Minimal time problem for a fed-batch bioreactor with saturating singular control

Térence Bayen, Francis Mairet, Marc Mazade

Minimal time problem for a fed-batch bioreactor with saturating singular control

Térence Bayen* Francis Mairet † Marc Mazade ‡

November 3, 2013

Abstract

This paper is devoted to the study of an optimal control problem under the presence of a *saturation point* on the singular locus. We consider the minimal time problem for a system describing a fed-batch reactor with one species and one substrate. Our aim is to find an optimal feedback control that steers the system to a given target in minimal time. The growth function is of Haldane type implying the existence of a singular arc. Unlike other studies on the minimal time problem governed by affine systems w.r.t. the control, we assume that the singular arc is non-necessary controllable everywhere. This brings interesting issues in terms of optimal synthesis. Thanks Pontryagin's Principle and numerical simulations, we provide an optimal synthesis of the problem.

1 Introduction

Minimal time control problems for affine systems with one input such as:

$$\dot{x} = f(x) + ug(x), \quad x \in \mathbb{R}^n, \quad |u| \leq 1, \tag{1.1}$$

have been investigated a lot in the literature, see e.g. [6] for $n = 2$ and references herein. One often encounters singular trajectories which appear when the switching function of the system is vanishing on a time interval. In order to find an issue to a minimal time control problem governed by (1.1), one usually requires a controllability assumption on the singular control u_s allowing the trajectory to stay on the singular arc. Hence, one may suppose that u_s verifies the following inequality:

$$|u_s| \leq 1. \tag{1.2}$$

However, one cannot in general show that this assumption holds. In fact, the expression of the singular control u_s in terms of the state and adjoint state does not always guarantee that (1.2) is satisfied. One can argue that it is enough to consider a larger admissible upper bound for the controls, but this seems rather artificial, and not necessarily feasible from a practical point of view. The objective of this work is to study a minimal time control problem in the plane where the singular control satisfies (1.2) only on a sub-domain of the state space. Our goal is to analyze how the optimal synthesis is modified.

The system that we consider in the present work is a fed-batch bioreactor with one species and one substrate. Our aim is to find an optimal feedback control that steers the system in minimal time to a given target where the substrate concentration is less than a prescribed value, see [13]. Finding an optimal feeding strategy can significantly increase the performance of the system and has several advantages from a practical point of view (see e.g. [1, 2, 7, 8, 10, 13]).

Whenever the growth function is of Monod type, then one can prove that the optimal feeding strategy is bang-bang [13]. This means that the reactor is filled until its maximum volume with the maximum input flow rate. Then, micro-organisms consume the substrate until reaching a reference value. In the case where the growth function is of Haldane type (in case of substrate inhibition), this strategy is not optimal. In fact, one

*Université Montpellier 2, Case courrier 051, 34095 Montpellier cedex 5, France (tbayen@math.univ-montp2.fr).
†INRIA 'BIOCORE' team, Sophia-Antipolis, 2004, route des Lucioles, 06902 Sophia Antipolis Cedex (francis.mairet@inria.fr).
‡Université Montpellier 2, Case courrier 051, 34095 Montpellier cedex 5, France (tbayen@math.univ-montp2.fr).

can prove (see [13]) that the optimal strategy is *singular*. It consists in reaching in minimal time a substrate concentration $\bar{s}$ corresponding to the maximum of the growth rate function, and which coincides with the singular set. Then, the substrate concentration is kept constant to this value until reaching the maximal volume.

In the present work, we are interested in studying the optimal synthesis for Haldane-type growth function whenever the singular arc is no longer admissible from a certain volume value. This can happen when the singular control becomes larger than the maximal input flow rate which is allowed in the system. It follows that there exists a volume value above which singular extremal trajectories are no longer admissible. Such a point is usually called *saturation point* [9]. Whereas in [1, 13], the maximal volume is reached by the singular arc, there exists a volume value above which it is not possible to keep the substrate concentration equal to $\bar{s}$ in the system. The main issue of the paper is to determine an optimal feedback control in this setting.

First, one cannot apply the clock form as we do not have a natural candidate for optimality in this case. Thanks to Pontryagin's Principle, we provide an optimal synthesis of the problem. We introduce solutions of the system backward in time with the maximum control that allow to determine where the switching time occurs for optimal trajectories. Our main result is that a singular extremal trajectory ceases to be optimal before reaching the saturation point (see e.g. [9]). This is rather non-intuitive and slightly different as in the controllable case [13]. We show that there exists a maximal volume value above which a singular trajectory is not globally optimal. Using numerical simulations, we determine switching curves when the control is saturating [5]. This allows to determine an optimal feedback control of the problem.

The paper is organized as follows. The first section states the optimal control problem. We also recall the optimality result of [13] and we apply Pontryagin's Principle. The second section is devoted to the optimal synthesis of the problem without controllability assumption. We first describe the curves that are solution of the system backward in time and that allow to determine properties of optimal trajectories. Then, we state our main results in the case where the singular arc is never controllable (Proposition 3.2) and whenever it is controllable only on a subset of the initial states (Proposition 3.3). The last section is devoted to numerical simulations. We exhibit a numerical switching curve for optimal controls that allows to provide an optimal feedback control of the problem under a uniqueness assumption (see Theorems 4.1 and 4.2).

2 General results

In this section, we state the optimal control problem and we recall the optimal synthesis as in [13] that will allow us to introduce the problem in absence of controllability. We also apply the Pontryagin Maximum Principle (PMP) [14] that will be used in the next section.

2.1 Statement of the problem

We consider a system describing a fed-batch bioreactor with one species and one substrate:

$$\begin{cases} \dot{x} = x\left(\mu(s) - \frac{u}{v}\right), \\ \dot{s} = -\mu(s)x + \frac{u}{v}(s_{in} - s), \\ \dot{v} = u, \end{cases} \tag{2.1}$$

where x represents the concentration of micro-organisms, s the concentration of substrate, and v is the volume of the tank. The input substrate concentration is denoted by $s_{in} > 0$, and u is the input flow rate in the system. For convenience, we have taken yield coefficient equal to one (by rescaling the equation). The function $s \longmapsto \mu(s)$ is the growth function of Monod or Haldane type (see [12, 15]). In the following, we consider that u takes values within the set:

$$\mathcal{U} := \{u : [0, +\infty) \to [0, u_{max}] \ ; \ u \text{ meas.}\}.$$

Here u_{max} denotes the maximum input flow rate in the system. By time scaling, we can take $u_{max} = 1$. The target we consider is defined by:

$$\mathcal{T} = \mathbb{R}_+^* \times [0, s_{ref}] \times \{v_m\},$$

where s_{ref} is a given substrate concentration. For $u \in \mathcal{U}$, let $t_{\xi_0}(u)$ the time to steer (2.1) from an initial condition $\xi_0 := (x_0, s_0, v_0) \in \mathbb{R}_+^* \times [0, s_{in}] \times [0, v_m]$. The optimal control problem becomes:

$$\inf_{u \in \mathcal{U}} t_{\xi_0}(u), \ \text{s.t.} \ \xi(t(u)) \in \mathcal{T}, \tag{2.2}$$

where $\xi(\cdot)$ denotes the unique solution of (2.1) for the control u that starts at ξ_0. One essential feature in the system (2.1) is that the quantity

$$M := v(x + s - s_{in}), \tag{2.3}$$

is conserved along any trajectory of (2.1), hence M is constant and equal to $v_0(x_0 + s_0 - s_{in})$. From (2.3), we obtain:

$$x = \frac{M}{v} + s_{in} - s, \tag{2.4}$$

and system (2.1) can be put into a two-dimensional system:

$$\begin{cases} \dot{s} = -\mu(s)(\frac{M}{v} + s_{in} - s) + \frac{u}{v}(s_{in} - s), \\ \dot{v} = u. \end{cases} \tag{2.5}$$

