Université Joseph Fourier GRENOBLE

Inria informatics mathematics

Getting out of steady state to understand growth regulatory strategies in microorganisms

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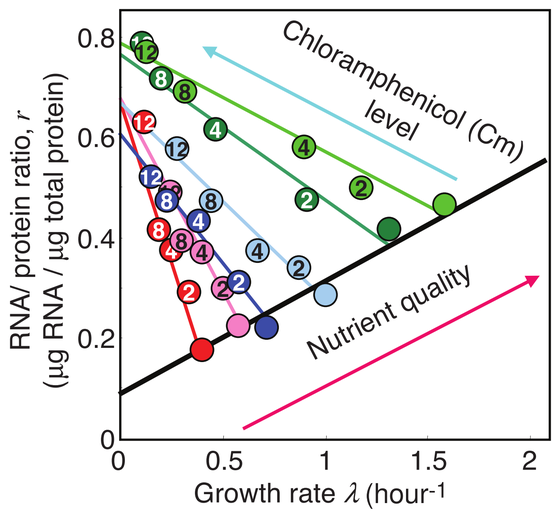
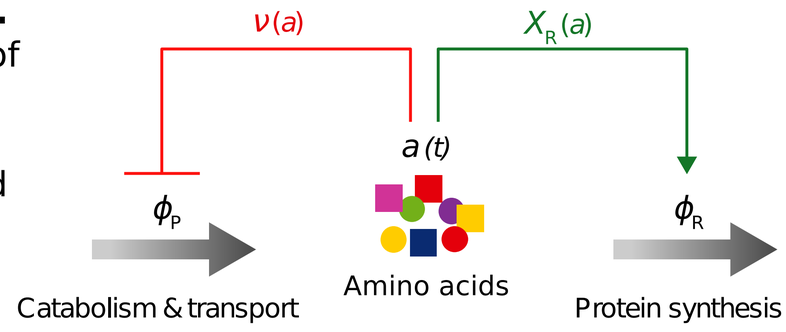
In constant environments, microorganisms follow general growth laws



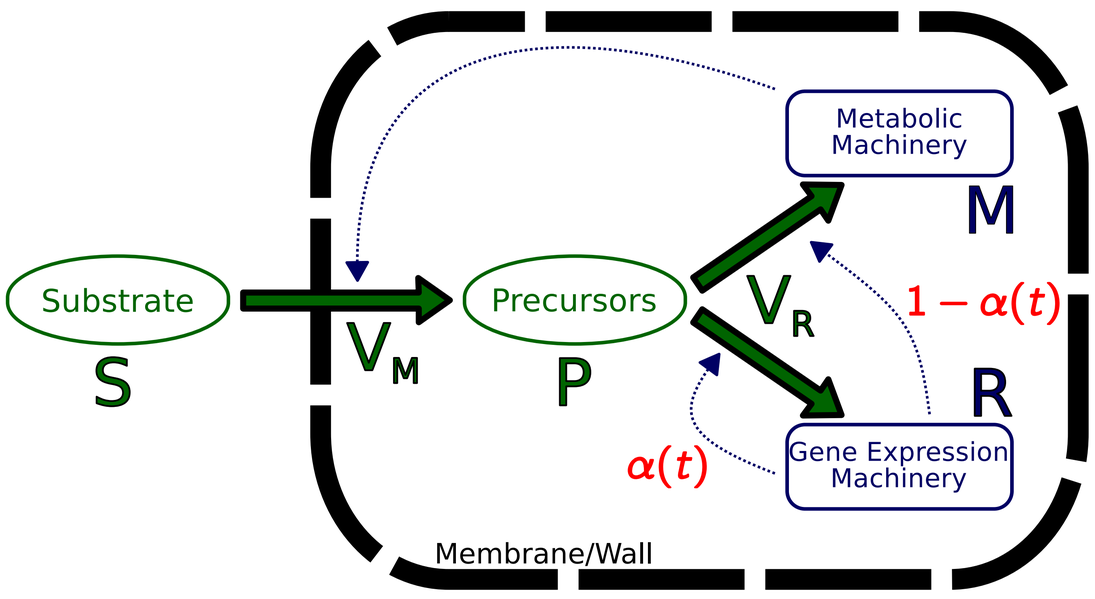
Ribosome concentration depends linearly on growth rate. This simple relation between nutrient quality and the synthesis of ribosomes is long known. Recently, Scott et al[1,2] showed that by applying the right perturbations (left figure), one can identify new growth laws and uncover the molecular mechanisms behind resource allocation (right figure). However, all these studies consider steady-state response to constant environments, while microorganisms have evolved in dynamically changing conditions.



