Predicting microbial cell composition and diauxic growth as optimal control strategies ⋆

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Abstract: Bacteria have evolved internal regulatory mechanisms allowing them to allocate resources to different cellular functions while dealing with the physiological limitations of the cell. In this preliminary work, we present a simple mathematical model of bacteria growing on n substitutable substrates aiming to capture these principles, focusing on the trade-off between metabolism and gene expression. The model is also able to capture a behavior known as diauxic growth, which is the sequential consumption of the nutrients in the environment resulting from the limitation of resources of the metabolic machinery. Under the hypothesis that cell regulatory mechanisms are tuned to maximize bacterial growth, we study the optimal allocation strategies through Optimal Control theory, by means of the Pontryagin's Maximum Principle. The optimal solutions are characterized by classical bang-singular-bang control structures, and can be expressed as feedback control laws, in accordance with previous results. We conclude the paper with numerical optimal trajectories of the model representing an environment with three substrates with different associated yields coefficients.

Keywords: diauxic growth, bacterial growth laws, bacterial resource allocation, optimal control

1. INTRODUCTION

A novel perspective in investigating the governing principles of microbial growth is to study the phenomenon from a resource allocation perspective. The approach is able to yield models accounting for the main cellular functions, while considering the intrinsic physical and biological limitations of cell physiology. There are numerous fundamental compromises arising from resource limitation. A widely studied problem is the trade-off between metabolism and gene expression (Weiße et al., 2015). Mathematical models of steady-state growth were able to reproduce empiric relations between cell composition and growth rate in steady-state conditions (Scott et al., 2010; Hui et al., 2015). In dynamical environments, Optimal Control theory allowed to predict natural resource allocation strategies from mathematical models in changing environments (Giordano et al., 2016; Yabo et al., 2022a,c), by assuming bacteria have evolved regulatory mechanisms to maximize growth rate (Dekel and Alon, 2005). The same approach has been applied to synthesize chemical compounds of interest by engineering synthetic pathways in microbial cells (Yegorov et al., 2018; Cinquemani et al., 2019; Yabo and Gouzé, 2020; Yabo et al., 2020, 2022b).

Another well-known behavior arising from resource limitation is a phenomenon called diauxie. The latter is the sequential (instead of simultaneous) consumption of nutrients in environments containing multiple substitutable substrates. Diauxic growth is a natural uptake pattern that bacteria have developed through evolution, which implies that it could be predicted as an optimal behavior with respect to a certain criterion (or cost function). Among the pioneering works in the subject, Dhurjati et al. (1985) and Ramakrishna et al. (1996) have developed simple mathematical models able to predict diauxie. More recently, there has also been numerical studies comparing different modelling techniques that were able to account for the phenomenon (Kremling et al., 2015, 2018). Mandli and Modak (2014) used Optimal Control theory to obtain feedback substrate uptake strategies using a bacterial growth model based on the classical work of Monod (1949). The study focuses on the case with two substitutable substrates, and proposes a very simple mathematical model where no cell composition is considered.

In this work, we extend these results by proposing a simple mathematical model of a microbial population growing on n substitutable substrates, which is a generalization of previous self-replicator bacterial growth models considering cell composition (Giordano et al., 2016; Yabo et al., 2022a). The paper starts with a definition of the model—in Section 2—including n metabolic controls that represent the distribution of proteins of the metabolic machinery over the n substrates, which are subject to a constraint accounting for the availability of enzymatic proteins. Additionally, the model considers the mass fractions of the cell dedicated to gene expression and metabolism, and thus it can account for the trade-off arising between these two cellular functions. As hypothesized in many bacterial growth studies, the natural objective is to maximize the biomass, which yields an OCP (Optimal Control Problem)—described in Section 3—with $n + 1$ degrees

