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Modelling and optimal control of an electro-fermentation process within a batch culture

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Abstract: The electro-fermentation is a novel process that consists in coupling a microbial fermentative metabolism with an electrochemical system. In such a process the electrodes act either as electron sinks or sources modifying the fermentation balance of a microbial fermentative metabolism and provide new options for the control of microbial activity. A theoretical framework for the analysis and control of fermentations using electro-fermentation is currently lacking. In this paper, we propose a simple electro-fermentation model in which a population of fermentative bacteria switch between two metabolic behaviors in response to different electrode potentials. We then mathematically analyze optimal strategies to maximize the production of one of the rising products in a batch fermentation using Pontryagin's Maximum Principle. The obtained results show that, in some experimental configurations, a dynamic control of the electrode potential is required for the maximization of the desired product. Consequences of the obtained optimal strategy for driving electro-fermentation experiments are discussed through a realistic example. This analysis also highlights that the transition rates between fermentation and electro-fermentation behaviors are currently unknown and would be crucial to quantify in order to apply such a control approach.

Keywords: Electro-fermentation; microbial electrochemical technologies; bioprocess models; batch culture; optimal control.

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1. Introduction

The knowledge of electroactive microorganisms has rapidly grown over the last 20 years with the development of microbial electrochemical technologies such as microbial fuel cells (MFC) and microbial electrolysis cells (MEC) for the production of electricity or hydrogen from organic matter [1]. The development of electromicrobiology has also led to several promising applications such as electro-fermentation (EF) in which reducing power provided by means of an electrode can redirect fermentation pathways [2]. In that case, the electrodes act as either electron sinks or sources modifying the fermentation balance of a microbial fermentative metabolism and providing new options for the control of microbial communities [3,4]. EF has been successfully applied on mixed culture fermentations and pure culture fermentations and has proven efficient for increasing yields in various products such as hydrogen, acetate, propionate, butyrate, lactate, 3-hydroxypropanoic acid, ethanol, 1,3-propanediol, 2,3-butandiol, butanol or acetone [5–16]. For example, a metabolic shift occurred in *Clostridium pasteurianum* when taking up electrons from an electrode poised at +0.045 V vs. SHE (Standard Hydrogen Electrode) with an increased production of reduced products such as butanol from glucose and 1,3-propanediol from glycerol [12]. From a biotechnological point of view, EF could lead to significant improvements of industrial fermentations using only a small amount of

36 electrical power. Moreover, the use of an electrode for the triggering of the EF effect in the
 37 fermentation system introduce the possibility of a dynamic control of the fermentation.
 38 However, mathematical models describing the EF effect are currently lacking. In EF,
 39 the voltage applied between electrodes is a variable that could be adjusted dynamically,
 40 typically with the objective of maximizing the total production over a time interval.
 41 We shall state and study such an optimization problem with the help of the theory of
 42 optimal control, for which several analytical and numerical tools are available. Optimal
 43 control has been successfully applied to various bioprocesses, providing practical control
 44 strategies, mostly in terms of feedback control (e.g. [17]), as we shall consider here.

45 Here we consider a pure cul-
 46 ture of a fermentative microorgan-
 47 ism growing on a limiting resource
 48 in a batch culture. As described
 49 above, the application of an exter-
 50 nal potential through the imple-
 51 mentation of an electrode in the
 52 bioreactor leads to a switching of
 53 the metabolism between two differ-
 54 ent metabolic pathways. This EF ef-
 55 fect is modeled by considering two
 56 microbial subpopulations produc-
 57 ing different metabolites (f_1, f_2)
 58 giving rise to two different prod-
 59 ucts (s_1, s_2). The switching be-
 60 tween the fermentation behaviors
 61 depends on the electrode potential

62 V . The control parameter is simply chosen in such a way that its variation between two
 63 constants values (which correspond to two different values of V) leads to a transition
 64 between the two considered metabolic behaviors. The bioreactor equations in batch
 65 culture are simply used to establish the model [18]. Based on this model, an optimal
 66 control problem for the maximization of the production of s_2 is formulated. The Pon-
 67 tryagin's Maximum Principle [17,19] is applied for the design of the optimal control
 68 strategy. The obtained results show that the optimal strategy is not trivial, in the sens
 69 that the control is not always constant (equal to that which correspond to f_2), where in
 70 some cases the metabolic behavior f_1 should be visited by the fermentative bacteria. The
 71 present mathematical analysis of the optimal strategies will serve as an experimental
 72 guide to design relevant experiments for testing if these strategies are eventually better,
 73 and thus contribute to the validation of the model.