What information can we gain from the dynamical study of resource allocation?

Self-replicator model

Allocation across 2 components



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

Two assumptions

Michaelis-Menten kinetics

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

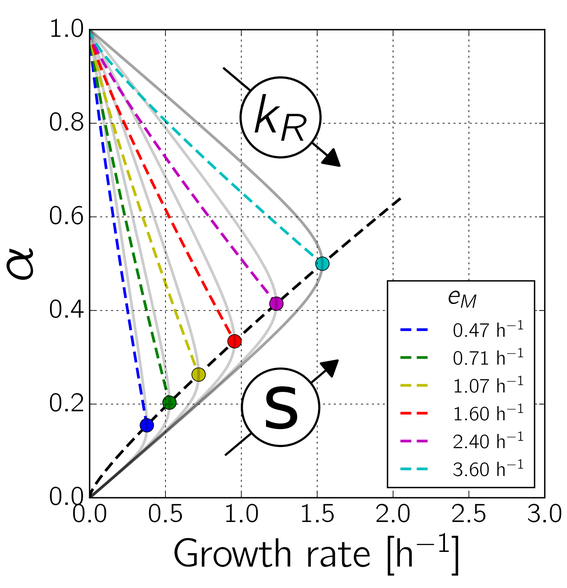
$$v_R = \frac{k_R p}{K_R + p} \cdot r$$

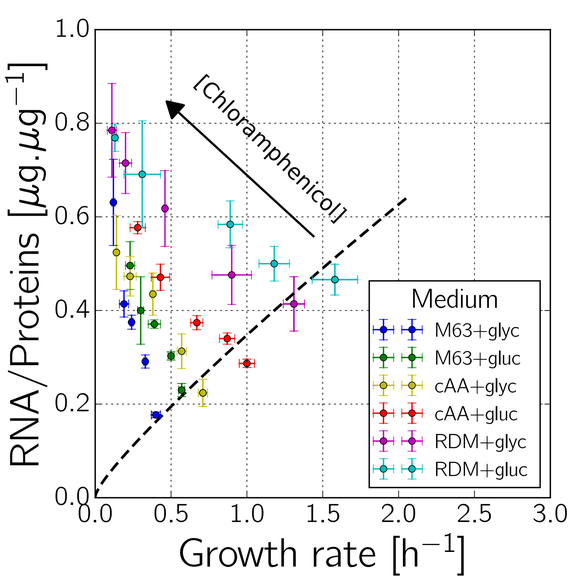
Constant total concentration of macromolecules

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

$$\mu = \beta v_R(x,t)$$

Optimal allocation predicts growth laws





Link with biological regulations?

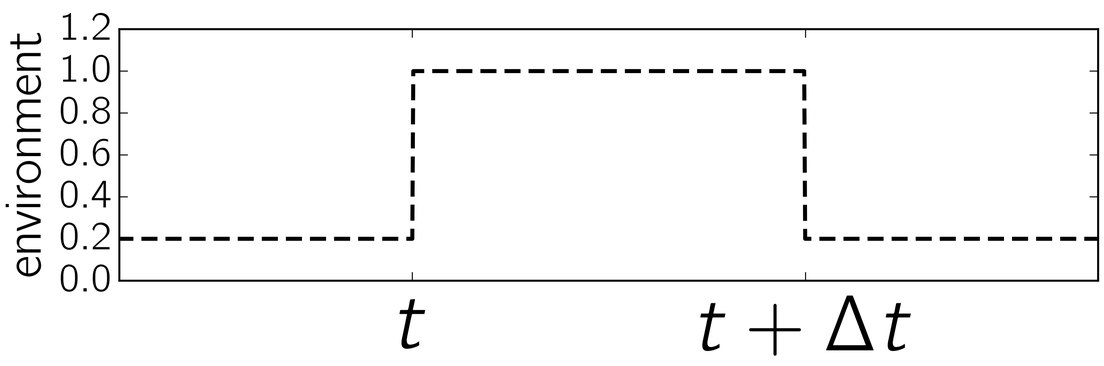
At steady state, the allocation that maximizes growth rate can be expressed as a function of **p (precursor concentration)** or **s (substrate concentration)**.

Mathematically equivalent cellular strategies that maximize growth rate in steady-state!

