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# Optimal resource allocation for bacterial growth with degradation <sup>\*</sup>

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**Abstract:** Understanding adaptation of bacterial growth for a changing environment is a fundamental biological problem which also has a great interest from the biotechnological point of view. This paper extends one of existing bacterial growth models by taking macromolecular degradation into account and provides new mathematical results. The related dynamic problem of maximizing biomass accumulation is stated in a specific way so that existence of optimal resource allocation strategies can be verified. A novel numerical algorithm for approximating switching curves of the chattering control in the state space is developed. Several realistic suboptimal feedback control laws are also constructed and successfully tested. The results of numerical simulations confirm validity of the new problem statement.

*Keywords:* bacterial growth, macromolecular degradation, resource allocation, optimal control, chattering, switching curves, suboptimal control.

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## 1. INTRODUCTION

In theoretical biology as well as in biotechnology, it is important to study mechanisms of bacterial adaptation for changes in availability of external nutrients (Schaechter et al. (2006); Venayak et al. (2015)). Several studies developed steady-state and dynamic mathematical models to investigate which control strategies microorganisms employ for achieving optimal resource allocation of their protein synthesis capacity over different cellular functions (Molenaar et al. (2009); Scott et al. (2014); Pavlov and Ehrenberg (2013); Giordano et al. (2016)). In particular, Giordano et al. (2016) proposed a model of a self-replicating prokaryotic cell population by distinguishing two basic cellular processes: metabolism (converting nutrients to precursors) and gene expression (converting precursors to proteins which constitute biomass). Dynamic optimization methods were used to obtain a resource allocation strategy leading to maximum biomass accumulation. The optimal control law was compared with several realistic suboptimal control strategies. For the sake of simplicity, the model of Giordano et al. (2016) ignored macromolecular degradation. The aim of this work is to develop an extended model with such a degradation as well as to provide wider theoretical and computational analysis of the related dynamic optimization problem.

The paper is organized as follows. First, we provide our problem statement and compare it with the statement

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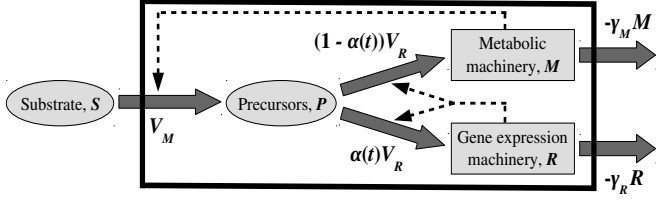
of Giordano et al. (2016). Then we describe the optimal steady state and verify existence of optimal open-loop resource allocation strategies (controls). Next, the latter are characterized via necessary optimality conditions, and a novel numerical algorithm for approximating switching curves of the chattering control in the state space is proposed. We also extend the suboptimal feedback controls of Giordano et al. (2016) to the current model with degradation. Finally, the results of numerical simulations are presented and discussed.

## 2. PROBLEM STATEMENT

Let  $P, M, R$  [g] be the total masses of precursor metabolites (amino acids), metabolic machinery (enzymes involved in nutrient uptake and conversion to precursors), and gene expression machinery (polymerase, ribosomes) in the considered self-replicating prokaryotic cell population, respectively. A scheme of the model is given in Fig. 1. Metabolic machinery converts external substrates into precursors, while gene expression machinery transforms precursors into macromolecules. The latter are involved either in metabolism or in gene expression itself. This leads to the system of ordinary differential equations

$$\begin{cases} \frac{dP(t)}{dt} = V_M(t) - V_R(t), \\ \frac{dM(t)}{dt} = (1 - \alpha(t))V_R(t) - \gamma_M M(t), \\ \frac{dR(t)}{dt} = \alpha(t)V_R(t) - \gamma_R R(t), \quad t \in [0, T], \end{cases} \quad (1)$$

where  $t$  is the time variable,  $T > 0$  is the time horizon,  $V_M(t), V_R(t)$  [ $g \cdot h^{-1}$ ] are the rates at which the precursors are formed by metabolism and utilized for gene expression,



**Fig. 1.** Scheme of the model.

respectively,  $\gamma_M \geq 0, \gamma_R \geq 0$  [ $h^{-1}$ ] are the degradation rates, and  $\alpha(\cdot)$  is a dimensionless resource allocation function. The latter satisfies the constraint  $0 \leq \alpha(t) \leq 1$  for all  $t \in [0, T]$  and determines the proportion of the precursors' mass used for supporting gene expression, so that  $1 - \alpha(t)$  is the proportion for metabolism. Note that system (1) extends the mathematical model of Giordano et al. (2016) by including degradation of macromolecules.

