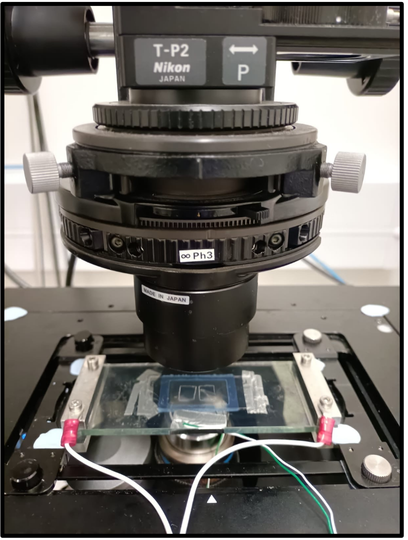
Xie, S., et al, Annual review of cell and developmental biology, May 2022.

Because it's fun



Disclaimer

This lecture will focus on the bacterium *E. coli* and "single-cell" data



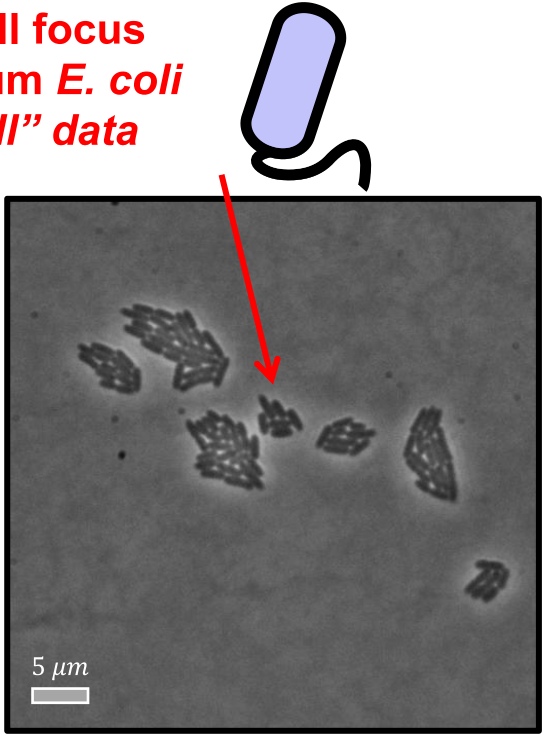


Image source: Mattia Corigliano

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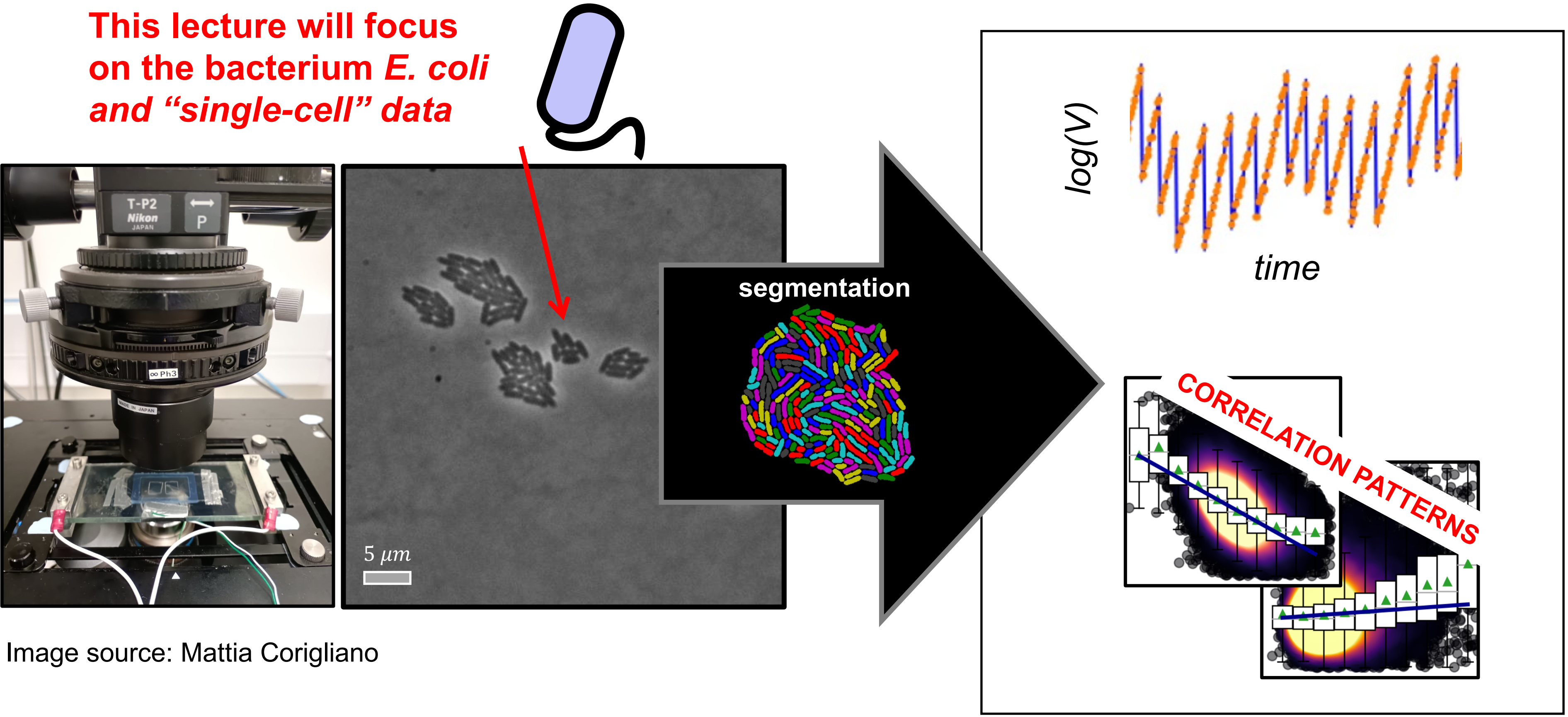
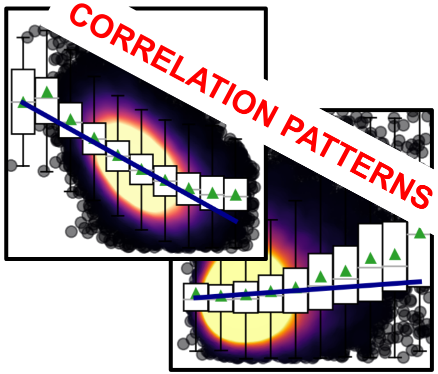


Image source: Mattia Corigliano

Book chapter question (I)

How single-cell correlation patterns can be used to understand cell-division behaviors?

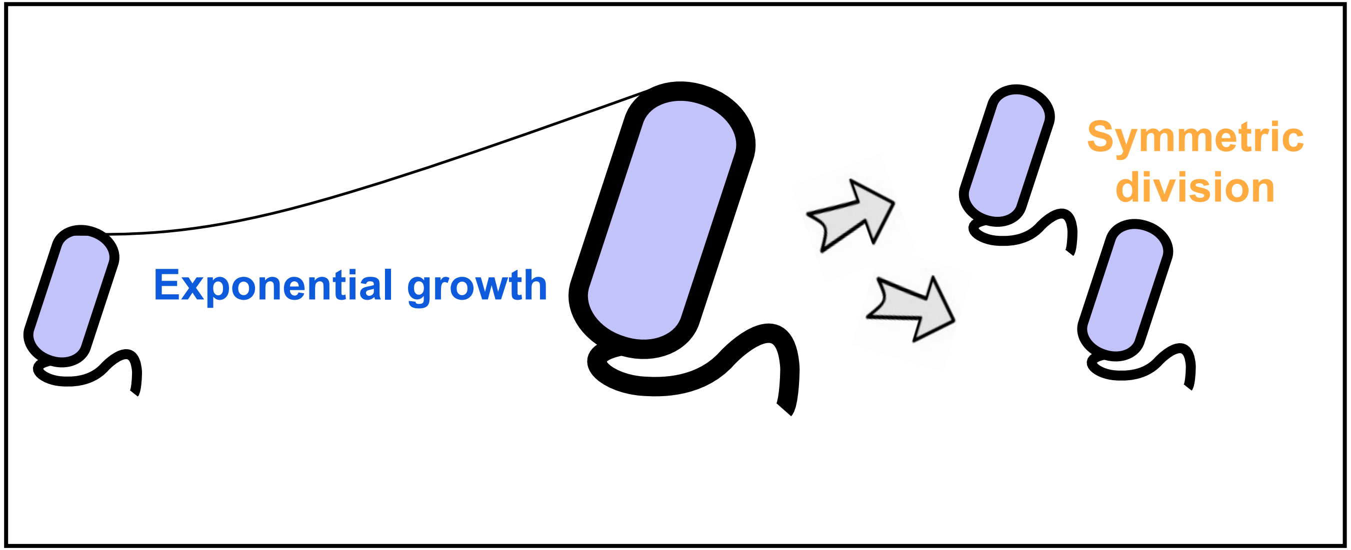


Quantitative approaches to cell division control

1. Linear response appoach
2. Hazard rate approach (if we have time)

(Sections 12.2, 12.3)

