



HAL
open science

Optimal cell growth under periodic environment

Javier Innerarity Imizcoz, Walid Djema, Francis Mairet, Jean-Luc Gouzé

► **To cite this version:**

Javier Innerarity Imizcoz, Walid Djema, Francis Mairet, Jean-Luc Gouzé. Optimal cell growth under periodic environment. MTNS 2024 - 26th International Symposium on Mathematical Theory of Networks and Systems, Aug 2024, Cambridge (Angleterre), United Kingdom. hal-04724783

HAL Id: hal-04724783

<https://inria.hal.science/hal-04724783v1>

Submitted on 7 Oct 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Optimal cell growth under periodic environment [★]

Javier Innerarity ^{*} Walid Djema ^{**} Francis Mairet ^{***}
Jean-Luc Gouzé ^{*}

^{*} *Inria Sophia Antipolis Méditerranée, MACBES Project-Team,
Université Nice Côte d'Azur, 06902 Sophia-Antipolis, France (email
jean-luc.gouze@inria.fr)*

^{**} *Inria Sophia Antipolis Méditerranée, BIOCORE Project-Team,
Université Nice Côte d'Azur, 06902 Sophia-Antipolis, France*

^{***} *Ifremer, PHYTOX, 44311 Nantes, France*

Abstract: We study the optimization of resource allocation in bacteria evolving in periodic environments. We use a dynamical model of the metabolism of these microorganisms with a control variable representing the allocation of protein precursors. We mathematically define the objective of maximizing the long-term growth of a given cell. We carry out a theoretical analysis of the resulting dynamical optimal control problem (DOCP), which we complete with a numerical resolution of its solution. Then we examine the effects of period and amplitude of the external forcing.

Keywords: Dynamical systems, Periodic Environment, Optimal Control, Microbial Growth, Nonlinear Biological Models.

1. INTRODUCTION

Bacteria and other microorganisms form the basis of every ecosystem. Also, they play a key role in many bio-industrial processes, such as food and drug production or waste-water treatment (Liao et al. (2016); Yegorov et al. (2019); Yabo et al. (2023)). Mathematical models have proved to be greatly effective to the study the dynamical behaviour of bacteria, while being able to reproduce and explain many experimental observations on their growth. For instance, Giordano et al. (2016) uses a low-dimensional self-replicator model of the metabolism of bacteria, in which the cell has to decide whether to allocate its precursor resources to the production of the macroproteins responsible for nutrient intake or to the ones responsible for the production of the macroproteins themselves.

Using optimal control theory is a natural way to approach these problems (Lenhart and Workman (2007)), which has been applied in a wide variety of biological contexts (Ewald et al. (2017); Caillaud et al. (2022)). With the appropriate objective function, it provides an ideal behavior, and a benchmark for the comparison of other metabolic regulation mechanisms. It is usual to assume that bacteria seek to maximize their growth rate, an assumption in accordance with the behavior observed in (Edwards et al. (2001); Ibarra et al. (2002)).

The first articles addressing the mathematical modelization of the metabolism of microorganisms studied their growth in steady-state conditions (Edwards et al. (2001);

Ibarra et al. (2002); Lewis et al. (2010); Scott et al. (2014); Maitra and Dill (2015)). Later studies used dynamical modeling of the response of bacteria after a single shift in their environment (Giordano et al. (2016); Pavlov and Ehrenberg (2013); van den Berg et al. (1998); Yabo et al. (2022); Ehrenberg et al. (2013); Yegorov et al. (2019)). These have been significant steps in the study of the mechanism of the optimization of resource allocation in micro-organisms. However, the type of conditions that these models represents is only in accordance with what microorganisms can face in a laboratory, where it is feasible to maintain a constant environment (Borirak et al. (2014)).

In a natural setting, it is not reasonable to assume that the environment of a given individual remains constant. We must therefore consider time-dependent environments if we want to properly study these mechanisms in a more realistic context.

For this reason, we will modify the model proposed in Giordano et al. (2016) by changing the parameter E_M , which represents the substrate availability in the environment of a given cell, to a periodic piecewise-constant function. This will yield a more realistic environmental input, able to capture cyclic changes in substrate concentration that are caused for example by day-night dynamics.