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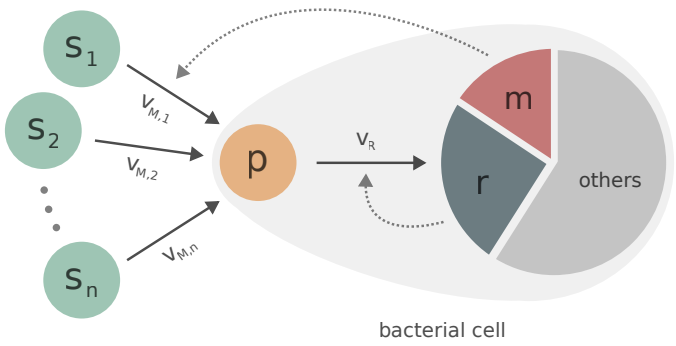

Fig. 1. Scheme of the bacterial model.

of freedom representing the n metabolic controls and cell composition. The resulting optimal strategies behind the studied regulatory mechanisms are characterized by bang-singular-bang structures, which can be written as functions of the state of the system. By application of Pontryagin's Maximum Principle (PMP), the approach successfully predicts the sequential uptake pattern as an optimal strategy in environments with multiple substrates, as well as the fractions of the cell allocated to gene expression and metabolism. These results—shown in Section 4—constitute an additional mathematical argument supporting the theory that regulatory mechanisms in bacteria are geared towards growth rate maximization. Finally, we provide numerical simulations—in Section 5—performed with Bocop (Team Commands, 2017), an optimal control solver, verifying the analytical results obtained.

2. MODEL DEFINITION

Based on Mandli and Modak (2014); Giordano et al. (2016); Yabo et al. (2022a), we write a dynamical model representing cell metabolism and gene expression in its minimal form, growing on n substitutable substrates. The model considers s_i as the concentration of the i-th substrate in the medium [g L^{-1}], the intracellular concentration of precursor metabolites p in the bacterial population [g L^{-1}], and the non-dimensional fraction of the culture volume occupied by the bacterial population $\mathcal{V}$. Reaction rates in the system depend on the time-varying quantities:

- $m(t)$: the fraction of the cell dedicated to proteins of the metabolic machinery, responsible for the uptake of substrates from the environment and the production of precursor metabolites.
- $r(t)$: the fraction of the cell dedicated to active proteins of the gene expression machinery, responsible for the synthesis of biomass $\mathcal{V}$.

Figure 1 shows a scheme of the model. The dynamical system writes

$$\begin{cases} \dot{s}_i = -v_i(s_i, m)\mathcal{V}, & i = 1, 2, \dots, n \\ \dot{p} = \sum_{i=1}^{n} Y_i v_i(s_i, m) - v_R(p, r)(p+1), \\ \dot{\mathcal{V}} = v_R(p, r)\mathcal{V}. \end{cases}$$

where v_i [h^{-1}] is the uptake rate and precursor synthesis rate associated to the i-th substrate—catalyzed by m—and v_R [h^{-1}] is the bacterial growth rate—catalyzed by r. Following (Scott et al., 2010; Hui et al., 2015), we suppose:

- The substrate uptake rate v_i is linear in m.
- The growth rate v_R is linear in r.
- The mass fraction $m + r$ is fixed.

According to empirical observations of microbial cells, $m + r \approx 0.43$, while the remainder of the cell (indicated in the Figure as *others*) corresponds to proteins that are not directly linked to growth (Hui et al., 2015). Without loss of generality, by rescaling mass fractions we can fix $m+r = 1$, and so the system can be rewritten as

$$\begin{cases} \dot{s}_i = -w_i(s_i)(1-r)\mathcal{V}, & i = 1, 2, \dots, n \\ \dot{p} = \sum_{i=1}^{n} Y_i w_i(s_i)(1-r) - w_R(p) r (p+1), \\ \dot{\mathcal{V}} = w_R(p) r \mathcal{V}. \end{cases}$$

where functions v_i and v_R have been expressed by taking into account the aforementioned linear relationships, and m has been replaced by $1-r$. The functions w_I satisfy the following properties:

Assumption 1. Function $w_I(x) : \mathbb{R}_+ \to \mathbb{R}_+$ is C^2 and it satisfies:

- $w_I(0) = 0$,
- $w_I'(x) > 0, \forall x \geq 0$,
- $w_I''(x) < 0, \forall x \geq 0$,
- $\lim_{x\to\infty} w_I(x) = k_I$.

