Dynamical Allocation of Cellular Resources as an Optimal Control Problem: Novel Insights into Microbial Growth Strategies

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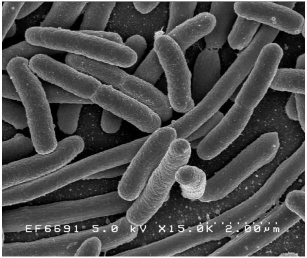
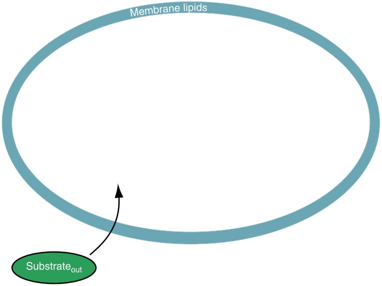
MICROBIAL GROWTH





Source picture: NIAID
Molenaar et al, MSB 2009

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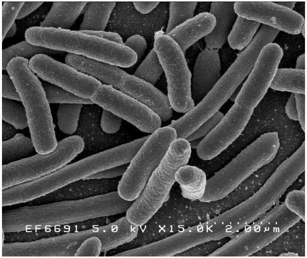
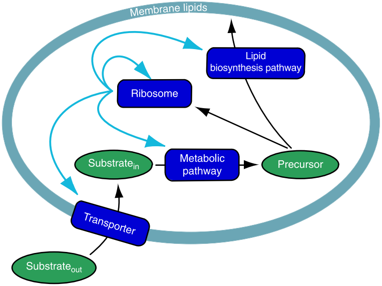
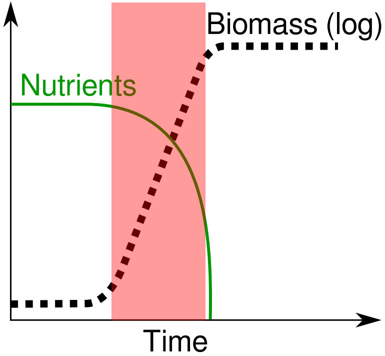


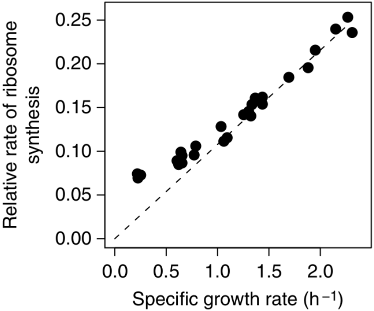


Cell composition is a resource allocation problem

Source picture: NIAID
Molenaar et al, MSB 2009

Molecular composition changes with the growth rate

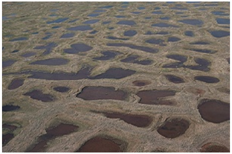


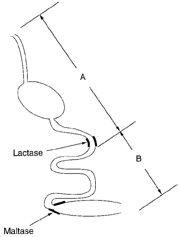


Empirical growth laws link the molecular composition with the **growth rate at balanced growth**

Molenaar et al, MSB 2009 ; from data in Gausing, JMB 1977

Do we find balanced growth in natural conditions?





Not so much.

Savageau (1998), Am. Natural., 122(6):732-44

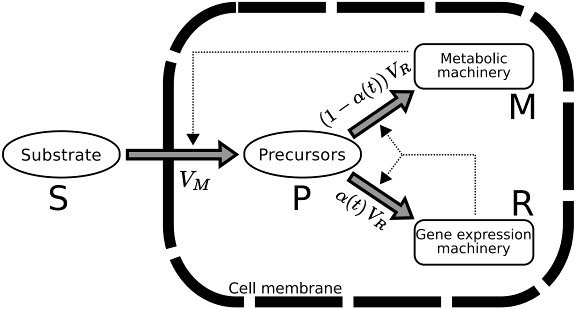
Project: a dynamical perspective on growth control strategies

- Is considering balanced-growth a critical assumption to understand growth control strategies?
- Can we gain additional information by extending growth rate studies to dynamical environments?

