Control in biology: topics in bacterial growth

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Joint work with

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ICIAM
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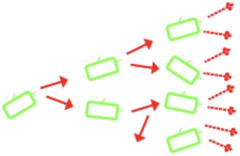
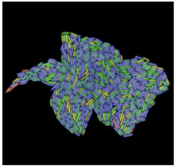
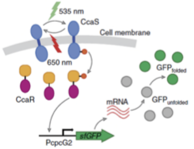
Model definition

Optimal control of microbial cells (ANR Maximic, PI H. de Jong)





Stewart *et al.* (2005), *PLoS Biol.*, 3(2): e45



Milias-Argeitis *et al.* (2019), *Nat Commun.*, 7:12546

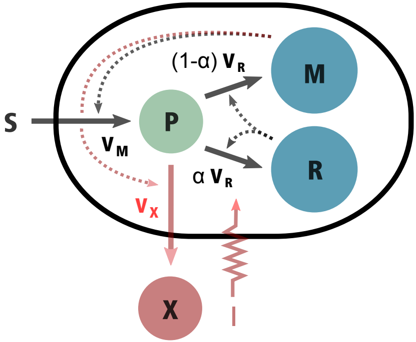
- Self-replicator model: biomass maximisation (Giordano *et al*'16)
- Genetic engineering of a strain of bacteria: light-induced control of growth
- New pathway to produce a metabolite of interest (Egorov *et al*'18)
- Competition between biomass maximisation and metabolite production

Yabo, A.; Caillau, J.-B.; Gouzé, J.-L. Optimal bacterial resource allocation: metabolite production in continuous bioreactors. *Math. Biosci. Eng.* **17** (2020), no. 6, 7074–7100

Yabo, A. G.; Caillau, J.-B.; Gouzé, J. L.; de Jong, H.; Mairet, F. Dynamical analysis and optimization of a generalized resource allocation model of microbial growth. *SIAM J. Appl. Dyn. Syst.* **21** (2022), no. 1, 137–165

Model definition

Self-replicator model



The model represents three chemical macroreactions between substrate (S), precursors (P), genetic machinery/ribosomes (R), metabolic machinery (M) and produced metabolite (X):

$$\mathrm{S} \xrightarrow{\mathrm{V_M}} \mathrm{P}$$

$$\mathrm{P} \xrightarrow{\mathrm{V_R}} \alpha \mathrm{R} + (1\text{-}\alpha)\mathrm{M}$$

$$\mathrm{P} \xrightarrow{\mathrm{V_X}} \mathrm{X}$$

New control: $u(t) := \alpha(t) I(t)$

Model definition

Continuous stirred-tank reactor dynamics

In terms of concentrations s, p, r, x (and using $m+r=1$) in the CSTR,

$$S_1 : \begin{cases} \dot{s} = D(s_{in} - s) - v_M(s, 1-r)\mathscr{V}, \\ \dot{p} = v_M(s, 1-r) - v_X(p, 1-r) - \mu(p, r)(p+1), \\ \dot{r} = (u - r)\,\mu(p, r), \\ \dot{x} = v_X(p, 1-r)\mathscr{V} - Dx, \\ \dot{\mathscr{V}} = (\mu(p, r) - D)\,\mathscr{V}, \end{cases}$$

where $\mathscr{V}$ is the volume of the cell population, D is the dilution rate, s_{in} is the substrate inflow, and

$$\mu(p, r) := \beta\, v_R(p, r)$$

($\beta =$inverse of cytoplasmic density) is the growth rate of the bacterial population.

Assumption. The synthesis rates v_M, v_R and v_X are *monotone increasing kinetics* (*e.g.* Michaelis-Menten, $v_R(p, r) := k_R rp/(K_R + p)$) and

$$v_X(p, 1-r) = c(r)\, v_R(p, r).$$

Asymptotic behaviour

Mass conservation

Proposition. The set

$$\Gamma = \left\{(s,p,r,x,\mathscr{V}) \in \mathbf{R}^5 \,:\, s_{in} \geq s \geq 0,\, p \geq 0,\, x \geq 0, 1 \geq r \geq 0,\, \mathscr{V} \geq 0\right\}$$

is positively invariant for the initial value problem.