2.1 Controlled dynamics

In order to be able to predict the optimal distribution of resources of the metabolic machinery, we define n time-varying functions $\delta_i \geq 0$ describing the fraction of enzymatic proteins assigned to the uptake of the i-th substrate. Thus, the controlled system becomes

$$\begin{cases} \dot{s}_i = -\delta_i w_i(s_i)(1-r)\mathcal{V}, & i = 1, 2, \dots, n \\ \dot{p} = \sum_{i=1}^{n} Y_i \delta_i w_i(s_i)(1-r) - w_R(p) r (p+1), \\ \dot{\mathcal{V}} = w_R(p) r \mathcal{V}. \end{cases} \quad \text{(S)}$$

where each individual function δ_i multiplies the fraction of proteins of the metabolic machinery m (or, in the new formulation, $1-r$). The metabolic controls are subject to the constraint

$$\sum_{i=1}^{n} \delta_i \leq 1. \quad \text{(C)}$$

representing the fact that the enzymatic proteins are limited to the fraction of the cell occupied by the metabolic machinery.

3. PROBLEM STATEMENT

We start by fixing the initial conditions of the system as

$$\begin{aligned} s_i(0) &= s_{i0} > 0, \quad i = 1, 2, \dots, n \quad \text{(IC)} \\ p(0) &= p_0 > 0, \\ \mathcal{V}(0) &= \mathcal{V}_0 > 0. \end{aligned}$$

Then, we write the dynamical optimization problem where the cost function to maximize is the biomass at final time t_f (for a fixed $t_f > 0$). The latter writes

$$\begin{cases} \textit{maximize } \mathcal{V}(t_f), \\ \textit{subject to dynamics of } (\mathrm{S}), \\ \qquad \textit{initial conditions } (\mathrm{IC}), \\ \qquad \textit{maximum control constraint } (\mathrm{C}), \\ \qquad r(\cdot) \in \mathcal{R}, \\ \qquad \delta_i(\cdot) \in \mathcal{D}, \quad i = 1, 2, \dots, n \end{cases} \tag{OCP}$$

where $\mathcal{R}$ and $\mathcal{D}$ are the sets of admissible controllers, described by Lebesgue measurable real-valued functions defined on the interval $[0, t_f]$ and satisfying the constraints associated to each control. We proceed to the study of the solutions of (OCP).

4. RESULTS

4.1 Application of the Pontryagin's Maximum Principle

Given that the optimal control problem has no terminal conditions, the controllability of the system is not relevant to problem (OCP). As the system is bounded, and the controls are included in compact and convex sets, Filippov's theorem ensures the existence of solutions (Agrachev and Sachkov, 2013). The state $x \in \mathbb{R}^{n+2}$, adjoint state $\lambda \in \mathbb{R}^{n+2}$ and control vector $u \in \mathbb{R}^{n+1}$ are defined as

$$\begin{aligned} x &\doteq (s_1, \dots, s_n, p, \mathcal{V}), \\ \lambda &\doteq (\lambda_{s_1}, \dots, \lambda_{s_n}, \lambda_p, \lambda_{\mathcal{V}}), \\ u &\doteq (\delta_1, \dots, \delta_n, r). \end{aligned}$$

For this class of OCPs, PMP ensures that there exist $\lambda^0 \leq 0$ and a piecewise absolutely continuous mapping $\lambda(\cdot) : [0, t_f] \to \mathbb{R}^n$, with $(\lambda(\cdot), \lambda^0) \neq (0, 0)$, such that the extremal $(x, \lambda, \lambda^0, u)$ satisfies the generalized Hamiltonian system

$$\begin{cases} \dot{x} = \dfrac{\partial}{\partial \lambda} H(\varphi, \lambda, \lambda^0, u), \\ \dot{\lambda} = -\dfrac{\partial}{\partial x} H(\varphi, \lambda, \lambda^0, u), \\ H(x, \lambda, \lambda^0, \tilde{u}) = \max\limits_{u} H(x, \lambda, \lambda^0, u), \end{cases} \tag{PMP}$$

for almost every $t \in [0, t_f]$. For this particular case, the Hamiltonian can be obtained by computing $\langle \lambda, F(x, u) \rangle$, where F is the right-hand side of system (S), which yields