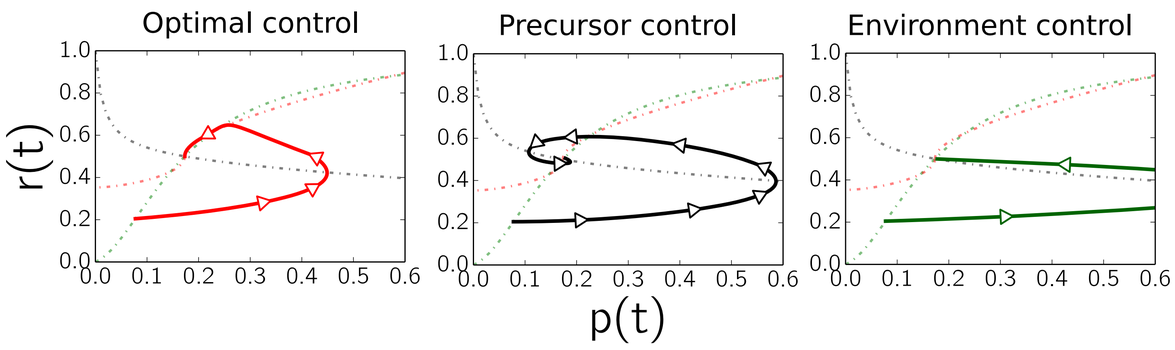
But do they optimize growth in dynamical conditions..?

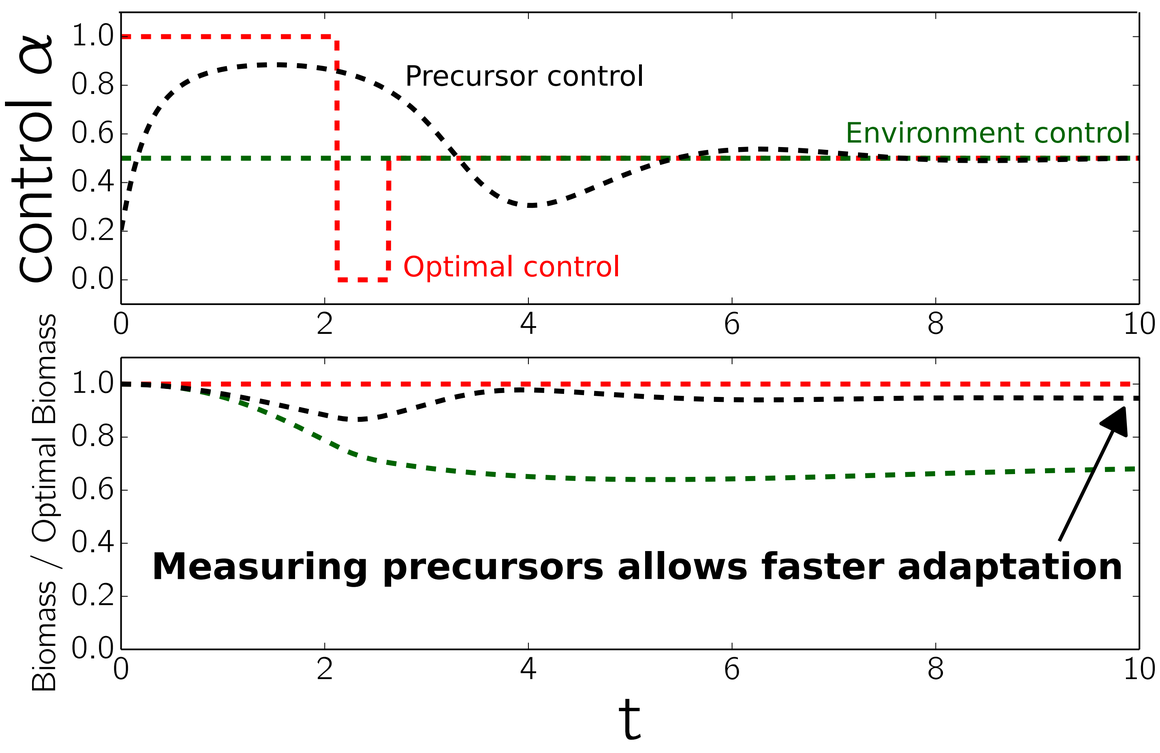
Dynamical optimization

Objective: biomass maximization during an environmental upshift



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





Thus, **simple steady-state strategies are not equivalent and not optimal in dynamical conditions.**

Can we explain this in terms of cellular strategies based on measuring several components? [3]

References

[1] Scott, M., Gunderson, C.W., Mateescu, E.M., Zhang, Z., and Hwa, T. (2010). Science (New York, N.Y.) 330, 1099–1102.
[2] Scott, M., Klumpp, S., Mateescu, E.M., and Hwa, T. (2014). Molecular Systems Biology 10, 747.
[3] Giordano, N., Mairet, F., Gouzé, JL., Geiselmann, J., de Jong, H. (in preparation)