74 The paper is organized as follows. In Section 2, we give the electro-fermentation
 75 model and introduce the optimization problem. A preliminary result analyzing the
 76 behavior of the optimal control in the case of proportional growth functions is given in
 77 Section 3. The main part of the paper is devoted to the synthesis of an optimal control
 78 strategy in two cases: case of identical growth functions in Section 4 and case of constant
 79 growth functions in Section 5. Finally, discussion and numerical simulations are given
 80 in Section 6.

81 2. Model description and optimization problem

82 In order to describe the switching between the two metabolic pathways described
 83 in the introduction, we suppose that the fermentative population is splitted into two
 84 sub-populations x_1 and x_2 in a commensal relationship to consume a substrate s . The
 85 sub-population x_1 with microbial growth rate μ_1 gives rise to a product s_1 and the sub-
 86 population x_2 with microbial growth rate μ_2 gives rise to a product s_2 . We suppose that in
 87 the absence of polarized electrodes the fermentation is mainly guided by the population
 88 x_1 and when the external voltage is sufficiently large the metabolic function switches to

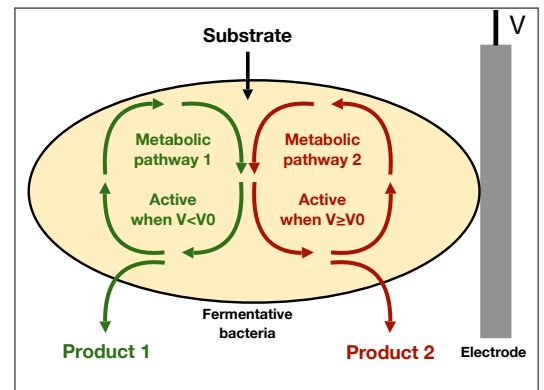


Figure 1. Scheme of the switching between the fermentation behaviors of a fermentative bacteria depending on the electrode potential V .

89 a metabolism guided by x_2 . This electro-fermentation process can be described by the
90 following system of ordinary differential equations:

$$\begin{aligned}\dot{s} &= -\frac{1}{Y_1}\mu_1(s)x_1 - \frac{1}{Y_2}\mu_2(s)x_2 \\ \dot{x}_1 &= \mu_1(s)x_1 - \alpha r_1 x_1 + (1-\alpha)r_2 x_2 \\ \dot{x}_2 &= \mu_2(s)x_2 + \alpha r_1 x_1 - (1-\alpha)r_2 x_2\end{aligned}\quad (1)$$

91 where Y_1, Y_2 are the yields coefficients, $r_1, r_2 > 0$ are positive constants and $\alpha \in \{0, 1\}$ is
92 a control variable which is directly related to the external potential V and satisfies the
93 following property:

$$\alpha = 0 \text{ if } V < V_0, \quad \text{and} \quad \alpha = 1 \text{ if } V \geq V_0, \quad (2)$$

94 where $V_0 > 0$ is a threshold on the external potential over which the metabolic pathway
95 is guided by x_2 . The value of the threshold potential V_0 depends on the microorganisms
96 x_1 and x_2 . We shall assume that growths do not present inhibition, which amounts to
97 consider the following hypothesis.

98 **Assumption 1.** *The growth functions μ_i are non decreasing with $\mu_i(s) > 0$ for $s > 0$.*

99 A classical model for the growth rates kinetics μ_i is given by the following Monod type
100 functions

$$\mu_i(s) = \frac{k_i s}{K_i + s}, \quad i = 1, 2 \quad (3)$$

101 for some positive real numbers k_i, K_i , for $i = 1, 2$.

102

103 Observe that, due to the migration phenomenon between the two sub-populations,
104 the relation between x_1 and x_2 is not simply reduced to a competition phenomenon.

105

106 We shall assume that the two sub-populations have the same conversion factor.

107 **Assumption 2.** $Y_1 = Y_2 = Y$.

108 Note that at the price of change of units of x_1 and x_2 , one can without loss of
109 generality assume that $Y = 1$; this is conventional when dealing with chemostat type
110 systems [20]. Therefore, we shall consider the simpler model

$$\begin{aligned}\dot{s} &= -\mu_1(s)x_1 - \mu_2(s)x_2 \\ \dot{x}_1 &= \mu_1(s)x_1 - \alpha r_1 x_1 + (1-\alpha)r_2 x_2 \\ \dot{x}_2 &= \mu_2(s)x_2 + \alpha r_1 x_1 - (1-\alpha)r_2 x_2,\end{aligned}\quad (4)$$

