Preprints of the 2012 20th Mediterranean Conference on
Control & Automation (MED), Barcelona, Spain, July 3-6,
2012

Minimal time control of fed-batch bioreactor with product inhibition

Térence Bayen and Pedro Gajardo and Francis Mairet

Abstract— **This paper is devoted to the minimal time control problem for fed-batch bioreactors, in presence of an inhibitory product, which is released by the biomass proportionally to its growth. We first consider a growth rate with substrate saturation and product inhibition, and we prove that the optimal strategy is *fill and wait* (bang-bang). We then investigate the case of the Jin growth rate which takes into account substrate and product inhibition. For this type of growth function, we can prove the existence of singular arc paths defining *singular strategies*. Several configurations are addressed depending on the parameter set. For each case, we provide an optimal feedback control of the problem (of type bang-bang or bang-singular-bang). These results are obtained gathering the initial system into a planar one by using conservation laws. Thanks to Pontryagin maximum principle, Green's theorem, and properties of the switching function, we obtain the optimal synthesis.**

I. INTRODUCTION

Fed-batch operation of bioreactor is a popular operating mode used in industry as the limiting substrate concentration can be easily controlled [11]. Moreover, it allows to reach a high concentration of cells or products, or a low concentration of substrate (for depollution). Defining an optimized feeding strategy is a real challenge which can be tackled using optimal control theory (see e.g. [12]). For the minimal time problem (i.e. given initial conditions, the goal is to define a feeding policy in order to reach a given substrate concentration with a completely full reactor in a minimal amount of time), the optimal synthesis has been proposed by [15] for increasing growth functions (e.g., the Monod kinetic, see [14], [19]) and nonmonotonic growth functions with one maximum point (e.g., Haldane kinetic, see [1], [19]) using Green's theorem, via the technique introduced in [13]. More recently, the problem for growth functions with two local maxima has been tackled numerically [17] and analytically [2] allowing impulsive controls (corresponding to instantaneous dilutions, see [7]).

In this paper, we consider the minimal time control problem for fed-batch bioreactors in presence of an inhibitory product. Optimal control problems with product inhibition have been tackled by [8] using Kelley's transformation [10] for specific rate of product formation which are not correlated to the specific growth rate. As an example, the optimal feeding strategy to maximize the amount of ethanol produced by *Saccharomyces cerevisiae* is provided. Contrary to [8], we consider in this work that the product is released by the biomass proportionally to its growth [6]. The growth rate function associated to this model is a smooth function $\mu(s,p)$ depending both on the substrate and product concentrations.

The paper is organized as follows. In Section II, the problem is stated, and we derive several general properties about extremal trajectories via the Pontryagin maximum principle. In Section III, we give the optimal strategy for the case of an inhibition by product only. Finally, Section IV is devoted to the case of an inhibition by product and substrate. As an example, we provide the optimal synthesis for the Jin growth rate [9].

II. STATEMENT OF THE PROBLEM AND GENERAL RESULTS

A. Formulation of the problem

A perfectly mixed bioreactor with product inhibition operated in fed-batch can be described by the following system (after a scaling):

$$\begin{cases}\dot{x} = \left(\mu(s,p) - \frac{u}{v}\right)x,\\ \dot{s} = -\mu(s,p)x + \frac{u}{v}(s_{in} - s),\\ \dot{p} = \mu(s,p)x - \frac{u}{v}p,\\ \dot{v} = u,\end{cases} \tag{1}$$

where x, s, and p are respectively the concentrations of biomass, substrate, and product, and v is the volume of the tank. Here u is the water input flow (which is a measurable control function taking values in $[0,1]$) and s_{in} is the concentration of substrate in the input flow. If (x,s,p,v) is a solution of (1), one can see that the functions $M := v(x+s-s_{in})$ and $N := v(p+s-s_{in})$ are constant. Therefore, we have $x = \frac{M}{v} - s + s_{in}$ and $p = \frac{N}{v} - s + s_{in}$, and the system can be gathered into a planar system with a drift and a single input u:

$$\begin{cases}\dot{s} = -h(s,v)\left(\frac{M}{v} - s + s_{in}\right) + \frac{u}{v}(s_{in} - s),\\ \dot{v} = u,\end{cases} \tag{2}$$

where $h(s,v) := \mu\left(s, \frac{N}{v} - s + s_{in}\right)$. Note that for $N = 0$, the system can be written with a growth function $h_0(s) := \mu\left(s, -s + s_{in}\right)$ depending only on the substrate concentration.

The optimal control problem can be stated as follows. We aim at finding a feeding strategy (that is a control $u(\cdot)$) steering system (2) in a minimal amount of time $t_f(u)$ to a given target $\mathcal{T}$:

$$\inf_{u\in\mathcal{U}} t_f(u), \text{ s.t. } \xi(t_f(u)) \in \mathcal{T}, \tag{3}$$

T. Bayen is with Université Montpellier 2, Case courrier 051, 34095 Montpellier cedex 5, France. `tbayen@math.univ-montp2.fr`

P. Gajardo and F. Mairet are with Departamento de Matemática, Universidad Técnica Federico Santa María, Avda. España 1680, Valparaíso, Chile. `pedro.gajardo@usm.cl, francis.mairet@usm.cl`

978-1-4673-2529-5/12/$31.00 ©2012 IEEE

where $\xi(\cdot) = (s(\cdot), v(\cdot))$, and $\mathcal{U}$ is the set of admissible controls u. In the present work, $\mathcal{T}$ is given by:

$$\mathcal{T} = \{\xi \in \mathbb{R}^2_+ \mid \text{s.t. } s(t_f) \leq s_{ref},\ v(t_f) = v_m\}, \tag{4}$$

where s_{ref} is a given substrate concentration, and v_m is the volume of the tank. This set is of particular interest for wastewater treatment.