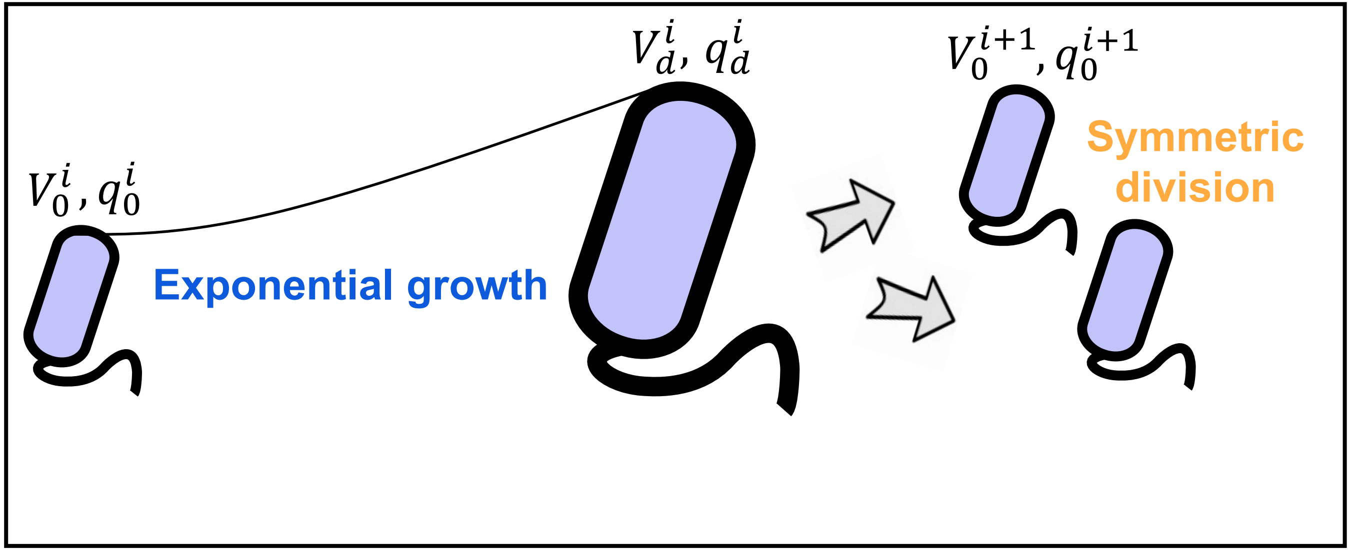
Known facts of *E.coli* growth and division



Known facts of *E.coli* growth and division

Notation

V_0^i	Volume at birth
V_d^i	Volume at division
q_0^i	Log. Volume at birth
q_d^i	Log. Volume at division
α^i	Growth rate
τ_d^i	Division time
G^i	Elongation



Def.

$$q_0^i \equiv \log V_0^i / V^*$$

$$G^i \equiv \alpha^i \tau_d^i = q_d^i - q_0^i$$

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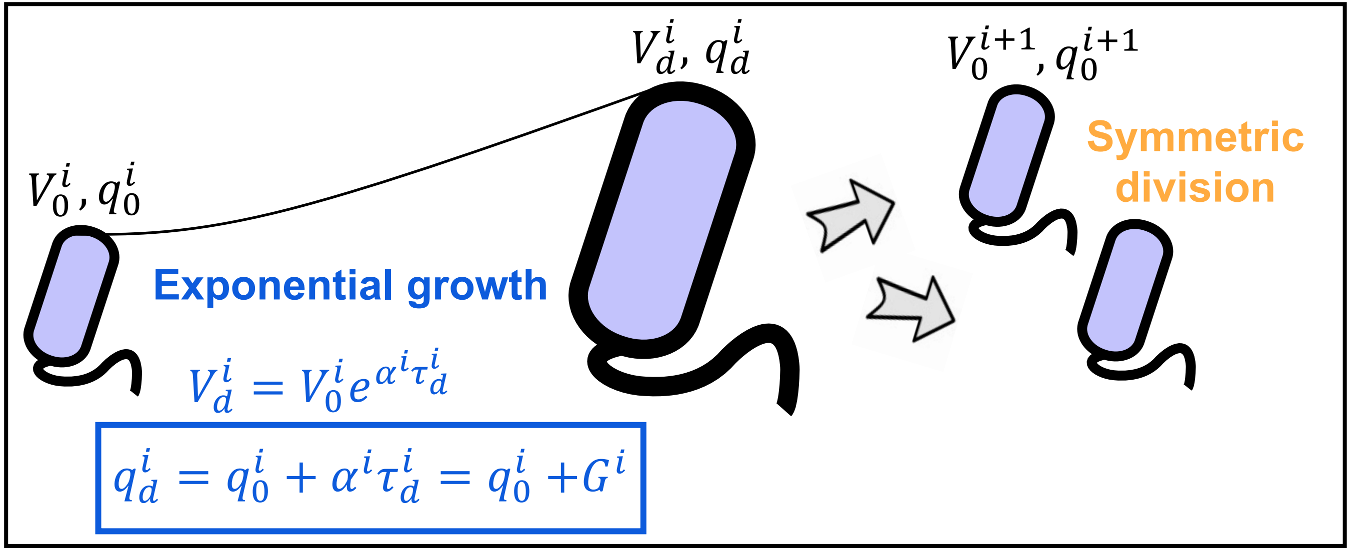

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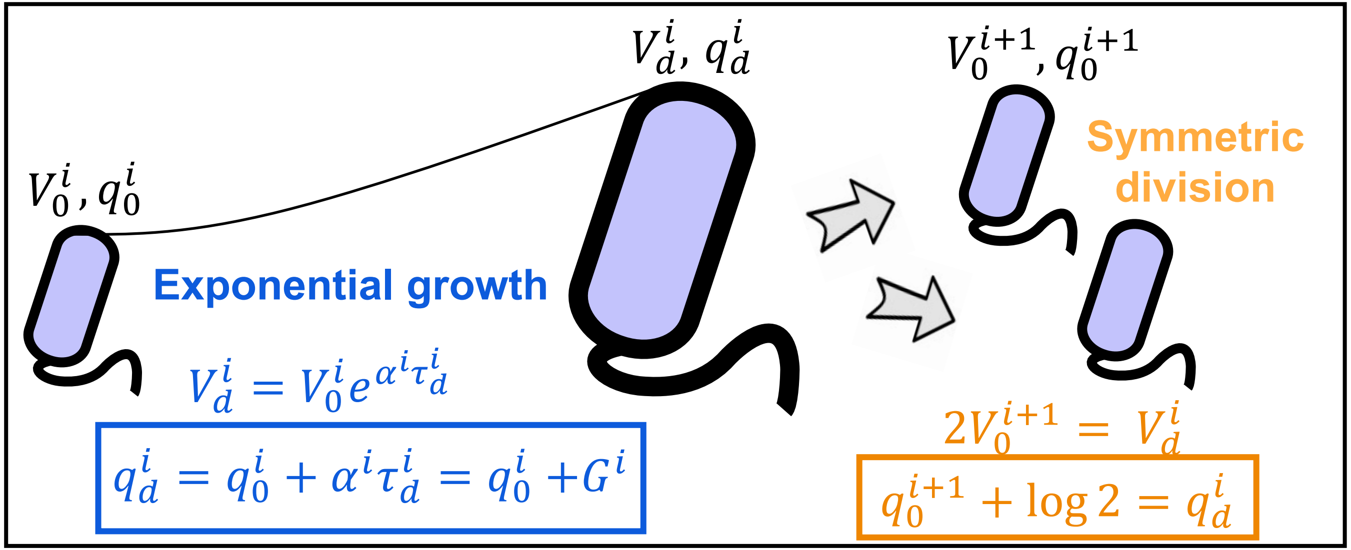

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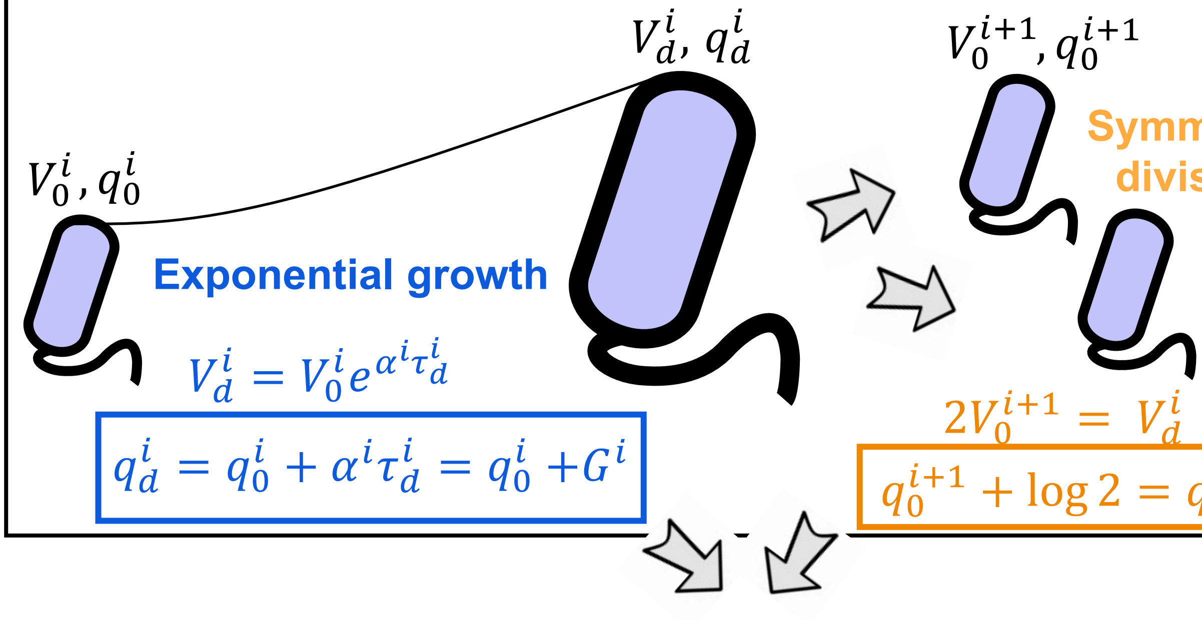


$$V_d^i = V_0^i e^{\alpha^i \tau_d^i}$$

$$q_d^i = q_0^i + \alpha^i \tau_d^i = q_0^i + G^i$$

$$2V_0^{i+1} = V_d^i$$

$$q_0^{i+1} + \log 2 = q_d^i$$

Def.