One can easily show that the set $[0, s_{in}] \times \mathbb{R}_+^*$ is invariant by (2.5). Notice that if we define x by (2.4), the micro-organisms concentration may not be positive. This can happen when $M \leq 0$ which means that initial conditions of micro-organisms and substrate are low. Therefore, we consider initial conditions for (2.5) in the domain $\mathcal{D}$ defined by:

$$\mathcal{D} := \left\{ (s, v) \in [0, s_{in}] \times (0, v_m] \ ; \ \frac{M}{v} + s_{in} - s > 0 \right\}.$$

We denote by $\partial\mathcal{D}$ the boundary of $\mathcal{D}$. In the rest of the paper, we also write $u(\cdot)$ a control in open loop and $u[\cdot]$ a feedback control depending on the state (s, v).

2.2 Optimal synthesis with controllability assumption

In this part, we review a result of [13] on optimal trajectories for problem (2.2) in the case where the singular arc is controllable. First, we consider the case where the growth function μ is of Monod type i.e. $\mu(s) = \frac{\bar{\mu}s}{k+s}$ with $\bar{\mu} > 0$ and $k > 0$ [12].

Theorem 2.1. *Assume that μ is of Monod type. Then, the optimal feedback control u_M steering any initial condition in $\mathcal{D}$ to the target $\mathcal{T}$ is:*

$$u_M[s, v] := \begin{cases} 1 & \text{if } v < v_m, \\ 0 & \text{if } v = v_m. \end{cases}$$

In other words, the optimal strategy is *fill and wait*, and it consists in filling the tank with maximum input flow rate until $v = v_m$, and then we let $u = 0$ until s reaches the value s_{ref} (if necessary). In the rest of the paper, we only consider the case where the growth function μ is of *Haldane type* i.e.

$$\mu(s) = \frac{\bar{\mu}s}{gs^2 + s + k},$$

with $\bar{\mu} > 0$, $g > 0$, and $k > 0$. In this case, μ has exactly one maximum over $\mathbb{R}_+$, that we denote $\bar{s}$, and we suppose that $\bar{s} > s_{ref}$ (which means that the reference concentration to achieve is sufficiently small). The optimal synthesis in this case is rather different as for Monod growth function.

Theorem 2.2. *Assume that μ is of Haldane type and that the following controllability assumption holds:*

$$\mu(\overline{s}) \left[\frac{M}{s_{in} - \overline{s}} + v_m \right] \leq 1. \tag{2.6}$$

Then, the optimal feedback control u_H to reach the target is given by

$$u_H[s, v] := \begin{cases} 0 & \text{if } v = v_m & \text{or} & s > \overline{s}, \\ 1 & \text{if } s < \overline{s} & \text{and} & v < v_m, \\ u_s(v) & \text{if } s = \overline{s} & \text{and} & v < v_m, \end{cases}$$

where

$$u_s(v) := \mu(\overline{s}) \left[\frac{M}{s_{in} - \overline{s}} + v \right]. \tag{2.7}$$

This can be proved by using either the Pontryagin Maximum Principle or the clock form [4, 11]. Here we have emphasized the controllability assumption (2.6) (see e.g. [1, 7]). The control u_s is *singular* (see section 2.3). It allows to maintain the substrate concentration equal to $\overline{s}$. It can be written $u_s(v) = \frac{\mu(\overline{s})x}{v(s_{in}-\overline{s})}$ so that $u_s \geq 0$. Therefore, assumption (2.6) is essential to ensure that $u_s(v)$ satisfies the upper bound $u_s(v) \leq 1$ for all $v \leq v_m$.

The objective of this paper is to provide an optimal synthesis of the problem whenever (2.6) is non-necessarily satisfied. Note that in practice, one should start the fed-batch with a high biomass concentration (i.e. high M) in order to speed up the process, so that condition (2.6) can no longer be satisfied.

2.3 Pontryagin maximum principle

In this part we apply the Pontryagin Maximum Principle on (2.2). Let $H := H(s, v, \lambda_s, \lambda_v, \lambda_0, u)$ the Hamiltonian of the system defined by:

$$H := -\lambda_s \mu(s) \left[\frac{M}{v} - (s - s_{in})\right] + u \left[\frac{\lambda_s(s_{in} - s)}{v} + \lambda_v\right] + \lambda_0.$$

If u is an optimal control and (s, v) the corresponding solution of (2.5), there exists $t_f > 0$, $\lambda_0 \leq 0$, and an absolutely continuous map $\lambda = (\lambda_s, \lambda_v) : [0, t_f] \to \mathbb{R}^2$ such that $(\lambda_0, \lambda) \neq 0$, $\dot{\lambda}_s = -\frac{\partial H}{\partial s}$, $\dot{\lambda}_v = -\frac{\partial H}{\partial v}$, that is:

$$\begin{cases} \dot{\lambda}_s = \lambda_s \left(\mu'(s)x - \mu(s) + \frac{u}{v}\right), \\ \dot{\lambda}_v = \lambda_s \left(\frac{-\mu(s)M + u(s_{in} - s)}{v^2}\right), \end{cases} \tag{2.8}$$

and we have the maximality condition:

$$u(t) \in \text{arg max}_{\omega \in [0,1]} H(s(t), v(t), \lambda_s(t), \lambda_v(t), \lambda_0, \omega), \tag{2.9}$$

for almost every $t \in [0, t_f]$. We call *extremal trajectory* a sextuplet $(s(\cdot), v(\cdot), \lambda_s(\cdot), \lambda_v(\cdot), \lambda_0, u(\cdot))$ satisfying (2.5)-(2.8)-(2.9), and *extremal control* the control u associated to this extremal trajectory. As t_f is free, the Hamiltonian is zero along an extremal trajectory. Following [1], one can prove that λ_s is always non-zero (it is therefore of constant sign from the adjoint equation), and that $\lambda_0 < 0$ (hence we take $\lambda_0 = -1$ in the following). Next, let us define the *switching function* ϕ associated to the control u by:

$$\phi := \frac{\lambda_s(s_{in} - s)}{v} + \lambda_v. \tag{2.10}$$

We obtain from (2.9) that any extremal control satisfies the following control law: for a.e. $t \in [0, t_f]$, we have

$$\begin{cases} \phi(t) < 0 \implies u(t) = 0 & \text{(No feeding)}, \\ \phi(t) > 0 \implies u(t) = 1 & \text{(Maximal feeding)}, \\ \phi(t) = 0 \implies u(t) \in [0, 1]. \end{cases}$$