Given the domain $\mathcal{D} = [0, s_{in}) \times (0, v_m]$, one can prove that the target can be reached from any initial condition $(s_0, v_0) \in \mathcal{D}$ by taking $u = 1$ until $v = v_m$ and then applying $u = 0$ until $s \leq s_{ref}$ if necessary.

In the following, we call $\mathcal{P}$ the optimal control problem (2)-(3), with initial condition $(s_0, v_0) \in \mathcal{D}$, and we apply Pontryagin maximum principle (PMP) on $\mathcal{P}$.

B. Pontryagin maximum principle

Let $H = H(s, v, \lambda_s, \lambda_v, \lambda_0, r, u)$ the Hamiltonian of the system:

$$\begin{aligned} H = -\lambda_s h(s,v)\left[\frac{M}{v} - (s - s_{in})\right] \\ + u\left[\frac{\lambda_s(s_{in} - s)}{v} + \lambda_v\right] + \lambda_0 \end{aligned} \tag{5}$$

If u denotes an optimal control and (s, v) the corresponding solution of (2), 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:

$$\begin{cases} \dot{\lambda}_s = \lambda_s\left(\frac{\partial h(s,v)}{\partial s}x - h(s,v) + \frac{u}{v}\right), \\ \dot{\lambda}_v = \lambda_s\left(\frac{\partial h(s,v)}{\partial v}x + \frac{-h(s,v)M + u(s_{in} - s)}{v^2}\right), \end{cases} \tag{6}$$

and we have the maximality condition:

$$u(t) \in \text{argmax}_{\omega \in [0,1]} H(s(t), v(t), \lambda_s(t), \lambda_v(t), \lambda_0, \omega), \tag{7}$$

for almost every $t \in [0, t_f]$. Without loss of generality, we may assume $\lambda_0 \neq 0$ (otherwise this would contradict the PMP) and by homogeneity, we can take $\lambda_0 = -1$. We call *extremal trajectory* a quintuplet $(s(t), v(t), \lambda_s(t), \lambda_v(t), u(t))$ satisfying (2)-(6)-(7), and *extremal control* the control u associated to this extremal trajectory. As t_f is free, the Hamiltonian is zero along an extremal trajectory.

Next, let us define the *switching function* ϕ associated to the control u by:

$$\phi(t) = \lambda_s \frac{s_{in} - s}{v} + \lambda_v. \tag{8}$$

We obtain from (7) that any extremal control satisfies the following control law: for a.e. $t \in [0, t_f]$, we have

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

If ϕ vanishes in an isolated point t_0, then u is *bang-bang* around t_0 (that is u switches from 0 or 1 to another extremal value 0 or 1 at time t_0). Whenever ϕ is zero on some time interval $I \subset [0, t_f]$ (such that $\text{meas}(I) > 0$), we say that u is a *singular control*, and the trajectory contains a *singular arc* (see e.g. [18]). A computation shows that

$$\dot{\phi}(t) = \lambda_s x \psi(s, v), \tag{9}$$

with

$$\psi(s, v) = \frac{s_{in} - s}{v}\frac{\partial h}{\partial s}(s, v) + \frac{\partial h}{\partial v}(s, v). \tag{10}$$

It follows that if I is a singular arc, we have $\dot{\phi} = 0$, on I, that is:

$$\psi \equiv 0, \tag{11}$$

as λ_s and x are non-zero.

The sign of λ_s is of particular interest in order to study the switching function.

Lemma 1: If (s_0, v_0) is in $\mathcal{D}$, then any optimal trajectory satisfies $\lambda_s < 0$.

Proof: From system (6), we have that if $\lambda_s(0) = 0$, then $\lambda_s(t)$ is always zero, and if $\lambda_s(0) \neq 0$, then $\lambda_s(t)$ is always non-zero and of constant sign. An optimal trajectory is a concatenation of arcs where $u = 0$ (no feeding), $u = 1$ (maximal feeding), or singular arcs satisfying $\phi = 0$. If the initial condition is in $\mathcal{D}$, any optimal trajectory contains at least an arc $u = 0$ or a singular arc (otherwise, the trajectory would not reach $\mathcal{T}$). Consequently, there exists an interval $[t_1, t_2]$ such that on this interval, one has:

$$H = -\lambda_s h(s,v)\left[\frac{M}{v} - (s - s_{in})\right] - 1 = 0$$

Now, if at some point t, we have $\lambda_s(t) \geq 0$, we get a contradiction. Hence, we have $\lambda_s < 0$. ■

Proposition 1: Consider two points A and B in $\mathcal{D}$, and two different trajectories T_a and T_b joining A to B, such that the trajectory T_b from A to B followed by the trajectory T_a from B to A is a positively oriented curve Γ. Let $\mathcal{A}$ be the region enclosed by Γ. If $\psi(s, v) \geq 0$ (resp. ≤ 0) for all $(s, v) \in \mathcal{A}$, then the cost J_a of trajectory T_a is bigger (resp. lower) than the cost J_b of trajectory T_b.