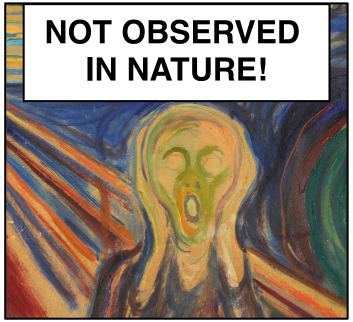
$$q_0^i \equiv \log V_0^i / V^*$$

$$G^i \equiv \alpha^i \tau_d^i = q_d^i - q_0^i$$

$$\boldsymbol{q_0^{i+1} = q_0^i + \delta G^i = q_0^i + \delta(\alpha^i \tau_d^i)}$$

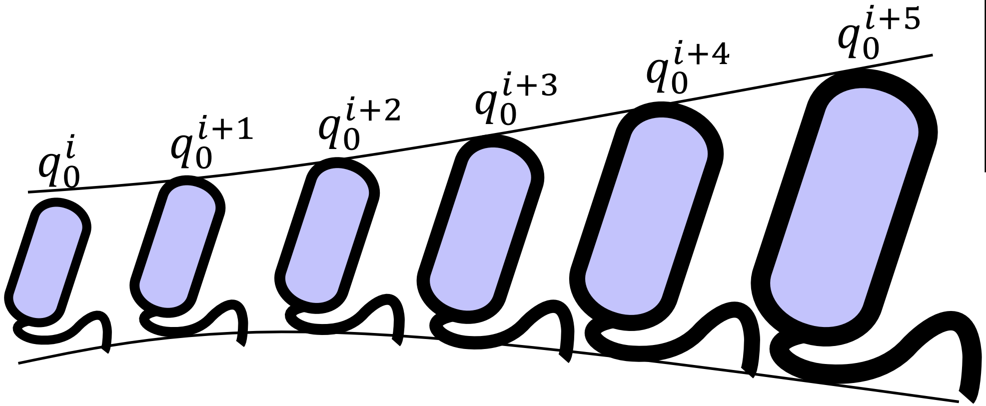
Division *per se* does not guarantee cell size homeostasis

Mechanisms must be in place to control cell size



$$q_0^{i+1} = q_0^i + \delta G^i = q_0^i + \delta(\alpha^i \tau_d^i)$$

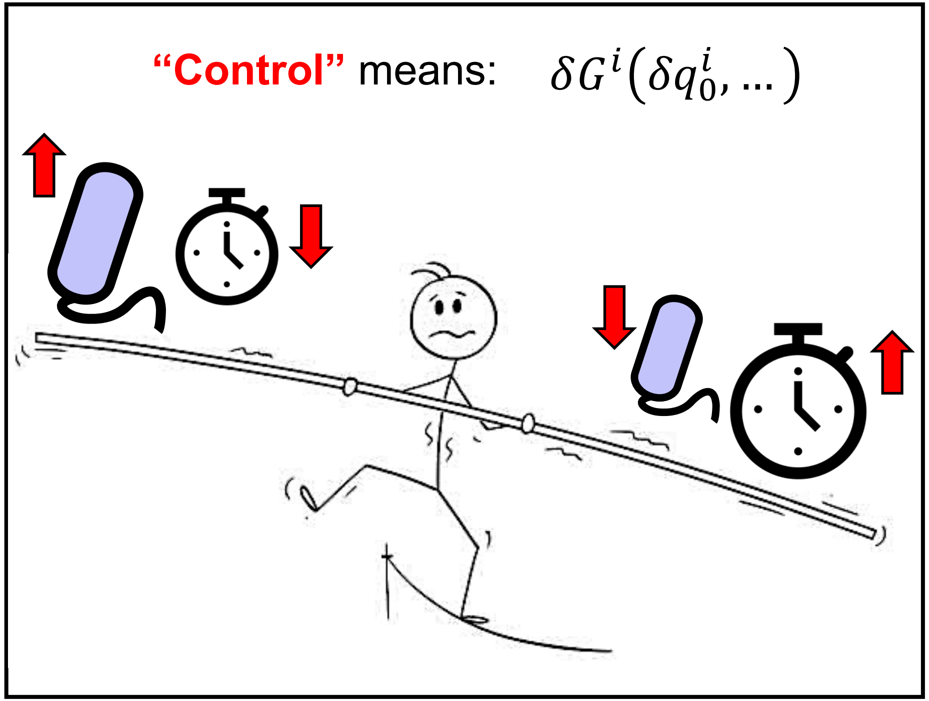
Random noise -> Random walk

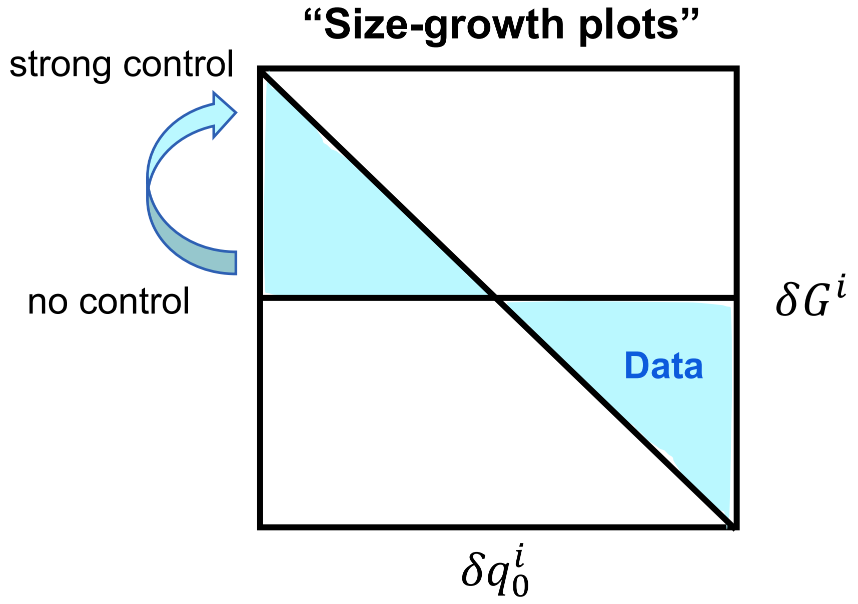


Exercise: what if cell growth is linear and /or cell division is asymmetric?

Amir A, Physical Review Letters **112** (2014)

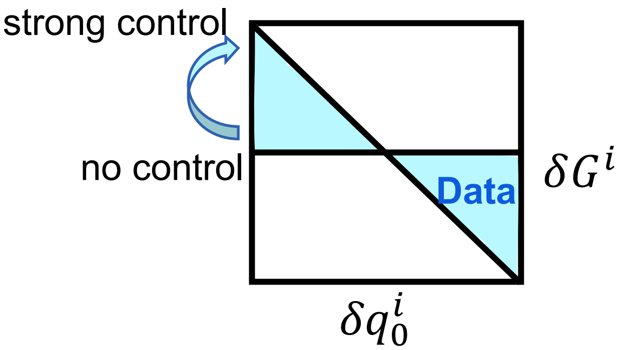
Mechanisms must be in place to control cell size





Book chapter question (I bis)

Can we set up a quantitative framework within which making sense of these plots?



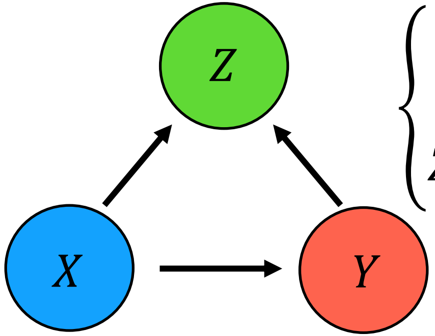
Quantitative approaches to cell division control

1. Linear response appoach

2. Hazard rate approach (if we have time)

(Sections 12.2, 12.3)

Linear-response 101



$$\begin{cases} X = \eta_X \\ Y = f_Y(X) + \eta_Y \\ Z = f_Z(X,Y) + \eta_Z \end{cases}$$

Central assumption:

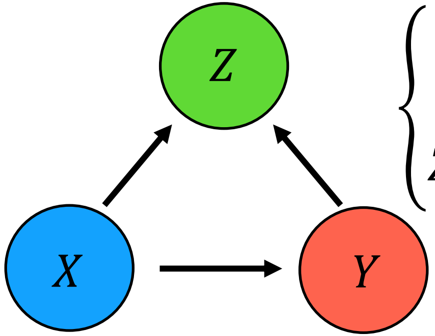
$$f_Y(X) \approx \langle Y \rangle - \lambda_{YX}\,\delta X$$

$$f_Z(X,Y) \approx \langle Z \rangle - \lambda_{ZX}\delta X \ - \lambda_{ZY}\delta Y$$

$$\lambda_{ab} \equiv -\frac{\partial f_a}{\partial b}(\langle b \rangle, \dots) \equiv \Lambda_{ab}\frac{\sigma_a}{\sigma_b}$$

Control parameters

Linear-response 101



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$$\lambda_{ab} \equiv -\frac{\partial f_a}{\partial b}(\langle b \rangle, \dots) \equiv \Lambda_{ab}\frac{\sigma_a}{\sigma_b}$$

Control parameters

Linear response

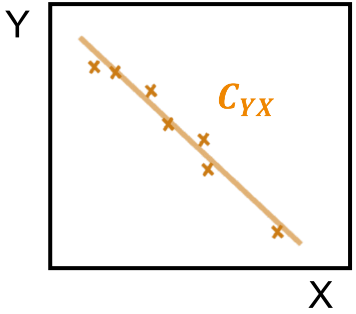
$$\begin{cases} \dfrac{\delta Y}{\sigma_Y} = -\Lambda_{YX}\dfrac{\delta X}{\sigma_X} + \eta_Y \\ \dfrac{\delta Z}{\sigma_Z} = -\Lambda_{ZX}\dfrac{\delta X}{\sigma_X} - \Lambda_{ZY}\dfrac{\delta Y}{\sigma_Y} + \eta_Z \end{cases}$$