The study is organized as follows. We introduce the model of interest in Section 2, where the environment is non-constant. Then, we state the dynamical optimal control problem (DOCP) in Section 3. We address this OCP through the application of a variant of Pontryagin's Maximum Principle (PMP) (Carlson et al. (2012)) in Section

^{*} We acknowledge the support of Ctrl-AB ANR project, and DS4H doctoral school of Unica for J.I.

4 and we numerically obtain the solution of the problem. In Section 5, we study how two key parameters of the environment, its period and amplitude, affect the solution of the OCP, and give interesting insights on the dynamical behaviour of the cells.

2. THE MATHEMATICAL MODEL

We use the self-replicator model proposed in (Giordano et al., 2016), which is schematized in Figure 1. It represents the metabolism of a given micro-organism. The external medium (E_M) of this cell has some substrate that the cell can absorb and convert into precursor metabolites (P) through some reactions catalyzed by the metabolic machinery (M). These precursors are then converted by the gene expression machinery (R) into the macromolecules that form R and M . The resource allocation parameter $\alpha(t)$ is the proportion of the precursor's mass used to build R at a given time.

The model can be simplified by dividing all the variables by the total volume of the cell (which is assumed to be proportional to the total macromolecular mass $M + R$) and supposing that reactions follow Michaelis-Menten dynamics. After normalization, the system reads as follows.

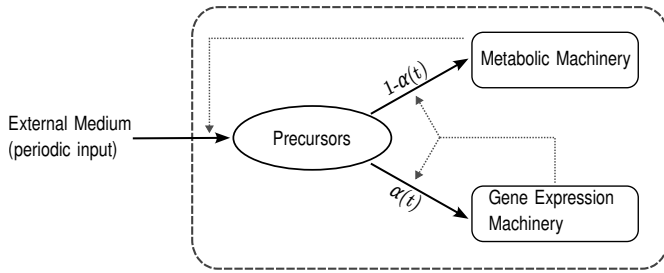


Fig. 1. Diagram of the model used in Giordano et al. (2016).

$$\begin{cases} \dot{p} = (1-r)E_M(t) - (1+p)\frac{p}{K+p}r \\ \dot{r} = (\alpha-r)\frac{p}{K+p}r, \end{cases} \quad (1)$$

where p and r are time-dependent variables. The first one represents the cytoplasmic concentration of P , whereas r is the concentration of R . The concentration of M does not appear in these equations as it can be defined by $m = 1 - r$, because the volume of the cell is defined by $M + R$. The resource allocation parameter $\alpha(t)$ will be the control exerted on the system. The parameter K is intrinsic to the metabolism of the cell, and will therefore be treated as a constant. In (Giordano et al., 2016) the parameter E_M , representing the richness of the external medium, is considered to be constant.

We propose to modify this system by setting E_M to be a piecewise-constant periodic input of period $T > 0$, described by

$$E_M(t) = \begin{cases} E_M^{\max}, & \text{if } t \in [0, T/2) \\ E_M^{\min}, & \text{if } t \in [T/2, T), \end{cases} \quad (2)$$

with $0 < E_M^{\min} < E_M^{\max}$. This definition of E_M yields a more realistic model, which takes into account the

always-changing conditions in which microorganisms usually evolve. Note that this particular environment is completely defined by three parameters, which are its period T and its maximal and minimal values E_M^{\max} and E_M^{\min} .

We define the average environmental capacity as

$$\bar{E}_M = \frac{1}{T} \int_0^T E_M(t) dt.$$

In this case we have that \bar{E}_M is the arithmetic mean of E_M^{\min} and E_M^{\max} .

