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

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SeMoVi
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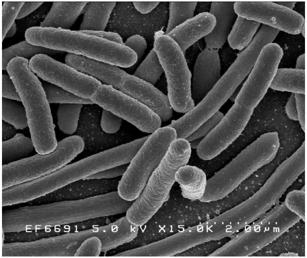
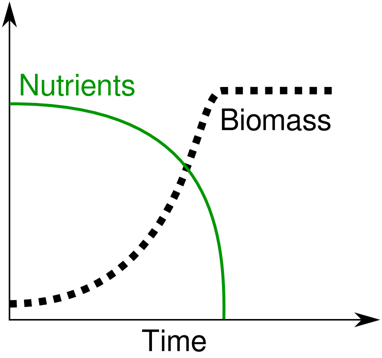
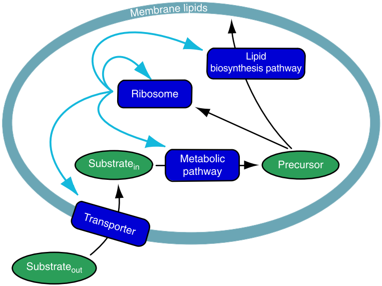
MICROBIAL GROWTH

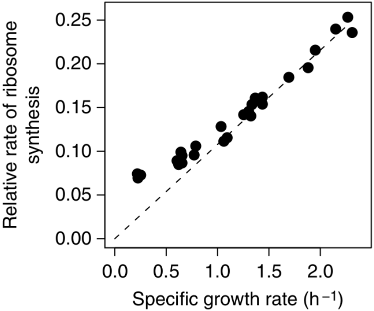




Source picture: NIAID

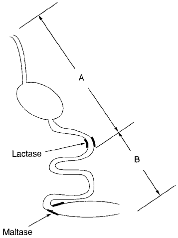
Molecular composition of a microorganism

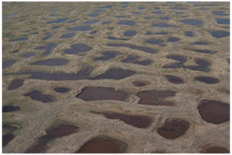




Molenaar et al, MSB 2009 ; from data in Gausing, JMB 1977

DO MICROORGANISMS LIVE IN CONSTANT ENVIRONMENTS?





Mostly, not.

Savageau (1998), Am. Natural., 122(6):732-44
Felix Andrews, CC BY-SA 3.0

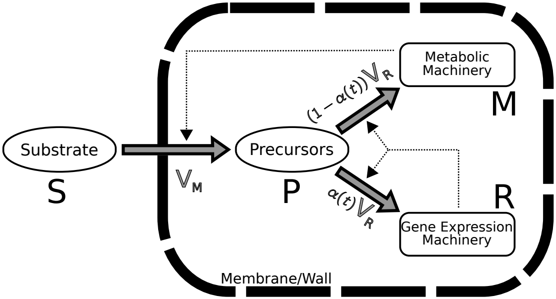
Our project: a dynamical perspective on growth control strategies

- 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*, in preparation

Two-dimensional dynamical system

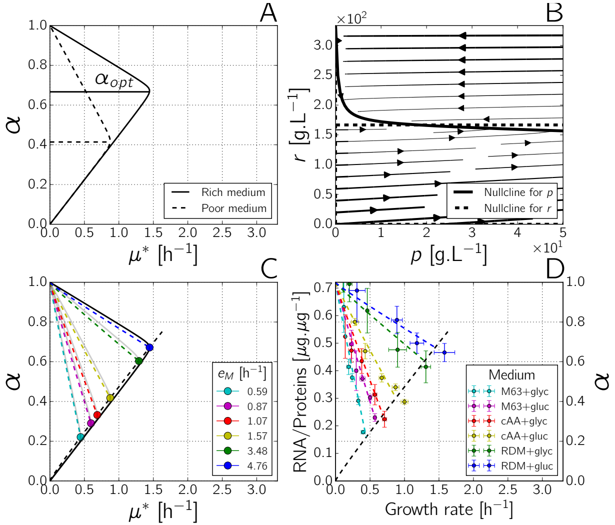
Volume: $\texttt{Vol} = \beta(M+R) \quad \Rightarrow \quad$ Growth rate: $\mu = \beta \dfrac{V_R}{\texttt{Vol}} = \beta v_R$