$$H = \left(\sum_{i=1}^{n} H_i \delta_i \right) + \left(H_r - \sum_{i=1}^{n} H_i \delta_i \right) r \tag{H}$$

where

$$\begin{aligned} &H_i(x, \lambda) \doteq w_i(s_i)(Y_i \lambda_p - \mathcal{V} \lambda_{s_i}), \qquad i = 1, 2, \dots, n \\ &H_r(x, \lambda) \doteq w_R(p)(\mathcal{V} \lambda_{\mathcal{V}} - (p+1)\lambda_p). \end{aligned}$$

The transversality conditions are given by the cost function as

$$\lambda(t_f) = (0, 0, \dots, 0, 0, -\lambda_0), \tag{TC}$$

and the dynamics of the adjoint system writes

$$\begin{cases} \dot{\lambda}_{s_i} = -\delta_i \dfrac{w_i'(s_i)}{w_i(s_i)}(1 - r) H_i, \quad i = 1, 2, \dots, n \\ \dot{\lambda}_p = w_R(p) r \left(\lambda_p - \dfrac{w_R'(p)}{w_R^2(p)} H_r \right), \\ \dot{\lambda}_{\mathcal{V}} = \left(\sum\limits_{i=1}^{n} \delta_i w_i(s_i) \right) (1 - r) \lambda_{s_i} - w_R(p) r \lambda_{\mathcal{V}}. \end{cases} \tag{AS}$$

As the set of controls should maximize the Hamiltonian, and the Hamiltonian is linear in the control r, it follows that the optimal cellular composition is given by

$$r = \begin{cases} 0 \ \textit{if } H_r < \sum\limits_{i=1}^{n} H_i \delta_i, \\ \\ 1 \ \textit{if } H_r > \sum\limits_{i=1}^{n} H_i \delta_i. \end{cases} \tag{1}$$

If $H_r = \sum_{i=1}^{n} H_i \delta_i$ over a subinterval of time, the arc is called a *singular arc* and the control law (1) given by the Hamiltonian does not provide enough information on the value of r. It is rather classical for this class of OCPs—where the Hamiltonian is linear in the control—that the optimal control solutions are concatenations of bang arcs ($r = 0$ and $r = 1$) and singular arcs. To further describe the structure of the solutions, we define the three possible arcs that can be found along the solutions:

- $\mathcal{G}$ (pure-growth arc): given by $H_r > \sum_{i=1}^{n} H_i \delta_i$, and thus $r = 1$.
- $\mathcal{S}$ (singular arc): it occurs when $H_r = \sum_{i=1}^{n} H_i \delta_i$ over a subinterval of time $[t_1, t_2] \subset [0, t_f]$.
- $\mathcal{M}$ (pure-metabolism arc): given by $H_r < \sum_{i=1}^{n} H_i \delta_i$, and so $r = 0$.

By evaluating the Hamiltonian at final time and using (TC), we can see that $H_i|_{t=t_f} = 0$ for $i = 1, 2, \dots, n$ and $H_r|_{t=t_f} > 0$, which indicates that the Hamiltonian is positive for every t, and thus we obtain the following result.

Lemma 1. An optimal process should finish with a $\mathcal{G}$ arc.

Now, let us analyze the arcs enabling substrate uptake ($\mathcal{S}$ and $\mathcal{M}$ arcs). In this case, $r < 1$, which means $H = \sum_{i=1}^{n} H_i \delta_i$. As a result, at least one function $H_i > 0$, in order to comply with the positivity of the Hamiltonian. Suppose the general case where

$$\max(H_1, H_2, \dots, H_n) = H_i,$$

for every i in a certain set $\mathcal{I} \doteq \{j, \dots, k\}$, where $\mathcal{I} \subset \{1, 2, \dots, n\}$. This includes the particular case where the solution of $\max(H_1, H_2, \dots, H_n)$ is unique, but also the case where multiple functions $H_j = \cdots = H_k$ are maximal. Then, using the positivity of the Hamiltonian and (C), one can see that

$$H = \sum_{i=1}^{n} H_i \delta_i = \max(H_1, H_2, \dots, H_n) \left(\sum_{i \in \mathcal{I}} \delta_i \right).$$

In the latter expression, it is clear that, in order to maximize the Hamiltonian, the sum of δ_i controls should be equal to 1, and so the Hamiltonian becomes $H = H_i$ for every $i = 1, 2, \dots, n$. This leads to a first result related to substrate uptake control:

Theorem 1. Every optimal control solution satisfies

$$\sum_{i=1}^{n} \delta_i = 1$$

along any arc enabling substrate uptake (i.e. $r \neq 1$).