According to Giordano et al. (2016), introduce the following quantities:

- inverse  $\beta > 0$  [ $L \cdot g^{-1}$ ] of the constant cytoplasmic density;
- volume of the cell population  $\mathcal{V}(t) = \beta \cdot (M(t) + R(t))$  [ $L$ ] (only the macromolecules constituting the cells are included here as opposed to the monomer precursors);
- intracellular characteristics  $v_M(t) = V_M(t)/\mathcal{V}(t)$  [ $g \cdot L^{-1} \cdot h^{-1}$ ],  $v_R(t) = V_R(t)/\mathcal{V}(t)$  [ $g \cdot L^{-1} \cdot h^{-1}$ ],  $p(t) = P(t)/\mathcal{V}(t)$  [ $g \cdot L^{-1}$ ],  $r(t) = R(t)/\mathcal{V}(t)$  [ $g \cdot L^{-1}$ ],  $m(t) = M(t)/\mathcal{V}(t)$  [ $g \cdot L^{-1}$ ];
- in the adopted representations  $v_M(t) = e_M m(t)$ ,  $v_R(t) = k_R r(t) p(t) / (K_R + p(t))$ , constant  $e_M > 0$  [ $h^{-1}$ ] specifies the environmental input, and  $k_R > 0$  [ $h^{-1}$ ],  $K_R > 0$  [ $g \cdot L^{-1}$ ] are the rate and half-saturation constants for gene expression machinery, respectively;
- new dimensionless time and state variables  $\hat{t} = k_R t$ ,  $\hat{p}(\hat{t}) = \beta p(t)$ ,  $\hat{r}(\hat{t}) = \beta r(t)$ ,  $\hat{m}(\hat{t}) = \beta m(t)$ ;
- auxiliary dimensionless parameters  $\hat{T} = k_R T$ ,  $E_M = e_M / k_R$ ,  $K = \beta K_R$ ,  $\Gamma_M = \gamma_M / k_R$ ,  $\Gamma_R = \gamma_R / k_R$ ;
- growth rate of the self-replicating system

$$\begin{aligned} \mu(t) &= \frac{1}{\mathcal{V}(t)} \cdot \frac{d\mathcal{V}(t)}{dt} = \\ &= k_R \left( \frac{\hat{p}(\hat{t}) \hat{r}(\hat{t})}{K + \hat{p}(\hat{t})} + (\Gamma_M - \Gamma_R) \hat{r}(\hat{t}) - \Gamma_M \right), \end{aligned}$$

and dimensionless variable  $\hat{\mu}(\hat{t}) = \mu(t) / k_R$ .

Then system (1) can be transformed into

$$\begin{cases} \frac{d\hat{p}(\hat{t})}{d\hat{t}} = (1 - \hat{r}(\hat{t})) E_M - \frac{\hat{p}(\hat{t}) \hat{r}(\hat{t})}{K + \hat{p}(\hat{t})} - \\ - \hat{p}(\hat{t}) \left( \frac{\hat{p}(\hat{t}) \hat{r}(\hat{t})}{K + \hat{p}(\hat{t})} + (\Gamma_M - \Gamma_R) \hat{r}(\hat{t}) - \Gamma_M \right), \\ \frac{d\hat{r}(\hat{t})}{d\hat{t}} = \alpha(\hat{t}) \frac{\hat{p}(\hat{t}) \hat{r}(\hat{t})}{K + \hat{p}(\hat{t})} - \Gamma_R \hat{r}(\hat{t}) - \\ - \hat{r}(\hat{t}) \left( \frac{\hat{p}(\hat{t}) \hat{r}(\hat{t})}{K + \hat{p}(\hat{t})} + (\Gamma_M - \Gamma_R) \hat{r}(\hat{t}) - \Gamma_M \right), \\ \hat{m}(\hat{t}) = 1 - \hat{r}(\hat{t}), \quad \hat{t} \in [0, \hat{T}]. \end{cases} \quad (2)$$

The initial conditions are

$$\hat{p}(0) = \hat{p}_0, \quad \hat{r}(0) = \hat{r}_0, \quad (3)$$

and the constraint on resource allocation functions is

$$0 \leq \alpha(\hat{t}) \leq 1 \quad \forall \hat{t} \in [0, \hat{T}]. \quad (4)$$

Similarly to Giordano et al. (2016), we state the optimal resource allocation (control) problem for (2)–(4) with the aim to maximize the biomass produced over the time interval  $[0, \hat{T}]$ , which leads to the functional

$$J(\alpha(\cdot)) = \int_0^{\hat{T}} \mu(t) dt = \int_0^{\hat{T}} \hat{\mu}(\hat{t}) d\hat{t} \rightarrow \max. \quad (5)$$

This maximum is searched over the set of all admissible open-loop controls  $\alpha(\cdot)$  which are measurable functions on  $[0, \hat{T}]$  fulfilling constraint (4).

Assume that the environment (i.e., the nutrient source) can change only via instantaneous shifts. Each nutrient upshift or downshift specifies a new separate optimal control problem (with a new value of the environmental input  $e_M$ ). In compliance with Giordano et al. (2016), the subject of the current investigation is one of such optimal control problems (for the new model) with a constant environmental input as a parameter.

The problem of Giordano et al. (2016) was stated with the infinite time horizon in the overtaking optimality sense according to Carlson et al. (1991). However, during the problem analysis, it was implicitly supposed that the optimal state trajectories should reach a certain rest point (with the maximum growth rate) and stay there all the remaining infinite time, even though a rigorous verification of this property as well as proving existence of optimal controls remained open challenging problems. Furthermore, numerical simulations could be conducted only for a finite time horizon, and they in fact indicated leaving the steady state a little time before the final instant. Giordano et al. (2016) intuitively treated these final subarcs as an artifact for the infinite-horizon study and, therefore, removed them from plots. Indeed, the general turnpike theory of Trélat and Zuazua (2015) informally leads to the hypothesis on disappearance of such “artifactual” subarcs in the infinite-horizon case, but a rigorous justification for that in the considered problem also was not given.