111 where $(s(0), x_1(0), x_2(0)) = (s_0, x_{10}, x_{20}) \in (\mathbb{R}_+ \setminus \{0\})^3$. Observe that one has $s(t) +$
112 $x_1(t) + x_2(t) = s(0) + x_1(0) + x_2(0) := c > 0$ at any $t \geq 0$. Therefore, we can consider
113 the reduced dynamics in the plane

$$\begin{aligned}\dot{x}_1 &= \mu_1(c - x_1 - x_2)x_1 - \alpha r_1 x_1 + (1-\alpha)r_2 x_2 \\ \dot{x}_2 &= \mu_2(c - x_1 - x_2)x_2 + \alpha r_1 x_1 - (1-\alpha)r_2 x_2.\end{aligned}\quad (5)$$

114 The objective is to maximize the total production of the sub-population x_2 over an
115 interval of time $[0, T]$, among functions $\alpha(\cdot)$ that are measurable time functions taking
116 values in $\{0, 1\}$, which amounts to maximize the criterion

$$J[\alpha(\cdot)] = \int_0^T \mu_2(s(t))x_2(t)dt, \quad (6)$$

117 where $T > 0$ is a fixed finite time horizon.

118 **Remark 1.** From the condition given by (2), the control variable α is constrained to take values
 119 in the non-convex set $\{0, 1\}$. In this case, one can not a priori guarantee the existence of optimal
 120 solutions for the problem (5)-(6). However, a technical approach consists into first considering
 121 the convexified problem, i.e., solve the problem with α taking values in the whole interval $[0, 1]$,
 122 for which the existence of solutions is guaranteed (see for instance [21]). Then, the optimal
 123 solution can be approached with an arbitrary precision via chattering controls [22], which consist
 124 in commuting rapidly between the values 0 and 1 so that the averaged dynamics behave close
 125 from that one with α different from 0 and 1.

126 We shall use the Maximum Principle of Pontryagin (PMP) [19] to obtain necessary
 127 optimality conditions. Defining the Hamiltonian

$$H(x, p, \alpha) = p_1\mu_1(c - x_1 - x_2)x_1 + (p_2 + 1)\mu_2(c - x_1 - x_2)x_2 + (p_2 - p_1)(\alpha r_1 x_1 - (1 - \alpha)r_2 x_2), \quad (7)$$

128 where $p = (p_1, p_2)$ is the adjoint vector, the Pontryagin Maximum Principle claims that
 129 for any optimal solution, there exists an absolutely continuous function $p : [0, T] \rightarrow \mathbb{R}^2$
 130 solution of the adjoint equation

$$\dot{p}(t) = -\partial_x H(x(t), p(t), \alpha(t)), \quad \text{a.e. } t \in [0, T] \quad (8)$$

131 with the terminal condition

$$p(T) = 0 \quad (9)$$

132 and an optimal control α^* that satisfy the maximization of the Hamiltonian

$$\bar{H}(x(t), p(t)) := \max_{\alpha} H(x(t), p(t), \alpha) = H(x(t), p(t), \alpha^*(t)), \quad \text{a.e. } t \in [0, T]. \quad (10)$$

133 In addition, the map $t \mapsto \bar{H}(x^*(t), p^*(t))$ is constant. Let

$$\phi(t) = p_2(t) - p_1(t) \quad (11)$$

134 be the switching function. From the maximization of the Hamiltonian, one gets the
 135 property for an optimal control

$$\alpha^*(t) = \begin{cases} 1 & \text{if } \phi(t) > 0, \\ 0 & \text{if } \phi(t) < 0, \end{cases} \quad \text{a.e. } t \geq 0 \text{ such that } \phi(t) \neq 0. \quad (12)$$

136 3. Sufficient condition for the absence of singular arc

137 In this section we give a sufficient condition under which any optimal solution
 138 of problem (5)-(6) does not admit singular arc. Recall that a singular arc is a piece of
 139 an optimal trajectory for which the switching function ϕ given by (11) vanishes in an
 140 interval of time $[t_1, t_2]$, for some $t_2 > t_1 \geq 0$. In that case, the maximization of the
 141 Hamiltonian (7) over $[t_1, t_2]$ becomes more difficult to study and additional techniques
 142 need to be involved in order to solve the problem on $[t_1, t_2]$. Accordingly to Remark 1,
 143 we can guarantee in absence of singular arc that the optimal solution is reached with
 144 α taking only values 0 and 1 (even though the number of switches might be large or
 145 infinite).

146 Suppose that the growth rate functions satisfy the following assumption.
 147

148 **Assumption 3.** *There exists a positive real $a \neq 1$ such that $\mu_1(s) = a\mu_2(s)$, for $s \geq 0$.*

149 Note that Assumption 3 is not unrealistic. Indeed, when the growth rates follow the
 150 Monod expression (3), the linear approximation

$$\mu_i(s) \simeq \frac{k_i}{K_i} s \quad (i = 1, 2)$$

151 is valid for relatively small values of s .