We assume $\mathscr{V}(0) > 0$ and $r(0) > 0$ (no growth otherwise).

Proposition. The ω-limit set of any solution of system S_1 with constant input $u(t) = \overline{u}$ lies in the set

$$\Omega := \left\{(s,p,r,x,\mathscr{V}) \in \mathbf{R}^5 \,:\, s + \left(p + \frac{r}{\overline{u}}\right)\mathscr{V} + x = s_{in}\right\}.$$

This result is used to define a limit system and reduce the dimension by two.

Asymptotic behaviour

Limiting system

As $r(t) \to \overline{u}$ when $t \to \infty$ and since x can be eliminated (Ω), we define

$$S_1' : \begin{cases} \dot{s} = D(s_{in} - s) - \overline{v}_M(s)\mathscr{V}, \\ \dot{p} = \overline{v}_M(s) - \overline{\mu}(p)(p + \overline{c} + 1), \\ \dot{\mathscr{V}} = (\overline{\mu}(p) - D)\mathscr{V}, \end{cases}$$

where

$$\overline{v}_M(s) := v_M(s, 1 - \overline{u}), \quad \overline{v}_R(p) := v_R(p, \overline{u}), \quad \overline{v}_X(p) := v_X(p, 1 - \overline{u}),$$
$$\overline{\mu}(p) := \mu(p, \overline{u}), \quad \overline{c} := c(\overline{u}).$$

We study the local and global stability properties of this reduced system.

Asymptotic behaviour

Local stability

Theorem. Define

$$\overline{f}(p) := \overline{v}_R(p) + \overline{v}_X(p) + \overline{\mu}(p)p = \overline{\mu}(p)(p + \overline{c} + 1),$$

and let p_w be the solution of $\overline{f}(p) = \overline{v}_M(s_{in})$. Then,

- If $\overline{\mu}(p_w) \geq D$:
  - The interior equilibrium E_i exists, is unique and locally stable.
  - The washout equilibrium E_w exists, is unique and locally unstable.
- If $\overline{\mu}(p_w) < D$:
  - The interior equilibrium E_i does not exist.
  - The washout equilibrium E_w exists, is unique and locally stable.

- The interior equilibrium $E_i := (s_i, p_i, \mathscr{V}_i)$ with

$$\overline{\mu}(p_i) = D, \quad \overline{v}_M(s_i) = \overline{f}(p_i), \quad \mathscr{V}_i := \frac{D(s_{in} - s_i)}{\overline{v}_M(s_i)}.$$

- The washout equilibrium is $E_w := (s_{in}, p_w, 0)$.

Asymptotic behaviour

Sketch of proof. If $\overline{\mu}(p_w) \geq D$,

$$J_i = \begin{bmatrix} -D - \overline{v}'_M(s)\mathscr{V}_i & 0 & -\overline{v}_M(s) \\ \overline{v}'_M(s) & \overline{f}'(p) & 0 \\ 0 & \overline{\mu}'(p)\mathscr{V}_i & 0 \end{bmatrix},$$

and the characteristic polynomial is

$$P_i(\lambda) = (\lambda + D)(\lambda^2 + \lambda \underbrace{\left(D + \overline{v}'_M(s)\mathscr{V}_i + (p + \overline{c} + 1)\overline{\mu}'(p)\right)}_{>0} + \underbrace{\overline{v}'_M(s)\mathscr{V}_i\,(p + \overline{c} + 1)\overline{\mu}'(p)}_{>0})$$

which, by Routh-Hurwitz criterion, implies that all eigenvalues have negative real part. If $\overline{\mu}(p_w) < D$,

$$J_w = \begin{bmatrix} -D & 0 & -\overline{c} \\ \overline{v}'_M(s) & -\overline{f}'(p) & 0 \\ 0 & 0 & \overline{\mu}(p_w) - D \end{bmatrix}$$

with characteristic polynomial

$$P_w(\lambda) = (\lambda + D)(\lambda + \overline{f}'(p))(\lambda - \overline{\mu}(p_w) + D). \quad \square$$