Let us propose another approach which is to take a sufficiently large finite time horizon  $\hat{T}$  and to fix the terminal state at  $\hat{t} = \hat{T}$  as the mentioned optimal steady state  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$ :

$$(\hat{p}, \hat{r})|_{\hat{t}=\hat{T}} = (\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*), \quad \hat{T} \in (0, +\infty) \text{ is fixed.} \quad (6)$$

A significant advantage of such a problem statement is that existence of an optimal open-loop control can be proved if  $\hat{T}$  is large enough. Certainly, minimum admissible  $\hat{T}$  should depend on initial state (3). Nevertheless, this does not appear to be a crucial shortcoming, because, as will be discussed below, some preliminary numerical simulations using suboptimal controls can help to choose suitable time horizons for initial states from physically realistic ranges.

For the model of this paper, we show that, in conformity with the results of Giordano et al. (2016), extremal state

trajectories can enter the optimal steady state only by chattering (a general theory of chattering optimal control is introduced by Zelikin and Borisov (1994)). We also develop a numerical algorithm for approximating the corresponding chattering switching curve in some neighborhood of the optimal steady state. By formulation, the algorithm does not depend on a particular time horizon, and, moreover, it gives the same results when applied to the related problem with  $\hat{T} = +\infty$  in the overtaking optimality sense. This is an important argument in favor of our statement of the optimal control problem with a sufficiently large finite  $\hat{T}$  and terminal condition (6).

Note that  $G = \{(\hat{p}, \hat{r}) : \hat{p} \geq 0, \hat{r} \in [0, 1]\}$  is a strongly invariant domain for controlled system (2),(4), i. e., for any initial state  $(\hat{p}_0, \hat{r}_0) \in G$  and for any measurable control  $\alpha : [0, +\infty) \rightarrow [0, 1]$ , there exists a unique state trajectory of (2) defined for all  $\hat{t} \geq 0$ , and the latter does not leave  $G$ . Hence, we can investigate optimal control problem (2)–(6) only for  $(\hat{p}, \hat{r}) \in G$ .

### 3. OPTIMAL STEADY STATE

In compliance with the approach of Giordano et al. (2016), let us first find the steady state  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*) \in G$  of system (2) at which the growth rate  $\mu$  takes the maximum value.

**Assumption 3.1.** *Macromolecules used in metabolism are less stable than those for gene expression:  $\Gamma_M \geq \Gamma_R$ . The degradation rates  $\Gamma_M, \Gamma_R$  are sufficiently small so that  $(1 - \Gamma_R)E_M > \Gamma_M, \Gamma_R \leq 1/K$ .*

Classical maximum conditions in one dimension and direct calculations lead to the following result.

**Theorem 3.1.** *Under Assumption 3.1, the optimal steady state together with the corresponding control and growth rate are represented as*

$$\left\{ \begin{array}{l} \hat{p}_{\text{opt}}^* = \frac{1}{(1 - \Gamma_R)E_M - \Gamma_M} \left( \Gamma_R E_M K + \right. \\ \quad \left. + \left( (\Gamma_R E_M K)^2 + \frac{1}{1 + \Gamma_M - \Gamma_R} K E_M \cdot \right. \right. \\ \quad \quad \left. \left. \cdot (E_M - (\Gamma_M - \Gamma_R)(1 - K\Gamma_R)) \cdot \right. \right. \\ \quad \quad \left. \left. ((1 - \Gamma_R)E_M - \Gamma_M) \right)^{\frac{1}{2}} \right) > 0, \\ \hat{r}_{\text{opt}}^* = \hat{r}^*(\hat{p}_{\text{opt}}^*) \in (0, 1), \\ \alpha_{\text{opt}}^* = \alpha^*(\hat{p}_{\text{opt}}^*) \in (0, 1), \\ \hat{\mu}_{\text{opt}}^* = \max_{\hat{p}^* \geq 0} \hat{\mu}^*(\hat{p}^*) = \hat{\mu}^*(\hat{p}_{\text{opt}}^*) > 0, \end{array} \right. \quad (7)$$

where the functions  $\hat{r}^* = \hat{r}^*(\hat{p}^*)$ ,  $\alpha^* = \alpha^*(\hat{p}^*)$ , and  $\hat{\mu}^* = \hat{\mu}^*(\hat{p}^*)$  are determined by

$$\left\{ \begin{array}{l} \hat{r}^*(\hat{p}^*) = \left( E_M + (1 + \hat{p}^*) \frac{\hat{p}^*}{K + \hat{p}^*} + (\Gamma_M - \Gamma_R)\hat{p}^* \right)^{-1} \cdot \\ \quad \cdot (E_M + \Gamma_M \hat{p}^*), \\ \alpha^*(\hat{p}^*) = \hat{r}^*(\hat{p}^*) - (\Gamma_M - \Gamma_R) \frac{K + \hat{p}^*}{\hat{p}^*} (1 - \hat{r}^*(\hat{p}^*)), \\ \hat{\mu}^*(\hat{p}^*) = \hat{r}^*(\hat{p}^*) \left( \frac{\hat{p}^*}{K + \hat{p}^*} + (\Gamma_M - \Gamma_R) \right) - \Gamma_M. \end{array} \right.$$

One can easily write an analytical expression for the Jacobian matrix  $D(\hat{p}, \hat{r}; \alpha)$  of system (2). The next assump-

tion guarantees asymptotic stability of the optimal steady state.