152

153 One has the following proposition.

154 **Proposition 1.** *Suppose that Assumption 3 holds. An optimal solution of the problem (6)-(4)*
 155 *has no singular arc.*

156 **Proof.** The adjoint equations are

$$\begin{aligned} \dot{p}_1 &= -p_1\mu_1(s) + p_1\mu_1'(s)x_1 + (p_2 + 1)\mu_2'(s)x_2 - \alpha r_1(p_2 - p_1) \\ \dot{p}_2 &= -(p_2 + 1)\mu_2(s) + p_1\mu_1'(s)x_1 + (p_2 + 1)\mu_2'(s)x_2 + (1 - \alpha)r_2(p_2 - p_1) \end{aligned} \quad (13)$$

157 with $s = c - x_1 - x_2$. If $\dot{\phi} = 0$ on a time interval, one has $p_1 = p_2$ and $\dot{\phi} = 0$, which gives

$$p_1 = a(p_2 + 1).$$

158 Therefore, p_1, p_2 have to be constant on this time interval, given by

$$p_1 = p_2 = \frac{a}{1 - a}.$$

159 Then, $\dot{p}_1 = \dot{p}_2 = 0$ gives the equations

$$\begin{aligned} p_1\mu_1'(s)x_1 + (p_2 + 1)\mu_2'(s)x_2 &= p_1\mu_1(s) \\ p_1\mu_1'(s)x_1 + (p_2 + 1)\mu_2'(s)x_2 &= (p_2 + 1)\mu_2(s) \end{aligned}$$

160 from which we obtain that $p_1\mu_1(s) = (p_2 + 1)\mu_2(s)$. Replacing p_1, p_2 by their expression
 161 and using Assumption 3 we obtain that $a = 1$ and thus a contradiction. \square

162 Thanks to Proposition 1, the optimal control of problem (5)-(6) is a sequence of
 163 commutation between $\alpha = 0$ and $\alpha = 1$.

164 4. Optimal synthesis with identical growth functions

165 We investigate here the simple case for which one can assume that the two sub-
 166 populations have exactly the same growth rate. Such an assumption might be considered
 167 quite unrealistic. However, it could happen that growth rates are indeed quite close
 168 to each other when the concentration s is not too large, which could then justify this
 169 assumption as a good approximation.

170 **Proposition 2.** *Consider the problem (6)-(5) and let $T > 0$. Assume that one has $\mu_1(s) =$
 171 $\mu_2(s) := \mu(s)$ for any $s > 0$. Then, the constant control $\alpha^* \equiv 1$ is optimal on $[0, T]$.*

172 **Proof.** Let $b = x_1 + x_2$. Then $b(\cdot)$ is the solution of

$$\dot{b} = \mu(c - b)b, \quad b(0) = x_1(0) + x_2(0) \quad (14)$$

173 whatever is the control $\alpha(\cdot)$. Then, the variable $X_2 = x_2/b$ is solution of

$$\dot{X}_2 = \alpha r_1(1 - X_2) - (1 - \alpha)r_2 X_2, \quad X_2(0) = x_2(0)/(x_1(0) + x_2(0)). \quad (15)$$

174 Note that at any time t , \dot{X}_2 is maximal for $\alpha = 1$, whatever is $X_2 \in [0, 1]$. Let $\bar{X}_2(\cdot)$ be the
 175 solution for the control α identically equal to 1. From standard results of comparison of
 176 solutions of scalar ordinary equations, one has $X_2(t) \leq \bar{X}_2(t)$ at any t , whatever is the
 177 control $\alpha(\cdot)$. Therefore, one has

$$J[\alpha(\cdot)] = \int_0^T \mu(c - b(t))b(t)X_2(t) dt \leq \int_0^T \mu(c - b(t))b(t)\bar{X}_2(t) dt = J[1]$$

178 and we conclude that the constant control $\alpha^* = 1$ is optimal. \square

179 Proposition 2 shows that, in the case of identical growth functions, the optimal
180 strategy in order to maximize (6) is by keeping α constantly equal to one, i.e., by keeping
181 an external potential sufficiently larger than V_0 .

182 5. Optimal synthesis with constant growth functions

183 We consider here distinct growth rates, but that we assume to be constant for
184 non-null concentration s .

185 **Assumption 4.** *One has $\mu_i(s) = a_i > 0$ for any $s > 0$ ($i = 1, 2$).*

186 Indeed, if one considers that population growths follows the classical Monod
187 function (3) and that the concentration $s(0)$ is quite large, having $\mu_i(s) = a_i$ can be a
188 good approximation on the finite time horizon $[0, T]$ (provided T not to be too large).