Correlation patterns

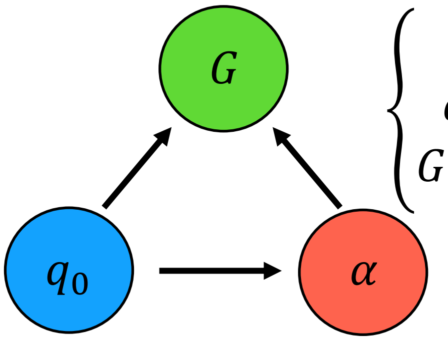
$$C_{YX} = -\Lambda_{YX}$$

$$C_{ZX} = -\Lambda_{ZX} + \Lambda_{ZY}\Lambda_{YX}$$

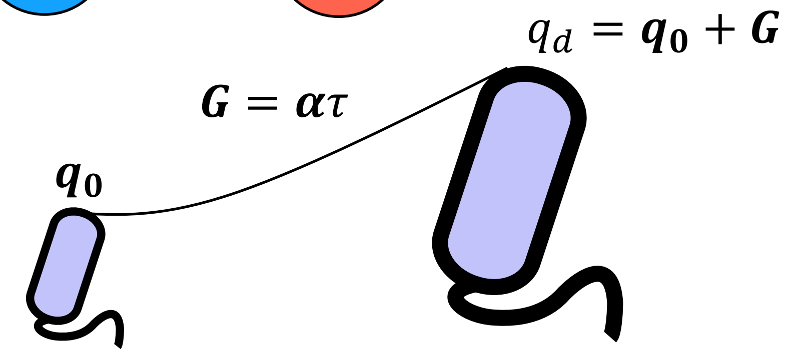
$$C_{ZY} = \Lambda_{ZX}\Lambda_{XY} - \Lambda_{ZY}$$



E.coli linear-response model of cell division control



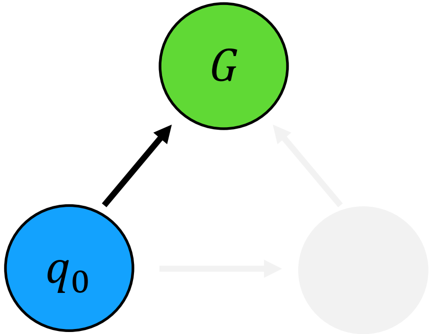
$$\begin{cases} q_0 = \eta_q \\ \alpha = f_\alpha(q_0) + \eta_\alpha \\ G = f_G(q_0, \alpha) + \eta_G \end{cases}$$



Grilli J., *et al.*, Frontiers in Microbiology **9** (2018)

E.coli linear-response model of cell division control

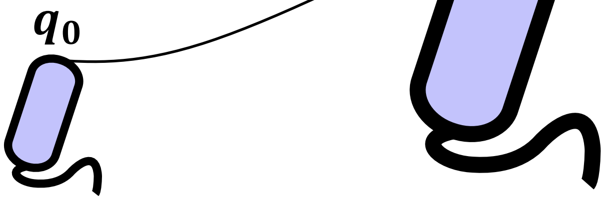
Even simpler because growth rate fluctuations are usually neglected



$$\begin{cases} q_0 = \eta_q \\ G = f_G(q_0) + \eta_G \end{cases}$$

$$q_d = \boldsymbol{q_0} + \boldsymbol{G}$$

$$\boldsymbol{G} = \boldsymbol{\alpha\tau}$$

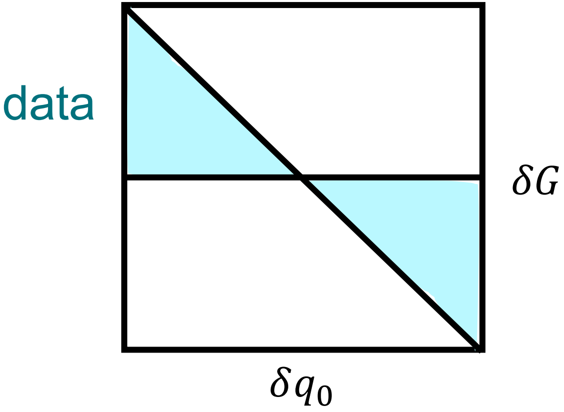


Linear response

$$\delta G = -\lambda_G \delta q_0 + \eta_G$$

$$\boldsymbol{\delta q_d = (1 - \lambda_G)\delta q_0 + \eta_G}$$

“Size-growth plots”



Grilli J., *et al.*, Frontiers in Microbiology **9** (2018)

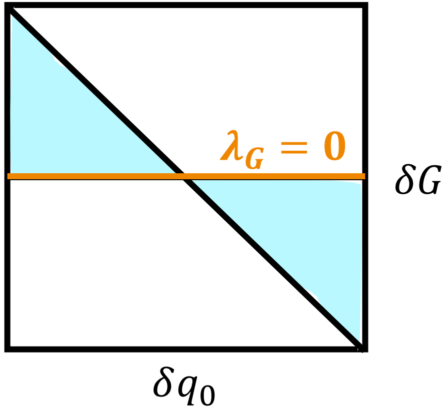
Control mechanisms

Linear response

$$\delta G = -\lambda_G \delta q_0 + \eta_G$$

$$\boldsymbol{\delta q_d = (1 - \lambda_G)\delta q_0 + \eta_G}$$

"Size-growth plots"



Timer: $\delta G^i = 0$

$$\delta \tau_d^i = 0 \rightarrow \tau_d^i = \langle \tau_d \rangle$$

$$\delta q_0^{i+1} = \delta q_0^i$$

Uncontrolled fluctuations

Amir A, Physical Review Letters **112** (2014)

Control mechanisms

Linear response

$$\delta G = -\lambda_G \delta q_0 + \eta_G$$

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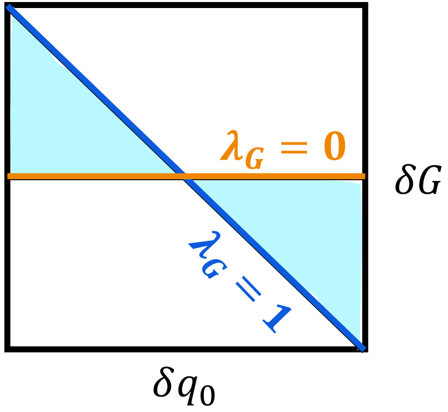

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$$\delta \tau_d^i = 0 \rightarrow \tau_d^i = \langle \tau_d \rangle$$

$$\delta q_0^{i+1} = \delta q_0^i$$

Uncontrolled fluctuations

Sizer: $\delta G^i = -\delta q_0^i$

$$\tau_d^i = \langle \tau_d \rangle - \alpha^{-1} \delta q_0^i$$

$$\delta q_0^{i+1} = 0 \rightarrow q_d^i = \langle q_d \rangle$$

Fluctuations controlled in one cell cycle

Amir A, Physical Review Letters **112** (2014)

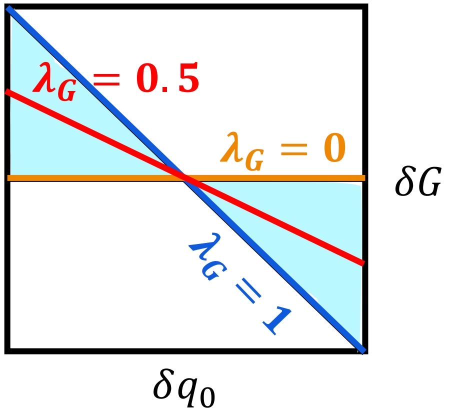
Control mechanisms

Linear response

$$\delta G = -\lambda_G \delta q_0 + \eta_G$$

$$\boldsymbol{\delta q_d = (1 - \lambda_G)\delta q_0 + \eta_G}$$

"Size-growth plots"



Amir A, Physical Review Letters **112** (2014)

Timer: $\delta G^i = 0$

$$\delta\tau_d^i = 0 \to \tau_d^i = \langle\tau_d\rangle$$

$$\delta q_0^{i+1} = \delta q_0^i$$

Uncontrolled fluctuations

Sizer: $\delta G^i = -\delta q_0^i$

$$\tau_d^i = \langle\tau_d\rangle - \alpha^{-1}\delta q_0^i$$

$$\delta q_0^{i+1} = 0 \to q_d^i = \langle q_d\rangle$$

Fluctuations controlled in one cell cycle

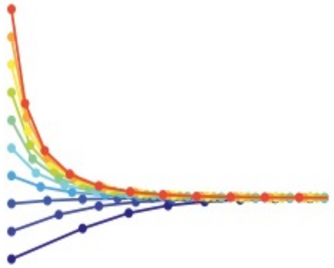
Adder: $\delta G^i = -\delta q_0^i/2$

$$\tau_d^i = \langle\tau_d\rangle - \delta q_0^i/2\alpha$$

$$\delta q_0^{i+1} = \delta q_0^i/2$$

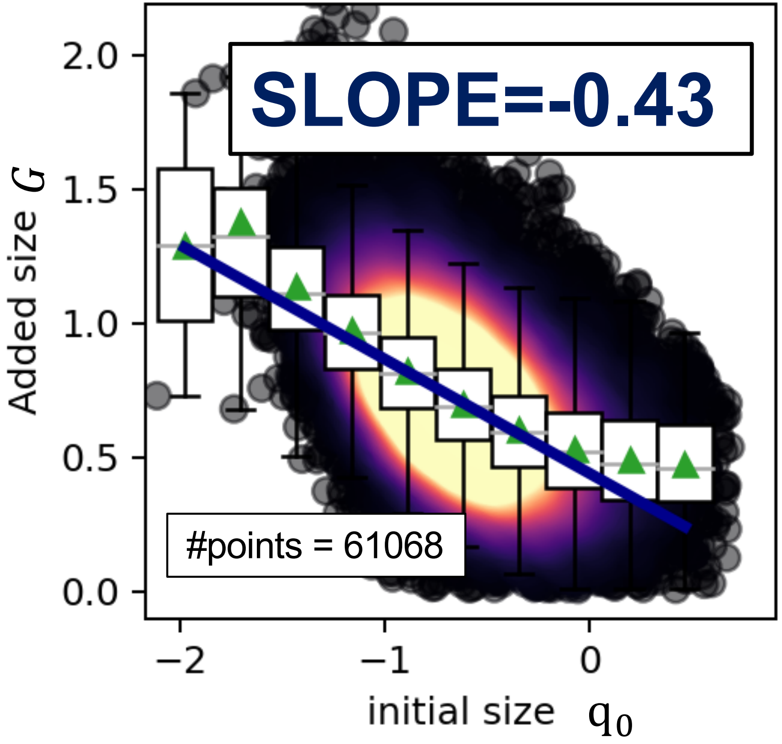
$$* \quad V_d^i = V_0^i + \Delta \quad *$$