**Assumption 3.2.** *The Jacobian matrix  $D(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*; \alpha_{\text{opt}}^*)$  at the optimal steady state has a negative trace and a positive determinant.*

Even if it is difficult to check this assumption analytically, numerical verification can easily be performed.

### 4. EXISTENCE OF OPTIMAL CONTROLS

The following restriction on the initial state implies that admissible state trajectories have positive coordinates for all  $\hat{t} > 0$ .

**Assumption 4.1.**  *$0 < \hat{r}_0 \leq 1$ , and  $\hat{p}_0 > 0$  if  $\hat{r}_0 = 1$ .*

We need to impose one more condition.

**Assumption 4.2.**  *$\alpha_{\text{opt}}^* > \Gamma_R$ .*

For the sake of brevity, let us give only a sketch of the proof that an optimal open-loop control exists. Due to the general existence theorem (Afanas'ev et al., 1996, Chapter VIII, §1, Theorem 1.1), it suffices to obtain existence of an admissible control such that terminal constraint (6) is fulfilled.

If  $(\hat{p}(\hat{t}_1), \hat{r}(\hat{t}_1)) \in \text{int } G$  at some time instant  $\hat{t}_1 \geq 0$  and there exists a constant  $\varepsilon \in (0, 1)$  such that  $\alpha(\hat{t}) \in [\varepsilon, 1 - \varepsilon]$  for all  $\hat{t} \geq \hat{t}_1$ , then the corresponding state trajectory of system (2) on the time interval  $[\hat{t}_1, +\infty)$  lies in a compact subset of  $G$ . In  $G$ , system (2) with  $\alpha = \alpha_{\text{opt}}^*$  has only two steady states: stable node or stable focus  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$  and unstable saddle  $(0, 1)$ . By using Dulac's theorem (Perko, 2001, Chapter 3, §3.9, Theorem 2) with the function

$$B(\hat{p}, \hat{r}) = \frac{1}{\hat{r} \left( E_M + (1 + \hat{p}) \frac{\hat{p}}{K + \hat{p}} + (\Gamma_M - \Gamma_R)\hat{p} \right)},$$

one can verify absence of periodic orbits in  $G$  for this system. Moreover, since  $(\hat{p}, \hat{r}) = (0, 1)$  is a saddle, the attracted set in its neighborhood consists of only one curve, which can be left (if  $(\hat{p}, \hat{r}) \neq (0, 1)$ ) by changing the control on a small time subinterval.

Now the following result can be proved with the help of Poincaré-Bendixson theorem (Perko, 2001, Chapter 3, §3.7, Theorem 1) and the sufficient local controllability condition (Lee and Markus, 1986, Chapter 6, §6.1, Theorem 1).

**Theorem 4.1.** *Under Assumptions 3.1, 3.2, 4.1, and 4.2, there exists an optimal open-loop control in problem (2)–(6) if time horizon  $\hat{T}$  is sufficiently large.*

It is clear that minimum admissible  $\hat{T}$  depends on initial state (3). A heuristic way of choosing a suitable  $\hat{T}$  is to integrate system (2) with  $\alpha = \alpha_{\text{opt}}^*$  numerically till a sufficiently small neighborhood of  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$  is reached and then to take  $\hat{T}$  somewhat greater than the final instant of the integration. Suboptimal feedback controls  $\alpha = g(\hat{p})$  and  $\alpha = h(\hat{p}, \hat{r})$  introduced in section 7 can also be used for this purpose.

## 5. NECESSARY OPTIMALITY CONDITIONS

According to Pontryagin et al. (1964), first-order necessary conditions for optimal open-loop controls are known as Pontryagin's maximum principle or, in short, PMP. For our problem (2)–(6), PMP leads to the Hamiltonian

$$\begin{aligned} H(\hat{p}, \hat{r}, \alpha, \psi_0, \psi_1, \psi_2) &= \psi_1 \left( (1 - \hat{r}) E_M - \frac{\hat{p}\hat{r}}{K + \hat{p}} - \right. \\ &- \hat{p} \left( \frac{\hat{p}\hat{r}}{K + \hat{p}} + (\Gamma_M - \Gamma_R)\hat{r} - \Gamma_M \right) \left. \right) + \psi_2 \left( \alpha \frac{\hat{p}\hat{r}}{K + \hat{p}} - \right. \\ &- \Gamma_R \hat{r} - \hat{r} \left( \frac{\hat{p}\hat{r}}{K + \hat{p}} + (\Gamma_M - \Gamma_R)\hat{r} - \Gamma_M \right) \left. \right) - \\ &- \psi_0 \left( \frac{\hat{p}\hat{r}}{K + \hat{p}} + (\Gamma_M - \Gamma_R)\hat{r} - \Gamma_M \right), \end{aligned}$$