189 The following definition will be useful in the following.

190 **Definition 1.** *Denote $L = \frac{a_1}{a_2}$ and $K = \frac{r_1 - a_1}{a_2}$ and define*

$$\tilde{\phi}(p_2) = \begin{cases} \frac{K + L - K(L - 1)p_2 - (L + K)(p_2 + 1)^{-K}}{K(K + 1)} & K \notin \{-1, 0\} \\ (1 - L)p_2 + L \log(p_2 + 1) & K = 0 \\ -L + L(p_2 + 1) + \log(p_2 + 1)(1 - L) & K = -1 \end{cases} \quad (16)$$

191 Define also, when $L > 1$, the number

$$\bar{\tau} := \frac{\log(\inf\{p_2 > 0; \tilde{\phi}(p_2) < 0\} + 1)}{a_2}. \quad (17)$$

192 **Remark 2.** *One can straightforwardly check that when $L > 1$ (that is when $a_1 > a_2$) one has*

$$\lim_{p_2 \rightarrow +\infty} \tilde{\phi}(p_2) = -\infty$$

193 *whatever is $K > -L$ (i.e. $r_1 > 0$). We deduce that $\bar{\tau}$ is well-defined.*

194 On has the following result.

195 **Proposition 3.** *Suppose that Assumption 4 holds. Consider the problem (6)-(5) and let $T > 0$.
196 One has the following two cases:*

- 197 • *If $a_1 \leq a_2$, then $\alpha^* = 1$ is optimal on $[0, T]$.*
- 198 • *If $a_1 > a_2$, then the control*

$$\alpha^*(t) = \begin{cases} 1 & \text{if } t \geq \min(0, T - \bar{\tau}) \\ 0 & \text{otherwise} \end{cases}$$

199 *is optimal on $[0, T]$.*

200 **Proof.** The adjoint equations are written

$$\begin{aligned}\dot{p}_1 &= -a_1 p_1 - \alpha r_1 (p_2 - p_1) \\ \dot{p}_2 &= -a_2 (p_2 + 1) + (1 - \alpha) r_2 (p_2 - p_1)\end{aligned}\quad (18)$$

201 Note that system (18) is decoupled from the dynamics of x_1, x_2 and can be studied
202 independently to the initial condition $(x_1(0), x_2(0))$. The switching function satisfies

$$\dot{\phi} = -a_2 + a_1 p_1 - a_2 p_2 + \phi (r_2 + \alpha (r_1 - r_2)). \quad (19)$$

203 At terminal time T , one has $\phi(T) = 0$ with $\dot{\phi}(T) = -a_2 < 0$. So we conclude about
204 the existence of the number

$$\bar{t}_1 := \inf\{t > 0; \phi(\tau) > 0, \tau \in (t, T)\}$$

205 and the optimality of $\alpha = 1$ on the interval $[\bar{t}_1, T]$. On this interval, one has

$$\begin{aligned}\dot{p}_2 &= -a_2 (p_2 + 1) \\ \dot{\phi} &= -a_2 + (a_1 - a_2) p_2 + (r_1 - a_1) \phi\end{aligned}\quad (20)$$

206 Note that $p_2(T) = 0$ implies that one has necessarily $p_2 > 0$ on $[\bar{t}_1, T]$.

207 If $a_1 \leq a_2$, ϕ cannot cross 0 from below because $\phi = 0$ implies $\dot{\phi} < 0$. We deduce
208 from (20) that ϕ is negative on $[\bar{t}_1, T)$, and thus \bar{t}_1 has to be equal to 0. We conclude that
209 $\alpha^* = 1$ is optimal on $[0, T]$.

210 Consider now the case $a_1 > a_2$. Let us show that an optimal solution cannot
211 present a singular arc, i.e. a time interval on which ϕ is identically null. If not, $\dot{\phi} = 0$
212 and $\phi = 0$ implies from equation (19) that p_2 has to be constant on such an interval
213 with $p_2 = a_2 / (a_1 - a_2) > 0$. But from equations (18) with $\dot{p}_2 = 0$ and $p_2 = p_1$, one
214 obtains $p_2 = -1 < 0$, and thus a contradiction. We deduce that an optimal solution is a
215 concatenation of arcs with $\alpha = 0$ or $\alpha = 1$. Note, from equation (19), that $\dot{\phi}$ is continuous
216 at switching times (with $\dot{\phi} = -a_2 + (a_1 - a_2) p_2 = -a_2 + (a_1 - a_2) p_1$). If $\bar{t}_1 > 0$, we
217 consider the number

$$\bar{t}_0 := \inf\{t > 0; \phi(\tau) < 0, \tau \in (t, \bar{t}_1)\}.$$

218 On the interval (\bar{t}_0, \bar{t}_1) , $\alpha = 0$ is optimal and one has

$$\begin{aligned}\dot{p}_1 &= -a_1 p_1 \\ \dot{\phi} &= -a_2 + (a_1 - a_2) p_1 + (r_2 - a_2) \phi.\end{aligned}\quad (21)$$