This result implies that every available protein of the metabolic machinery should be used to metabolize the available substrates of the medium, which is a rather natural result. In this context, a i-th control with $i \in \mathcal{I}$ is denoted an active control. In next section, we proceed to analyze the structure of the optimal solutions.

4.2 Summary of the main results

While in this case it is possible to obtain a full description of the optimal solution in feedback form, the details of the computations through PMP are not displayed in this preliminary work. In this section, we provide a brief summary of the main results regarding the structure of the optimal control. For notation purposes, let us first define the following regions of the state space:

$$\max(Y_1 w_1(s_1), Y_2 w_2(s_2), \dots, Y_n w_n(s_n)) > \frac{w_R^2(p)}{w_R'(p)}, \quad (\mathrm{S}^+)$$

$$\max(Y_1 w_1(s_1), Y_2 w_2(s_2), \dots, Y_n w_n(s_n)) < \frac{w_R^2(p)}{w_R'(p)}, \quad (\mathrm{P}^+)$$

$$\max(Y_1 w_1(s_1), Y_2 w_2(s_2), \dots, Y_n w_n(s_n)) = \frac{w_R^2(p)}{w_R'(p)}, \quad (\mathrm{SP})$$

Then, we have a main result regarding the structure of the optimal solutions.

Theorem 2. The only admissible structures of the optimal control are:

- A single $\mathcal{G}$ for any initial conditions
- $\mathcal{M} - \mathcal{G}$ for initial conditions in (S^+)
- $\mathcal{M} - \mathcal{S} - \mathcal{G}$ for initial conditions in (S^+)
- $\mathcal{G} - \mathcal{S} - \mathcal{G}$ for initial conditions in (P^+)

The first two cases ($\mathcal{G}$ and $\mathcal{M} - \mathcal{G}$) occur when the state cannot reach (SP), which can be due to a small t_f with respect to the reaction rates of the system. As the latter is rather a degenerate case, in this paper we focus on the solutions allowing singular arcs ($\mathcal{M}-\mathcal{S}-\mathcal{G}$ and $\mathcal{G}-\mathcal{S}-\mathcal{G}$). Additionally, the presence of the final arc is optimal for fixed-horizon bioprocesses, and its duration is reduced as $t_f \to \infty$ (and $p \to 0$ at the end of the singular arc). Therefore, the final $\mathcal{G}$ arc can be neglected in infinite-time approaches [1], in particular when aiming to study the "long-term" perspective of bacterial growth. In this context, we can formalize the following result.

Theorem 3. The optimal long-term feedback control law for cellular composition is

$$(r, m) = \begin{cases} (0, 1) & \text{if } (s, p) \in (\mathrm{S}^+), \\ (1, 0) & \text{if } (s, p) \in (\mathrm{P}^+), \\ (r_{\text{sing}}, 1 - r_{\text{sing}}) & \text{if } (s, p) \in (\mathrm{SP}), \end{cases}$$

with

$$r_{\text{sing}}(s_j, \dots, s_k, p, \mathcal{V}) = \frac{\mathcal{V} + \phi \frac{w_R(p)}{w_R'(p)}}{\mathcal{V} + \phi \left(p + 1 + \frac{w_R(p)}{w_R'(p)} \right)},$$

where ϕ is a function that depends only on the state, defined as

$$\phi(s_j, \dots, s_k, p) \doteq \left(2w_R'(p) - \frac{w_R(p)}{w_R'(p)} w_R''(p) \right) \times \left[\sum_{j \in \mathcal{I}} \frac{1}{w_i'(s_j)} \right]^{-1};$$

