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## Optimal resource allocation for bacterial  $\bm{\mathsf{u}}$  resource anocation for  $\bm{\mathsf{v}}$ <br>growth with degradation  $^\star$  $\overline{O}$  resource all resource allocation for backerial resource allocation for backerial resource allocation for backerial resource and the stress of d resource allocation for b Optimal resource allocation for bacterial Optimal resource allocation for bacterial

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Abstract: Understanding adaptation of bacterial growth for a changing environment is a<br>fundamental biological problem which also has a great interest from the biotechnological point rundamental biological problem which also has a great interest from the biotechnological point<br>of view. This paper extends one of existing bacterial growth models by taking macromolecular or view. This paper extends one of existing bacterial growth models by taking macromolecular<br>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 or maximizing biomass accumulation is stated in a specific way so that existence or optimal<br>resource allocation strategies can be verified. A novel numerical algorithm for approximating essuite anotation strategies can be verified. A nover numerical agorithm for approximating<br>switching curves of the chattering control in the state space is developed. Several realistic switching curves of the chattering control in the state space is developed. Several realistic<br>suboptimal feedback control laws are also constructed and successfully tested. The results of numerical simulations confirm validity of the new problem statement. Abstract: Understanding adaptation of bacterial growth for a changing environment is a degradation into account and provides new mathematical results. The related dynamic problem suboptimal feedback control laws are also constructed and successfully tested. The results of  $\sim$  1 fully fundamental biological problem which also has a great interest from the biotechnology from the biotechnology  $\mu$ 

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

## 1. INTRODUCTION 1. INTRODUCTION 1. INTRODUCTION 1. INTRODUCTION

In theoretical biology as well as in biotechnology, it is In theoretical biology as well as in biotechnology, it is In theoretical biology as well as in biotechnology, it is In theoretical biology as well as in biotechnology, it is<br>important to study mechanisms of bacterial adaptaion for<br>changes in availability of external nutrients (Schaechter<br> $(2000)$  M important to study ineclianisms of bacterial adaptator for<br>changes in availability of external nutrients (Schaechter enanges in availability of external interests (schaechter<br>et al. (2006); Venayak et al. (2015)). Several studies develet al. (2000), vehayak et al. (2015)). Several studies devel-<br>oped steady-state and dynamic mathematical models to oped steady-state and dynamic mathematical models to ploy for achieving optimal resource allocation of their protein synthesis capacity over different cellular functions (Molenaar et al.  $(2009)$ ; Scott et al.  $(2014)$ ; Pavlov and (Molendal et al.  $(2009)$ , Scott et al.  $(2014)$ , I aviov and<br>Ehrenberg (2013); Giordano et al. (2016)). In particular Ememberg (2013), Giordano et al. (2016)). In particu-<br>lar, Giordano et al. (2016) proposed a model of a selfar, Giordano et al. (2010) proposed a moder or a sen-<br>replicating prokaryotic cell population by distinguishing replicating provided by distinguishing<br>two basic cellular processes: metabolism (converting nutritwo basic central processes. Inetabolism (converting nutri-<br>ents to precursors) and gene expression (converting precurents to precursors) and gene expression (converting precursors to proteins which constitute biomass). Dynamic optisors to proteins which constitute biomass). Dynamic opti-<br>mization methods were used to obtain a resource allocation strategy leading to maximum biomass accumulation. The strategy leading to maximum biomass accumulation. The strategy leading to maximum biomass accumulation. The strategy leading to maximum biomass accumulation. The<br>optimal control law was compared with several realistic optimal control law was compared with several realistic<br>suboptimal control strategies. For the sake of simplicity, suboptimal control strategies. For the sake of simplicity,<br>the model of Giordano et al. (2016) ignored macromolecular degradation. The aim of this work is to develop an ular degradation. The aim of this work is to develop an ular degradation. The aim of this work is to develop an ular 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. protein synthesis capacity over different cellular functions<br>(Malaysex at al. (2009); Saatt at al. (2014); Paylax and ular degradation. The aim of this work is to develop an<br>extended model with such a degradation as well as to the related dynamic optimization problem. the related dynamic optimization problem. the related dynamic optimization problem. replicating prokaryotic cell population by distinguishing mization methods were used to obtain a resource allocation the model of Giordano et al. (2016) ignored macromolec-

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

 $\frac{1}{\sqrt{1 + \frac{1}{\sqrt{1 +$ This work was supported in part by the project RESET (Biom-<br>formatique, ANR-11-BINF-0005) and program LABEX SIGNALIFE 10 BIOCORE ANN-11-BINT-0000) and program LABEX SIGNAT<br>(ANR-11-LABX-0028-01).