We say that t_0 is a *switching point* if the control u is non-constant in any neighborhood of t_0 which implies that $\phi(t_0) = 0$. Whenever the control u switches either from 0 to 1 or from 1 to 0 at time t_0, we say that the control is *bang-bang* around t_0. We will write B_0 an arc bang $u = 0$ and B_1 an arc bang $u = 1$. Whenever ϕ is zero on a non-trivial interval $I \subset [0, t_f]$, we say that u is a *singular control*, and that the trajectory contains a *singular arc*. We will write SA a time interval where the trajectory is singular. The sign of $\dot{\phi}$ is fundamental in order to obtain the optimal synthesis. By taking the derivative of ϕ, we get:

$$\dot{\phi} = \frac{\lambda_s x(s_{in} - s)\mu'(s)}{v}.$$

Moreover, we can show that $\lambda_s < 0$ (see e.g. [1, 7]). This implies that any extremal trajectory satisfies the property:

$$s(t) > \overline{s} \implies \dot{\phi}(t) > 0 \ ; \ s(t) < \overline{s} \implies \dot{\phi}(t) < 0. \tag{2.11}$$

Now, if an extremal trajectory contains a singular arc on some time interval $I := [t_1, t_2]$, then we have $\phi = \dot{\phi} = 0$ on I, hence we have $\mu'(s) = 0$ and $s = \overline{s}$ on I, hence the singular locus is the line segment

$S := \{\bar{s}\} \times [0, v_m]$. By solving $\dot{s} = 0$, we obtain the expression of the singular control given by (2.7), see e.g. [2]. Moreover, we can estimate the time of a singular trajectory as follows (see e.g. [1]):

$$t_2 - t_1 = \frac{1}{\mu(\bar{s})} \ln \left(\frac{M + v(t_2)[s_{in} - \bar{s}]}{M + v(t_1)[s_{in} - \bar{s}]} \right). \tag{2.12}$$

3 Optimal synthesis without controllability assumption

In this part, we provide a description of optimal trajectories for problem (2.2) when (2.6) is not satisfied. We first introduce a partition of $\mathcal{D}$ that will allow us to describe where optimal trajectories have a switching point.

3.1 Partition of the domain $\mathcal{D}$

In view of (2.6) that can be also written $v_m \leq \frac{1}{\mu(\bar{s})} - \frac{M}{s_{in} - \bar{s}}$, we introduce a mapping $\eta : (0, s_{in}) \to \mathbb{R}$ by

$$\eta(s) := \frac{1}{\mu(s)} - \frac{M}{s_{in} - s}.$$

By definition of η, we have:

$$u_s(v) = 1 \iff v = \eta(s).$$

Now, if define a point v^* by $v^* := \eta(\bar{s})$, the singular arc is controllable provided that $v^* \leq v_m$. In the following, we make the following assumption of v^*:

(H1) We suppose that $v^* < v_m$.

The point $(\bar{s}, v^*)$ is called *saturation point*, see e.g. [5, 9]. It follows that the singular arc is controllable only if the volume is less than v^* i.e. the admissible part of the singular arc is $\{\bar{s}\} \times [0, v^*]$. Indeed, for $v > v^*$ equality (2.7) no longer defines a control in $[0, 1]$. Next, we will consider the two following cases:

- Case 1: $v^* \leq 0$,
- Case 2: $0 < v^* < v_m$.

Remark 3.1. *Case 1 means that the singular arc is never controllable over* $(0, v_m]$. *As the function* η *can take negative values,* v^* *can be negative.*

We now introduce curves that are solutions of (2.5) with $u = 1$ that will provide a partition of initial states.

Definition 3.1. *We define* $\hat{\mathcal{C}}$, *resp.* $\check{\mathcal{C}}$ *as the restriction to the set* $\mathcal{D}$ *of the orbit of system* (2.5) *with* $u = 1$ *that passes though the point* $(\bar{s}, v_m)$, *resp.* $(\bar{s}, v^*)$.

Hence, $\hat{\mathcal{C}}$ is the graph of a mapping $v \longmapsto \hat{\gamma}(v)$ that is the unique solution of the equation:

$$\frac{ds}{dv} = -\mu(s) \left[\frac{M}{v} + s_{in} - s \right] + \frac{s_{in} - s}{v}, \tag{3.1}$$

over $(0, v_m]$ (recall that the point $(\bar{s}, v_m) \in \partial\mathcal{D}$) with initial condition $\hat{\gamma}(v_m) = \bar{s}$. Similarly, $\check{\mathcal{C}}$ is the graph of a mapping $v \longmapsto \check{\gamma}(v)$ that is the unique solution of (3.1) over $(0, v_m]$ such that $\check{\gamma}(v^*) = \bar{s}$.

The curves $\hat{\mathcal{C}}$ and $\check{\mathcal{C}}$ will play a major role in the optimal synthesis contrary to the case where the singular arc is controllable (see Fig. 2 and Table 1 for parameter values). In fact, they will indicate sub-domains where optimal trajectories have a switching point. As $\mathcal{D}$ is not backward invariant by (2.5), we call $\hat{v}$, resp. $\check{v}$ the first volume value such that $\hat{\gamma}(\hat{v}) \notin (0, s_{in})$, resp. $\check{\gamma}(\check{v}) \notin (0, s_{in})$. The next proposition is concerned with monotonicity properties of $\hat{\gamma}$ and $\check{\gamma}$ (see Fig. 1 and 2).

Proposition 3.1. *(i) The curve* $\hat{\gamma}$ *is either decreasing on* $[\hat{v}, v_m]$, *either there exists a unique* $v_1 \in (\hat{v}, v_m)$ *such that* $\hat{\gamma}(v_1) \in (0, s_{in})$ *and* $\frac{d\hat{\gamma}}{dv}(v_1) = 0$. *Moreover, in the latter case,* $\hat{\gamma}$ *is increasing on* $[\hat{v}, v_1]$ *and is decreasing on* $[v_1, v_m]$.
(ii) The mapping $\check{\gamma}$ *is increasing on* $(\check{v}, v^*]$ *and decreasing on* $[v^*, v_m]$ *and* $\frac{d\check{\gamma}}{dv}(v^*) = 0$.