219 Note that one has $p_1(\bar{t}_1) = p_2(\bar{t}_1) > 0$, which implies $p_1(t) > p_1(\bar{t}_1)$ for $t \in [\bar{t}_0, \bar{t}_1)$. As ϕ
220 changes its sign at \bar{t}_1 (from negative to positive values), one has necessarily $\dot{\phi}(\bar{t}_1) \geq 0$
221 (with $\phi(\bar{t}_1) = 0$). If $\bar{t}_0 > 0$, one should have $\phi(\bar{t}_0) = 0$ with $\dot{\phi}(\bar{t}_0) = -a_2 + (a_1 -$
222 $a_2) p_1(\bar{t}_0) > -a_2 + (a_1 - a_2) p_1(\bar{t}_1) = \dot{\phi}(\bar{t}_1) \geq 0$, which contradicts the change of sign
223 of ϕ at \bar{t}_0 . We conclude that one has necessarily $\bar{t}_0 = 0$ and thus the optimal solution
224 consists in at most one switch from $\alpha = 0$ to $\alpha = 1$.

225 Finally, let us consider the dynamics (20) in the backward time $\tau = T - t$:

$$\begin{aligned}\frac{dp_2}{d\tau} &= a_2 (p_2 + 1), \quad p_2(0) = 0 \\ \frac{d\phi}{d\tau} &= a_2 - (a_1 - a_2) p_2 - (r_1 - a_1) \phi, \quad \phi(0) = 0.\end{aligned}\quad (22)$$

226 Note that the map $\varphi : \tau \mapsto p_2(\tau)$ defines a diffeomorphism from \mathbb{R}^+ to \mathbb{R}^+ . The solution
227 ϕ can then be parameterized by p_2 , as solution of the non-autonomous scalar differential
228 equation

$$\frac{d\tilde{\phi}}{dp_2} = 1 - L \frac{p_2}{p_2 + 1} - K \frac{\tilde{\phi}}{p_2 + 1}, \quad \tilde{\phi}(0) = 0, \quad (23)$$

229 where L and K are given by Definition 1. The solution of (23) can be made explicit as
 230 given by (16). As it is underlined by Remark 2, when $L > 1$ (that is when $a_1 > a_2$) the
 231 number $\bar{\tau}$ is well-defined. Then, we have that $\phi(\bar{\tau}) = 0$ with $\phi(\tau) > 0$ for $\tau \in (0, \bar{\tau})$.
 232 Therefore, one gets $\bar{t}_1 = \max(0, T - \bar{\tau})$ and the control

$$\alpha^*(t) = \begin{cases} 1 & \text{if } t \geq \min(0, T - \bar{\tau}) \\ 0 & \text{otherwise} \end{cases}$$

233 is optimal. \square

234 **Remark 3.** Let us underline that when μ_i are constant functions, the optimal synthesis does
 235 not depend on the initial state. Also, it is worth noting that in this case the optimal control α^*
 236 does not depend on r_2 , the migration rate constant from population x_2 to population x_1 . This is
 237 clearly recognizable from the statement of Proposition 3 and Definition 1.

238 6. Numerical simulations and discussions

239

240 6.1. Constant growth rates

241 Let us consider system (5) where the growth rate functions follow Assumption 4
 (constant values) with values given in table 1. In this case the switching time $\bar{\tau}$ introduced

a_1	a_2	r_1	r_2	Y_1	Y_2	T
2	1/2	1	0.1 - 0.5	1	1	2

Table 1: Numerical values of the different parameters: case of constant growth rates.

242

243 by equation (17) is given by $\bar{\tau} = \log(4)$ and the optimal control is given by

$$\alpha^*(t) = \begin{cases} 1 & \text{if } t \geq \min(0, 2 - \log(4)) \\ 0 & \text{otherwise.} \end{cases}$$