Asymptotic behaviour

Global analysis

Proposition. The ω-limit set of any solution of the limiting system S_1' lies in the set

$$\Omega' := \left\{(s,p,\mathscr{V}) \in \mathbf{R}^3 \,:\, s + (p+\overline{c}+1)\mathscr{V} = s_{in}\right\}$$

As $s = s_{in} - \mathscr{V}(p+\overline{c}+1)$, one can further reduce S_1' to

$$S_1'' : \left\{ \begin{array}{l} \dot{p} = \overline{v}_M(s(\cdot)) - \overline{\mu}(p)(p+\overline{c}+1), \\ \dot{\mathscr{V}} = (\overline{\mu}(p) - D)\mathscr{V}. \end{array} \right.$$

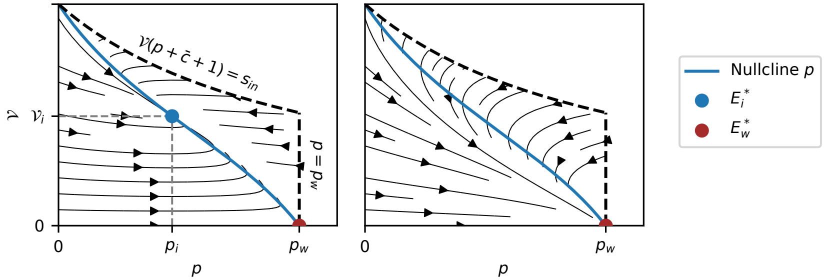
Proposition. Every solution of the limiting system S_1'' converges to

- $E_i^* := (p_i, \mathscr{V}_i)$ if $\overline{\mu}(p_w) \geq D$,
- $E_w^* := (p_w, 0)$ if $\overline{\mu}(p_w) < D$.

Sketch of proof. Bendixson-Dulac criterion allows to discard periodic orbits and cycles of equilibria as

$$\begin{aligned} \frac{\partial}{\partial p}\dot{p} + \frac{\partial}{\partial \mathscr{V}}\dot{\mathscr{V}} =& \frac{\partial}{\partial p}\overline{v}_M(s(\cdot)) - \overline{\mu}(p) - \overline{\mu}'(p)(p+\overline{c}+1) + \overline{\mu}(p) - D \\ =& \overline{v}_M'(s(\cdot))\frac{\partial s(\cdot)}{\partial p} - \overline{\mu}'(p)(p+\overline{c}+1) - D < 0. \quad \square \end{aligned}$$

Asymptotic behaviour



Results on asymptotically autonomous systems (Thieme'92) eventually allow to relate the asymptotic behaviour of the 2-dimensional limiting system S_1'' to the behaviour of the full 5-dimensional system S_1.

Theorem. Every solution of system S_1 converges to

- the extended interior equilibrium $\hat{E}_i := (s_i, p_i, \overline{u}, x_i, \mathscr{V}_i)$, $x_i := \overline{c}\mathscr{V}_i$, if $\overline{\mu}(p_w) \geq D$,
- the extended washout equilibrium $\hat{E}_w := (s_{in}, p_w, \overline{u}, 0, 0)$ otherwise.

Dynamic optimisation

Metabolite production

Maximisation of the metabolite X is considered over a finite time horizon:

$$\text{maximize } D\mathscr{V}_{\mathrm{ext}} \int_0^T x(t)\,\mathrm{d}t,$$

resorting to $(q := (s, p, r, x, \mathscr{V}) \in \mathbf{R}^5)$

$$(\mathrm{OCP}) : \left\{ \begin{array}{rl} \text{maximize} & \displaystyle\int_0^T x(t)\,\mathrm{d}t \\ \text{subject to} & \dot{q}(t) = F(q(t), u(t)), \\ & q(0) = q_0, \quad q(T) \text{ free}, \\ & u(t) \in [0,1]. \end{array} \right.$$

Proposition. Existence holds.