Proof: Using Green's theorem, we obtain:

$$J_b - J_a = \oint_\Gamma dt = \iint_{\mathcal{A}} -\frac{\psi(s, v)}{\mu(s, p)^2 x} ds dv. \tag{12}$$

If $\psi \geq 0$ (resp. $\psi \leq 0$), it follows that $J_b - J_a \leq 0$ (resp. $J_b - J_a \geq 0$) from the integral above, which proves the result (see [13] and [15] for more details). ■

The expression of $\psi(s, v)$ will be important in the following in order to apply this proposition. First, we have:

$$\frac{\partial h}{\partial s}(s, v) = \frac{\partial \mu}{\partial s}(s, p) + \frac{\partial p}{\partial s}\frac{\partial \mu}{\partial p}(s, p) = \frac{\partial \mu}{\partial s}(s, p) - \frac{\partial \mu}{\partial p}(s, p)$$

and:

$$\frac{\partial h}{\partial v}(s, v) = \frac{\partial p}{\partial v}\frac{\partial \mu}{\partial p}(s, p) = -\frac{N}{v^2}\frac{\partial \mu}{\partial p}(s, p).$$

Consequently, we obtain:

$$\psi(s, v) = \frac{s_{in} - s}{v}\frac{\partial \mu}{\partial s}(s, p) - \frac{N + v(s_{in} - s)}{v^2}\frac{\partial \mu}{\partial p}(s, p). \tag{13}$$

978-1-4673-2529-5/12/$31.00 ©2012 IEEE

C. Legendre-Clebsch necessary condition

To study the optimality of a singular arc, we can use Legendre-Clebsch necessary condition, see e.g. [18]. If u is a singular optimal control, we must have:

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}H_u \geq 0, \tag{14}$$

where $H_u = \phi$. Moreover, if $\frac{\partial}{\partial u}\frac{d^2}{dt^2}H_u > 0$ along the singular arc, it is standard that a singular control can be computed by derivating two times the switching function (see e.g. [3]). A computation shows that:

$$\begin{aligned}\frac{\partial}{\partial u}\frac{d^2}{dt^2}H_u = \lambda_s x\Big(&-2\frac{s_{in}-s}{v^2}\frac{\partial h}{\partial s} + \frac{(s_{in}-s)^2}{v^2}\frac{\partial^2 h}{\partial s^2} \\ &+ 2\frac{(s_{in}-s)}{v}\frac{\partial^2 h}{\partial s \partial v} + \frac{\partial^2 h}{\partial v^2}\Big).\end{aligned} \tag{15}$$

In the case where $h(s,v) = h_0(s)$, condition (11) implies that $h_0'(s) = 0$, hence the concentration of substrate $s(t)$ is constant and is equal to a critical point $\tilde{s}$ of h_0 (if it exists). Moreover, (15) becomes

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}H_u = \lambda_s x\frac{s_{in}-s}{v^2}h''(s),$$

hence, only local maxima of h_0 are candidates for optimality (see [2],[17]).

III. INHIBITION BY PRODUCT ONLY

In this section, we study problem $\mathcal{P}$ in the case of inhibition by the product which means that the mapping $s \longmapsto \mu(s,p)$ is increasing with respect to s for all p, and that the mapping $p \longmapsto \mu(s,p)$is decreasing with respect to p for all $s > 0$.

Property 1: In the case of inhibition by product only, the optimal strategy is *fill and wait.*

Proof: Since $N + v(s_{in} - s) = vp \geq 0$, we get from (13) that $\psi(s,v) > 0$ for all $(s,v) \in \mathcal{D}$. Therefore, $\dot{\phi}(t) \neq 0$, so the optimal strategy does not contain a singular arc. Using Proposition 1, we can conclude that the optimal strategy is $u = 1$ until v_m, and then $u = 0$ (strategy fill and wait). ■

Remark 1: Using the same approach, we can show that this strategy is also optimal for bioprocesses in which microbial growth is represented by the Contois model $\mu(s,x)$, see [4]:

$$\mu(s,x) = \mu_m\frac{s}{kx+s}.$$

In particular μ is increasing with respect to s and decreasing with respect to x. This growth rate is widely used in wastewater treatment as it is suitable to represent hydrolysis, which is generally the limiting step for particulate waste treatment.

IV. INHIBITION BY PRODUCT AND SUBSTRATE

In this section, we consider inhibition by product and substrate, using as an example the growth rate proposed by Jin et al. (see [9]):

$$\mu(s,p) = \mu_m\frac{s}{k_1+s}e^{-k_2 p - k_3 s}. \tag{16}$$

Remark 2: The study of (16) in this framework is a first attempt to study more general growth functions decoupled in (s,p) (that is $\mu(s,p) = f(s)g(p)$) in the context of minimal time problems for fed-batch bioreactors. However, dealing with a more general growth function seems more delicate and is out of the scope of the paper.

In the case where μ is given by (16), we obtain by (13):

$$\psi(s,v) = \mu_m\frac{e^{-k_2 p - k_3 s}}{v(k_1+s)}\Psi(s,v), \tag{17}$$

with:

$$\Psi(s,v) = (s_{in}-s)\left(\frac{k_1}{k_1+s} + s(k_2-k_3)\right) + \frac{k_2 N s}{v}.$$

This expression will allow to characterize singular arcs in the next section.