3. STATEMENT OF THE DYNAMIC OPTIMAL CONTROL PROBLEM

As stated above, we seek the resource allocation strategy that will maximize the volume increase of the cell. The quantity

$$\mu(t) = \frac{pr}{K+p}(t),$$

is the exponential growth rate of the cell. That is, if we call its volume Vol , then

$$Vol(t) = Vol(0) \exp \int_0^t \mu(\tau) d\tau \quad \forall t \geq 0.$$

Therefore, the quantity to be maximized is

$$\int \mu(t) dt,$$

The objective of our dynamic optimal control problem (DOCP) is thus to find

α_{opt} such that $\liminf_{t_f \rightarrow \infty} (J_{t_f}(\alpha_{opt}) - J_{t_f}(\alpha)) \geq 0 \quad \forall \alpha \in U_\infty$,

where

$$J_{t_f}(\alpha) = \int_0^{t_f} \frac{pr}{K+p} dt,$$

$$U_\infty = \{\alpha : [0, +\infty) \rightarrow [0, 1] \mid \alpha \text{ is measurable}\}$$

and the system $(p, r)(t)$ follows System (1).

We also consider the related problem of optimization over one period of E_M with periodic boundary conditions and see that the infinite-horizon optimization problem is numerically equivalent to a periodic one.

4. APPLICATION OF PONTRYAGIN'S MAXIMUM PRINCIPLE

4.1 Optimality Conditions

For the theoretical analysis of the optimization problem, we will use the Infinite Horizon Maximum Principle (Carlson et al. (2012)), an extension of Pontryagin's Maximum Principle. We set the Hamiltonian

$$\begin{aligned} H &= H(p, r, \lambda_p, \lambda_r, \lambda_0, \alpha, t) = \lambda_p \dot{p} + \lambda_r \dot{r} + \lambda_0 \left(\frac{pr}{K+p} \right) \\ &= \lambda_p \left[(1-r)E_M(t) - \frac{(1+p)pr}{K+p} \right] + \lambda_r \frac{(\alpha-r)pr}{K+p} + \lambda_0 \frac{pr}{K+p} \end{aligned}$$

We compute adjoint variables $(\lambda, \lambda_0) = (\lambda_p, \lambda_r, \lambda_0) \neq 0$, $\lambda_0 \geq 0$ and apply the PMP.

4.2 Analysis of Optimal Controls

The above conditions allow to find the possible values of α_{opt}

Theorem 1. The optimal control α_{opt} is given by

$$\alpha_{opt}(t) = \begin{cases} 1 & \text{if } \lambda_r > 0 \\ 0 & \text{if } \lambda_r < 0 \\ \alpha_{opt}^*(E_M(t)) & \text{if } \lambda_r = 0, \end{cases}$$

where

$$\alpha_{opt}^*(E_M) = \frac{E_M + \sqrt{KE_M}}{E_M + 2\sqrt{KE_M} + 1}.$$

If $\lambda_r = 0$ on a time interval $t \in [t_1, t_2]$, with $t_1 < t_2$, we say that the controls has a singular arc at $[t_1, t_2]$. In that case, the system must lie at the equilibrium point $(p_{opt}^*, r_{opt}^*)(E_M(t))$, where

$$p_{opt}^*(E_M) = \sqrt{KE_M}$$

and $r_{opt}^*(E_M) = \alpha_{opt}^*(E_M)$.

We study the relation to static optimal problem, Kelley conditions, and observe chattering phenomena.

We now compute the optimal control by means of a direct numerical resolution with software BOCOP (Team Commands (2017)).

Figure 2 shows the optimal control α_{opt} found for this piece-wise constant periodic environment. We see from the plot that the optimal control seems to tend to a limit cycle.

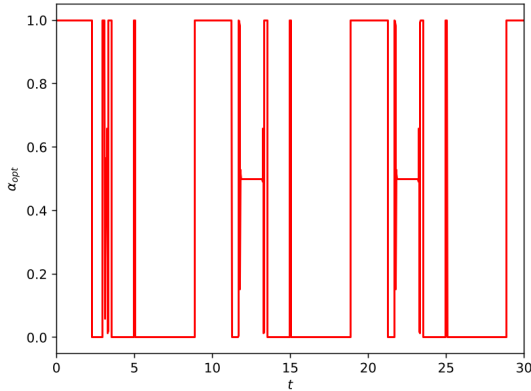


Fig. 2. The optimal control for a finite final time of $t_f = 40$. The plot of α_{opt} over the last period has been omitted.