adjoint system

$$\begin{cases} \frac{d\psi_1(\hat{t})}{d\hat{t}} = - \frac{\partial H(\hat{p}(\hat{t}), \hat{r}(\hat{t}), \alpha(\hat{t}), \psi_0, \psi_1(\hat{t}), \psi_2(\hat{t}))}{\partial \hat{p}}, \\ \frac{d\psi_2(\hat{t})}{d\hat{t}} = - \frac{\partial H(\hat{p}(\hat{t}), \hat{r}(\hat{t}), \alpha(\hat{t}), \psi_0, \psi_1(\hat{t}), \psi_2(\hat{t}))}{\partial \hat{r}}, \\ \psi_0 \equiv 0 \text{ or } \psi_0 \equiv -1, \\ (\psi_0, \psi_1(\hat{t}), \psi_2(\hat{t})) \neq (0, 0, 0) \quad \forall \hat{t} \in [0, \hat{T}] \end{cases}$$

(one can easily write a complete representation of the right-hand side here), and Hamiltonian maximum condition

$$\alpha_{\text{extr}}(\hat{t}) = \begin{cases} 0, & \psi_2(\hat{t}) < 0, \\ 1, & \psi_2(\hat{t}) > 0, \\ \text{unknown}, & \psi_2(\hat{t}) = 0, \end{cases}$$

which holds necessarily for an optimal open-loop control. An admissible process  $(\alpha(\cdot), \hat{p}(\cdot), \hat{r}(\cdot), \psi_0, \psi_1(\cdot), \psi_2(\cdot))$  satisfying PMP is called extremal. It is called normal if  $\psi_0 < 0$  and abnormal if  $\psi_0 = 0$ . Since system (2) is autonomous, the Hamiltonian is conserved along any extremal process.

If  $\psi_2(\cdot)$  vanishes over some time subinterval, then the corresponding control and part (arc) of the related extremal state trajectory are called singular. Zelikin and Borisov (1994); Schattler and Ledzewicz (2015) indicate a key role of singular regimes for optimal control problems arising in many applied areas such as economics, engineering, biology, and medical sciences. In conformity with Giordano et al. (2016), let us exclude abnormal extremal processes from consideration in view of the fact that they do not allow singular regimes and, therefore, do not admit a clear biological interpretation.

The following properties of normal extremal processes can be obtained from PMP.

**Theorem 5.1.** *Adopt Assumptions 3.1, 3.2, 4.1 and 4.2. Consider a normal extremal process  $(\alpha(\cdot), \hat{p}(\cdot), \hat{r}(\cdot), -1, \psi_1(\cdot), \psi_2(\cdot))$ . A switching of the control may appear only when  $\psi_2(\cdot)$  reaches zero. For such a switching instant, if the expression*

$$\begin{aligned} \left. \frac{d\psi_2(\hat{t})}{d\hat{t}} \right|_{\psi_2(\hat{t})=0} &= \psi_1(\hat{t}) \left( E_M + \frac{(1 + \hat{p}(\hat{t}))\hat{p}(\hat{t})}{K + \hat{p}(\hat{t})} + \right. \\ &+ (\Gamma_M - \Gamma_R)\hat{p}(\hat{t}) \left. \right) - \left( \frac{\hat{p}(\hat{t})}{K + \hat{p}(\hat{t})} + \Gamma_M - \Gamma_R \right) \end{aligned}$$

*is negative, then the switching occurs in the direction from  $\alpha = 1$  to  $\alpha = 0$ , and the opposite switching direction takes place when this expression is positive. Any singular*

*arc coincides with the optimal steady state  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$ , satisfies Kelley condition, and has the second order, i. e., it can be entered or left only by chattering arcs with infinite numbers of switchings. For a chattering arc, switchings from  $\alpha = 1$  to  $\alpha = 0$  happen only in the region*

$$\{(\hat{p}, \hat{r}) \in (0, +\infty) \times (0, 1] : \hat{r} > \hat{r}^*(\hat{p})\}, \quad (8)$$

*and switchings in the opposite direction happen only in the region*

$$\{(\hat{p}, \hat{r}) \in (0, +\infty) \times (0, 1] : \hat{r} < \hat{r}^*(\hat{p})\} \quad (9)$$

*(function  $\hat{r}^* = \hat{r}^*(\hat{p})$  is defined in Theorem 3.1).*

## 6. CHATTERING SWITCHING CURVE

A local structure of entering chattering arcs near the optimal steady state  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$  can be described by some switching curve  $\Sigma$  such that the corresponding feedback control takes value 0 on one side of  $\Sigma$  and value 1 on the other side. In turn, the optimal steady state divides  $\Sigma$  into two subcurves  $\Sigma_0$  and  $\Sigma_1$ , so that switchings in the direction from  $\alpha = 1$  to  $\alpha = 0$  happen only on  $\Sigma_0$  and switchings in the opposite direction happen only on  $\Sigma_1$ . By virtue of Theorem 5.1,  $\Sigma_0$  is contained in set (8), while  $\Sigma_1$  is contained in set (9).