A. Case $N = 0$

For future reference, let us define a polynomial ρ by $\rho(s) = s^2 + k_1 s + \frac{k_1}{k_2-k_3}$. The discriminant of ρ reads: $\Delta = k_1(k_1 - \frac{4}{k_2-k_3})$, and whenever $\Delta \geq 0$, let $\bar{s} = \frac{-k_1+\sqrt{\Delta}}{2}$ the positive root of ρ. Notice that $\rho' \geq 0$.

The next proposition gives an optimal synthesis of the problem for $N = 0$ which is closely related to the one obtained in [15].

Proposition 2: (i). If $\Delta \leq 0$ or $\bar{s} \geq s_{in}$, the optimal strategy is *fill and wait* (bang-bang).

(ii). If $\Delta > 0$ and $\bar{s} < s_{in}$, the optimal strategy is the singular arc strategy $\overline{s}$, defined as follows (see figure 1):

$$u(s_0,v_0) = \begin{cases} \bar{u} \text{ if } s_0 = \bar{s} \text{ and } v_0 < v_m, \\ 0 \text{ if } s > \bar{s} \text{ or } v_0 = v_m, \\ 1 \text{ if } s < \bar{s} \text{ and } v_0 < v_m, \end{cases}$$

where control $\overline{u}$ is such that $s(t) = \bar{s},\ \forall t > t_0$.

Proof: If $N = 0$, it follows from (17) that a singular arc is possible if: $\rho(s) = 0$. If $\Delta \leq 0$, the equation $\rho = 0$ does not have any positive root, so a singular arc is not possible, and $\psi(s,v) > 0$ for all $(s,v) \in \mathcal{D}$. If $\Delta > 0$, there exists a positive root $\bar{s}$ of $\rho = 0$ which defines a singular arc, and $\psi(s,v) > 0$ (resp. < 0) if $s < \bar{s}$ (resp. $> \bar{s}$). Using proposition 1, we can conclude that the optimal strategy is:

- *fill and wait* if $\Delta \leq 0$ or $\bar{s} \geq s_{in}$,
- the singular arc strategy $\bar{s}$ if $\Delta > 0$ and $\bar{s} < s_{in}$.

■

Remark 3: Following [2],[17], the control $\bar{u}$ can be obtained solving (2) when the substrate concentration is constant equal to $\overline{s}$. It follows that:

$$\overline{u}(v) = h_0(\overline{s})\left(v + \frac{M}{s_{in}-\overline{s}}\right).$$

Hence, the singular arc is admissible provided that $\overline{u}(v) \in [0,1]$ for all $v \in (0, v_m]$. Thus, if:

$$h_0(\overline{s})\left(v_m + \frac{M}{s_{in}-\overline{s}}\right) < 1, \tag{18}$$

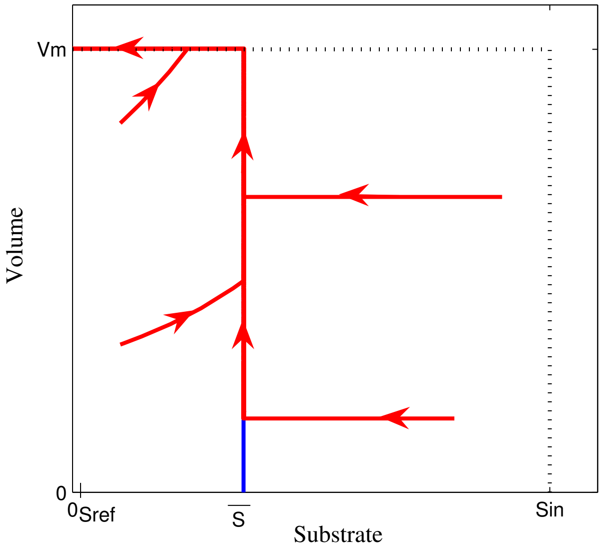

Fig. 1. Optimal trajectories (in red) for various initial conditions for the Jin growth rate with $N = 0$ (see Proposition 2). In blue, the line $s = \bar{s}$. Parameter values used for simulation are given in Table I.

then the singular arc is admissible. This assumption is generally used for minimal time control of fed-batch reactor with nonmonotonic growth rate (see e.g. [7]).

B. *Case* $N \neq 0$

Let us first characterize singular arcs. From (17), we obtain that along a singular arc, substrate concentration and volume are related by $v = \tilde{v}(s)$ with:

$$\tilde{v}(s) = -N \frac{s(k_1+s)k_2}{(s_{in}-s)\left[k_1 + s(k_1+s)(k_2-k_3)\right]}. \tag{19}$$

Remark 4: One has $\Psi(s,v) = \frac{k_2 N s}{v}\left(1 - \frac{v}{\tilde{v}(s)}\right)$.

The derivative of $\tilde{v}(s)$ writes:

$$\frac{\partial \tilde{v}}{\partial s} = \frac{\tilde{v}(s)}{s_{in}-s} - \frac{N k_1 k_2 (k_1 + 2s)}{(s_{in}-s)\left[k_1 + s(k_2-k_3)(k_1+s)\right]^2}.$$

Using (2), the singular control can be expressed by:

$$\tilde{u}(s) = \frac{x(s)\tilde{v}(s)h(s,\tilde{v}(s))}{s_{in}-s}\left[1 - \tilde{v}(s)\frac{(k_2-k_3)^2}{N k_1 k_2}\frac{\rho^2(s)}{\rho'(s)}\right] \tag{20}$$

where $x(s) = \frac{M}{\tilde{v}(s)} + (s_{in} - s)$. We now make the following assumption on the system:

Hypothesis 1: The singular control is always admissible.