Exponentially controlled fluctuations



Evidence of adder-like correlations

E.Coli cells implement the adder strategy



[Data from Mattia's experiments]

Evidence of adder-like correlations

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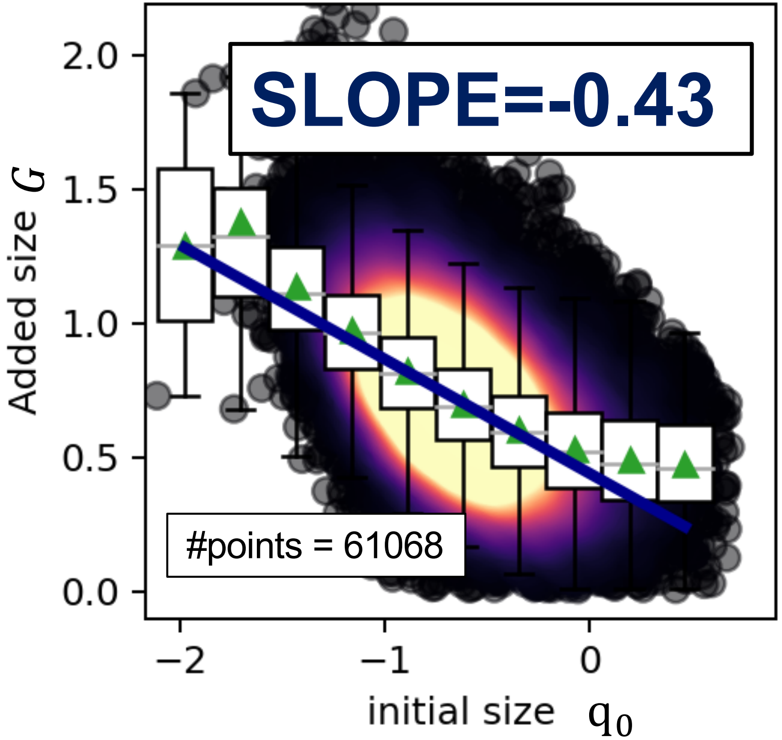
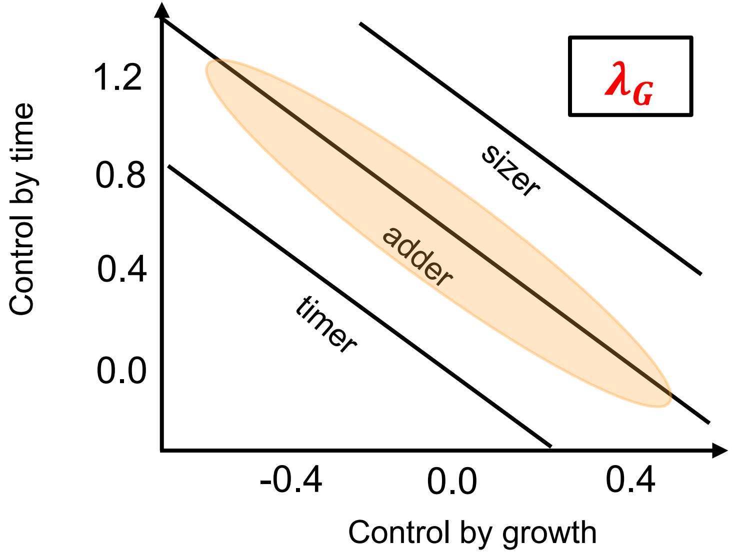


[Data from Mattia's experiments]

$$\delta G^i = \langle \alpha \rangle \delta \tau_d^i + \langle \tau_d \rangle \delta \alpha^i$$



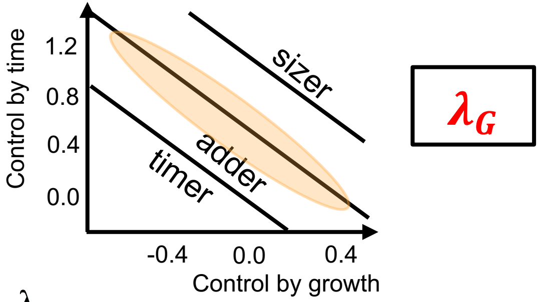
[Adapted from Cadart *et al.* Nat Commun. (2018)]

Data from different species in different conditions

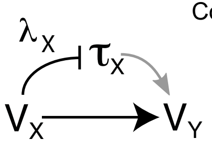
Features of linear response framework

A general solvable framework which:

❑ Allows us to interpret and compare control strategies of different species in different conditions

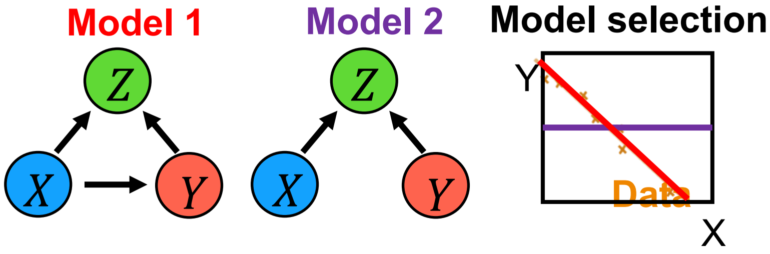


❑ Can be easily modified to describe more refined cell cycle models (cell cycle subperiods)



$$\delta q_Y^i = (1-\lambda_Y)\delta q_X^i + \eta^i$$

❑ Relates correlation patterns in data to couplings/mechanisms in models:
- propose mechanisms
- select scenarios



Features of linear response framework

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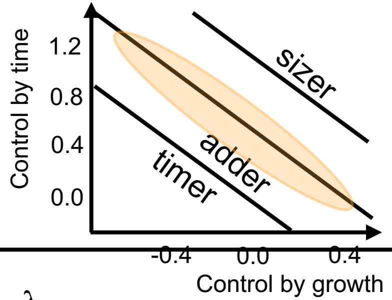
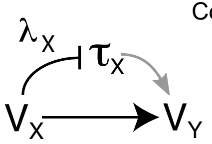


λ_G

Next

- ❑ Can be easily modified to describe more refined cell cycle models (cell cycle subperiods)



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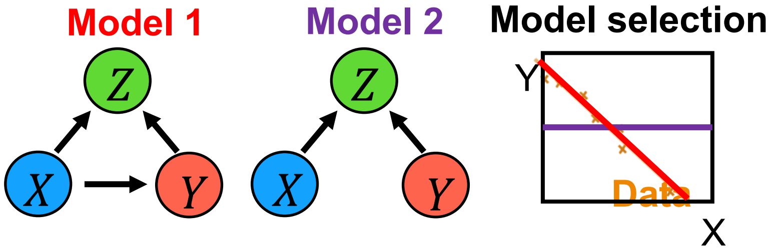
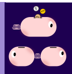




Book chapter question (II)

What sets the decision to divide?
What is the rate-limiting process setting cell division?

Coordination of cell division with different cell-cycle processes

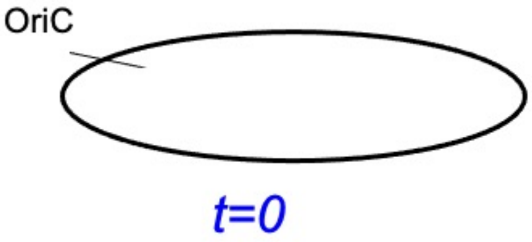
(Sections 12.4)

What is the rate-limiting process setting cell division?

'Traditional answer' *based on population averages*

(Replication + segregation) is rate-limiting for division

(Schaechter et al 1958, Cooper & Helmstetter 1968, Donachie 1969)



Chromosome Cycle

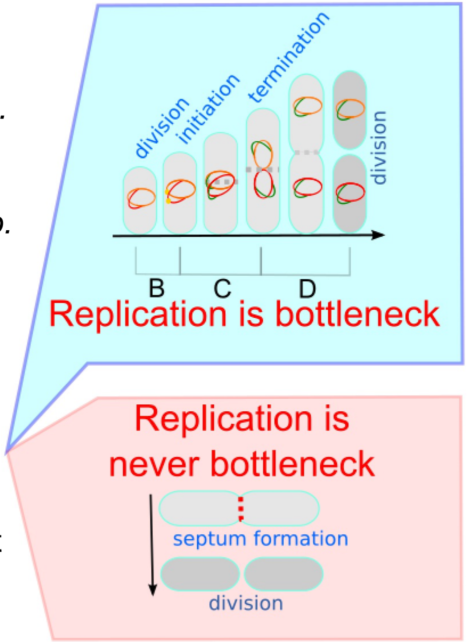
Division a "constant" time C+D after initiation of DNA replication

True for *single cells* ?

What is the rate-limiting process setting cell division?

For single cells two opposite views were proposed

Wallden *et al.* *Cell* (2016)
Ho & Amir *Front. Microb.* (2015)



Harris &Theriot *Cell* (2016), TIM (2018)

What is the rate-limiting process setting cell division?