The optimal control starts with a first transient phase on the interval $[0, T]$ and then becomes periodic, with the same period as E_M . During its first period, it presents a very brief constant singular arc included in the interval over which the environmental variable is maximal. This singular arc is longer during the phase where α_{opt} becomes periodic. In both cases, the singular arc is preceded and followed by bang-bang arcs, with chattering occurring in between. This is in accordance with the theoretical study carried out before.

5. EFFECT OF THE PERIOD AND AMPLITUDE OF THE ENVIRONMENT

In this section, we will study how two of the parameters defining the environment given by Equation (2) affect the resulting long-term volume increase given by the solution of our DOCP. To do so, we define the environmental input E_M by giving, instead of its two possible values, its average \bar{E}_M and its amplitude $E_M^{\max} - E_M^{\min}$. The condition that E_M^{\min} be positive thus becomes $E_M^{\max} - E_M^{\min} \leq 2\bar{E}_M$.

In order to measure the asymptotic volume increase rate, we will use the equivalent average exponential growth rate over a period of the limit cycle. This rate can be defined over any time interval $[0, t]$ as

$$\bar{\mu}(t) = \frac{\log(\text{Vol}(t)) - \log(\text{Vol}(0))}{t} = \frac{\int_0^t \mu(\tau) d\tau}{t},$$

such that $\text{Vol}(t) = \text{Vol}(0)e^{\bar{\mu}(t)t}$. If, as we will do in this section, we focus on $\bar{\mu}(T)$, the average growth rate over a period of duration T of the environmental input, we obtain that $\text{Vol}(t)$ behaves asymptotically as $e^{\bar{\mu}(T)t}$.

It is especially interesting to investigate whether, for a fixed \bar{E}_M , there exist some T and $E_M^{\max} - E_M^{\min}$ that maximize the average exponential increase in biomass that the solution of the optimal control problem with those parameters yields.

We use the BOCOP solver to find the value of the parameters T and $E_M^{\max} - E_M^{\min}$ that maximize this average growth $\bar{\mu}(T)$ over a period, assuming the control $\alpha = \alpha_{opt}^*$. The average growth rate $\bar{\mu}$ to be maximized can be expressed as a function of the variables in normalized time as

$$\bar{\mu} = \int_0^1 \frac{pr}{K+p}(\tau) d\hat{t}.$$

As before, we take the constants $K = 0.003$ and $\bar{E}_M = 0.6$ for the numerical resolution of this problem. We now seek to optimize over three variables: the resource allocation parameter $\alpha : [0, +\infty) \rightarrow [0, 1]$ and the real parameters $T \in (0, +\infty)$ and $E_M^{\max} - E_M^{\min} \in [0, 2\bar{E}_M]$.

When initialized with the right initial conditions, the BOCOP software (Team Commands (2017)) gives a solution of $(T, E_M^{\max} - E_M^{\min}) \approx (0.26, 1.2 = 2\bar{E}_M)$, which results in an average growth rate of $\bar{\mu}_{opt}^* \approx 0.3571$, slightly better than in a constant environment ($\mu_{opt}^* \approx 0.3561$).

From an ecological point of view, it is very interesting to obtain that there exist periods that give a better average growth rate than constant environments. That can be compared to experimental results.

REFERENCES

- Borirak, O., Bekker, M., and Hellingwerf, K.J. (2014). Molecular physiology of the dynamic regulation of carbon catabolite repression in escherichia coli. *Microbiology*, 160(6), 1214–1223.
- Caillau, J.B., Djema, W., Gouzé, J.L., Maslovskaya, S., and Pomet, J.B. (2022). Turnpike property in optimal microbial metabolite production. *Journal of Optimization Theory and Applications*, 194(2), 375–407.