Proof. Let us first prove (i). For $v \in (\hat{v}, v_m]$, we can rewrite (3.1) as follows:

$$\frac{ds}{dv} = \frac{\mu(s)(s_{in} - s)}{v}[\eta(s) - v].$$

When $v = v_m$, we have $\eta(\hat{\gamma}(v_m)) = \eta(\bar{s}) = v^* < v_m$, therefore, we have $\frac{d\hat{\gamma}}{dv} < 0$ in a neighborhood of v_m. Now, if $\hat{\gamma}$ is non-monotone on $(\hat{v}, v_m)$, then necessarily $v \longmapsto \frac{d\hat{\gamma}}{dv}$ is vanishing on $(\hat{v}, v_m]$. Assume that there exist $0 < v_2 < v_1 < v_m$ such that $\hat{\gamma}(v_1) \in (0, s_{in})$, $\hat{\gamma}(v_2) \in (0, s_{in})$ and $\frac{d\hat{\gamma}}{dv}(v_1) = \frac{d\hat{\gamma}}{dv}(v_2) = 0$. Without any loss of generality, we can assume that $\frac{d\hat{\gamma}}{dv}(v) > 0$ for $v \in (v_2, v_1)$. This gives using $\eta(\hat{\gamma}(v_2)) = v_2$:

$$\eta(\hat{\gamma}(v)) - \eta(\hat{\gamma}(v_2)) > v - v_2, \; v \in (v_2, v_1),$$

and by dividing by $v - v_2$ (with $v > v_2$), we obtain that $\frac{d}{dv}\eta(\hat{\gamma}(v))_{|v=v_2} \geq 1$. On the other hand, we find $\eta'(\hat{\gamma}(v_2))\frac{d\hat{\gamma}}{dv}(v_2) = 0$, which gives a contradiction. Therefore, there exists at most one value v_1 for which $\frac{d\hat{\gamma}}{dv}(v_1) = 0$, and $\hat{\gamma}(v_1) \in (0, s_{in})$. Also, by derivating (3.1) and using the fact that $\frac{d\hat{\gamma}}{dv}(v_1) = 0$ we get:

$$\frac{d^2\hat{\gamma}}{dv^2}(v_1) = -\frac{\mu(\hat{\gamma}(v_1))(s_{in} - \hat{\gamma}(v_1))}{v_1},$$

which is non-zero. In fact, we have seen that $\hat{\gamma}(v_1) > 0$. Moreover we have $\hat{\gamma}(v_1) \neq s_{in}$ from (3.1) (if $M \neq 0$, then $\frac{d\hat{\gamma}}{dv}(v_1) \neq 0$ whenever $\hat{\gamma}(v_1) = s_{in}$; if $M = 0$, then, $\hat{\gamma}(v) < s_{in}$ for all v by Cauchy-Lipschitz Theorem). We deduce that at point v_1, the monotonicity of $\hat{\gamma}$ is changing. The conclusion of (i) follows.
Let us prove (ii). By definition of v^*, we have $\frac{d\check{\gamma}}{dv}(v^*) = 0$. By a similar argument as for (i), one can prove that v^* is the unique zero of $v \longmapsto \frac{d\check{\gamma}}{dv}(v)$ on $(\check{v}, v_m]$. Thus $v \longmapsto \zeta(v) := \eta(\check{\gamma}(v)) - v$ has exactly one zero on $(\hat{v}, v_m]$. Moreover, we find $\frac{d\zeta}{dv}(v^*) = -1$, therefore ζ is decreasing in a neighborhood of v^*. It follows that $\check{\gamma}$ is increasing on $[\hat{v}, v^*]$ and decreasing on $[v^*, v_m]$, and the result follows. □

Remark 3.2. *(i) Proposition 3.1 (ii) implies that the curve $\check{\mathcal{C}}$ leaves the domain $\mathcal{D}$ through the line-segment $\{0\} \times [0, v_m]$, see Fig 2.*
(ii) Proposition 3.1 (i) implies that the curve $\hat{\mathcal{C}}$ leaves the domain $\mathcal{D}$ either through the line-segment $\{0\} \times [0, v_m]$, the line segment $[0, s_{in}] \times \{0\}$ or through the line-segment $\{s_{in}\} \times [0, v_m]$, see Fig. 1.
(iii) We can show that there exist values of M for which the two cases mentioned in Proposition 3.1 (ii) occur. In fact, by changing v into $w := -\ln v$, (3.1) can be gathered into a planar dynamical system. The stable manifold Theorem (see e.g. [15]) shows that $\lim_{v \to 0} \hat{\gamma}(v)$ is either finite or $\pm\infty$ When this limit is $\pm\infty$, $\hat{\gamma}$ leaves $\mathcal{D}$ through $\{0\} \times [0, v_m]$ or $\{s_{in}\} \times [0, v_m]$. We have not detailed this point for brevity.
(iv) For instance, if $M = 0$, Cauchy-Lipschitz Theorem implies that $\lim_{v \to 0} \hat{\gamma}(v) = -\infty$.

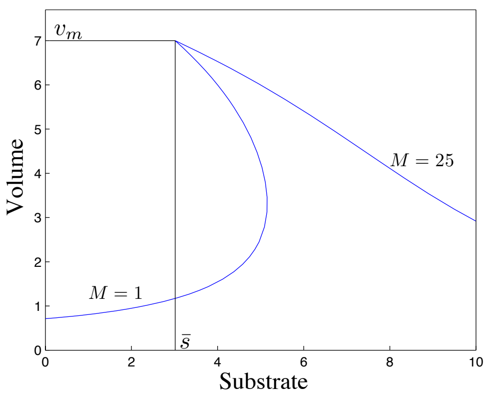


Figure 1: The curve $\hat{\mathcal{C}}$ leaves the domain $\mathcal{D}$ through $\{0\} \times [0, v_m]$ when $M = 1$, and through $\{s_{in}\} \times [0, v_m]$ when $M = 25$, see Proposition 3.1 (i).

When M is such that $\lim_{v\to 0}\hat{\gamma}(v) = -\infty$, the trajectory leaves the domain $\mathcal{D}$ through the line-segment $\{0\}\times[0,v_m]$. Hence, there exists a volume value v_* such that $\hat{\gamma}(v_*) = \overline{s}$, see Fig. 1. From the definition of v^*, the volume v_* necessarily satisfies $0 < v_* < v^*$. In fact, for any volume value v such that $v^* < v \leq v_m$, one has $\frac{ds}{dt}_{|u=1}(\bar{s}) < 0$, thus $\hat{\mathcal{C}}$ necessarily intersects the singular arc below v^*.

3.2 Optimal synthesis without controllability of the singular arc

In the case where $v^* \leq 0$ (case 1), we have the following optimality result (see also Fig. 2).

Proposition 3.2. *Suppose (H1) and that $v^* \leq 0$ (case 1). Then, given initial states $(s_0, v_0) \in \mathcal{D}$, optimal controls satisfy the following:*

(1) If $s_0 \leq \overline{s}$, then, there exists $t_0 > 0$ such that $u = 1$ on $[0, t_0]$, $u = 0$ on $[t_0, t_f]$ where t_0 is such that $v(t_0) = v_m$ and $s(t_f) = s_{ref}$.