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

Model with concentration variables (dimensionless):

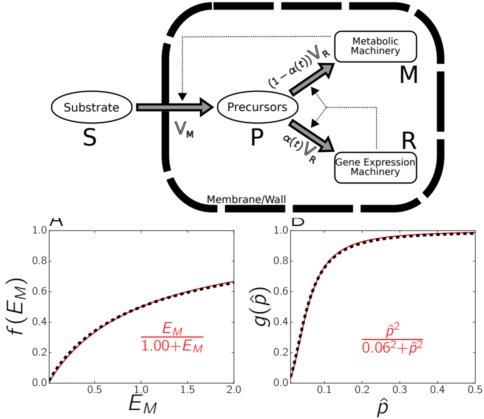
$$
\begin{aligned}
\text{Precursors:} \quad \frac{d\hat{p}}{d\hat{t}} &= E_M \cdot (1-\hat{r}) - \frac{\hat{p}}{K+\hat{p}} \cdot \hat{r} \cdot (1+\hat{p}) \\
\text{GEM:} \quad \frac{d\hat{r}}{d\hat{t}} &= \frac{\hat{p}}{K+\hat{p}} \cdot \hat{r} \cdot (\alpha - \hat{r})
\end{aligned}
$$

Model predicts the steady-state growth laws



Giordano *et al*, in preparation; from data in Scott *et al*, Science, 2010

Alternative control strategies for optimal resource allocation



The two strategies are equivalent for steady-state growth!

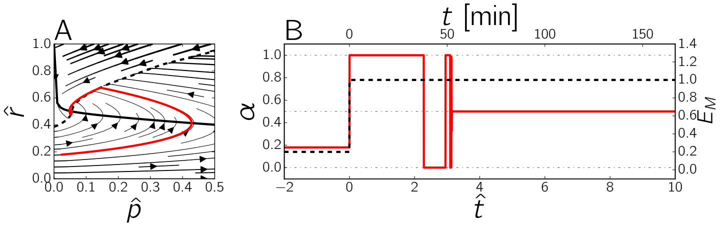
Giordano *et al*, in preparation

What if we optimize during a growth transition?

New objective: maximize biomass during a transition (upshift at $t = 0$)

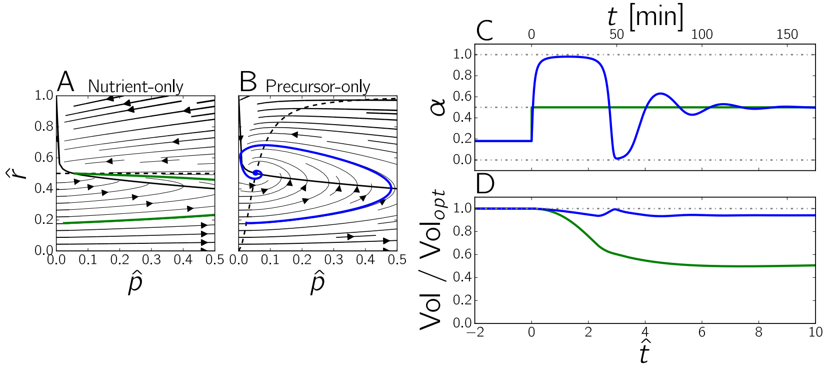
$$J(\alpha) = \int_0^{\tau} \mu(t, \hat{p}, \hat{r}, \alpha)\, dt$$

Optimal solution: bang-bang-singular regulatory strategy



Giordano *et al*, in preparation

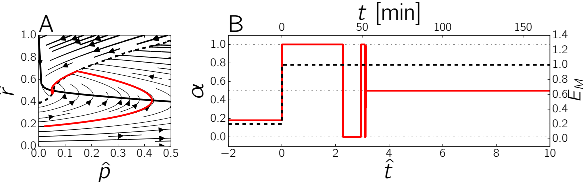
Performance of control strategies during growth transition