Remark 5: If the singular control is optimal, it must satisfy (14). From (15), we obtain:

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}H_u = \lambda_s x \mu_m \frac{e^{-k_2 p - k_3 s}}{v(k_1+s)}\gamma(s,v),$$

where $\gamma(s,v) := \frac{k_1 k_2 N \rho'(s)(s_{in}-s)}{(k_2-k_3)v^2\rho(s)(k_1+s)}$. As $\lambda_s < 0$, we obtain that if the singular arc is optimal, then we must have

$$-N(k_2-k_3)\rho(s) \geq 0. \tag{21}$$

From (19), we have that if $\tilde{v}(s) \geq 0$, then (21) is satisfied.

Remark 6: Following [2],[17] and (18), it is standard to assume that

$$\max_{0 \leq s \leq \bar{s}} \frac{x(s)\tilde{v}(s)h(s,\tilde{v}(s))}{s_{in}-s} < 1, \tag{22}$$

where $\bar{s} = \tilde{v}^{-1}(v_m)$. This condition ensures that $\dot{s} > 0$ in (2) whenever $u = 1$. However, from (20), this condition is not sufficient in order to define admissible singular arcs as in the case where $N = 0$.

In the following, we assume that hypothesis 1 holds in this case. From (20) and (22), one can see that this assumption is always satisfied if s is small enough and that (20) defines a control $\tilde{u} \leq 1$ if $N > 0$.

In order to determine the optimal feeding strategy, we consider the following cases:

- Case 1: $N < 0$,
- Case 2: $N > 0$ and $k_2 - k_3 > 0$,
- Case 3: $N > 0$, $k_2 - k_3 < 0$, and $\bar{s} \geq s_{in}$,
- Case 4: $N > 0$, $k_2 - k_3 < 0$, and $\bar{s} < s_{in}$.

For each case, we can now provide the optimal synthesis:

Property 2: For Case 1, the optimal strategy is the singular arc strategy $\tilde{v}(s)$ (see figure 2), defined as follows:

- if $s > \tilde{v}^{-1}(v)$ or $v = v_m$, then $u = 0$.
- if $v = \tilde{v}(s)$ and $v < v_m$, then $u = \tilde{u}(s,v)$.
- if $s < \tilde{v}^{-1}(v)$ and $v < v_m$, then $u = 1$.

Proof: If $k_2 - k_3 > 0$, then $\tilde{v}(s)$ is positive and increasing on $(0, s_{in})$. If $k_2 - k_3 < 0$, we have two subcases: if $\bar{s} \geq s_{in}$, then $\tilde{v}(s)$ is also positive and increasing on $(0, s_{in})$ while if $\bar{s} < s_{in}$, then $\tilde{v}(s)$ is positive and increasing on $(0, \bar{s})$, and negative on $(\bar{s}, s_{in})$ (one has $\tilde{v}(s) \to +\infty$ when $s \to \bar{s}$). One can check that $\psi(s,v) > 0$ for $s < \tilde{v}^{-1}(v)$ and $\psi(s,v) < 0$ for $s > \tilde{v}^{-1}(v)$. Consequently, proposition 1 implies that the optimal feeding strategy is the singular arc strategy $\tilde{v}(s)$. ■

TABLE I

PARAMETER VALUES USED FOR SIMULATIONS WITH THE JIN GROWTH RATE (SEE FIGURES 1, 2, AND 3)

	v_m	s_{in}	s_{ref}	M	N	k_1	k_2	k_3
Case $N = 0$	0.3	100	1	20	0	20	0.01	0.02
Case 1	0.3	100	1	20	-10	20	0.02	0.01
Case 4	0.5	100	1	20	10	36	0.1	0.2

Property 3: For Cases 2 and 3, the optimal strategy is *fill and wait*.

Proof: We have $\tilde{v}(s) < 0$ for $s \in (0, s_{in})$, so a singular arc is not possible and the optimal control is bang-bang. Given that $\psi(s,v) > 0$ in the domain $\mathcal{D}$, we conclude the proof by using Proposition 1. ■

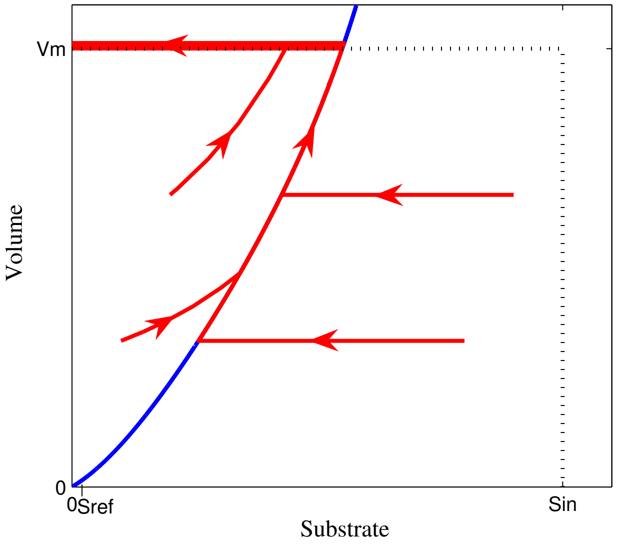

Fig. 2. Optimal trajectories (in red) for various initial conditions for the Jin growth rate, Case 1 (see Property 2). In blue, the curve $s \longmapsto \tilde{v}(s)$. Parameter values used for simulation are given in Table I.