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Wallden *et al.* *Cell* (2016)
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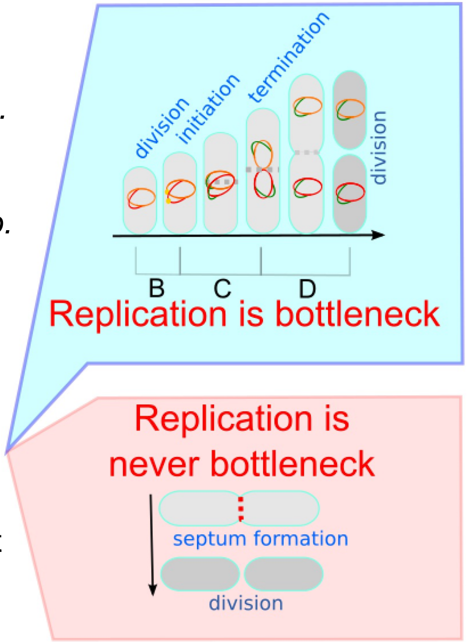
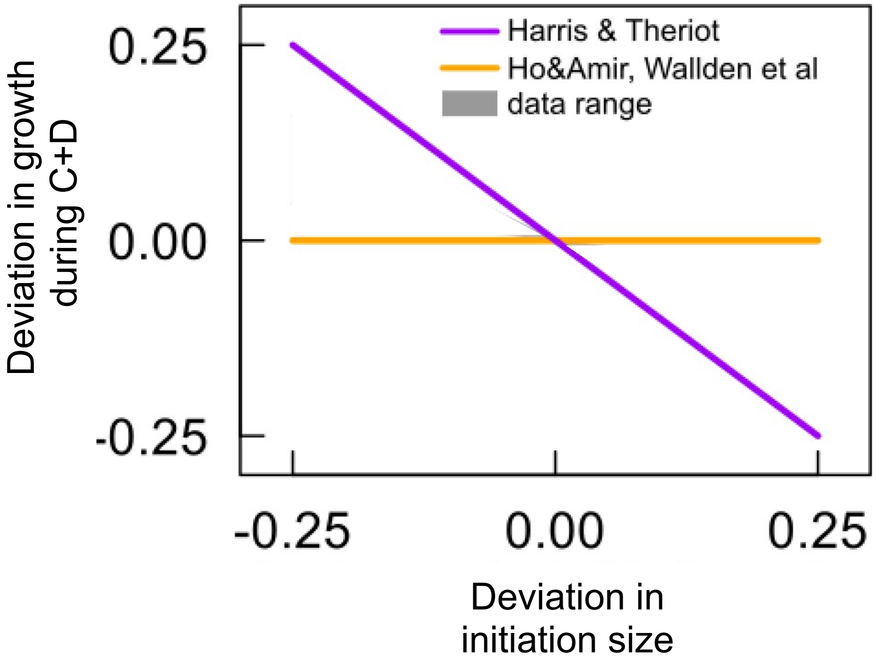
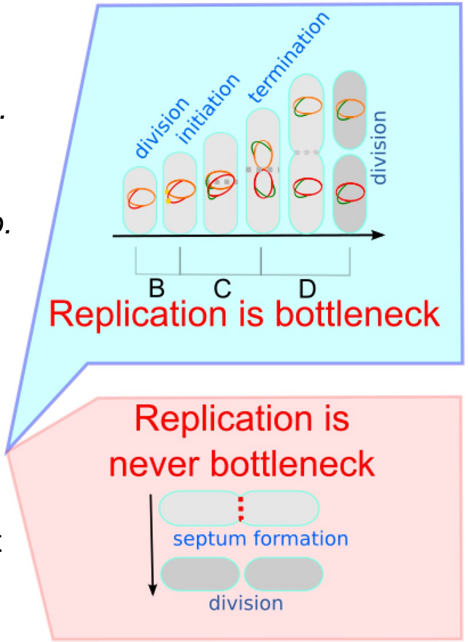




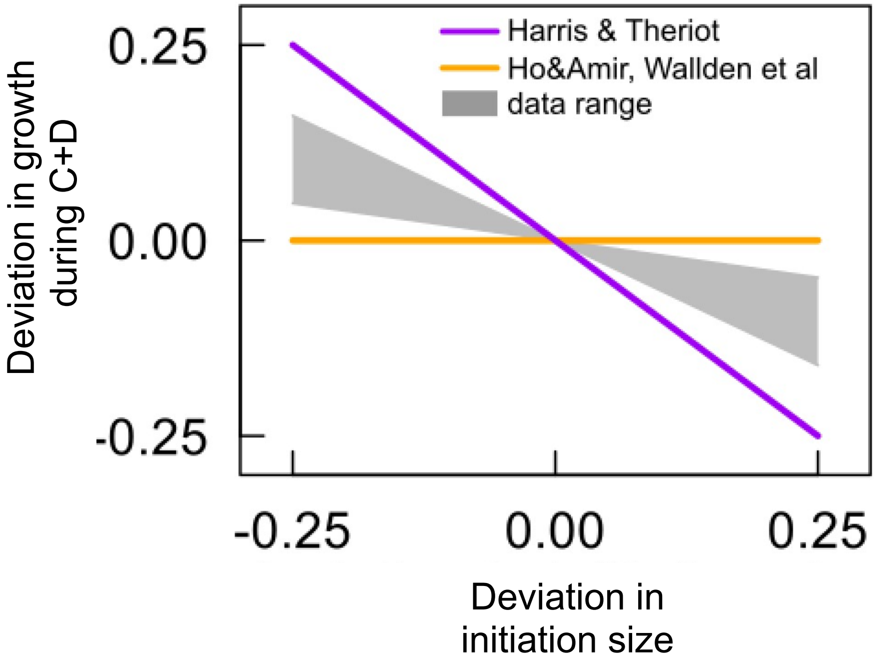
What is the rate-limiting process setting cell division?

Wallden *et al.* *Cell* (2016)
Ho & Amir *Front. Microb.* (2015)



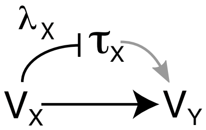
Harris &Theriot *Cell* (2016), TIM (2018)

They both fail to reproduce relevant correlation patterns (but they didn't know)!



Generalization of replication-limiting models

Recipe



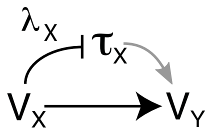
$$\delta q_Y^i = (1 - \lambda_Y)\delta q_X^i + noise$$

$$1 - \lambda_Y \equiv \widetilde{\lambda_Y}$$

Generalization of replication-limiting models

"Wallden et al. *Cell* (2016)"

Recipe

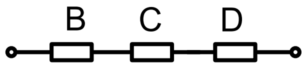


$$\delta q_Y^i = (1-\lambda_Y)\delta q_X^i + noise$$

$$1-\lambda_Y \equiv \widetilde{\lambda_Y}$$

intervals in series

"BCD" models



$$\delta q_B^i = \widetilde{\lambda_B}\delta q_0^i + \eta_B^i$$

$$\delta q_C^i = \widetilde{\lambda_C}\delta q_B^i + \eta_C^i$$

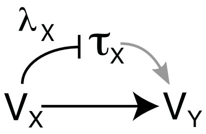
$$\delta q_D^i = \widetilde{\lambda_D}\delta q_C^i + \eta_D$$

$$\widetilde{\lambda_G} = \widetilde{\lambda_{C+D}}\,\widetilde{\lambda_B}$$

$$\widetilde{\lambda_I} = \widetilde{\lambda_G}$$

Generalization of replication-limiting models

Recipe



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"Wallden et al. *Cell* (2016)"

intervals in series

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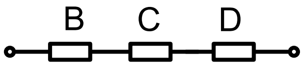

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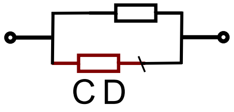
$$\widetilde{\lambda_I} = \widetilde{\lambda_G}$$

Ho & Amir *Front. Microbiol.* (2015)

intervals in parallel

"ICD" models



$$\delta q_B^i = \widetilde{\lambda_I}\delta q_B^{i-1} + \eta_B^i$$

$$\delta q_C^i = \widetilde{\lambda_C}\delta q_B^i + \eta_C^i$$

$$\delta q_D^i = \widetilde{\lambda_D}\delta q_C^i + \eta_D^i$$

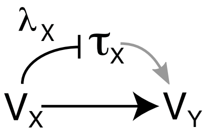
$$\widetilde{\lambda_G} = \widetilde{\lambda_{C+D}}\,\widetilde{\lambda_B}$$

$$\widetilde{\lambda_I} = \widetilde{\lambda_{C+D}}\widetilde{\lambda_B}$$

Generalization of replication-limiting models

“Wallden et al. *Cell* (2016)” Ho & Amir *Front. Microbiol.* (2015) Micali G et al., Cell reports **25** (2018)

Recipe

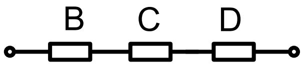


$$\delta q_Y^i = (1-\lambda_Y)\delta q_X^i + noise$$

$$1-\lambda_Y \equiv \widetilde{\lambda_Y}$$

intervals in series

"BCD" models



$$\delta q_B^i = \widetilde{\lambda_B}\delta q_0^i + \eta_B^i$$
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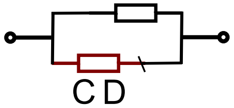
intervals in parallel