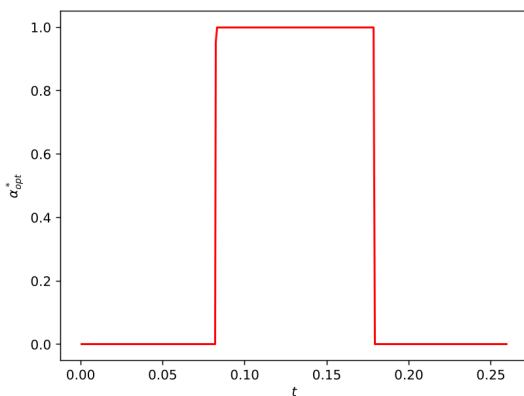


Fig. 3. Plot of the optimal control α_{opt} for the environmental input defined by Equation (2) with the optimal parameters $(T, E_M^{\max} - E_M^{\min}) \approx (0.26, 1.2 = 2\bar{E}_M)$.

- Carlson, D.A., Haurie, A.B., and Leizarowitz, A. (2012). *Infinite horizon optimal control: deterministic and stochastic systems*. Springer Science & Business Media.
- Edwards, J.S., Ibarra, R.U., and Palsson, B.O. (2001). In silico predictions of escherichia coli metabolic capabilities are consistent with experimental data. *Nature biotechnology*, 19(2), 125–130.
- Ehrenberg, M., Bremer, H., and Dennis, P.P. (2013). Medium-dependent control of the bacterial growth rate. *Biochimie*, 95(4), 643–658.
- Ewald, J., Bartl, M., and Kaleta, C. (2017). Deciphering the regulation of metabolism with dynamic optimization: an overview of recent advances. *Biochemical Society Transactions*, 45(4), 1035–1043. doi:10.1042/BST20170137.
- Giordano, N., Mairet, F., Gouzé, J.L., Geiselman, J., and de Jong, H. (2016). Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies. *PLOS Computational Biology*, 12. doi:10.1371/journal.pcbi.1004802.
- Ibarra, R.U., Edwards, J.S., and Palsson, B.O. (2002). Escherichia coli k-12 undergoes adaptive evolution to achieve in silico predicted optimal growth. *Nature*, 420(6912), 186–189.
- Lenhart, S. and Workman, J.T. (2007). *Optimal control applied to biological models*. CRC press.
- Lewis, N.E., Hixson, K.K., Conrad, T.M., Lerman, J.A., Charusanti, P., Polpitiya, A.D., Adkins, J.N., Schramm, G., Purvine, S.O., Lopez-Ferrer, D., et al. (2010). Omic data from evolved e. coli are consistent with computed optimal growth from genome-scale models. *Molecular systems biology*, 6(1), 390.
- Liao, J.C., Mi, L., Pontrelli, S., and Luo, S. (2016). Fueling the future: microbial engineering for the production of sustainable biofuels. *Nature Reviews Microbiology*, 14(5), 288–304.
- Maitra, A. and Dill, K.A. (2015). Bacterial growth laws reflect the evolutionary importance of energy efficiency. *Proceedings of the National Academy of Sciences*, 112(2), 406–411.
- Pavlov, M.Y. and Ehrenberg, M. (2013). Optimal control of gene expression for fast proteome adaptation to environmental change. *Proceedings of the National Academy of Sciences*, 110(51), 20527–20532.
- Scott, M., Klumpp, S., Mateescu, E.M., and Hwa, T. (2014). Emergence of robust growth laws from optimal regulation of ribosome synthesis. *Molecular systems biology*, 10(8), 747.
- Team Commands, I.S. (2017). Bocop: an open source toolbox for optimal control. <http://bocop.org>.
- van den Berg, H.A., Kiselev, Y.N., Kooijman, S., and Orlov, M.V. (1998). Optimal allocation between nutrient uptake and growth in a microbial trichome. *Journal of Mathematical Biology*, 37, 28–48.
- Yabo, A.G., Caillaud, J.B., Gouzé, J.L., De Jong, H., and Mairet, F. (2022). Dynamical analysis and optimization of a generalized resource allocation model of microbial growth. *SIAM Journal on Applied Dynamical Systems*, 21(1), 137–165.
- Yabo, A.G., Caillaud, J.B., and Gouzé, J.L. (2023). Optimal bacterial resource allocation strategies in batch processing.
- Yegorov, I., Mairet, F., De Jong, H., and Gouzé, J.L. (2019). Optimal control of bacterial growth for the maximization of metabolite production. *Journal of mathematical biology*, 78, 985–1032.