For Case 4, $\tilde{v}(s)$ is negative on the interval $(0, \bar{s})$, and positive on $(\bar{s}, s_{in})$ with two vertical asymptotes for $s = \bar{s}$ and $s = s_{in}$ (see figure 3). Moreover, a computation shows that there exists a unique minimum of $\tilde{v}(s)$ on $(\bar{s}, s_{in})$ that we call (s_d, v_d). If $v_d > v_m$, one can easily show that the optimal strategy is *fill and wait* (in this case, the singular is not admissible), so we will only consider the case $v_d < v_m$. In order to define the optimal strategy, we divide the domain $\mathcal{D}$ in five regions A, B, C, D, E as represented in figure 3:

- the blue curve is the mapping $s \longmapsto \tilde{v}(s)$ on $(\bar{s}, s_{in})$,
- the green curve L_1 is the solution of (2) with $u = 1$ which passes through the point (s_d, v_d),
- the dot-dashed curve L_2 is the set of points $\hat{s}(v) > s_0(v)$ for $v > v_d$ such that:

$$\int_{s_0(v)}^{\hat{s}(v)} \frac{\psi(s,v)}{h(s,v)^2(M/v + s_{in} - s)} ds = 0$$

  where $s_0(v)$ is such that $v = \tilde{v}(s_0)$ and $s_0(v) < s_d$,
- the green curve L_3 is the solution of (2) with $u = 1$ which passes through the intersection between L_2 and the line $v = v_m$.

Notice that from remark 4 we have $\psi(s,v) > 0$ for $(s,v) \in A$, and $\psi(s,v) < 0$ otherwise.

Remark 7: Given the definition of $\hat{s}(v)$, the curve L_2 starts at the point (s_d, v_d). Nevertheless, it is not clear that $\hat{s}(v)$ will always exist for all $v \in [v_d, v_m]$. In this case, the curve L_2 will end at $s = s_{in}$ for some volume $v \in (v_d, v_m)$, and the region D will not exist (but the same optimal synthesis holds).

Hypothesis 2: For any volume $v \in (v_d, v_m)$, we have $\frac{d\hat{s}(v)}{dv} > \frac{s_{in} - \hat{s}(v)}{v}$.

If this hypothesis holds, then a trajectory starting in E can not go in $C \cup D$. According to various numerical simulations, this assumption seems to be always true. Table II presents a numerical verification of this hypothesis with the parameter set used for simulations (given in Table I).

TABLE II

NUMERICAL VERIFICATION OF HYPOTHESIS 2 WITH THE PARAMETER SET USED FOR SIMULATIONS (GIVEN IN TABLE I).

v	$v_d = 0.17$	0.2	0.3	0.40	$v_m = 0.5$
$\frac{d\hat{s}(v)}{dv}$	2.1e3	605	132	71	40
$\frac{s_{in} - \hat{s}(v)}{v}$	330	238	86	42	23

Property 4: For Case 4 under hypothesis 2, we have:
(i). If $(s_0, v_0) \in A \cup B \cup E$, the optimal strategy is the singular arc strategy $\tilde{v}(s)$, defined as follows:

- if $(s_0, v_0) \in A$, then $u = 0$.
- if $v_0 = \tilde{v}(s_0)$ with $s_0 \leq s_d$, then $u = \tilde{u}$.
- if $(s_0, v_0) \in B$, then $u = 1$.

(ii). If $(s_0, v_0) \in C$, the optimal strategy is $u = 1$ until reaching L_2, and then the singular arc strategy $\tilde{v}(s)$.
(iii). If $(s_0, v_0) \in D$, the optimal strategy is *fill and wait.*

Proof: First, let us prove (i) for $(s_0, v_0) \in A \cup B$. The region $A \cup B$ is invariant: any trajectory starting in $A \cup B$ will stay in it. Indeed, if we consider the trajectory $u = 1$ starting at (s, v) such that $s > s_d$ and $v = \tilde{v}(s)$, we have:

$$\frac{\partial v}{\partial s} > \frac{v}{s_{in} - s} > \frac{\partial \tilde{v}}{\partial s},$$

which proves that $A \cup B$ is invariant. Moreover, this last equation shows that a trajectory cannot follow the singular arc for $s > s_d$. Given that $\psi(s,v) < 0$ in A and $\psi(s,v) > 0$ in B, we can apply proposition 1 and conclude that, if $(s_0, v_0) \in A \cup B$, then the singular arc strategy is optimal.