"ICD" models



$$\delta q_B^i = \widetilde{\lambda_I}\delta q_B^{i-1} + \eta_B^i$$
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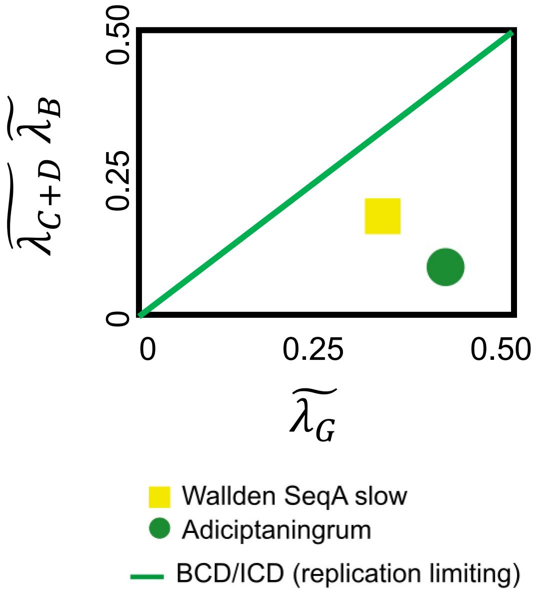
$$\widetilde{\lambda_G} = \widetilde{\lambda_{C+D}}\,\widetilde{\lambda_B}$$
$$\widetilde{\lambda_I} = \widetilde{\lambda_{C+D}}\widetilde{\lambda_B}$$

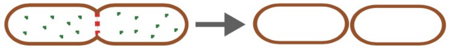
→ Replication is not always rate-limiting for cell division



The concurrent-cycles model

Micali G et al., Cell reports **25** (2018)
Micali G et al., Science Advance **4** (2018)

Replication agnostic process



$$q_H^i = q_H^* + \widetilde{\lambda}_H (q_0^i - q_0^*)$$

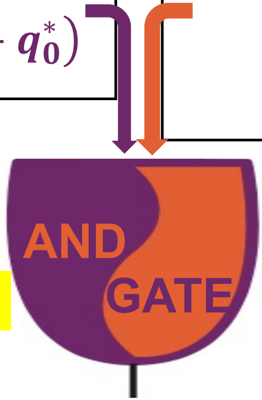
Replication centric process

$$q_R^i = q_R^* + \delta q_I^i$$

$$\delta q_I^{i+1} = \widetilde{\lambda}_I \delta q_I^i$$

$$q_d^i = max(q_H^i, q_R^i)$$

$$q_d^i \approx q_H^i \sigma^i + q_R^i (1 - \sigma^i)$$



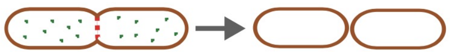
p_H probability of inter -division process being bottleneck

Division set by bottleneck process

The concurrent-cycles model

Micali G et al., Cell reports **25** (2018)
Micali G et al., Science Advance **4** (2018)

Replication agnostic process



$$q_H^i = q_H^* + \widetilde{\lambda}_H (q_0^i - q_0^*)$$

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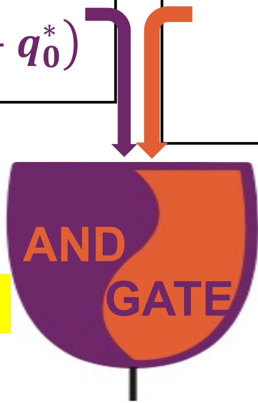
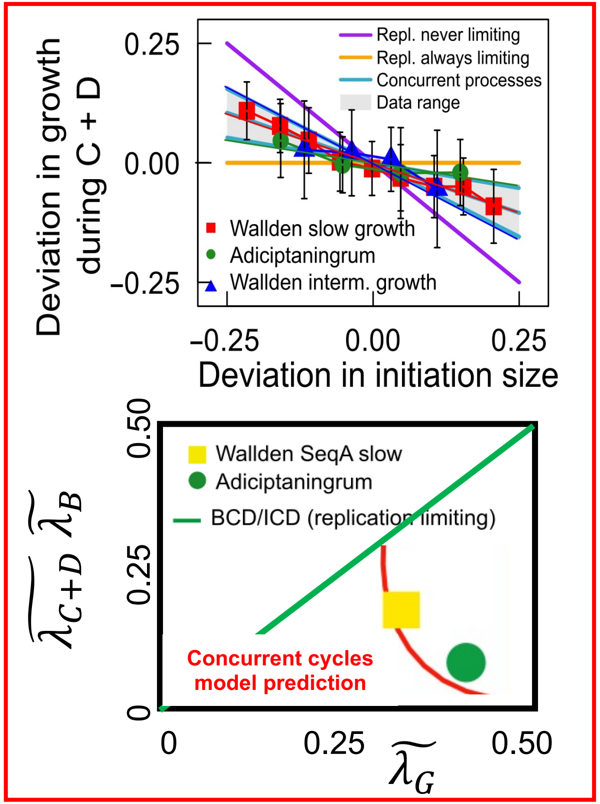


p_H probability of inter -division process being bottleneck

Division set by bottleneck process

Recapitulates all correlation patterns!

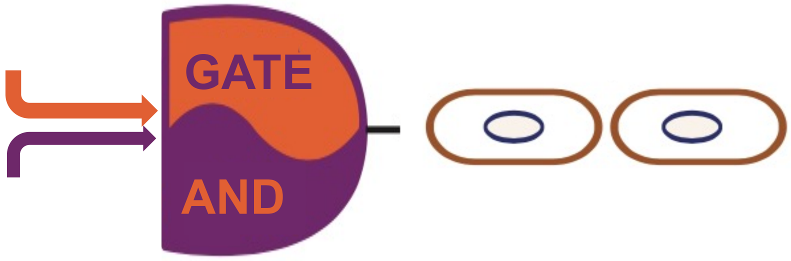


Recap on cell division coordination

1. Replication is not rate-limiting for cell division
(all models based on this assumption fail with data)

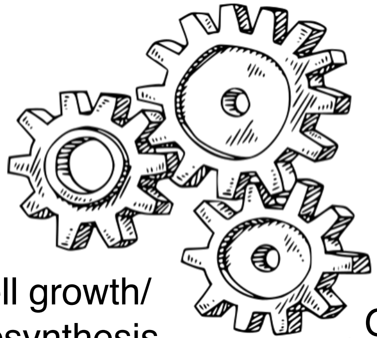
2. "Chromosome agnostic" models
(assuming that replication is never the bottleneck)
are also falsified by the data

3. Concurrent processes set cell division



Book chapter question (III)

Link with cell growth and biosynthesis? How do we go beyond studying correlation patterns?



Crosstalk between cell cycle control and cell growth/biosynthesis

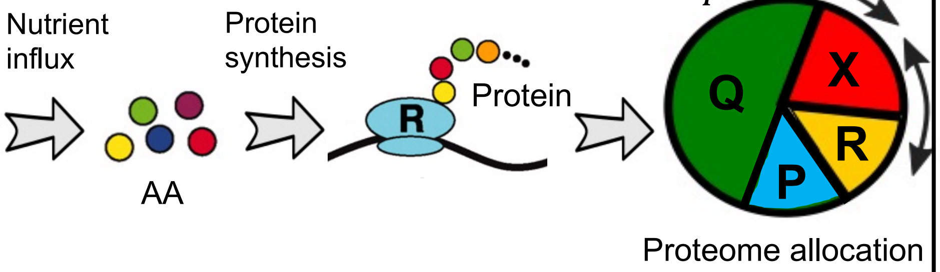
(Sections 12.4)

Diana Serbanescu, Nikola Ojkic, and Shiladitya Banerjee. *The FEBS Journal*, 2021.
François Bertaux, Julius von Kügelgen, Samuel Marguerat, and Vahid Shahrezaei. *PLoS Computational Biology*, 16 (9), September 2020.
Parth Pratim Pandey, Harshant Singh, and Sanjay Jain. *Physical review. E*, 101:062406, June 2020.

Unified whole-cell coarse grained model

"Biosynthesis level"

$$\phi_i \equiv \frac{M_i}{M_P}$$



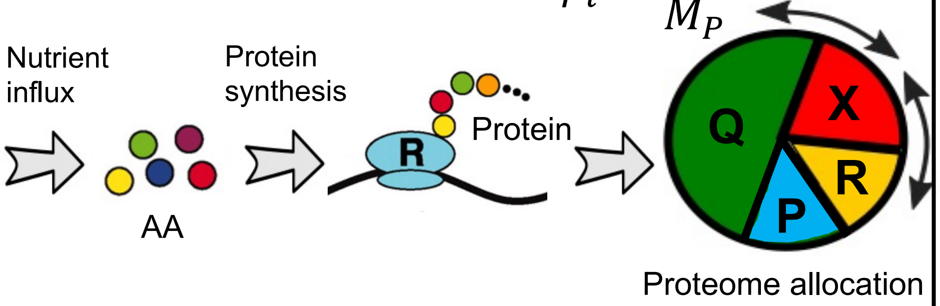
$$\frac{dA}{dt} = \frac{1}{m_A}\left(k_n P - a k_t R f_a + \sum d_{P_i} P_i\right)$$

$$\frac{dP_i}{dt} = \frac{1}{m_{P_i}}\left(a k_t f_{P_i} R\, f_a - d_{P_i} P_i\right)$$

Unified whole-cell coarse grained model

"Biosynthesis level"

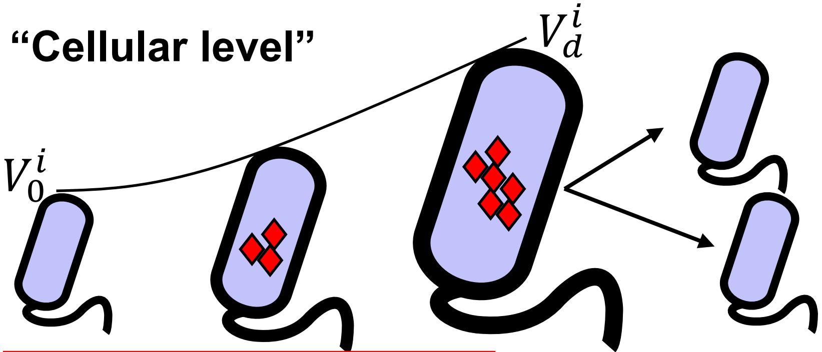
$$\phi_i \equiv \frac{M_i}{M_P}$$

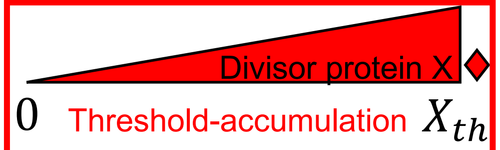


$$\frac{dA}{dt} = \frac{1}{m_A}\left(k_n P - a k_t R f_a + \sum d_{P_i} P_i\right)$$

$$\frac{dP_i}{dt} = \frac{1}{m_{P_i}}\left(a k_t f_{P_i} R\, f_a - d_{P_i} P_i\right)$$

"Cellular level"





$$X \nearrow X_{th}$$

$$V \rightarrow V/2 \qquad X \rightarrow 0$$

$$\frac{dV}{dt} = \lambda V$$

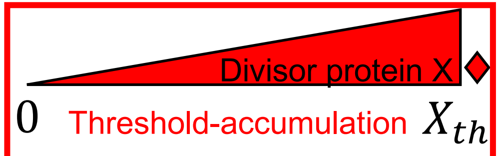
$$\frac{dX}{dt} = k_X V - \frac{d_X}{m_X} X$$

A molecular mechanism for the adder

Molecular mechanism to obtain
an adder (**threshold-accumulation**):

Division is set by the accumulation of a divisor protein N up to a threshold value.