and the optimal i-th substrate uptake control is

$$\delta_i = \frac{1}{\sum_{j \in \mathcal{I}} \frac{w_i'(s_i)}{w_j'(s_j)}},$$

for every i-th control satisfying

$$\max(Y_1 w_1(s_1), \dots, Y_n w_n(s_n)) = Y_i w_i(s_i).$$

5. NUMERICAL SIMULATIONS

In this section, we show simulations obtained with Bocop of a system describing a medium with 3 substrates at the same initial concentration $s_1(0) = s_2(0) = s_3(0)$ and with different associated yields $Y_1 > Y_2 > Y_3$. The discretization algorithm used for the time variable is Gauss II (implicit, 2-stage, order 4) with 10000 time steps. For the computations, we define the synthesis rates as Michaelis-Menten kinetics in terms of the mass fractions as

$$w_R(p) = k_R \frac{p}{K_R + p}, \qquad w_i(s_i) = k_i \frac{s_i}{K_i + s_i},$$

where K_R and K_i are the half-saturation constants of the synthesis rates measured in g L^{-1}. Model parameters are fixed to $k_R = k_1 = k_2 = 10$ h^{-1}, $K_R = 1$ g L^{-1}, $K_1 = K_2 = 0.05$ g L^{-1}, $Y_1 = 1$, $Y_2 = 0.6$ and $Y_3 = 0.1$. Initial conditions are set to $s_1(0) = s_2(0) = s_3(0) = 0.003$, $p(0) = 0.001$ and $\mathcal{V}(0) = 0.005$. Figure 2 illustrates the resulting optimal metabolic controls and the optimal resource distribution (between r and m), while Figure 3 shows the system states associated to the same trajectory. As expected, the optimal trajectory exhibits the diauxic growth pattern, as the substrates are consumed sequentially starting from the one with the highest yield s_1. Moreover, the curve r shows the optimal mass fraction of ribosomal proteins in the cell, which follows a $\mathcal{M} - \mathcal{S} - \mathcal{G}$ structure, as the initial conditions are in (S^+). It is noteworthy that these results are purely theoretical: in real living organisms, cellular compositions is governed by macrochemical reactions, and thus it is expected to be a continuous function. However, this approach provides an ideal scenario which can serve as a gold standard in terms of optimality. Figure 4 confirms the theoretical findings: the optimal arc at each time instant is decided by the state, which is first in (S^+) until it reaches (SP) and protein synthesis starts. The same holds for the metabolic control activation pattern, where each substrate control δ_i is activated when $\max(Y_1 w_1(s_1), \dots, Y_n w_n(s_n))$ decreases until it matches the next maximum value.

6. DISCUSSION

We presented an approach capable of predicting the distribution of resources and exhibiting the diauxie behavior through a simple mathematical model of microbial cells growing on n substrates. The main hypothesis of the problem is that both these features are governed by regulatory

[1] See Giordano et al. (2016) for a discussion on infinite horizons and overtaking optimality

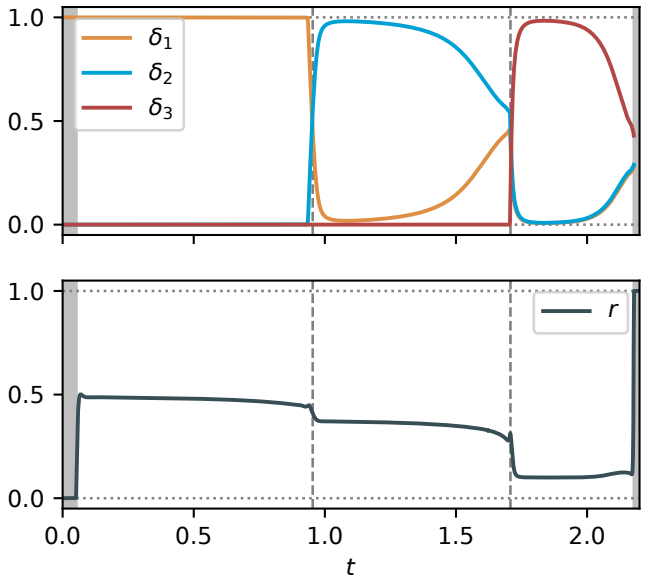

Fig. 2. Optimal metabolic controls and resource distribution control associated to the simulated optimal trajectory. The initial and final arcs are indicated with gray shaded areas, while the activation of metabolic controls is marked with dashed vertical lines.