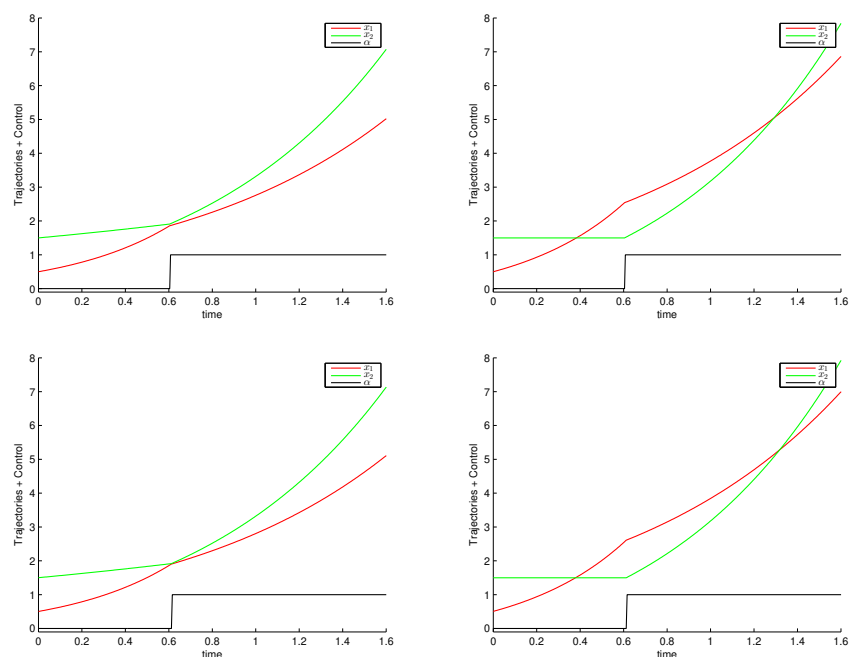


Figure 2. Exact optimal control (top) and optimal control computed with Bocop (top) for $r_2 = 0.1$ (left) and $r_2 = 0.5$ (right).

244 As underlined in Remark 2, the optimal control α^* does not depend on the migration
 245 rate constant r_2 . On Figure 2, we plot (with Matlab) the optimal control given by
 246 Proposition 3 together with the optimal trajectories in the two cases $r_2 = 0.1$ (bottom-left)
 247 and $r_2 = 0.5$ (bottom-right). As a verification, these plots are also compared with the
 248 ones obtained with Bocop [23], which is a numerical optimization software dedicated to
 249 optimal control problems (using direct method) on Figure 2 (top).
 250

251 6.2. Monod growth rates

252 In this section, we consider system (5) with variable growth rate functions instead
 of constants ones, using the Monod expression (3).

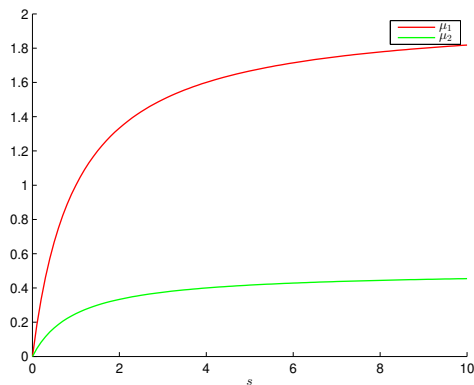


Figure 3. Kinetic growth rates of Monod type.

253

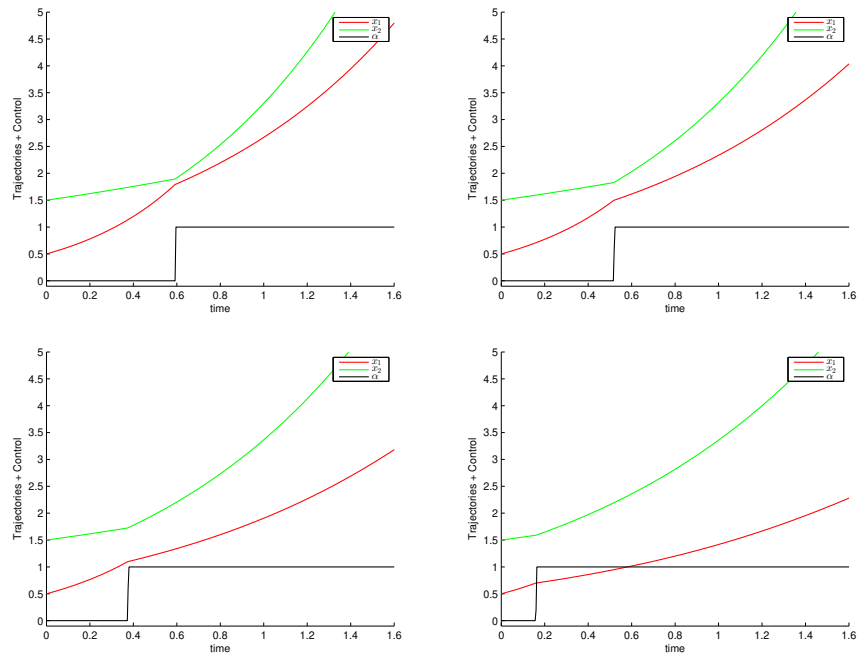


Figure 4. Optimal control computed with Bocop for $c = 100$ (top-left), $c = 30$ (top-right), $c = 20$ (bottom-left), and $c = 15$ (bottom-right).