(2) If $\overline{s} < s_0 < \hat{\gamma}(v_0)$, then, there exists $t_0 > 0$ such that $u = 0$ on $[0, t_0]$, $u = 1$ on $[t_0, t_1]$, $u = 0$ on $[t_1, t_f]$ where $t_0 \geq 0$, $\overline{s} < s(t_0) < s_0$, $v(t_1) = v_m$, and $s(t_f) = s_{ref}$.

(3) If $s_0 \geq \hat{\gamma}(v_0)$, then, there exists $t_0 > 0$ such that $u = 0$ on $[0, t_0]$, $u = 1$ on $[t_0, t_1]$, $u = 0$ on $[t_1, t_f]$ with $t_0 > 0$, $\overline{s} < s(t_0) < \hat{\gamma}(v_0)$, $v(t_1) = v_m$, and $s(t_f) = s_{ref}$.

Proof. Consider an optimal trajectory $(s(\cdot), v(\cdot), u(\cdot))$ starting at some point $(s_0, v_0) \in \mathcal{D}$. In the present case, the control u can only take the value 0 or 1 from the PMP (the singular arc is not admissible in $\mathcal{D}$).

First, assume $s_0 \leq \overline{s}$. Given the non-controllability assumption $v^* \leq 0$, we can show that $s(t) \leq \overline{s}$ for all t. We thus have $u = 1$ in a neighborhood of $t = 0$. Otherwise, we would have $u = 0$ together with $\phi(0) \leq 0$, and from (2.11) we would have for all t, $\phi(t) < 0$ which is not possible (as the trajectory would not reach the target). It follows that we have $u = 1$ in a neighborhood of $t = 0$. The same argument shows that the trajectory cannot switch to $u = 0$ before reaching v_m. This proves the first item.

Assume now that $\overline{s} < s_0 < \hat{\gamma}(v_0)$. If $\phi(0) < 0$, then we have $u = 0$, and the trajectory necessarily switches to $u = 1$ before reaching $\overline{s}$ (otherwise we would have a contradiction by the previous case). Now, we have $u = 1$ on some time interval $[t_0, t_1]$. Again, the previous case shows that the trajectory cannot switch to $u = 0$ at some time t' such that $s(t') \leq \overline{s}$ with $v(t') < v_m$. As $\phi(t_0) \geq 0$ and $\dot{\phi}(t) > 0$ whenever $s(t) > \overline{s}$ (recall (2.11)), we obtain that the trajectory cannot switch to $u = 0$ at some time t'' such that $s(t'') > \overline{s}$. Therefore, we have $u = 1$ until v_m, and the conclusion follows.

Now, take $s_0 > \hat{\gamma}(v_0)$. Then, we must have $u = 0$ in a neighborhood of $t = 0$. Ootherwise we would have $\phi(0) > 0$ which implies that $\phi(t) > 0$ for all t and a contradiction from (2.11). The same argument shows that the trajectory cannot switch to $u = 1$ at some substrate concentration $s(t_0) \geq \hat{\gamma}(v_0)$. Using the first item, we obtain that the trajectory necessarily switches at some time t_0 such that $\overline{s} < s(t_0) < \hat{\gamma}(v_0)$. By the second case, we obtain directly that $u = 1$ on some time interval $[t_0, t_1]$ with $v(t_1) = v_m$. This concludes the proof. □

Remark 3.3. *In the second case of proposition 3.2, the switching time t_0 from $u = 0$ to $u = 1$ may be zero and it can be found numerically, see section 4.*

Next, we consider case 2 where $0 < v^* < v_m$. We make the following assumption on M:

(H2) The constant M is such that there exists a unique $0 < v_* < v^*$ such that $\hat{\gamma}(v_*) = \overline{s}$.

It is easy to see that for initial conditions such that $v_0 > v^*$, optimal controls are given by proposition 3.2. Indeed, the admissible part of the singular arc is defined only for $v_0 \leq v^*$). Therefore, we only consider initial states such that $v_0 < v^*$. The next Proposition is illustrated on Fig. 2.

Proposition 3.3. *Suppose (H1) and that $0 < v^* < v_m$ (case 2). In addition, suppose that (H2) is satisfied. Then, given initial states $(s_0, v_0) \in \mathcal{D}$ such that $v_0 < v^*$, optimal controls satisfy the following:*

(1) If $s_0 \leq \check{\gamma}(v_0)$, then, there exists $t_0 > 0$ such that we have $u = 1$ on $[0, t_0]$, $u = 0$ on $[t_0, t_f]$ where t_0 is such that $v(t_0) = v_m$.

(2) If $\check{\gamma}(v_0) < s_0 < \hat{\gamma}(v_0)$ and $s_0 \leq \overline{s}$, then, there exists $t_0 > 0$ such that we have $u = 1$ on $[0, t_0]$, $u = u_s$ on $[t_0, t_1]$, $u = 1$ on $[t_1, t_2]$, $u = 0$ on $[t_2, t_f]$, where $s(t_0) = \overline{s}$, $t_1 - t_0 \geq 0$, $v(t_1) < v^*$, and $v(t_2) = v_m$.

(3) *If $\hat{\gamma}(v_0) \leq s_0 < \overline{s}$, then, there exists $0 < t_0 < t_1 < t_2$ such that we have $u = 1$ on $[0, t_0]$, $u = u_s$ on $[t_0, t_1]$, $u = 1$ on $[t_1, t_2]$, $u = 0$ on $[t_2, t_f]$ where $s(t_0) = \overline{s}$, $v(t_1) \in (v_*, v^*)$, $v(t_2) = v_m$.*

(4) *If $s_0 \geq \overline{s}$ and $v_0 \leq v_*$, then, there exists $0 < t_0 < t_1 < t_2$ such that we have $u = 0$ on $[0, t_0]$, $u = u_s$ on $[t_0, t_1]$, $u = 1$ on $[t_1, t_2]$, $u = 0$ on $[t_2, t_f]$ where $s(t_0) = \overline{s}$, $v(t_1) \in (v_*, v^*)$, and $v(t_2) = v_m$.*

(5) *If $s_0 \geq \overline{s}$, and $v_0 > v_*$, then, the optimal control is one of the following types:*

- *either $u = 0$ on $[0, t_0]$, $u = u_s$ on $[t_0, t_1]$, $u = 1$ on $[t_1, t_2]$, $u = 0$ on $[t_2, t_f]$ where $s(t_0) = \overline{s}$ and $0 < t_0 < t_1$, $v(t_2) = v_m$,*
- *either $u = 0$ on $[0, t_0]$, $u = 1$ on $[t_0, t_1]$, $u = 0$ on $[t_1, t_f]$ where $t_0 \geq 0$, $\overline{s} < s(t_0) < \hat{\gamma}(v_0)$, $v(t_1) = v_m$.*

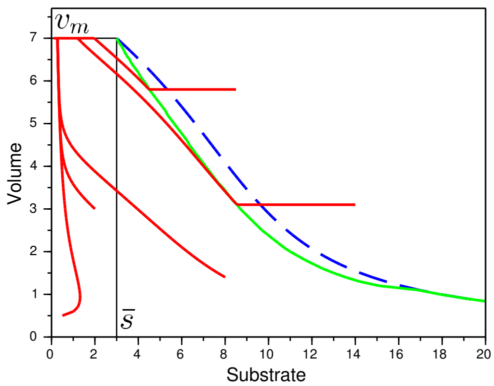
Proof. The proof of the first item is the same as the first one of the previous Proposition.