Dynamic optimisation

Extremal flow

We write the (normal) Hamiltonian in terms of state $q := (s, p, r, x, \mathscr{V})$ and costate $\lambda := (\lambda_s, \lambda_p, \lambda_r, \lambda_x, \lambda_{\mathscr{V}})$:

$$H(q, \lambda, u) = -\lambda^0 x + \langle \lambda, F(q, u) \rangle,$$

where F is the right-hand side of S_1. As the dynamics is control-affine, $H = H_0 + uH_1$ with

$$\begin{aligned} H_0 = & \lambda_s \left(D(s_{in} - s) - v_M(s, 1-r)\mathscr{V} \right) + \lambda_p \Big(v_M(s, 1-r) - v_X(p, 1-r) - \mu(p, r)(p+1) \Big) \\ & - r\lambda_r \mu(p, r) + \lambda_x (v_X(p, 1-r)\mathscr{V} - Dx) + \lambda_{\mathscr{V}} (\mu(p, r) - D)\mathscr{V} - \lambda^0 x, \\ H_1 = & \lambda_r \mu(p, r). \end{aligned}$$

By virtue of Pontrjagin's maximum principle, a.e. one has

$$u(t) = \begin{cases} 0 & \text{if } H_1(q(t), \lambda(t)) < 0, \\ 1 & \text{if } H_1(q(t), \lambda(t)) > 0, \end{cases}$$

and the control is singular if H_1 vanishes along a whole subarc.

Dynamic optimisation

Singular arcs

Along a singular arc

$$0 = \dot{H}_1 = \frac{\partial H_1}{\partial q}\dot{q} + \frac{\partial H_1}{\partial \lambda}\dot{\lambda} = \sum_{i=1}^{n}\left(\frac{\partial H}{\partial \lambda_i}\frac{\partial H_1}{\partial q_i} - \frac{\partial H}{\partial q_i}\frac{\partial H_1}{\partial \lambda_i}\right) = \{H, H_1\} = \{H_0, H_1\} := H_{01}$$

and

$$0 = \dot{H}_{01} = H_{001} + uH_{101}.$$

Proposition. Singular arcs are at least of order two.

$$\begin{aligned} H_{101} = & \mu(p,r)\left[\dot{\lambda}_r \mu_r(p,r) + \lambda_r \frac{\partial}{\partial r}\left(\mu_r(p,r)\dot{r} + \mu_p(p,r)\dot{p}\right)\right] \\ & - \lambda_r \mu_r(p,r)\frac{\partial H_{01}}{\partial \lambda_r} - \lambda_r \mu_p(p,r)\frac{\partial H_{01}}{\partial \lambda_p} \end{aligned}$$

which is also equal to 0 when $H_1 = 0$. $\square$

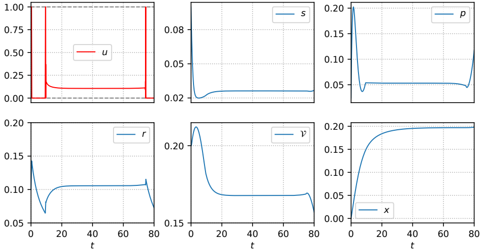
In the case of an order two singular control ($H_{10001} < 0$ along the arc, generalized Legendre-Clebsch condition)

$$u = -\frac{H_{00001}}{H_{10001}}.$$

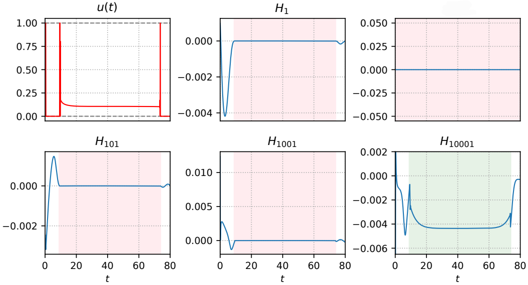
Although the order is *local* (H_{101} is not everywhere zero), one expects connection between bang and singular arcs through Fuller phenomenon.