254 Using the numerical solver Bocop, we simulate the optimal control together with
 255 the optimal trajectories in similar conditions than before with model parameters given
 256 in Table 2, and for different values of initial control $c = s(0) + x_1(0) + x_2(0)$. Observe
 257 that, in this example, the growth kinetic functions μ_1 and μ_2 satisfy Assumption 3. Thus,

k_1	k_2	K_{s_1}	K_{s_2}	r_1	r_2	Y_1	Y_2	T
2	1/2	1	1	1	0.1	1	1	2

Table 2: Numerical values of the different parameters: case of Monod type growth rates (3).

258 thanks to Proposition 1, no singular arcs are present in this case. We observe in Figure 4
 259 that the optimal trajectories have the same structure than for constant growth rates given
 260 by Proposition 3, but here the optimal switching time depends on the initial condition.

261 6.3. Consequences for the control of electro-fermentation experiments

262 We have proposed a model describing the effect of electro-fermentation on the
 263 metabolic profile of a fermentative bacteria in a batch culture. Fermentation and electro-
 264 fermentation behaviors (f_1, f_2) , each gives rise to different products (s_1, s_2) . The switch-
 265 ing between the fermentation behaviors depends on the electrode potential V . As
 266 shown in Proposition 2, the optimal control strategy is trivial in the case where the
 267 electro-fermentation f_2 growth rate is higher or equal to the fermentation f_1 growth rate
 268 ($a_2 \geq a_1$). This indicates that in some experimental configurations a dynamic control
 269 is not necessary to optimize the system. For example, in the case of *Clostridium au-*
 270 *toethanogenum* electro-fermentation with $[\text{Co}(\text{trans-diammac})]^{3+}$ as mediator reported by
 271 Kracke *et al.* [13], the electro-fermentation led to a 35-fold increase in lactate production
 272 but the growth rate was not significantly impacted. In that case the optimization of lac-
 273 tate production is straightforward and requires a constant polarization of the electrode at
 274 the electro-fermentation potential (-603 mV vs. Standard Hydrogen Electrode). However,
 275 in other cases the electro-fermentation growth rate is lower than the fermentation growth
 276 rate ($a_2 < a_1$). In those cases, the dynamic control strategy proposed in Proposition
 277 3 would be required to optimize the production of the targeted product. This is the
 278 case, for example, for the electro-fermentation of glucose by *Clostridium pasteurianum*
 279 reported by Choi *et al.* [12]. In that case, they reported a 2.4-fold increase of butanol
 280 production associated with a 1.6-fold decrease in growth rate. Using values estimated
 281 in their experiments $a_1 = 0.41 \text{ h}^{-1}$ and $a_2 = 0.25 \text{ h}^{-1}$, and assuming a relatively high
 282 transition rate $r_1 = 1 \text{ h}^{-1}$ the switching time $\bar{\tau}$ is then calculated using equation (17):
 283 $\bar{\tau} \approx 5 \text{ h}$. This means that the optimal production of butanol would then be obtained with
 284 a first period of fermentation without polarization of the electrode followed by 5 h of
 285 electro-fermentation. In the experiment reported by Choi *et al.* [12], according to Figure 3,
 286 the fermentation starts after a 15 h lag phase and ends around 23 h. The optimal control
 287 would then correspond to polarizing the electrode at +45 mV vs. Standard Hydrogen
 288 Electrode after 18 h. This calculation also shows that the estimation of the true value of
 289 the transition rate r_1 would be crucial for such a control approach.

290 7. Conclusion and perspectives

291 We propose a model describing the metabolic switching holding in an electro-
 292 fermentation process within a pure batch culture. Based on this model, an optimal
 293 control problem is formulated in order to maximize the production of one of the rising
 294 fermentation products. The Pontryagin's Maximum Principle is applied for the analysis
 295 of the optimization problem. A preliminary result analyzing the behavior of the optimal
 296 control in the case of proportional growth functions is given. An optimal control is syn-
 297 thesised in two particular cases: similar and constant (but different) growth rate kinetics.
 298 The obtained results show that the optimal control strategy is far from being trivial, in the
 299 sense that undesirable metabolic pathways may be visited by the fermentative bacteria
 300 for the maximization of a desired fermentation product. Consequences of the obtained
 301 optimal strategy for driving electro-fermentation experiments are discussed through a
 302 realistic example. This study is elaborated under the hypothesis of identical yield factors.
 303 The optimality for the case of different yield factors with more general growth kinetics,

304 is an open problem, that will be explored in a near future. This theoretical approach
305 also underscores the importance of evaluating biological parameters such as transition
306 rates between fermentation mode and electro-fermentation mode for the application of
307 the optimal control. The proposed model as well as the optimal control law need to be
308 confronted with experimental data, and this will be the subject of future experimental
309 investigation within the LBE laboratory.

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