mechanism tuned by natural selection to maximize bacterial growth rate, and thus "long-term" biomass. This yields an OCP that can be analyzed by means of PMP. While all the computations are not detailed in this preliminary paper, an overview of the main results is provided, as well as numerical simulations confirming the theoretical results. An extension of this work is contemplated, including comparisons to experimental data and to more complex models where the fractions of the cell dedicated to gene expression and metabolism are solutions of differential equations, and thus cellular composition is described by smooth (and not discontinuous) functions.

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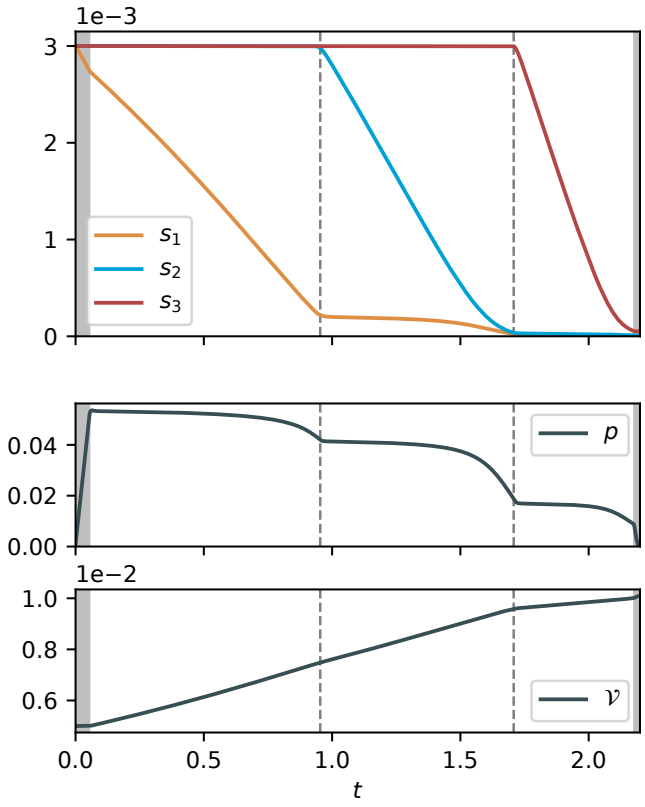

Fig. 3. Concentration of the available substrates s_1, s_2 and s_3 exhibiting sequential consumption. Additionally, the change of yield between substrates directly influences the slope of the biomass curve $\mathcal{V}$. The initial and final arcs are indicated with gray shaded areas, while the activation of metabolic controls is marked with dashed vertical lines.

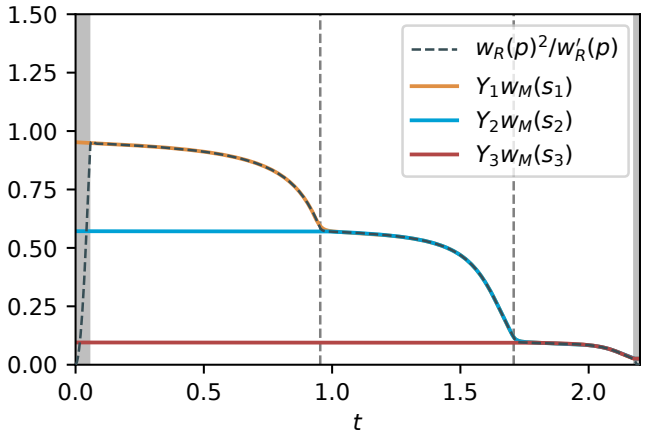

Fig. 4. Comparison of the values of the curves behind metabolic control activation, which confirms the results of Theorem 3. The initial and final arcs are indicated with gray shaded areas, while the activation of metabolic controls is marked with dashed vertical lines.

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