Let us briefly describe how  $\Sigma$  can be approximated. According to Naumov (2003), if the directions specified by the vectors  $(d\hat{p}/d\hat{t}, d\hat{r}/d\hat{t}) \Big|_{(\hat{p}, \hat{r})=(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*), \alpha=0}$

and  $(d\hat{p}/d\hat{t}, d\hat{r}/d\hat{t}) \Big|_{(\hat{p}, \hat{r})=(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*), \alpha=1}$  coincide with each other, then this is in fact the direction of the tangent line to  $\Sigma$  at  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$ . The latter is vertical, because  $\alpha(\cdot)$  does not explicitly appear in the first equation of (2). Hence, in a small closed neighborhood of  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$ ,  $\Sigma$  can be approximated as a short vertical line segment  $L$ . Since we know the value  $\hat{\mu}_{\text{opt}}^*$  of the Hamiltonian at the optimal steady state, then, from its conservation property and switching condition  $\psi_2 = 0$ , we can derive an explicit representation  $\psi_1 = \psi_{1,L}(\hat{p}, \hat{r})$  for  $(\hat{p}, \hat{r}) \in L \setminus \{(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)\}$ . Integrating dynamic and adjoint equations in reverse time with the starting positions  $\psi_1 = \psi_{1,L}(\hat{p}, \hat{r})$ ,  $\psi_2 = 0$ ,  $(\hat{p}, \hat{r}) \in L \setminus \{(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)\}$  allows us to find the switching points in the state space (where  $\psi_2$  changes sign) and thereby to characterize  $\Sigma_0$  and  $\Sigma_1$ . The results of related numerical simulations are presented in section 8.

## 7. SUBOPTIMAL FEEDBACK CONTROLS

For the model without degradation, Giordano et al. (2016) proposed and tested three suboptimal feedback control laws. They were based on biological arguments and designed so that the system eventually approached the optimal steady state by using either “measurements” of nutrients and precursors or the imbalance between precursors and gene expression machinery. These were the nutrient-only strategy  $\alpha = f(E_M)$ , precursor-only strategy  $\alpha = g(\hat{p})$ , and on-off strategy  $\alpha = h(\hat{p}, \hat{r})$ . In particular, the on-off law turned out to be in good agreement with the control strategy of the signalling molecule ppGpp (in the enterobacterium *Escherichia coli*) approximated via experimental data and a specific kinetic model.

The nutrient-only, precursor-only, and on-off controls allow extensions to the current model with nonzero degradation

rates, while preserving reasonable biological interpretations. The nutrient-only strategy is merely  $\alpha = \alpha_{\text{opt}}^* = \text{const}$ . The on-off strategy is represented in terms of the precursor-only strategy as follows:

$$h(\hat{p}, \hat{r}) = \begin{cases} 0, & \hat{r} \geq g(\hat{p}), \\ 1, & \hat{r} < g(\hat{p}), \\ \alpha_{\text{opt}}^*, & (\hat{p}, \hat{r}) = (\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*). \end{cases}$$

Hence, it suffices to construct  $g(\hat{p})$ .

For the case  $\gamma_M = \gamma_R = 0$ , Giordano et al. (2016) obtained  $E_M = (\hat{p}_{\text{opt}}^*)^2 / K$  from the representation  $\hat{p}_{\text{opt}}^* = \sqrt{E_M K}$  and then determined  $g = g(\hat{p})$  by substituting  $E_M = \hat{p}^2 / K$  into the expression for  $\alpha_{\text{opt}}^*$ . In our case, (7) does not give such a trivial representation of  $E_M$  in terms of  $\hat{p}_{\text{opt}}^*$ . However, one can verify that, for some sufficiently small constant  $\mathcal{E}_M > 0$ , function  $\hat{p}_{\text{opt}}^* = \hat{p}_{\text{opt}}^*(\mathcal{E}_M)$  has a positive derivative and, therefore, strictly increases on the infinite interval  $(\mathcal{E}_M, +\infty)$ . Then the inverse  $E_M = E_M(\hat{p}_{\text{opt}}^*)$  can be constructed numerically on some finite interval. Suppose that the latter is sufficiently large and contains the optimal steady state for the considered environmental input. Outside this finite interval, specify  $E_M = E_M(\hat{p}_{\text{opt}}^*)$  arbitrarily. By substituting the obtained function of variable  $\hat{p}$  into the expression for  $\alpha_{\text{opt}}^*$  (see Theorem 3.1), we get  $g = g(\hat{p})$ .

Now consider system (2) with the substituted precursor-only feedback control and given environmental input. By construction,  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$  is a steady state of this system, and it is asymptotically stable under the next assumption.

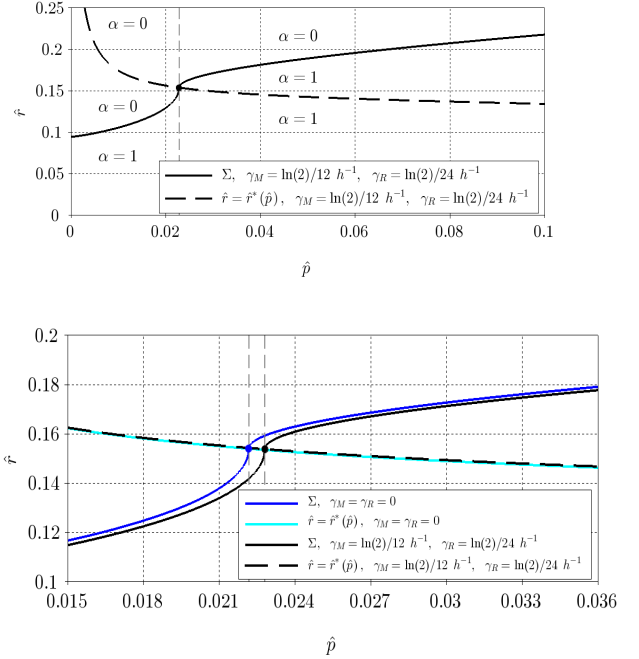
**Assumption 7.1.** *For the Jacobian matrix of system (2) with the substituted feedback control  $\alpha = g(\hat{p})$ , the trace and determinant at point  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$  are negative and positive, respectively.*

