Moving away from steady state to understand growth regulatory strategies in microorganisms

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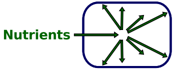
Microbes grow by assimilating nutrients from the environment



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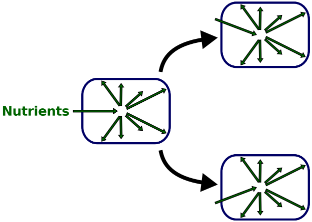

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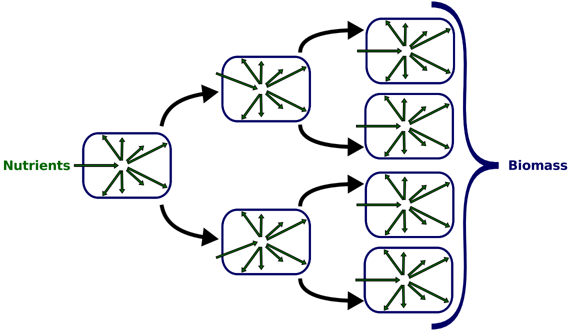

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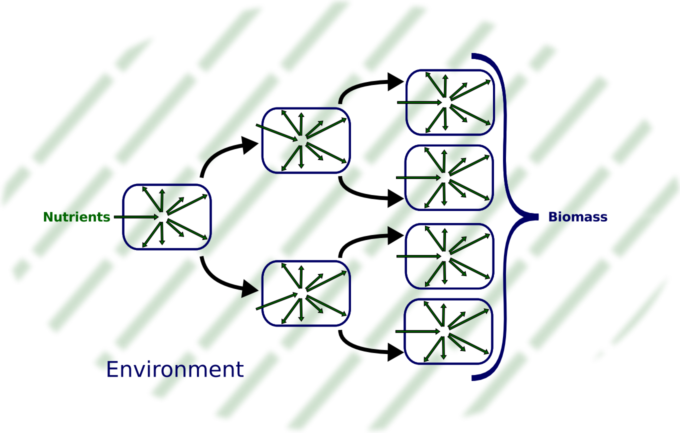
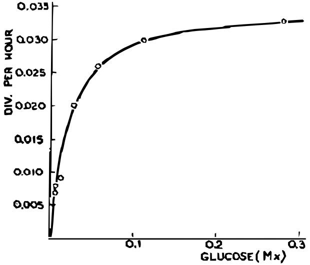
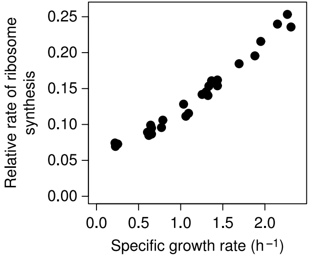


Growth rate and cell composition change with the environment





Monod, J. (1949) The growth of bacterial cultures, Annu Rev Microbiol

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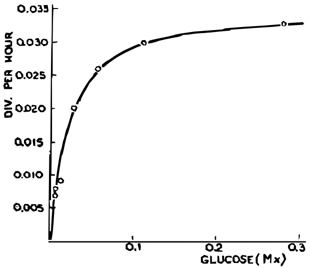

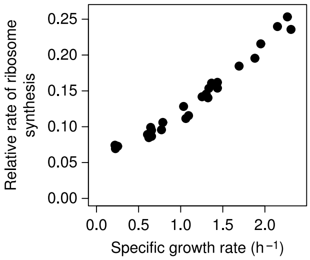

Resource allocation changes with the environment

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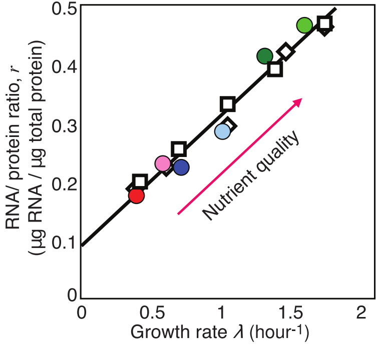
General growth laws predict physiology based on growth rate maximization



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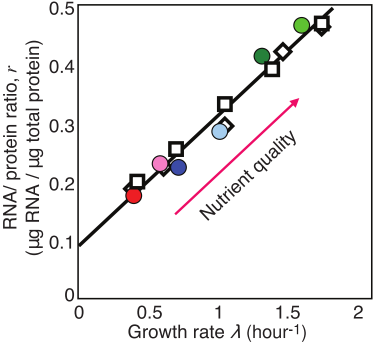