Now, when $\check{\gamma}(v_0) < s_0 < \hat{\gamma}(v_0)$ and $s_0 \leq \overline{s}$, the trajectory cannot switch from $u = 1$ to $u = 0$ before reaching $s = \overline{s}$. Therefore, we have two cases when the trajectory reaches $s = \overline{s}$: the trajectory either crosses the singular arc, or the control becomes singular. In the latter, the trajectory switches to $u = 1$ before reaching v^* and we have $u = 1$ until $v = v_m$ (otherwise we would have $u = 0$ at the point $(\overline{s}, v^*)$ and the trajectory would not reach the target from (2.11)). Notice that $t_1 = t_0$ is possible. This means that the time interval where the trajectory is singular can be zero.

If $\hat{\gamma}(v_0) < s_0 < \overline{s}$, the proof is the same as for the second item except that the trajectory cannot leave the singular arc with $u = 1$ before v_* (otherwise the trajectory reaches $v = v_m$ with $u = 1$ and $\phi > 0$, and the trajectory cannot switch to $u = 0$ at $v = v_m$ from (2.11)).

The proof of the fourth item is the same as the third one except that the trajectory starts with $u = 0$ until reaching the singular arc. Similarly as in the previous item, the trajectory cannot switch to $u = 1$ before reaching $s = \overline{s}$.

The last region is given by initial conditions such that $s_0 \geq \overline{s}$, and $v_0 > v_*$. The same arguments as before can be used except that Pontryagin's Principle is not sufficient to exclude two type of trajectories. First observe that we have $u = 0$ on some time interval $[0, t_0]$ as before (with $s(t_0) < \hat{\gamma}(t_0)$, otherwise the trajectory would not reach the target from (2.11)). When the trajectory crosses the curve $\hat{\gamma}$, we have two sub-cases. Either the trajectory switches to $u = 1$ before reaching $s = \overline{s}$ (as in Proposition 3.2), either the trajectory switches to the singular arc for $s = \overline{s}$. After the first switching times, the behavior of the trajectory is exactly as for the second item, and we can conclude from the other cases. □



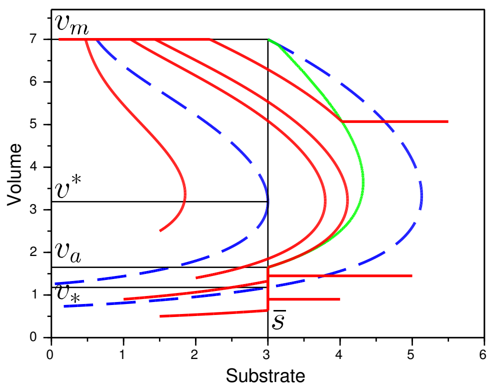


Figure 2: Optimal trajectories (in solid red lines) for various initial conditions without controllability assumption. Left: case 1 ($v^* \leq 0$), see Proposition 3.2 for the description of optimal controls; right: case 2 ($0 < v^* < v_m$), see Proposition 3.3. In blue dashed lines, trajectories $\hat{\mathcal{C}}$ and $\check{\mathcal{C}}$ which pass through $(\overline{s}, v^*)$ and $(\overline{s}, v_m)$. In green, the mapping $v_0 \longmapsto s_b(v_0)$ (see Section 4).

Table 1: Parameter values (arbitrary units) of simulations for the optimal synthesis without the controllability assumption of the singular arc (see Fig. 2 and 3)

v_m	s_{in}	s_{ref}	M	$\bar{\mu}$	k	g
7	10	0.1	25 (case 1) 1 (case 2)	0.5	1	0.11

Remark 3.4. *(i) Propositions 3.2 and 3.3 do not explicitly provide a switching curve for the optimal control. Nevertheless, in case 1, Proposition 3.2 shows that the control has no more than two switching points and that optimal controls are of type of type $B_0B_1B_0$ or B_1B_0. In case 2, Proposition 3.3, shows that optimal controls can also be of type $B_0SAB_1B_0$ with three switching points.*
(ii) For the last item of Proposition 3.3, the optimal trajectory is either $B_0SAB_1B_0$ or $B_0B_1B_0$. The next section will clarify this point and will provide an estimation of the switching time t_0 for items 2, 3, and 4.

We now investigate the loss of optimality of the singular arc.

Proposition 3.4. *Suppose (H1) and that $0 < v^* < v_m$ (case 2). In addition, suppose that (H2) is satisfied. Then, there exists $v_a \in (v_*, v^*)$ such that any optimal trajectory starting at the point $(\bar{s}, v_0)$ with $v_0 \leq v_*$ leaves the singular arc for $v = v_a$.*

Proof. If, the trajectory leaves the singular arc for a volume value less than v_*, then, we have $u = 1$ until reaching $v = v_m$. From Proposition 3.3, we have $\phi > 0$ at $v = v_m$ in contradiction with the fact that the trajectory switches to $u = 0$. Hence, it leaves the singular arc for a volume value $v > v_*$. Notice that if a singular trajectory reaches $v = v^*$ at a time t', then we have $\phi(t') = \dot{\phi}(t') = 0$. For $t > t'$, we have $s(t) < \bar{s}$ for any control u (this follows from the definition of v^*). Hence, we have $\dot{\phi}(t) < 0$, and we deduce that $\phi(t) < 0$ for $t > t'$. Hence we have $u = 0$ using (2.9). As the trajectory necessarily has a switching point in order to reach the target, we obtain a contradiction. □

Unlike in the controllable case [1, 13] where singular trajectories are optimal until $v = v_m$, the previous proposition shows that singular extremal trajectories are not optimal until the saturation point (see also [5, 9]). If an initial state (s_0, v_0) is such that $s_0 = \bar{s}$ and $v_0 \in (v_a, v^*)$, then the associated optimal control necessarily satisfies $u = 1$.

Remark 3.5. *If the point on the singular arc where singular extremal cease to be optimal is non-unique, we take for v_a the one that is maximal.*

4 Numerical simulations

In this section, we provide an optimal feedback control of the problem based on numerical simulations. We will focus only on case 2 assuming (H1) and (H2).

