Optimal allocation of bacterial resources in a bioreactor

Introduction to optimal control problems

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Summary

Summary

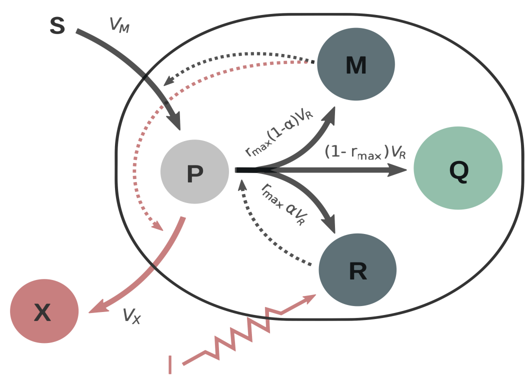
» Introduction to the problem

The study of living micro-organisms

* Bacteria's resource management and compound production in batch bioprocessing are explored using mathematical models, revealing insights at the biology-engineering crossroads.
* How can one know how to maximise the needs of a bacteria for its optimal development ?

Summary

» Definition of the model



The self-replicator model

» Definition of the model

- Initial mass of **substrate** S
- Transformed into **precursors metabolites** P
- P produces M, Q and R which catalyze other productions
- Creation of X, **metabolites of interest**

» Definition of the model

$$
\begin{cases}
\dot{S} &= -V_M \\
\dot{P} &= V_M - V_X - V_R \\
\dot{R} &= r_{max}\mathbf{u}V_r \\
\dot{M} &= r_{max}\mathbf{(1\text{-}u)}V_R \\
\dot{Q} &= (1 - r_{max})V_R \\
\dot{X} &= V_X
\end{cases}
\tag{SRM-D}
$$

Summary

» Understanding optimal control theory

First approach

- Optimal control theory deals with objects that are to be **controlled** meaning that they depend on external factors.
- Example for a plant growth :
  - Temperature
  - Lightning
  - Water
  - and much more ...
- These are some of the many "controls" that one can try to adjust to maximise the plant growth.

» Understanding optimal control theory

Mathematical explanation

- Let's say we want to maximise a plant's height. This can be modelled as follows : Let $u \in \mathbb{R}$, $x \in \mathbb{R}^2$, $t \in [t_0, t_f]$, $x(t_0) = [h_0, s_0]$, h_0 being the height of the plant at time $= 0$ and s_0 the thickness of the stem at time $= 0$.
- An example of the control u could be for example the light intensity variation over time, or the variation of temperature over time.

$$\begin{cases} \dot{x}(t) = F_0(x(t)) + u(t) \cdot F_1(x(t)) \\ h(t_f) \longrightarrow max \end{cases}$$

Summary

* Introduction to the problem
* Definition of the model
* Understanding optimal control theory
* The biomass maximisation case
* Calculation of Lie brackets
* Conclusion

» The biomass maximisation case

Finite-time problem

$$\begin{cases} \dot{s} = -w_M(s)(1-r)\mathcal{V} \\ \dot{p} = w_M(s)(1-r) - w_R(p)(1+p)r \\ \dot{r} = (u-r)w_R(p)r \\ \dot{\mathcal{V}} = w_R(p)r\mathcal{V} \end{cases} \tag{WTB-M}$$

» The biomass maximisation case

Finite-time problem

The numerical simulations of (WTB-M) were already done for an infinite-time problem. As a result, we solved the OCP problem for a finite-time horizon.

» The biomass maximisation case

Definition of $(BM - OCP)$

The problem in a finite-time case is modelled as follows

$$\begin{cases} \mathcal{V}(t_f) \longrightarrow max \\ \text{using the dynamics of (WTB-M)} \\ \text{using initial conditions (IC)} \\ u \in \mathcal{U} \end{cases} \qquad \text{(BM-OCP)}$$

With (IC) being

$$s(0) = s_0 > 0, p(0) = p_0 > 0, x(0) = 0, r(0) = r_0 \in (0, 1), \\ \mathcal{V}(0) = \mathcal{V}_0 > 0 \qquad \text{(IC)}$$