For proving (i), it remains to consider the case where the initial condition is in E. First, consider a sequence $u = 0$ (at a given constant volume v) on a time interval $[t_0, t_1]$. We have for all $t \in [t_0, t_1]$:

$$\lambda_s(t) = \frac{-1}{h(s,v)x}, \quad \dot{\phi}(t) = \frac{-\psi(s,v)}{h(s,v)}. \qquad (23)$$

Take $v > v_d$, and let $s(t_0)$, $s(t_1)$ the two substrate concentrations such that $s(t_0) = \hat{s}(v)$, $v = \tilde{v}(s(t_1))$, and $s(t_1) < s_d$. We obtain from (23):

$$\int_{t_0}^{t_1} \dot{\phi}(t) dt = \int_{s(t_0)}^{s(t_1)} \frac{\psi(s,v)}{h(s,v)^2(M/v + s_{in} - s)} ds = 0$$

Therefore, a sequence $u = 0$ that contains two switches at t_0 and t_1 is candidate for optimality.
Finally, take $(s_0, v_0) \in E$. As we have in this region $\dot{\phi} < 0$, we only have two candidates for optimality C_1 and C_2:

- C_1: if $\phi(t_0) < 0$, then $u = 0$ until reaching A.
- C_2: if $\phi(t_0) > 0$, then the trajectory starts with $u = 1$. In order to reach the target, this trajectory must switch at a time t_1 (with $\phi(t_1) = 0$). Then, is satisfies $u = 0$

until reaching A (as $\dot{\phi} < 0$, only one switch is possible in E).

For both strategies, we must have $u = 0$ until reaching the singular arc $\tilde{v}$ at a time t_2 with a substrate concentration $s(t_2) < s_d$ (see above in region A). However, the second trajectory C_2 satisfies $s(t_1) < \hat{s}(v(t_1))$, hence we have

$$\begin{aligned}\phi(t_2) &= \int_{t_1}^{t_2} \dot{\phi}(t)dt = \int_{s(t_1)}^{s(t_2)} \frac{\psi(s,v)}{h(s,v)^2(M/v + s_{in} - s)} ds,\\ &> \int_{s(t_1)}^{\hat{s}(v)} \frac{\psi(s,v)}{h(s,v)^2(M/v + s_{in} - s)} ds = 0,\end{aligned}$$

where $v = v(t_1) = v(t_2)$. Thus, we get a contradiction. Therefore, the first candidate C_1 is optimal, which concludes the proof of (i).

Now consider (ii) and (iii) (i.e. let $(s_0, v_0) \in C \cup D$ a given initial condition at time t_0). First, if $v_0 < v_d$, we have $u(t_0) = 1$. Otherwise, we would have $u(t_0) = 0$, thus $\phi(t_0) < 0$ and $\dot{\phi}(t) < 0$, and the trajectory would not reach the target (as the control cannot switch).

Secondly, assume $v_d < v_0 < v_m$. If $u(t_0) = 0$, then the trajectory must switch at a time t_1 (in order to reach the target). As $\dot{\phi} < 0$ in $C \cup D \cup E$, the switch should be in A. Following the proof of (i), the trajectory will switch to the singular arc at a time t_1 such that $\tilde{v}(s(t_1)) = v(t_0)$ with $s(t_1) < s_d$. But we have:

$$\begin{aligned}\phi(t_1) &= \phi(t_0) + \int_{t_0}^{t_1} \dot{\phi}_{u=0}(s,v)dt\\ &< \int_{\hat{s}(v(t_0))}^{s(t_1)} \frac{\psi(s,v)}{h(s,v)^2(M/v + s_{in} - s)} ds = 0,\end{aligned}$$

as $s(t_0) > \hat{s}(v(t_0))$, which is a contradiction. Therefore, we have $u(t_0) = 1$ and a switch is possible only in the two following cases:

- If $(s(t_0), v(t_0)) \in C$, then the trajectory switches for $s = \hat{s}(v)$,
- If $(s(t_0), v(t_0)) \in D$, then the trajectory switches at volume $v = v_m$.

This concludes the proof. ■

V. DISCUSSION

Given model uncertainties that arise in bioprocesses and the lack of online sensors, the practical implementation of such optimal strategies is not straightforward. The first challenge is to determine which case applies since it depends on model parameters and initial conditions which are generally poorly known. Then, a robust approach should be used to implement the optimal strategy. For inhibition by product only (Section III) and inhibition by product and substrate with $N = 0$ (Section IV-A), the optimal strategy is either *fill and wait* (which implementation is straightforward), either a singular strategy which consists at regulating $s = \bar{s}$, i.e. maintaining the specific growth rate at its maximum. Implementation of the second strategy has been tackled in the case of nonmonotonic growth rate by Moreno et al. [16]. Their method - called *Event-Driven Time Optimal Control* (ED-TOC) - consists in the approximation of the singular control by a bang-bang control where the switching instants are determined by the variations of the specific growth rate (which is estimated via online measurement of the dissolved oxygen concentration). This strategy has been validated experimentally with the removal of the toxic organic compound 4-chlorophenol in a lab-scale bioreactor. Other methods have been proposed for nonmonotonic growth rate such as adaptive extremum seeking [5] but their experimental implementation has not yet been carried out (probably because of a higher complexity). Thereby, the ED-TOC strategy seems to be a good candidate for the practical implementation of the optimal strategy for $N = 0$. This case is of particular interest since N tends to zero when repeated fed-batch cultures are carried out (assuming that the new fed-batch culture starts, after a partial discharge of the reactor, with the substrate and product concentrations reached at the end of the previous culture).