4.1 Determination of the maximal optimal volume

Our aim in this part is to determine the optimal volume v_a, above which a singular arc is not optimal. For $v_0 \in [v_*, v^*]$, consider the strategy $u = u_s$ from v_* to v_0, $u = 1$ until v_m and then $u = 0$ until s_{ref}. The time $t_a(v_0)$ of this strategy is (recall (2.12), see also [1]):

$$t_a(v_0) = \frac{\ln\left(\frac{M+v_0(s_{in}-\bar{s})}{M+v_*(s_{in}-\bar{s})}\right)}{\mu(\bar{s})} + v_m - v_0 + \int_{s_{ref}}^{s^\dagger(v_0)} \frac{d\sigma}{\mu(\sigma)\left(\frac{M}{v_m} + s_{in} - \sigma\right)}, \tag{4.1}$$

where $s^\dagger(v_0)$ is the substrate concentration when this trajectory reaches $v = v_m$: it is defined as the value for $v = v_m$ of the solution of (3.1) that starts at $s = \bar{s}$ with $v = v_0$. Hence, $s^\dagger(v_0)$ can be computed after solving the Cauchy problem:

$$\frac{ds}{dv} = -\mu(s)\left[\frac{M}{v} + s_{in} - s\right] + \frac{s_{in} - s}{v}, \; s(v_0) = \bar{s}. \tag{4.2}$$

We now show that $v_0 \longmapsto t_a(v_0)$ admits a minimum $v_a \in [v_*, v^*]$ that we will characterize hereafter. First, (4.2) can be equivalently written as $\frac{ds}{dv} = g(v,s)$ where g is the right hand-side of (4.2). By the classical dependence of the solution of an ODE on parameters, we denote by $s(v,\bar{s},v_0)$ the unique solution of (4.2). It is standard that $v_0 \in \mathbb{R}_+^* \longmapsto s(v,\bar{s},v_0)$ is of class C^1 for all $v > 0$. It follows by composition that $v_0 \longmapsto t_a(v_0)$ is of class C^1 on $[v_*, v^*]$. Consequently, it admits a minimum on this interval. By differentiating $s(v,\bar{s},v_0)$ w.r.t. v_0, we get:

$$\frac{\partial s}{\partial v_0}(v,\bar{s},v_0) = -g(v_0,\bar{s})e^{\int_{v_0}^{v} \frac{\partial g}{\partial s}(s(w,v_0,\bar{s}),w)dw},$$

using a classical result on the dependance w.r.t. initial conditions of a solution of an ordinary differential equation. Hence $\frac{ds^\dagger}{dv_0}(v_0) = \frac{\partial s}{\partial v_0}(v_m,\bar{s},v_0)$.

Now, we know from the PMP that $v_0 = v^*$ and $v_0 = v_*$ are not admissible (see also Proposition 3.3), hence v_a necessarily satisfies $\frac{dt_a}{dv_0}(v_a) = 0$. So, if we put $\theta(v_0) := \int_{v_0}^{v_m} \frac{\partial g}{\partial s}(w, s(w,\bar{s},v_0))dw$, we obtain by taking the derivative of (4.1) w.r.t. v_0:

$$\frac{dt_a}{dv_0}(v_0) = \frac{v^* - v_0}{\frac{M}{s_{in}-\bar{s}} + v_0}\left[1 - \frac{\mu(\bar{s})(\frac{M}{v_0} + s_{in} - \bar{s})}{\mu(s^\dagger)(\frac{M}{v_m} + s_{in} - \bar{s})}e^{\theta(v_0)}\right]$$

This equation allows to obtain numerically the volume $v_a \in (v_*, v^*)$ above which extremal trajectories stop to be singular. As an example, we find $v_a \simeq 1.67$ (see Fig. 3 and Table 1 for the values of the parameters).

Remark 4.1. *Other methods could be investigated to determine v_a, for instance using the theory of conjugate points [3].*

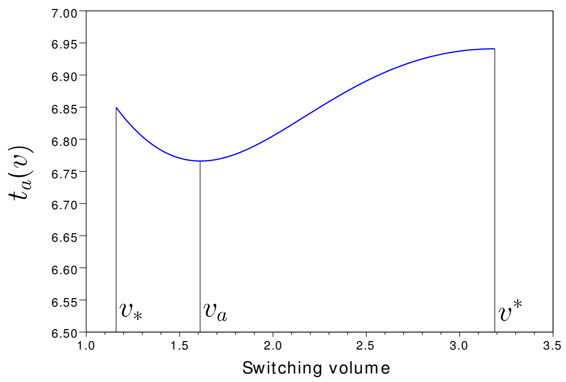


Figure 3: Time $t_a(v)$ to reach the target from $(\bar{s}, v_*)$ with the strategy: singular arc until the switching volume v, $u = 1$ until v_m, $u = 0$ until s_{ref}. We find that $t_a(v)$ has a unique minimum for $v = v_a$ (see Section 4)

4.2 Determination of the switching curve and the feedback control

To determine the optimal switching time for the trajectories $B_0B_1B_0$ starting with $s_0 > \bar{s}$, we proceed as follows. For each $v_0 \in (v_*, v_m)$, we search numerically $s_b(v_0) \in [\bar{s}, \hat{\gamma}(v_0)]$ which minimizes the time $t_b(s_b)$ to reach the target starting from $(\hat{\gamma}(v_0), v_0)$ with the strategy: $u = 0$ until s_b, $u = 1$ until v_m, $u = 0$ until s_{ref}. The application $s_b \longmapsto t_b(s_b)$ can we written:

$$t_b(s_b) = \int_{s_b}^{\hat{\gamma}(v_0)} \frac{d\sigma}{\mu(\sigma)\left(\frac{M}{v_0} + s_{in} - \sigma\right)} + \int_{s_{ref}}^{s_b^\dagger} \frac{d\sigma}{\mu(\sigma)\left(\frac{M}{v_m} + s_{in} - \sigma\right)},\ s_b \in [\bar{s}, \hat{\gamma}(v_0)],$$

where $s_b^\dagger$ is the solution of (3.1) that starts at point (s_b, v_0) evaluated at $v = v_m$. Numerical simulations indicate that for each value of v_0, the point $s_b(v_0)$ where t_b is minimal is unique. This allows us to define a curve $\mathcal{C}_b$ whose graph is the mapping $v_0 \longmapsto s_b(v_0)$, represented in green on Fig. 2. Moreover, we find that for $v_0 < v_a$, we have $s_b(v_0) = \bar{s}$, while $s_b(v_0) > \bar{s}$ for $v_0 \in (v_a, v_m)$. This result allows to conclude numerically which structure is optimal whenever $s_0 > \bar{s}$ and $v_0 > v_*$ (see the last case of Proposition 3.3):

- if $v_0 \leq v_a$, the optimal strategy is $u = 0$ on $[0, t_0]$, $u = u_s$ on $[t_0, t_1]$, $u = 1$ on $[t_1, t_2]$, $u = 0$ on $[t_2, t_f]$ where $s(t_0) = \bar{s}$, $v(t_1) = v_a$, $v(t_2) = v_m$.
- if $v_0 > v_a$, the optimal strategy is $u = 0$ on $[0, t_0]$, $u = 1$ on $[t_0, t_1]$, $u = 0$ on $[t_1, t_f]$ where $t_0 \geq 0$, $s(t_0) = \min(s(0), s_b(v_0))$, $v(t_1) = v_m$.