» The biomass maximisation case

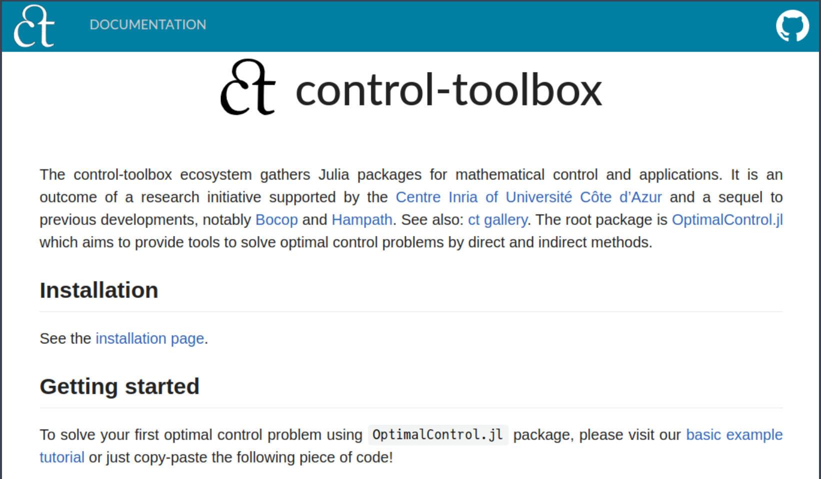
Numerical definition of the problem

What we mathematically expressed in the previous slide is defined in a dozen of lines using the control-toolbox package :

```
@def ocp begin # definition of the optimal control problem

    t ∈ [ t0, tf ], time
    x ∈ R⁴, state
    u ∈ R, control

    s = x₁
    p = x₂
    r = x₃
    V = x₄

    x(t0) == [ s0, p0, r0, V0 ]

    s(t) ≥ 0
    p(t) ≥ 0
    0 ≤ r(t) ≤ 1
    V(t) ≥ 0
    0 ≤ u(t) ≤ 1

    ẋ(t) == F0(x(t)) + u(t) * F1(x(t))

    V(tf) → max

end;
```

» The biomass maximisation case

A peek at the control-toolbox



DOCUMENTATION

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.

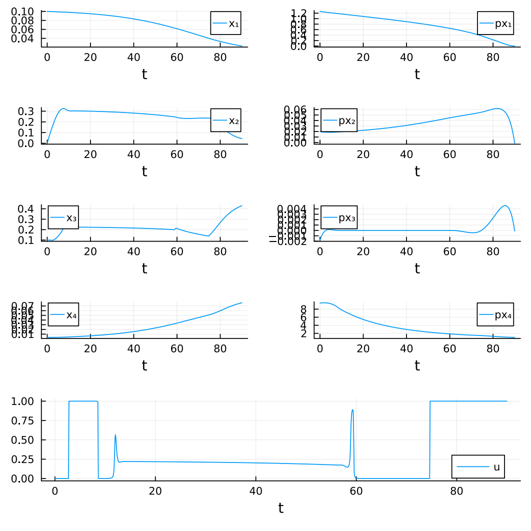
Getting started

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!

The control-toolbox project

» The biomass maximisation case

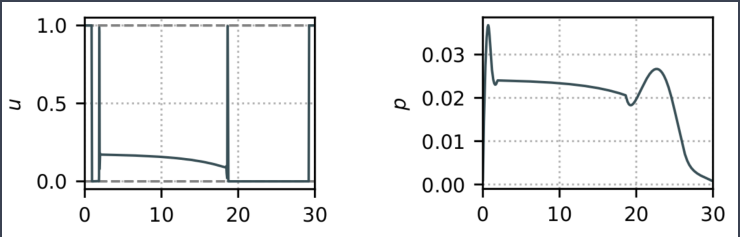
Results of the numerical simulations



Numerical simulations of (BM-OCP)

» The biomass maximisation case

Results of the numerical simulations



Numerical simulations of (BM-OCP)

Summary

» Calculation of Lie brackets

Proposition to be proved

Proposition 4.4

If the *Lie* bracket F_{101} belongs to the span of F_1 and F_{01}, then singular extremals must be of (local) order at least two.

» Calculation of Lie brackets

Lie brackets applied to our case

Since our problem is modelled as follows

$$\varphi(x) = F_0(x) + u \cdot F_1(x)$$

with $x = \left(s\ p\ r\ \mathcal{V}\right)^t$ with respect to (WTB-M)
our goal was to compute the *Lie* brackets $F_{01} = [F_0, F_1]$ and $F_{101} = [F_1, F_{01}]$ and to make sure that

$$rank(F_1(\varphi), F_{01}(\varphi)) = 2 = rank(F_1(\varphi), F_{01}(\varphi), F_{101}(\varphi))$$

A *Lie* bracket is defined for vector fields as $[X, Y] = Y'X - X'Y$
e.g. in a linear case :

$$X(x) = A \cdot x,\ \ Y(x) = B \cdot x$$
$$[X, Y](x) = (BA - AB)(x)$$

» Calculation of Lie brackets

* The calculation of *Lie* brackets are involving determinants of 4×4 matrices which can be quite tricky to do by hand.
* Hence, we decided to use symbolic calculation with `Julia`