By using the framework of Filippov (1988) related to differential equations with discontinuous right-hand sides, one can also prove that, under the adopted assumptions, the optimal steady state is asymptotically stable for system (2) with the substituted on-off control  $\alpha = h(\hat{p}, \hat{r})$ .

## 8. NUMERICAL SIMULATIONS

For numerical simulations, take  $e_M = 0.59 \text{ h}^{-1}$  (poor M63+glycerol medium),  $\beta = 0.003 \text{ L} \cdot \text{g}^{-1}$ ,  $k_R = 3.6 \text{ h}^{-1}$ , and  $K_R = 1 \text{ g} \cdot \text{L}^{-1}$  according to Giordano et al. (2016). Set the average half-life time of a macromolecule as 12 h for metabolic machinery and 24 h for more stable gene expression machinery. Then  $\gamma_M = \ln(2)/12 \text{ h}^{-1}$  and  $\gamma_R = \ln(2)/24 \text{ h}^{-1}$ . Such degradation rates conform with the relevant orders of magnitude given by Mandelstam (1958). Also choose  $\hat{T} = k_R T = 20$ . Initial state (3) is taken as the optimal steady state for the higher environmental input  $e_M' = 1.57 \text{ h}^{-1}$  (cAA+glucose medium), i. e., the system is considered after a nutrient downshift. One can check that Assumptions 3.1, 3.2, 4.1, 4.2, and 7.1 hold for such parameters.

Fig. 2 illustrates the chattering switching curves approximated via the algorithm of section 6 for the mentioned degradation rates and also in case  $\gamma_M = \gamma_R = 0$ . A noticeable difference can be seen only near the corresponding optimal steady states. Fig. 3 shows time evolution of the



**Fig. 2.** *Chattering switching curve.*

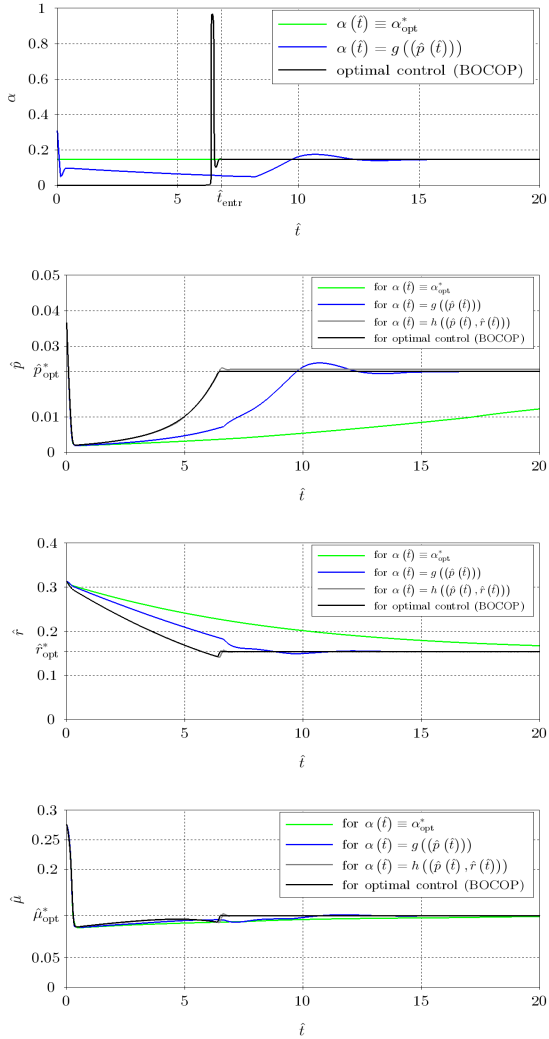
suboptimal and approximate optimal processes for the case of nonzero degradation rates. The optimal open-loop control was computed by using the Bocop software of Bonnans et al. (2012). As in the numerical results of Giordano et al. (2016) related to the case  $\gamma_M = \gamma_R = 0$ , the growth rate integral for the on-off control is very close to the optimal value reached by chattering, which may explain that such a strategy has appeared through biological evolution.

The optimal open-loop control has also been computed for the greater time horizon  $\hat{T} = 40$ . On the time interval before the previous horizon  $\hat{T} = 20$ , the evolution is almost identical, and then the control continues to keep the system at the optimal steady state till the end (the corresponding figure is omitted for the sake of brevity). Thus, validity of our problem statement is confirmed by this result as well as by the existence result of section 4 and independence of the algorithm of section 6 from a particular time horizon.