1. Production rate proportional to volume
2. Target number of divisor proteins
3. Starting from zero



$$\frac{dX}{dt} = k_X V - \frac{d_X}{m_X} X$$

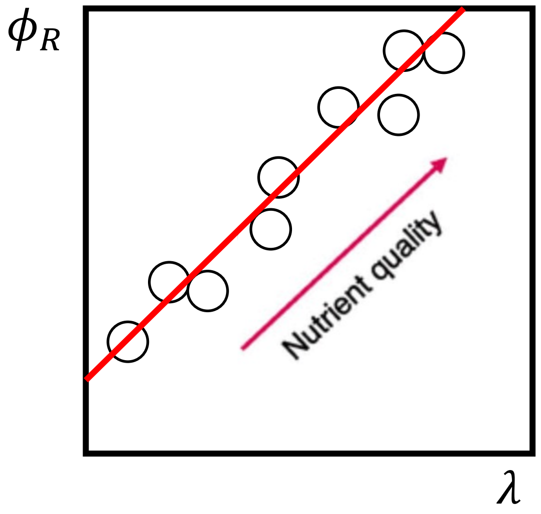
$$X(t) = \frac{k_X V_0}{\lambda + d_X/m_X}\left(2^{\frac{t}{\tau_d}} - 2^{-\frac{d_X}{m_X \lambda} t/\tau_d}\right)$$

$\lambda \gg d_X/m_X$

$$\boldsymbol{\Delta V \approx X_{th}\frac{\lambda}{k_X}} = \text{const.}$$ **Adder**

Growth laws and trade-offs between protein sectors

First growth law



$$\lambda \propto (\phi_R - \phi_R^{min})$$

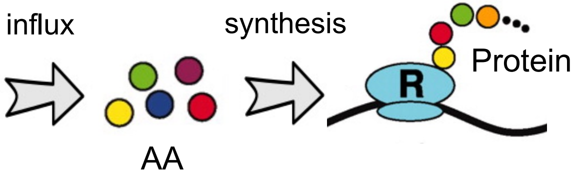
Matthew Scott et al., Science 330,1099-1102(2010).

Derivation:

$$\lambda = \frac{1}{M}\frac{dM}{dt} = \frac{1}{M}\frac{dM_{prot}}{dt} + \frac{1}{M}\frac{dM_A}{dt} = \cdots = \frac{\boldsymbol{k_n P(t)}}{\boldsymbol{M}}$$

At steady state fluxes are balanced:

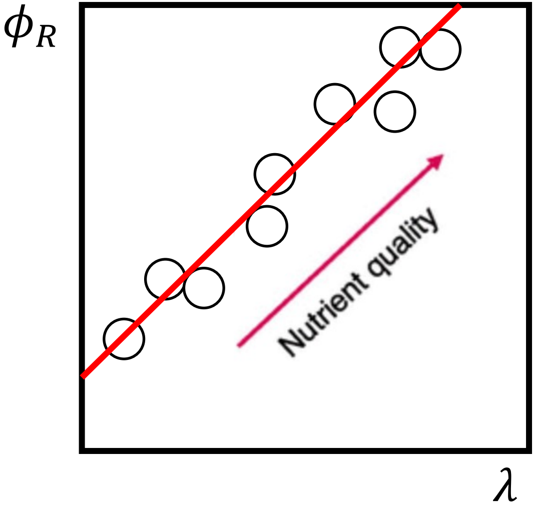
$$\frac{k_n P^*}{M} = \frac{a k_t R^* f_a}{M}$$



$$\boldsymbol{\lambda^* = \frac{a k_t}{m_R}\frac{M_P}{M}(\phi_R - \phi_R^{inact})}$$

Growth laws and trade-offs between protein sectors

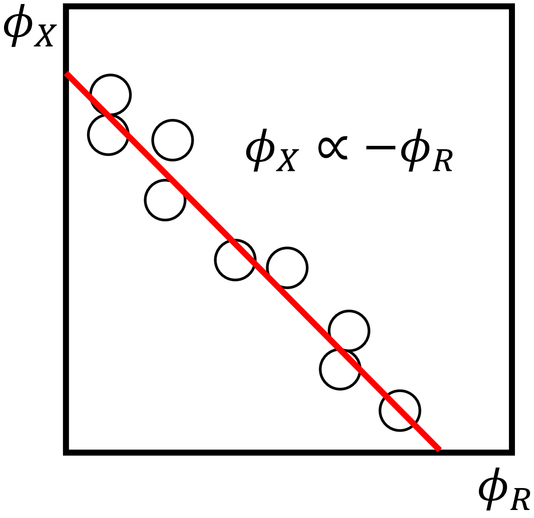
First growth law



$$\lambda \propto \left(\phi_R - \phi_R^{min}\right)$$

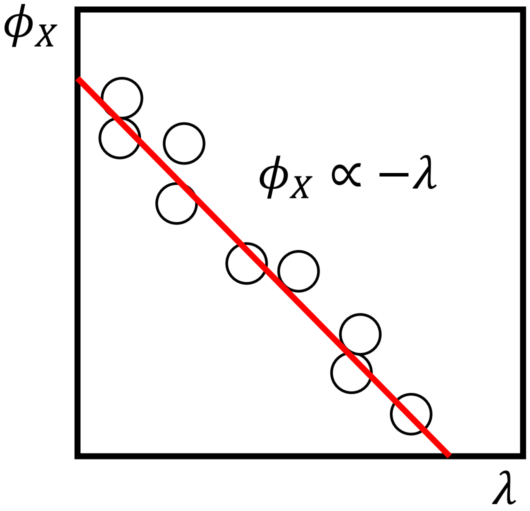
Matthew Scott et al., Science 330,1099-1102(2010).

Trade-offs between growth and division



$$\phi_X = -\frac{K_n + K_t}{K_n}\phi_R + \frac{K_t\phi_R^{min} + K_n\phi_R^{max}}{K_n}$$

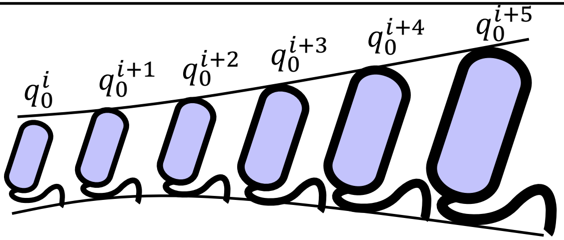
Growth law for the division sector

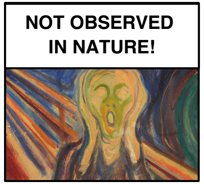


$$\lambda = \frac{K_n K_t}{K_n + K_t}\frac{M_{prot}}{M}\left(\phi_R^{max} - \phi_R^{min} - \phi_X\right),$$

Take Home messages

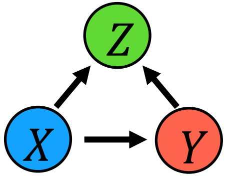
1. Cell division *per se* does not guarantee homeostasis (in *E.coli*).
Control mechanisms must be in place.

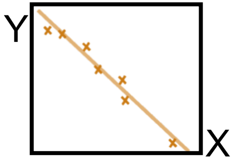


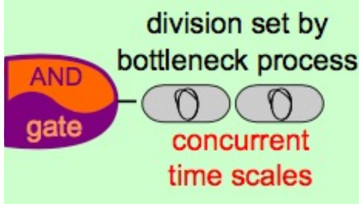


2. The Linear-response framework is helpful in making sense of single-cell correlation patterns and studying the decision to divide.

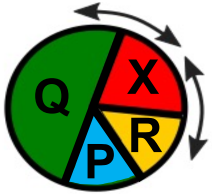
$$\delta q_Y^i = (1-\lambda_Y)\delta q_X^i + \eta^i$$



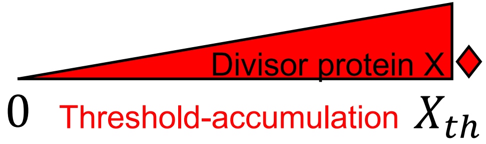




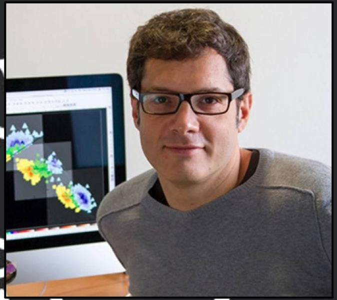
3. We are able to integrate gene-expression models with cell control strategies into a unified quantitative framework



Proteome allocation



I thank



Marco Cosentino
Lagomarsino, IFOM

Jacopo Grilli
ICTP

Gabriele Micali
Humanitas

…and you for the attention!