Tools:

- A simple model of resource allocation
- Optimal control theory
- Fluorescent reporters of gene expression (experiments)

SELF-REPLICATOR MODEL OF RESOURCE ALLOCATION



Two biochemical (macro)reactions:

$$\text{Metabolism:} \quad S \xrightarrow{V_M} P$$
$$\text{Macromolecule synthesis:} \quad P \xrightarrow{V_R} \alpha R + (1-\alpha)M$$

Giordano *et al*, Plos Comp Biol 2016

TWO-DIMENSIONAL DYNAMICAL SYSTEM

Assuming...

$$\text{Volume: } \texttt{Vol} = \beta(M+R) \quad \Rightarrow \quad \text{Growth rate: } \mu = \beta \frac{V_R}{\texttt{Vol}} = \beta v_R$$

$$\text{Michaelis-Menten kinetics} \quad \Rightarrow \quad v_R = \frac{k_R \cdot p}{K_R + p} \cdot r$$

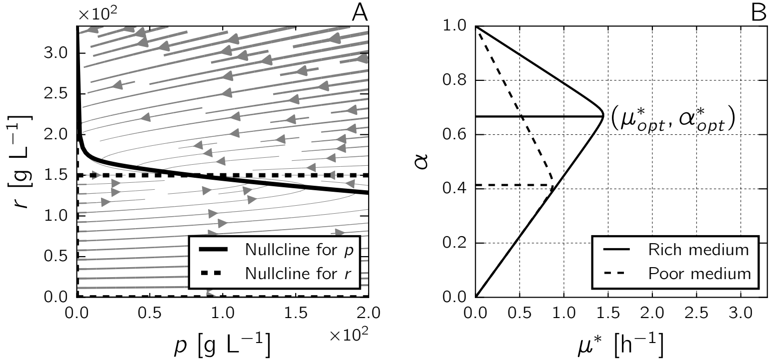
We obtain the following (dimensionless) system:

$$\text{Precursors:} \quad \frac{d\hat{p}}{d\hat{t}} = E_M \cdot (1-\hat{r}) - \frac{\hat{p}}{K+\hat{p}} \cdot \hat{r} \cdot (1+\hat{p})$$

$$\text{GEM:} \quad \frac{d\hat{r}}{d\hat{t}} = \frac{\hat{p}}{K+\hat{p}} \cdot \hat{r} \cdot (\alpha - \hat{r})$$

How does the cell choose α (relative GEM production)?

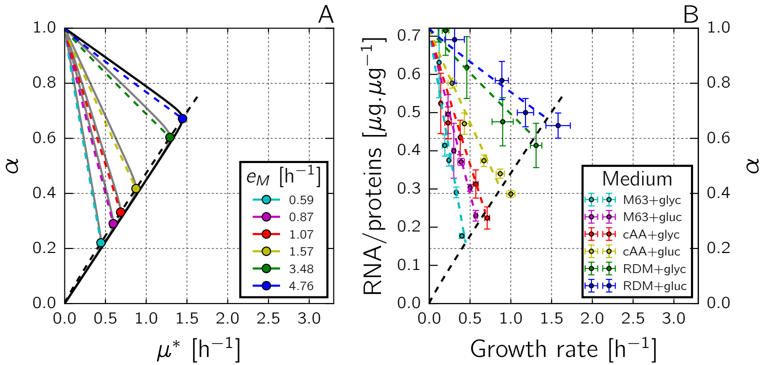
MODEL HAS A SINGLE STABLE STEADY-STATE



For each environment, a single value of α is "optimal"

Giordano *et al*, Plos Comp Biol 2016

Model predicts the steady-state growth laws

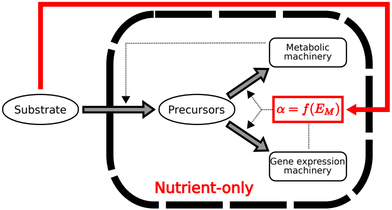


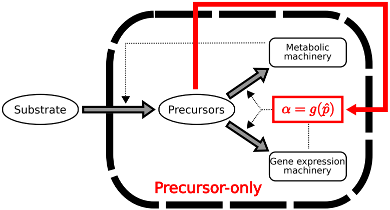
Choosing the "optimal" α for each environment predicts the empirical growth laws

Giordano *et al*, Plos Comp Biol 2016; from data in Scott *et al*, Science, 2010

Alternative control strategies for optimal resource allocation

Only two possible candidates...





$$f(E_M) = \frac{E_M + \sqrt{K\,E_M}}{E_M + 2\sqrt{K\,E_M} + 1} \qquad g(\hat{p}) = \frac{\hat{p}}{\hat{p} + \frac{K}{K+\hat{p}}(1+\hat{p})}$$

... which are exactly equivalent for steady-state growth!