## 9. CONCLUSION

In this paper, the bacterial growth model of Giordano et al. (2016) was generalized by taking degradation of macromolecules into account. The related dynamic optimization problem was stated in a different way so that existence of optimal open-loop controls could be proved. A novel numerical algorithm for approximating switching curves of the chattering control in the state space was proposed and tested. Moreover, the suboptimal feedback control laws of Giordano et al. (2016) were extended to the new model.

One possible extension of our model is to include additional terms representing the fact that some of degraded proteins are recycled into precursors and thereby stay in cells. From the practical point of view, it is also relevant to consider bacterial populations growing in bioreactors, and the model can be extended by introducing one more



**Fig. 3.** Time evolution of the suboptimal and approximate optimal processes for  $\gamma_M = \ln(2)/12 \text{ h}^{-1}$  and  $\gamma_R = \ln(2)/24 \text{ h}^{-1}$ . In the top subfigure, the on-off control is not illustrated because of a huge amount of its switchings when the state approaches  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$ .

reaction, which transforms cellular resources into a certain product of biotechnological interest. Then it is reasonable to use the fact that, by regulating an external inducer (chemical or light), it becomes possible to affect internal cellular processes and, consequently, biotechnological production. The dynamic optimization problem can be stated as seeking for an optimal inducing strategy that maximizes the production. These are subjects for future investigation.

Finally, let us discuss one more possible further development. Our numerical results indicated that the qualitative structures of optimal and suboptimal control strategies were similar to those for the case of zero degradation rates, even though there was some quantitative difference for a poor environmental input. The model parameters for the simulations in fact corresponded to a normal-temperature case. Nevertheless, the results of Farewell and Neidhardt (1998) showed a significant increase in protein degradation at high temperatures. Thus, for a future work, it is worth investigating to derive suitable parameter values and to

conduct numerical experiments for our model in a high-temperature case so as to test robustness of the resource. This can also have a great interest for bioengineering.

## REFERENCES

- Afanas'ev, V. N., Kolmanovskii, V. B., and Nosov, V. R. *Mathematical Theory of Control Systems Design*. Kluwer Academic Publishers: Dordrecht, 1996.
- Bonnans, F., Martinon, P., and Grélard, V. *Bocop — A collection of examples*. 2012. E-print: <https://hal.inria.fr/hal-00726992>.
- Carlson, D. A., Haurie, A. B., and Leizarowitz, A. *Infinite Horizon Optimal Control: Deterministic and Stochastic Systems*. Springer-Verlag: Berlin, Heidelberg, 1991.
- Farewell, A. and Neidhardt, F. C. Effect of temperature on in vivo protein synthetic capacity in *Escherichia coli*. *J. Bacteriol.* 1998; **180**(17):4704–4710.
- Filippov, A. F. *Differential Equations with Discontinuous Right-hand Sides*. Kluwer Academic: Dordrecht, 1988.
- Giordano, N., Mairet, F., Gouzé, J.-L., Geiselmann, J., and de Jong, H. Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies. *PLoS Comput. Biol.* 2016; **12**(3):e1004802.
- Lee, E. B. and Markus L. *Foundations of Optimal Control Theory*. Krieger Publishing: Malabar, 1986.
- Mandelstam, J. Turnover of protein in growing and non-growing populations of *Escherichia coli*. *Biochem. J.* 1958; **69**(1):110–119.
- Molenaar, D., van Berlo, R., de Ridder, D., and Teusink, B. Shifts in growth strategies reflect tradeoffs in cellular economics. *Mol. Syst. Biol.* 2009; **5**:323.
- Naumov, G. V. Construction of the switching curve for optimal control problems with chattering control. *Izv. RAN: Teor. Sist. Upr.* 2003; **3**:46–51 (in Russian).
- Pavlov, M. Y. and Ehrenberg, M. Optimal control of gene expression for fast proteome adaptation to environmental change. *Proc. Natl. Acad. Sci. USA* 2013; **110**(51):20527–32.
- Perko, L. *Differential Equations and Dynamical Systems*. Springer-Verlag: New York, 2001.
- Pontryagin, L. S., Boltyansky, V. G., Gamkrelidze, R. V., and Mishchenko, E. F. *The Mathematical Theory of Optimal Processes*. Macmillan: New York, 1964.
- Schaechter, M., Ingraham, J. L., and Neidhardt, F. C. *Microbe*. ASM Press: Washington, DC, 2006.
- Schattler, H. and Ledzewicz, U. *Optimal Control for Mathematical Models of Cancer Therapies: An Application of Geometric Methods. Interdisciplinary Applied Mathematics*, **42**. Springer-Verlag: New York, 2015.
- Scott, M., Klumpp, S., Mateescu, E. M., and Hwa, T. Emergence of robust growth laws from optimal regulation of ribosome synthesis. *Mol. Syst. Biol.* 2014; **10**:747.
- Trélat, E. and Zuazua, E. The turnpike property in finite-dimensional nonlinear optimal control. *J. Differential Equations* 2015; **258**(1):81–114.
- Venayak, N., Anesiadis, N., Cluett, W. R., and Mahadevan, R. Engineering metabolism through dynamic control. *Curr. Opin. Biotech.* 2015; **34**:142–152.
- Zelikin, M. I. and Borisov, V. F. *Theory of Chattering Control with Applications to Astronautics, Robotics, Economics, and Engineering*. Birkhauser: Boston, 1994.