Dynamic optimisation

Fuller phenomenon



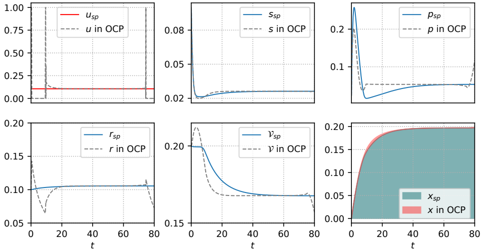
Generalized Legendre-Clebsch condition



Dynamic optimisation

Turnpike property

$$(SP_X): \begin{cases} \text{maximize} & \overline{x} \\ \text{subject to} & F(\overline{q},\overline{u}) = 0, \\ & 0 \le \overline{u} \le 1. \end{cases}$$



A Lagrange pair $(\overline{q},\overline{u},\overline{\lambda})$ of (SP_X) defines a hyperbolic equilibrium of the Hamiltonian singular flow on $\Sigma'' := \{(q,\lambda) \mid H_1 = H_{01} = H_{001} = H_{00001} = 0\}$,

$$H_s(q,\lambda) := H(q,\lambda,u_s(q,\lambda)), \quad u_s(q,\lambda) := -\frac{H_{00001}}{H_{10001}}(q,\lambda).$$

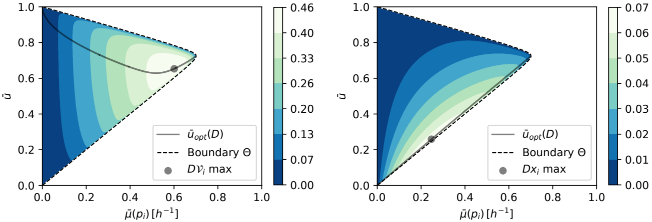
See Trélat-Zuazua'14, Pighin'16 in the regular case, ongoing work with S. Maslovskaya, W. Djema, J.-B. Pomet in the singular case (JOTA 2022).

Static optimisation

Metabolite production vs. biomass maximisation

Maximisation is now performed wrt. the static control $\overline{u}$ plus the dilutation rate D of the CSTR:

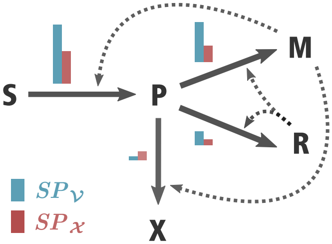
$$(SP_{\mathscr{V}}) : \begin{cases} \text{maximize} & D\overline{\mathscr{V}} \\ \text{subject to} & F(\overline{q},\overline{u}) = 0, \\ & 0 \leq \overline{u} \leq 1, \end{cases} \quad (SP_X) : \begin{cases} \text{maximize} & D\overline{x} \\ \text{subject to} & F(\overline{q},\overline{u}) = 0, \\ & 0 \leq \overline{u} \leq 1. \end{cases}$$

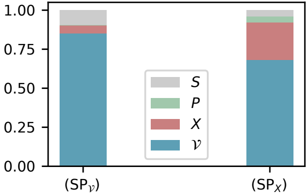


Proposition. Any solution of the two static problems lies in the region of existence of the interior equilibrium, $\overline{\mu}(p_w) > D$.

Static optimisation

Discussion





- 20% decrease of biomass ($\mathscr{V}$) but 500% increase of produced metabolite (X)
- Difference between static and "gold standard" dynamic optimisation negligible for large fixed final time ($< 1\%$)
- Richer models: ubiquity of Fuller and (singular) turnpike phenomena
- Second order conditions in the Fuller case: preliminary approach in Agrachev-Beschastnyi'2020
- Reproducible research: ct (= control toolbox) initiative control-toolbox.org

control-toolbox.ork

control-toolbox

The control-toolbox ecosystem gathers Julia packages for mathematical control and applications. It is an outcome of a research initiative supported by the Centre Inria of Université Côte d'Azur and a sequel to previous developments, notably Bocop and Hampath. See also: ct gallery. The root package is OptimalControl.jl which aims to provide tools to solve optimal control problems by direct and indirect methods.

Installation

See the installation page.

Getting started

To solve your first optimal control problem using `OptimalControl.jl` package, please visit our basic example tutorial or just copy-paste the following piece of code!

```
using OptimalControl

@def ocp begin
    t ∈ [ 0, 1 ], time
    x ∈ R², state
    u ∈ R, control
    x(0) == [ -1, 0 ]
    x(1) == [ 0, 0 ]
    ẋ(t) == [ x₂(t), u(t) ]
    ∫( 0.5u(t)^2 ) → min
end

sol = solve(ocp)
plot(sol)
```

Free Azat Miftakhov

- caseazatmiftakhov.org