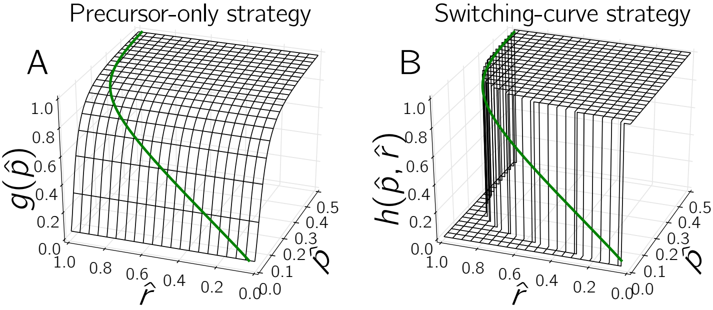


Control strategies are no longer equivalent in dynamic environment.

Giordano *et al*, in preparation

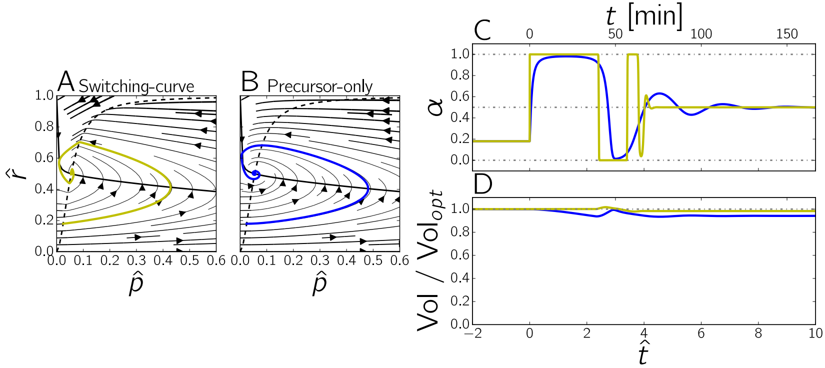
AND IF WE CAN MEASURE SEVERAL VARIABLES?





Giordano *et al*, in preparation

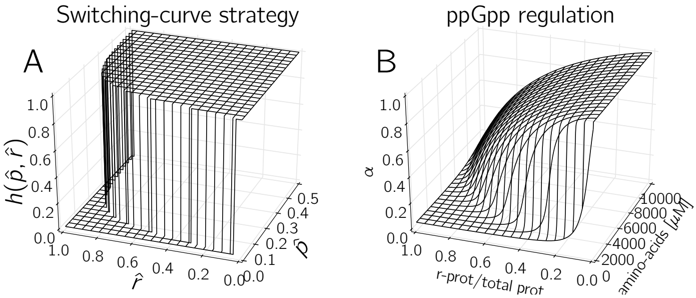
Is a strategy measuring two variables better?



Giordano *et al*, in preparation

Does the strategy correspond to actual regulatory mechanisms?

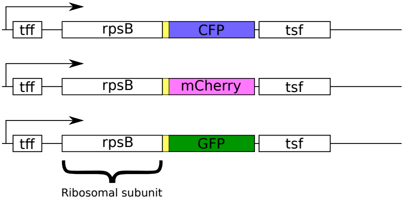
If we take a model of the ppGpp regulatory system in *E. coli* (Bosdriesz *et al*, 2015)...

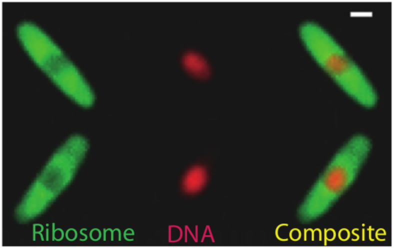


... we obtain a likely candidate.

Giordano *et al*, in preparation

EXPERIMENTAL VALIDATION: OBSERVING THE DYNAMICS OF α IN BACTERIAL CELLS





Bakshi et al, Molecular Microbiology 2012

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 dynamic conditions
  - Complex strategies are beneficial during growth transitions
  - The widespread ppGpp system might actually be a simple way for the cell to gain information on several variables

Perspective

- Can we observe experimentally an oscillatory pattern of ribosome synthesis during transitions?
- Is there a fundamental relation between environment dynamics and complexity of regulations?
- Can we apply this approach to maximize industrial production yields?