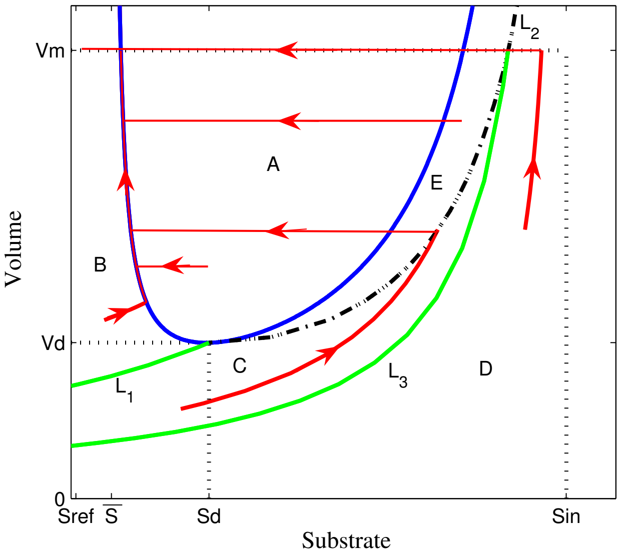

Fig. 3. Optimal trajectories (in red) for various initial conditions for the Jin growth rate, Case 4 (see Property 4 and the paragraph above this property for the definition of the curves L_i). In blue, the curve $\tilde{v}(s)$. Parameter values used for simulation are given in Table I.

Finally, for $N \neq 0$, the optimal trajectory (see Section IV-B) should follow the singular arc path $\tilde{v}(s)$ defined by $\psi = 0$. Implementation of this strategy is more problematic given the uncertain framework. Nevertheless, note that ψ (see Equation 10) is actually the directional derivative of the specific growth rate $h(s,v)$ along the vector $(\frac{s_{in}-s}{v}, 1)$ in the (s,v) plan, which corresponds to a trajectory $u = 1$ (assuming $u >> h(s,v)x$). Thus, along a sequence $u = 1$, the observed growth rate goes through a maximum when the trajectory cross the curve $\tilde{v}(s)$. This is a first hint that an ED-TOC strategy can be adapted to this case. This will deserve further investigations.

VI. CONCLUSION

This paper has tackled the minimal time control problem for fed-batch bioreactors, in presence of an inhibitory product, which is released by the biomass proportionally to its growth. Thanks to Pontryagin maximum principle, Green's theorem, and properties of the switching function, we have provided the optimal strategy, which is of type bang-bang or bang-singular-bang depending on the parameter set.

ACKNOWLEDGEMENTS

This work was supported by Programa de Financiamiento Basal from the Center of Mathematical Modeling, Universidad de Chile and was developed in the context of DYMECOS INRIA associated team. P. Gajardo and F. Mairet were partially supported by FONDECYT-Chile program (N 1080173 and N 3120117 respectively), and by INRIA Chile - CIRIC. The first author thanks the team DYMECOS for partial financial support.

REFERENCES

[1] J. F. ANDREWS, *A mathematical model for the continuous culture of microorganisms utilizing inhibitory substrates*, Biotechnology Bioengineering, vol. 10, pp. 707–723, 1968.

[2] T. BAYEN, P. GAJARDO, F. MAIRET, *Optimal synthesis for the minimum time control problems of fed-batch bioprocesses for growth functions with two maxima*, http://hal.archives-ouvertes.fr/hal-00655534/fr/, submitted to Journal of Optimization Theory and Applications.

[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] D.E. CONTOIS, *Kinetics of bacterial growth: Relationship between population density and specific growth rate of continuous cultures. Journal of General Microbiology, 21, pp.40–50, 1959.*

[5] P. COUGNON, D. DOCHAIN, M. GUAY, M. PERRIER, *On-line optimization of fedbatch bioreactors by adaptive extremum seeking control*, Journal of Process Control, vol. 21, 10, pp. 1526–1532, 2011.

[6] P.M. DORAN, *Bioprocess engineering principles*, Academic Press, 1995.

[7] 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.

[8] J. HONG, *Optimal substrate feeding policy for a fed batch fermentation with substrate and product inhibition kinetics*, Biotechnology and bioengineering, 28, pp. 1421–1431, 1986.

[9] C.K. JIN, H.L. CHIANG, S.S. WANG, *Steady state analysis of the enhancement in ethanol productivity of a continuous fermentation process employing a protein-phosphotifind complex as a protecting agent*, Enzyme Microbiol. Technol., vol. 3, pp. 249–257, 1981.

[10] H.J. KELLEY, *A transformation approach to singular subarcs in optimal trajectory and control problems*, SIAM J. on Control and Optimization , vol. 2, pp. 234–240, 1964.

[11] 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.

[12] C. LIU, *Optimal control for nonlinear dynamical system of microbial fed-batch culture*, Journal of computational and applied mathematics, 232, pp. 252–261, 2009.

[13] A. MIELE, *Application of Green's Theorem to the extremization of linear integrals*, Symp. on Vehicle Systems Optimization, Garden City, L. I. New York, pp. 26–35, 1961.

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

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

[16] J.A. MORENO, M.J. BETANCUR, G. BUITRÓN, I. MORENO-ANDRADE, *Event-driven time-optimal control for a class of discontinuous bioreactors*, Biotechnology and bioengineering, 94, pp. 803–814, 2006.

[17] A. RAPAPORT, D. DOCHAIN, , *Minimal time control of fed-batch processes for growth functions with several maxima*, IEEE Transactions on Automatic Control, vol. 56, 11, pp. 2671-2676, 2011.

[18] H. M. ROBBINS, *A Generalized Legendre-Clebsch Condition for the Singular Cases of Optimal Control*, IBM J. of Research and Development 11, pp. 361–372, 1967.

[19] H. L. SMITH, P. WALTMAN, *The theory of the chemostat, Dynamics of microbial competition*, cambridge University Press, 1995.