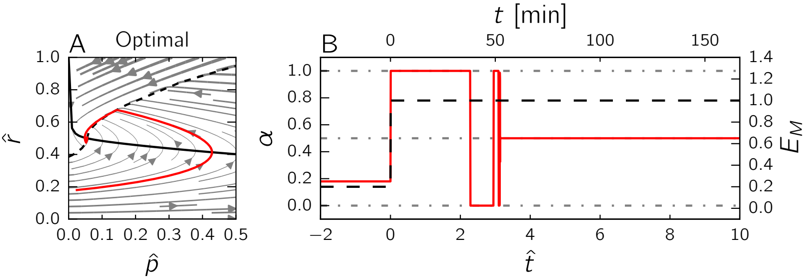
Giordano *et al*, Plos Comp Biol 2016

AND DURING GROWTH TRANSITIONS?

New objective: producing as much biomass as possible **during an environmental transition**

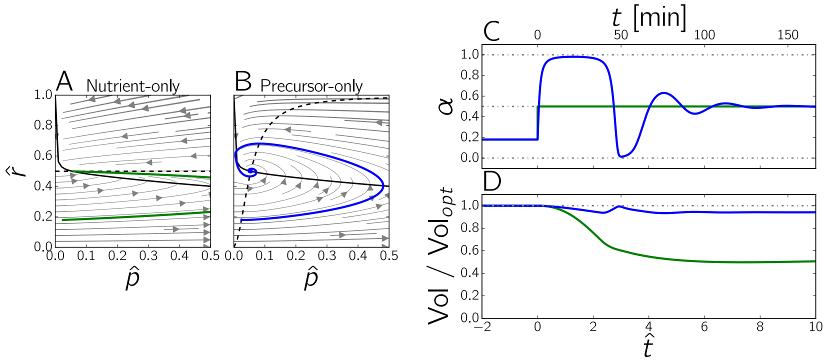
$$J(\alpha) = \int_0^{\tau} \mu(t, \hat{p}, \hat{r}, \alpha)\, dt$$

The optimal solution is a bang-bang-singular regulatory strategy



Giordano *et al*, Plos Comp Biol 2016

Performance of control strategies during growth transition

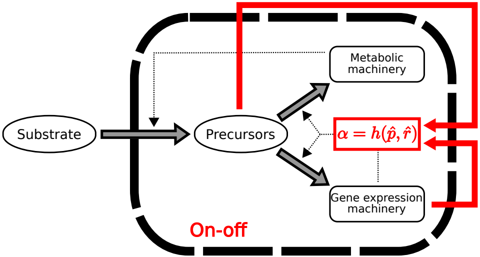


Measuring precursors leads to a higher biomass production

Giordano *et al*, Plos Comp Biol 2016

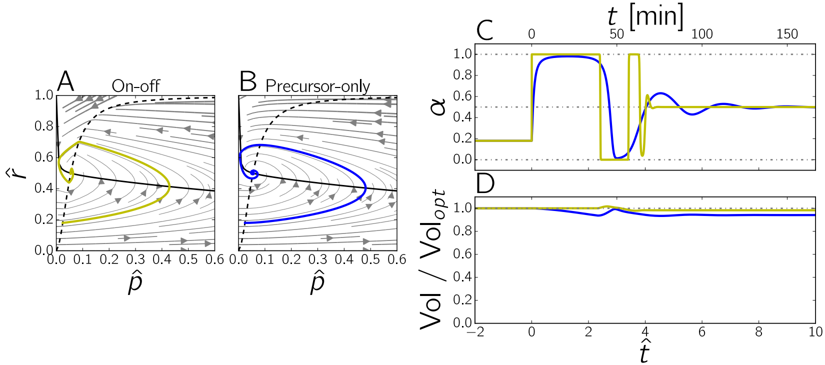
But the cell is not that constrained...

Is a strategy measuring two (or more) variables better?