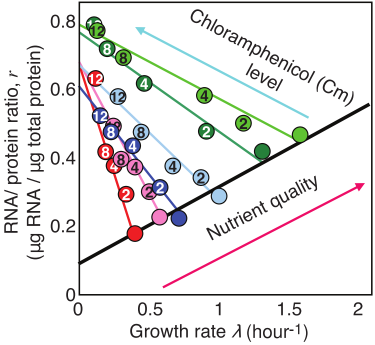

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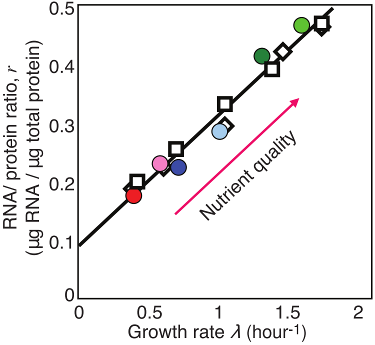

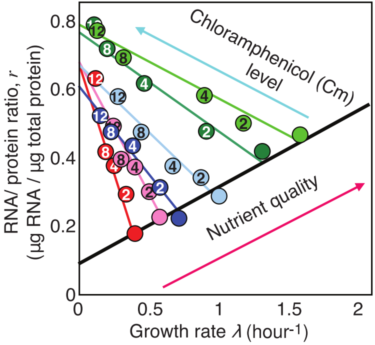

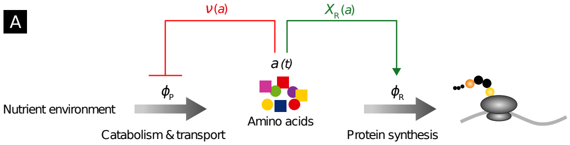

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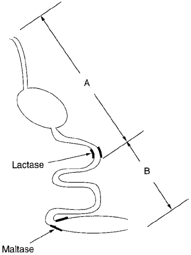
Steady-state and dynamic optimization

- Most growth laws and data concern steady-state growth
  $\rightarrow$ convenient, well-controlled, robust and reproducible
- However, most bacteria live (and evolve) in changing environment



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

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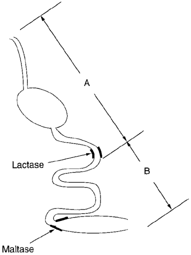
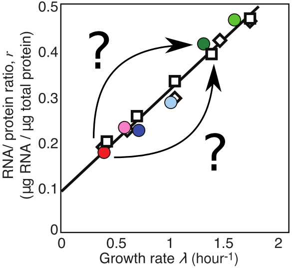




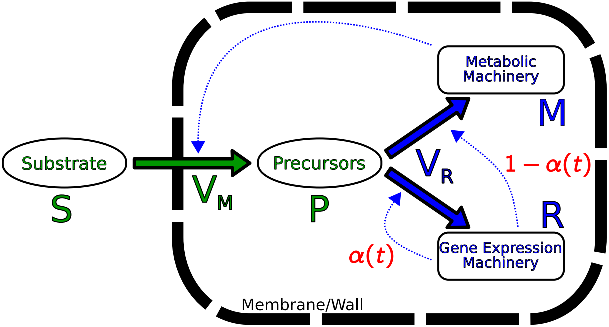
What new information (if any) can we gain from studying the dynamics of growth?

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

Plan

- A self-replicator model of resource allocation
- Equivalent regulatory strategies at steady state can be discriminated in dynamical conditions

Self-replicator formalism



Biochemical (macro)reactions:

$$S \xrightarrow{V_M} P$$
$$P \xrightarrow{V_R} \alpha R + (1-\alpha) M$$

Inspired by Molenaar, D. et al (2009), Mol Syst Biol

Dynamics of the self-replicating system

$$\frac{d}{dt}\begin{bmatrix} p(t) \\ r(t) \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & -1 \\ 0 & \alpha \end{bmatrix} \cdot \begin{bmatrix} v_M(p,r,s,t) \\ v_R(p,r,t) \end{bmatrix}}_{\texttt{reactions}} - \underbrace{\mu(p,r,t) \cdot \begin{bmatrix} p(t) \\ r(t) \end{bmatrix}}_{\texttt{dilution}}$$

$$v_M = \frac{k_M \cdot s}{K_M + s} \cdot (1/\beta - r)$$

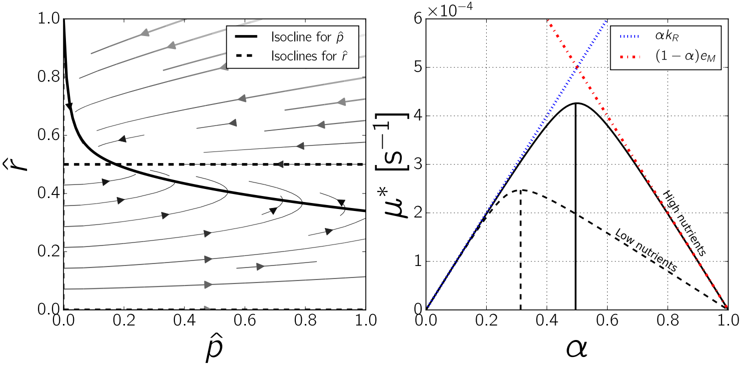
$$v_R = \frac{k_R \cdot p}{K_R + p} \cdot r$$

$$\texttt{Vol}(t) = \beta \cdot (M(t) + R(t))$$

Growth rate is given by total macromolecular synthesis:

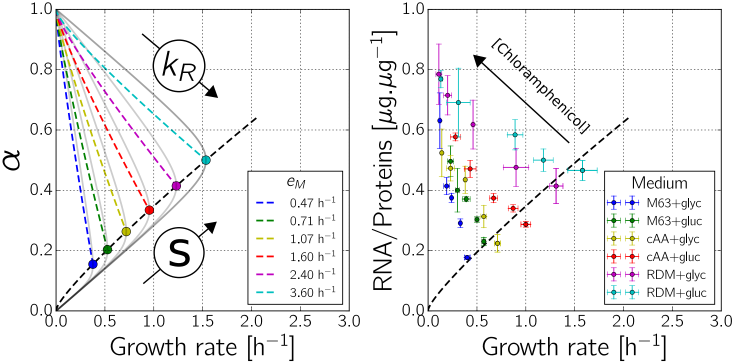
$$\mu = \frac{1}{\texttt{Vol}} \frac{d\texttt{Vol}}{dt} = \frac{1}{M+R} \frac{d(M+R)}{dt} = \beta \cdot v_R(p,r,t)$$

Transition towards a stable steady state



For any environment ($\frac{k_M \cdot s}{K_M + s} = e_M$) $\rightarrow$ a single resource allocation α maximizes the growth rate

Maximizing growth rate at steady state yields growth laws



Parameters: order of magnitudes extracted from literature. Qualitative behaviors are not parameter sensitive. Data in right figure from Scott et al (2010), Science.

Regulatory strategies: biological implementation of optimal resource allocation

If the cell can measure any variable, which one would allow to maximize growth rate in any environment?

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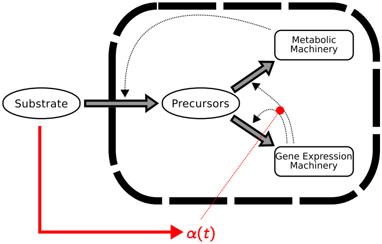
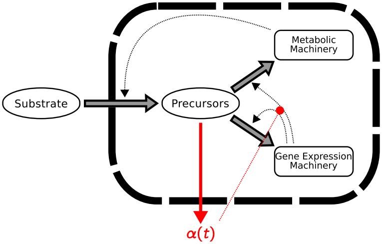


$$\alpha_{opt} = f(E_M)$$



$$\alpha_{opt} = g(p)$$

Both strategies are equivalent at steady state

Optimal regulatory strategies during growth transitions

Are those regulatory strategies also optimal (and equivalent) during growth transitions?

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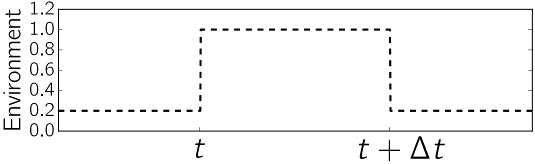
- Environmental conditions: **nutrient upshift**

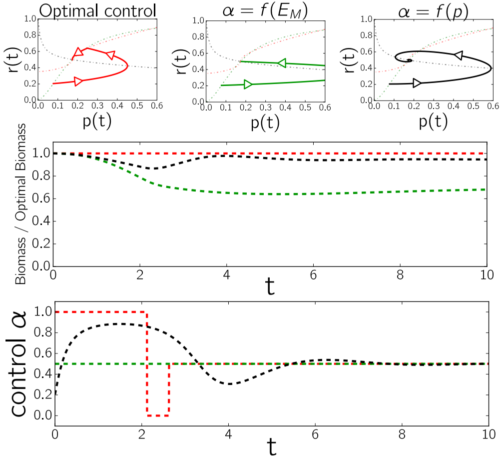


- Objective function: **biomass produced**

$$\max_{\alpha \in \mathcal{U}} J(\alpha) := \int_{\tau}^{\tau+\Delta\tau} \mu(p, r, \alpha) dt$$

- Mathematical tools from control theory used to derive optimal strategy: **Pontryagin's maximum principle**

Regulatory strategies are not equivalent during growth transitions



Measuring precursors is closer to optimal strategy than measuring the environment

Conclusions

- Steady-state growth laws can be reproduced from first principles
- Without additional assumptions, we cannot discriminate between strategies that sense the environment (external input) or the precursor abundance (internal variable)
- However, formulation of dynamical optimal control problem shows that measuring internal variables enables faster adaptation
- What about regulatory strategies that measure several components?
- Is there a *growth law* linking the dynamics of the environment with the complexity of regulatory strategies across the diversity of microorganisms?