Calculation of Lie brackets

Calculations by hand

$$F_{01} = \begin{pmatrix} -\nu w_R(p)\frac{k_A K_A}{(K_A+s)^2} & -\nu w_A(s)\frac{k_R K_R}{(K_R+p)^2} & w_A(s)\times\nu & -w_R(p)w_A(s) \\ w_R(p)\frac{k_A K_A}{(K_A+s)^2} & w_R^2(p)+\frac{(p+1)\left(2p k_R^2(K_R+p)^2-k_R^2p^2(2p+2K_R)\right)}{(K_R+p)^4} & -w_A(s)-w_R(p)(p+1) & 0 \\ \frac{(1-r)k_A k_R K_A K_R}{(K_R+p)^2(K_A+s)^2} & -\frac{2k_R K_R w_A(s)(1-r)}{(K_R+p)^3}-\frac{k_R^2K_R^2 r(p+1)+rK_R k_R w_R(p)(K_R+p)^2-k_R K_R w_R(p) r(p+1)(2p+2K_R)}{(K_R+p)^4} + (2-r^2)\frac{2p k_R^2(K_R+p)^2-k_R^2p^2(2p+2K_R)}{(K_R+p)^4} & -2r w_R(p) & 0 \\ 0 & -\nu\frac{\left(2p k_R^2(K_R+p)^2-k_R^2p^2(2p+2K_R)\right)}{(K_R+p)^4} & \nu w_R(p) & -w_R^2(p) \end{pmatrix}$$

» Calculation of Lie brackets

Calculations by hand

$$F_{01}' \times F_1 = \begin{pmatrix} r\vartheta w_1(s) w_R(p) \\ -r w_R(p) w_1(s) - r w_R^2(p)(p+1) \\ -2r^2 w_R^2(p) \\ r\vartheta w_R^2(p) \end{pmatrix}$$

$$F_1' \times F_{01} = \begin{pmatrix} 0 \\ 0 \\ \dfrac{r h_R K_R w_R(p)\,\big(w_1(s) + w_R(p)(p+1)\big) + w_R(p) h_R K_R\big((1-r) w_1(s) - w_R(p) r (p+1)\big) + 2 w_R^2(p)(K_R+p)^2 - \overbrace{r^2 w_R^2(p)(K_R+p)^2}}{(K_R+p)^2} \\ 0 \end{pmatrix}$$

$$F_{101} = [F_1, F_{01}] = \begin{pmatrix} r\vartheta w_1(s) w_R(p) \\ -r w_R(p) w_1(s) - r w_R^2(p)(p+1) \\ -2r^2 w_R^2(p) - \left(\dfrac{r h_R K_R w_R(p)\big(w_1(s) + w_R(p)(p+1)\big) + w_R(p) h_R K_R\big((1-r) w_1(s) - w_R(p) r (p+1)\big) + 2 w_R^2(p)(K_R+p)^2 - r^2 w_R^2(p)(K_R+p)^2}{(K_R+p)^2}\right) \\ r\vartheta w_R^2(p) \end{pmatrix}$$

$$\boxed{\text{rang}\{(F_1, F_{01})\} = \text{rang}\{(F_1, F_{01}, F_{101})\} = 2 \quad \forall \varphi, \forall h_R, K_R, h_1, K_1.}$$

» Calculation of Lie brackets

Using Symbolics in Julia, we found that *rank*$(F_1, F_{01}) = 2$, since we obtain at least one non-null minor.

$$-\frac{-k_r p r \frac{p^2 k_r^2 r v}{(K_r+p)^2}}{K_r + p}$$

$$0$$

An example of 2 minors

» Calculation of Lie brackets

Lie brackets using Symbolics

And also that $rank(F_1, F_{01}, F_{101}) = 2$ because all the minors are null this time.

$$\frac{p^2 k_r^2 k_m r s v \frac{-k_r p r \frac{k_r p r \left(\frac{-k_r p (1+p)}{K_r+p} + \frac{-k_m s}{K_m+s} \right)}{K_r+p}}{K_r+p}}{(K_r+p)^2 (K_m+s)} + \frac{-k_r k_m p r s v \frac{-r^2 p^3 k_r^3 \left(\frac{-k_r p (1+p)}{K_r+p} + \frac{-k_m s}{K_m+s} \right)}{(K_r+p)^3}}{(K_r+p)(K_m+s)}$$

$$0$$

$$\frac{-v^2 r^3 p^5 k_r^5 k_m s}{(K_r+p)^5 (K_m+s)} + \frac{r^2 p^3 k_r^3 k_m s v \frac{p^2 k_r^2 r v}{(K_r+p)^2}}{(K_r+p)^3 (K_m+s)}$$

$$\frac{-r^3 p^5 k_r^5 v \left(\frac{-k_r p (1+p)}{K_r+p} + \frac{-k_m s}{K_m+s} \right)}{(K_r+p)^5} + \frac{r^2 p^3 k_r^3 \frac{p^2 k_r^2 r v}{(K_r+p)^2} \left(\frac{-k_r p (1+p)}{K_r+p} + \frac{-k_m s}{K_m+s} \right)}{(K_r+p)^3}$$

The four minors for $(F_1 \; F_{01} \; F_{101}$

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» Conclusion

This project was for us a glance at what research really is :

* hand-calculations are not always possible
* Julia is great for mathematicians
* we liked working in english as it helped us getting better