Giordano *et al*, Plos Comp Biol 2016

PERFORMANCE OF AN "ON-OFF" STRATEGY

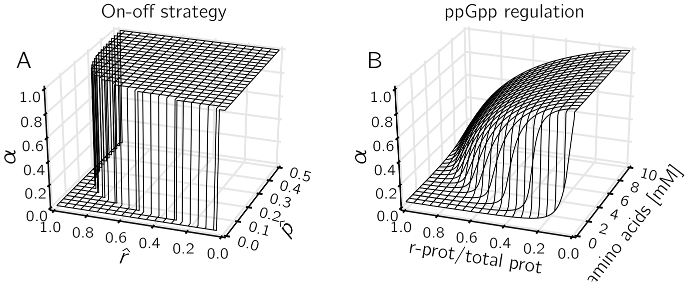


A feedback control on two variables improves the transition

Giordano *et al*, Plos Comp Biol 2016

Does the strategy correspond to actual regulatory mechanisms?

If we take a model of the ppGpp regulatory system in *E. coli* (Bosdriesz *et al*, 2015)...



... we obtain a likely candidate.

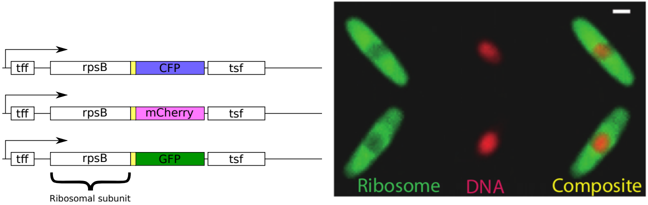
Giordano *et al*, Plos Comp Biol 2016

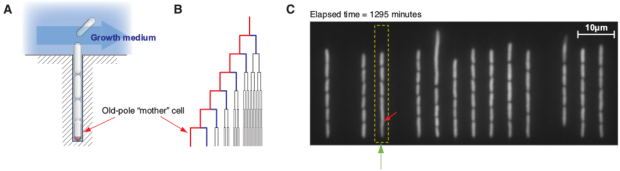
Conclusion

- Is considering balanced-growth a critical assumption to understand growth control strategies?
  - Yes, because strategies are equivalent at steady state
- Can we gain additional information by extending growth rate studies to dynamical environments?
  - Yes, because they become distinguishable in dynamical conditions
  - Complex strategies are beneficial during growth transitions
  - The widespread ppGpp system might actually be a cheap way for the cell to gain information on several variables

COMING SOON!

Experimental validation: observing the dynamics of α in bacterial cells

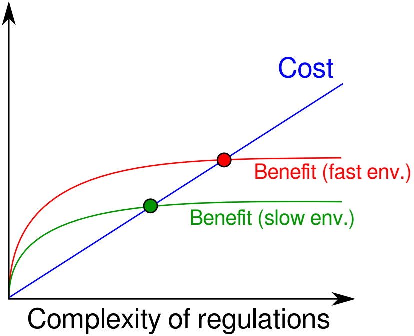


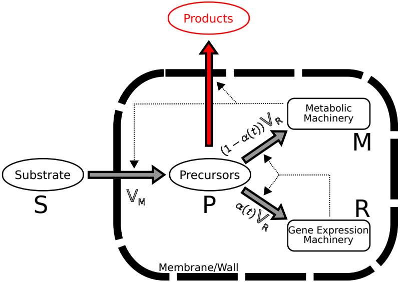


Bakshi *et al*, Mol. Microb. 2012; Wang *et al*, Current Biology 2010

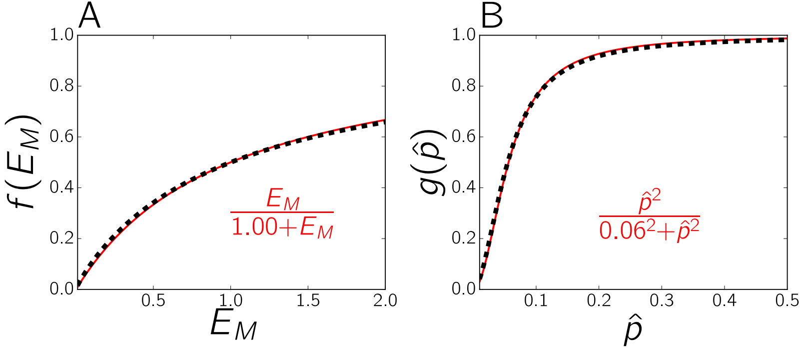
Food for thought (a.k.a. Perspective)

- Is there a fundamental relation between environment dynamics and complexity of regulations?
- Can we apply this approach to maximize industrial production yields?





Control strategies can be approximated by biologically relevant functions



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Giordano *et al*, Plos Comp Biol 2016