Dynamic optimization of resource allocation in microorganisms

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Growth and macromolecular composition

- Macromolecular composition of cell varies with growth rate

- Phenomenological **growth laws** capture variation of macromolecular composition with growth rate
- Explanation of growth laws based on **optimization principle**
  - Bacteria have evolved so as to distribute limited resources over cellular processes in order to optimize growth (biomass)

Steady-state and dynamic optimization

- Most growth laws and data concern **steady state** (balanced growth)
  - Well-controlled and reproducible in laboratory

- However, most bacteria evolve in **dynamic** environment
  Example: *E. coli* in human colon

Towards dynamic growth laws

- **Aim**: study optimal allocation of resources to gene expression machinery and metabolism during growth-phase transitions
  - Which allocation is optimal for sustaining maximal growth (biomass)?
  - Simple model of cell: bacteria as **self-replicators**

Molenaar et al. (2009), *Mol. Syst. Biol.*, 5:323

- Tools from **optimal control theory**
Self-replicator model of cell

- Reaction scheme:
  \[ S \xrightarrow{V_M} P \]
  \[ nP \xrightarrow{V_R} \alpha R + (1 - \alpha)M \]

- Stochiometry model with extensive variables:
  \[ \frac{d}{dt} \begin{bmatrix} P \\ M \\ R \end{bmatrix} = \begin{bmatrix} 1 & -n & 0 \\ 0 & 1 - \alpha & 1 \\ 0 & \alpha & 0 \end{bmatrix} \cdot \begin{bmatrix} V_M \\ V_R \end{bmatrix} = N \cdot V \]

- Volume and growth rate:
  \[ Vol = \beta(M + R) \]
  \[ \mu = \frac{1}{Vol} \frac{dVol}{dt} = \frac{1}{M + R} \frac{d(M + R)}{dt} \]
Reformulated self-replicator model of cell

- Definition of intensive variables:

\[ p = \frac{P}{V_{ol}}, \quad m = \frac{M}{V_{ol}}, \quad \text{and} \quad r = \frac{R}{V_{ol}} \]

- Kinetics:

\[ v_M = k_M \frac{s}{K_M + s} m = e_M \left(\frac{1}{\beta} - r\right), \]
\[ v_R = k_R \frac{p}{K_R + p} r, \]
\[ \mu = \frac{V_R}{R + M} = \beta v_R. \]

- Model with **intensive** (dimensionless) variables:

\[
\begin{align*}
\frac{dp}{dt} &= E_M \cdot (1 - r) - (1 + p) \frac{p}{K+p} r, \\
\frac{dr}{dt} &= (\alpha - r) \frac{p}{K+p} r.
\end{align*}
\]
Steady-state analysis of model

- Control parameter $\alpha$ determines fractional distribution of resources over metabolic and gene expression subsystems.

- **Result:** for constant $\alpha$, the system has a single steady state with growth rate $\mu^*(p^*, r^*, \alpha)$.

\[
\begin{align*}
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\]
Steady-state analysis of model

**Result:** system admits single maximum growth rate for value \( \alpha = \alpha_{\text{opt}} \in [0, 1] \)
- Maximum varies with medium quality, represented by parameter \( e_M \)
Dynamic optimal control problem

- Bacterial cell has to reallocate resources after change in environment to reach optimal growth rate (change $\alpha$)

- What is the best dynamic resource allocation strategy?
- **Optimal control problem** for biomass

$$
\max_{\alpha \in \mathcal{U}} J(\alpha) := \int_{0}^{+\infty} \mu(p, r, \alpha, t)dt
$$

with set of admissible controls: $\mathcal{U} = \{ \alpha : \mathbb{R}^+ \rightarrow [0, 1] \}$
Pontryagin Maximum Principle

\[ H := \lambda_p E_M (1 - r) - \frac{p}{K + p} r \left[ \lambda_p (1 + p) + \lambda_r r + \lambda_0 \right] + \alpha \lambda_r \frac{p}{K + p} r. \]

\[ \dot{\lambda}_p = \frac{K}{(K + p)^2} r \left[ \lambda_p (1 + p) + \lambda_r (r - \alpha) + \lambda_0 \right] + \frac{p}{K + p} r \lambda_p, \]

\[ \dot{\lambda}_r = \lambda_p E_M + \frac{p}{K + p} \left[ \lambda_p (1 + p) + \lambda_r (2r - \alpha) + \lambda_0 \right]. \]