of Giordano et al. (2016). Then we describe the optimal of Giordano et al. (2010). Then we describe the optimal<br>steady state and verify existence of optimal open-loop resource allocation strategies (controls). Next, the latter resource anotation strategies (controls). Next, the latter<br>are characterized via necessary optimality conditions, and are characterized via hecessary optimality conditions, and<br>a novel numerical algorithm for approximating switching a novel numerical algorithm for approximating switching<br>curves of the chattering control in the state space is curves of the chattering control in the state space is<br>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. are presented and discussed. are presented and discussed. are presented and discussed. steady state and verify existence of optimal open-loop are characterized via necessary optimality conditions, and

## 2. PROBLEM STATEMENT 2. PROBLEM STATEMENT 2. PROBLEM STATEMENT 2. PROBLEM STATEMENT

Let  $P, M, R$  [g] be the total masses of precursor metabo-Let  $I$ ,  $M$ ,  $I$  [g] be the total masses of precursor metapo-<br>lites (amino acids), metabolic machinery (enzymes inries (animo acids), metabolic machinery (enzymes m-<br>volved in nutrient uptake and conversion to precursors), voived in nutrient uptake and conversion to precursors),<br>and gene expression machinery (polymerase, ribosomes) in and gene expression machinery (polymerase, rhotsomes) in<br>the considered self-replicating prokaryotic cell population, In the considered sen-replicating prokaryout cen 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 precursors, while gene expression machinery transforms precursors, while gene expression machinery transforms precursors, while gene expression machinery transforms<br>precursors into macromolecules. The latter are involved effectured in metabolism or in gene expression itself. This leads to the system of ordinary differential equations respectively. A scheme of the model is given in Fig. 1. to the system of ordinary differential equations to the system of ordinary differential equations to the system of ordinary differential equations Ţ the considered self-replicating prokaryotic cell population,

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

where t is the time variable,  $T > 0$  is the time horizon, where t is the time variable,  $T > 0$  is the time horizon,<br> $V_M(t)$ ,  $V_R(t)$   $[g \cdot h^{-1}]$  are the rates at which the precursors are formed by metabolism and utilized for gene expression, are formed by metabolism and utilized for gene expression, are formed by metabolism and utilized for gene expression, where t is the time variable,  $T > 0$  is the time horizon,  $\frac{d\mathbf{t}}{dt} = \alpha(t) \mathbf{v}_R(t) - \gamma_R \mathbf{v}_R(t), \quad t \in [0, 1],$ <br>where t is the time variable,  $T > 0$  is the time horizon, where t is the time variable,  $T > 0$  is the time horizon,<br>  $V_M(t)$ ,  $V_R(t)$   $[g \cdot h^{-1}]$  are the rates at which the precursors  $V_M(t)$ ,  $V_R(t)$  [g · h<sup>-1</sup>] are the rates at which the precursors<br>are formed by metabolism and utilized for gene expression

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Fig. 1. Scheme of the model.

respectively,  $\gamma_M \geq 0, \gamma_R \geq 0$  [h<sup>-1</sup>] 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  $V(t) = \beta \cdot (M(t) + R(t))$ [L] (only the macromolecules constituting the cells are included here as opposed to the monomer precursors);
- intracellular characteristics  $v_M(t) = V_M(t)/V(t)$  $[g \cdot L^{-1} \cdot h^{-1}], \quad v_R(t) = V_R(t)/\mathcal{V}(t) \quad [g \cdot L^{-1} \cdot h^{-1}].$  $p(t) = P(t)/\mathcal{V}(t) \quad [g \cdot L^{-1}], \quad r(t) = R(t)/\mathcal{V}(t)$ <br>  $[g \cdot L^{-1}], \quad m(t) = M(t)/\mathcal{V}(t) \quad [g \cdot L^{-1}];$
- 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  $e_M > 0$  $\left[\tilde{h}^{-1}\right]$  specifies the environmental input, and  $k_R > 0$  $\left[h^{-1}\right], K_R > 0 \left[g \cdot L^{-1}\right]$  are the rate and halfsaturation 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  $\hat{T} = k_B T$ ,  $E_M =$  $e_M/k_R$ ,  $K = \beta K_R$ ,  $\Gamma_M = \gamma_M/k_R$ ,  $\Gamma_R = \gamma_R/k_R$ ;
- growth rate of the self-replicating system

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

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

Then system (1) can be transformed into

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

The initial conditions are

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

\nthe constraint on resonance allocation functions is

and the constraint on resource allocation functions is

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

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

$$
J(\alpha(\cdot)) = \int_{0}^{T} \mu(t)dt = \int_{0}^{\hat{T}} \hat{\mu}(t) dt \longrightarrow \max. \quad (5)
$$

This maximum is searched over the set of all admissible open-loop controls  $\alpha(\cdot)$  which are measurable functions on  $\left[0,\hat{T}\right]$  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 infinitehorizon 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  $(\hat{p}_{\text{opt}}^*, \hat{r}_{\text{opt}}^*)$ :

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

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