In case 2, numerical simulations together with Proposition 3.3 provide the following result.

Theorem 4.1. *Suppose (H1) and that $0 < v^* < v_m$ (case 2). In addition, suppose that (H2) is satisfied. If for each $v_0 \in [v_*, v_m]$, there exists a unique minimum $s_b(v_0)$ of $t_b(v_0)$ with $s_b(v) = \bar{s}$ for $v \in [v_*, v_a]$, then the optimal feedback steering any initial state in $\mathcal{D}$ to the target is given by:*

$$u_2[s, v] := \begin{cases} 0 & \text{if } \ s > s_b(v), \ \ v \geq v_a, \\ 1 & \text{if } \ s \leq s_b(v), \ \ v_m > v \geq v_a, \\ 0 & \text{if } \ s > \bar{s}, \ \ v < v_a, \\ 1 & \text{if } \ s < \bar{s}, \ \ v < v_a, \\ u_s(v) & \text{if } \ s = \bar{s}, \ \ v < v_a. \end{cases}$$

The switching curve is depicted on Fig. 2 (right). We see that for $v < v_a$, the optimal feedback is as in Theorem 2.2 whereas for $v > v_a$, the feedback control is either 0 or 1 depending where the state is w.r.t. the curve $v \longmapsto s_b(v)$.

In case 1, we have a similar result based on numerical simulations (conducted in case 2) together with Proposition 3.2.

Theorem 4.2. *Suppose (H1) and that $v^* \leq 0$ (case 2). If for each $v_0 \in [v_a, v_m]$, there exists a unique minimum $s_b(v_0)$ of $t_b(v_0)$, then the optimal feedback steering any initial state in $\mathcal{D}$ to the target is given by:*

$$u_1[s, v] := \begin{cases} 0 \text{ if } \ s \geq s_b(v) \ \text{ or } \ v = v_m, \\ 1 \text{ if } \ s < s_b(v) \ \text{ and } \ v < v_m. \end{cases}$$

The switching curve is depicted on Fig. 2 (left). To conclude, based on the optimal synthesis (Proposition 3.3) and the computations of the mapping $v_0 \longmapsto s_b(v_0)$ and v_a, optimal trajectories for various initial conditions (s_0, v_0) are represented on Fig. 2. Moreover, the curve $v_0 \longmapsto s_b(v_0)$ is the switching curve for optimal trajectories and it allows to give an optimal feedback control. We have shown that, without the controllability assumption, the optimal synthesis is quite different as the one of Theorem 2.2. In particular, we have pointed out that it is not optimal for a trajectory to stay on the singular arc until the saturating point.

5 Conclusion

We have studied an optimal control problem for a fed-batch bioprocess that exhibits a singular arc with a saturating point. This situation can arise for example when the initial biomass concentration is high. Thanks to the Pontryagin Maximum Principle and numerical simulations, we have obtained an optimal synthesis of the problem. We have pointed out that there exists a volume value above which any singular trajectory is not globally optimal. Moreover, it appears that there exist switching curves that provide an optimal feedback control of the problem. A more detailed insight into the determination of the switching curves (for instance using the theory of conjugate points [3]) could be the basis of future works. The analysis of the problem reveals that the determination of the optimal synthesis without controllability assumption is more intricate as in the case where the singular arc is always controllable. We believe that this kind of study can be the starting point to study optimal control problems in a more general setting in presence of non-controllable singular arcs.

Acknowledgements

We would like to thank Professor C. Lobry and A. Rapaport for helpful discussions on the subject.

References

[1] T. Bayen, P. Gajardo, F. Mairet, *Optimal synthesis for the minimal time control problems of fed-batch processes for growth functions with two maxima*, J. Optim. Theory and Applications, vol. 158, 2, pp. 521–553, 2013.

[2] T. Bayen, F. Mairet, *Minimal time control of fed-batch bioreactor with product inhibition* Bioprocess and Biosystems Engineering, vol. 36, 10, pp. 1485-1496, 2013.

[3] B. Bonnard, J.-B. Caillau, E. Trélat, Second order optimality conditions in the smooth case and applications in optimal control, ESAIM Control Optim. Calc. Var. 13, 2, pp. 207–236, 2007.

[4] B. Bonnard, M. Chyba, *Singular Trajectories and their role in Control Theory*, Springer, SMAI, vol. 40, 2002.

[5] B. Bonnard, M. Chyba, D. Sugny, *Time-Minimal Control of Dissipative Two-Level Quantum Systems: The Generic Case*, IEEE Trans. Automat. Contr., 54(11) pp. 2598–2610, 2009.

[6] U. Boscain, B. Piccoli, *Optimal Syntheses for Control Systems on 2-D Manifolds*, Springer SMAI, vol. 43, 2004.

[7] D. Dochain, A. Rapaport, *Minimal time control of fed-batch processes for growth functions with several maxima*, IEEE Trans. Automat. Contr., 56(11), pp. 2671–2676, 2011.

[8] P. Gajardo, H. Ramirez, A. Rapaport, *Minimal time sequential batch reactors with bounded and impulse controls for one or more species*, SIAM J. Control Optim., vol. 47, 6, pp. 2827–2856, 2008.

[9] U. Ledzewicz, H. Schättler, Anti-angiogenic therapy in cancer treatment as an optimal control problem, SIAM J. on Control and Optimization, 46 (3), 2007, pp. 1052–1079.

[10] J. Lee, S.Y. Lee, S. Park, A.P.J. Middelberg, *Control of fed-batch fermentations*, Biotechnology advances, vol. 17, 1, pp. 29–48, 1999.

[11] A. Miele, *Application of Green's Theorem to the extremization of linear integrals. Symp. on Vehicle Systems Optimization*, Garden City, New York, 1961.

[12] J. Monod, *Recherches sur la Croissance des Cultures Bactériennes*, Hermann, Paris 1942.

[13] J. A. Moreno, *Optimal time control of bioreactors for the wastewater treatment*, Optim. Control Appl. Meth., 20, pp. 145–164, 1999.

[14] L. Pontryagin, V. Boltyanski, R. Gamkrelidze, E. Michtchenko, *The Mathematical Theory of Optimal Processes*, Wiley Interscience, New York, 1962.

[15] H.L. Smith, P. Waltman, The theory of the chemostat, Dynamics of microbial competition, Cambridge University Press, 1995.