The maximization condition is given by:

\[ \alpha(t) \in \arg\max_{\nu \in [0, 1]} H(x(t), \lambda(t), \lambda_0, \nu), \]

a.e. \( t \in [0, +\infty). \)

The switching function:

\[ \phi := \lambda_r \frac{p}{K + p} r \]

\[ \begin{cases} \alpha = 1 & \iff \phi > 0, \\ \alpha = 0 & \iff \phi < 0. \end{cases} \]
Characterization of singular arcs

- The singular arc corresponds to the optimal steady-state:

\[ \phi(t) = \dot{\phi}(t) = 0, \quad \forall t \in [t_1, t_2] \quad \Rightarrow \quad (p(t), r(t)) = (p_{opt}, r_{opt}) \]

- Kelley condition:

\[ (-1)^q \frac{\partial}{\partial \alpha} \frac{d^{2q}}{dt^{2q}} \phi(t) < 0 \quad \text{for } q = 2 \quad \Rightarrow \quad \text{Chattering arc (Fuller’s phenomena)} \]

- Optimal strategy: Turnpike?
How to compute the switching curve?

- The tangent of the switching curve at \((p_{\text{opt}}, r_{\text{opt}})\) is vertical (Naumov, 2003) → approximation of the switching curve as a vertical line in a small neighborhood of \((p_{\text{opt}}, r_{\text{opt}})\).

- From Hamiltonian conservation property and switching condition \(\lambda_r = 0\), we can derive an explicit representation

\[
\lambda_p = \lambda_{p,L}(p, r)
\]

- Backward integration starting from

\[
(p(0), r(0), \lambda_p(0), \lambda_r(0)) = (p_{\text{opt}}, r_{\text{opt}} + \epsilon, \lambda_{p,L}(p_{\text{opt}}, r_{\text{opt}} + \epsilon), 0)
\]
How to compute the switching curve?

- Backward integration starting from

\[(p(0), r(0), \lambda_p(0), \lambda_r(0)) = (p_{opt}, r_{opt} + \epsilon, \lambda_p, L(p_{opt}, r_{opt} + \epsilon), 0)\]
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How to compute the switching curve?

- Validation on Fuller’s problem:
  
  - minimize \( \int_0^T x_1^2(t) \, dt \) given

  \[
  \begin{cases}
  \dot{x}_1 &= x_2, \\
  \dot{x}_2 &= u,
  \end{cases}
  \]

  - Analytical expression of the switching curve (represented in blue):
    \[ x_1 = \pm \zeta x_2^2 \]
    with \( \zeta = \sqrt{\left(\sqrt{33} - 1\right) / 24} \)

  - Numerical method (red dotted line)
Optimal strategy: turnpike

- Numerical solutions by a direct method (using Bocop, developed by Inria Commands)
Simple feedback control strategies

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Precursor</th>
<th>On-Off</th>
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</table>
| $\alpha = f(E_M)$ | $\alpha = g(\hat{p})$ | $\alpha = \begin{cases} 
0, & \text{if } \hat{r} > g(\hat{p}) \\
1, & \text{if } \hat{r} < g(\hat{p}) 
\end{cases}$ |

\[
\alpha = \frac{E_M}{1.00 + E_M}
\]

\[
\alpha = \frac{\hat{p}^2}{0.19^2 + \hat{p}^2}
\]

\[
\alpha = 0
\]

\[
\alpha = 1
\]
Comparison of control strategies

- Nutrient-only
- Precursor-only
- On-Off

Graphs showing the comparison of control strategies with plots of parameters over time.
Biological implementation?

- Regulation of resource allocation via ppGpp (Bosdriesz et al., 2015)
Biological implementation?

- Regulation of resource allocation via ppGpp (Bosdriesz et al., 2015)
- Quasi steady-state approximation:
  - Fast variables: ppGpp, tRNA
Conclusions and perspectives

- Study of resource allocation in bacteria in dynamic condition
- Optimal strategy: turnpike with chattering
- Numerical method to determine the switching curve
- Near-optimal strategy: switch depending on the inbalance between precursors and ribosomes
- Implementation via ppGpp

- Next step:
  - Experimental test of control strategy using fluorescent reporters
  - Optimization of the production of valuable compounds

Yegorov, I.; Mairet, F.; Gouzé, J.-L. Optimal resource allocation for bacterial growth with degradation. IFAC 2017 world congress