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Optimal control of cell mass and maturity in a model of follicular ovulation

Frédérique Clément* Jean-Michel Coron† Peipei Shang‡

Abstract

In this paper, we study optimal control problems associated with a scalar hyperbolic conservation law modeling the development of ovarian follicles. Changes in the age and maturity of follicular cells are described by a 2D conservation law, where the control terms act on the velocities. The control problem consists in optimizing the follicular cell resources so that the follicular maturity reaches a maximal value in fixed time. Formulating the optimal control problem within a hybrid framework, we prove necessary optimality conditions in the form of Hybrid Maximum Principle. Then we derive the optimal strategy and show that there exists at least one optimal bang-bang control with one single switching time.

Keywords: optimal control, conservation law, biomathematics.

2000 MR Subject Classification: 35L65, 49J20, 92B05.

1 Introduction

This work is motivated by natural control problems arising in reproductive physiology. The development of ovarian follicles is a crucial process for reproduction in mammals, as its biological meaning is to free fertilizable oocyte(s) at the time of ovulation. During each ovarian cycle, numerous follicles are in competition for their survival. Few follicles reach an ovulatory size, since most of them undergo a degeneration process, known as atresia (see for instance [29]). The follicular cell population consists of proliferating, differentiated and apoptotic cells, and the fate of a follicle is determined by the changes occurring in its cell population in response to an hormonal control originating from the pituitary gland.

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A mathematical model, using both multiscale modeling and control theory concepts, has been designed to describe the follicle selection process on a cellular basis (see [14]). The cell population dynamics is ruled by a conservation law, which describes the changes in the distribution of cell age and maturity.

Cells are characterized by their position within or outside the cell cycle and by their sensitivity to the follicle stimulating hormone (FSH). This leads one to distinguish 3 cellular phases. Phase 1 and 2 correspond to the proliferation phases and Phase 3 corresponds to the differentiation phase, after the cells have exited the cell cycle.

The cell population in a follicle f is represented by cell density functions $\rho_{j,k}^f(t, x, y)$ defined on each cellular phase $Q_{j,k}^f$, where $j = 1, 2, 3$ denotes Phase 1, Phase 2 and Phase 3, $k = 1, 2, \dots$ denotes the number of the successive cell cycles (see figure 1). The cell density functions satisfy the following conservation laws:

$$\frac{\partial \rho_{j,k}^f}{\partial t} + \frac{\partial (g_f(u_f) \rho_{j,k}^f)}{\partial x} + \frac{\partial (h_f(y, u_f) \rho_{j,k}^f)}{\partial y} = -\lambda(y, U) \rho_{j,k}^f \text{ in } Q_{j,k}^f, \quad (1)$$

where $Q_{j,k}^f = \Omega_{j,k}^f \times [0, T]$, with

$$\begin{aligned} \Omega_{1,k}^f &= [(k-1)a_2, (k-1)a_2 + a_1] \times [0, y_s], \\ \Omega_{2,k}^f &= [(k-1)a_2 + a_1, ka_2] \times [0, y_s], \\ \Omega_{3,k}^f &= [(k-1)a_2, ka_2] \times [y_s, y_m]. \end{aligned}$$

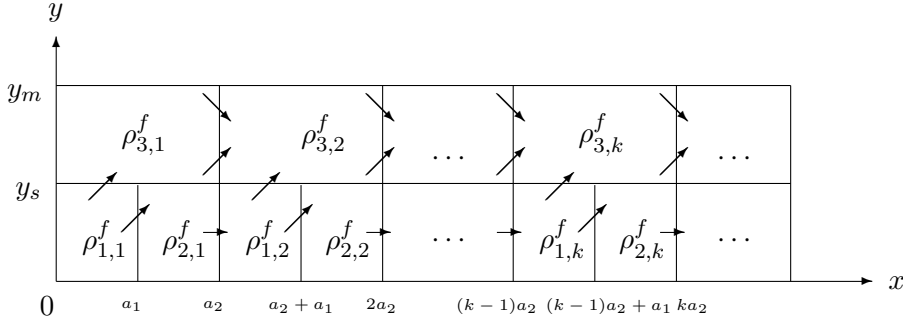


Figure 1: Cellular phases on the age-maturity plane for each follicle f . The domain consists of the sequence of $k = 1, 2, \dots$ cell cycles. Variable x denotes the age of the cell and variable y denotes its maturity. Number y_s is the threshold value at which cell cycle exit occurs and y_m is the maximal maturity. The top of the domain corresponds to the differentiation phase and the bottom to the proliferation phase.

Let us define

$$M_f(t) := \sum_{j=1}^3 \sum_{k=1}^N \int_0^{+\infty} \int_0^{+\infty} y \rho_{j,k}^f(t, x, y) dx dy \quad (2)$$

as the maturity on the follicle scale, and

$$M(t) := \sum_f M_f(t) \quad (3)$$

as the maturity on the ovarian scale.

The velocities of aging g_f and maturation h_f as well as the loss term λ depends on the mean maturity of the follicle f through a local control $u_f(t, M_f, M)$ which represents intrafollicular bioavailable FSH level and the mean maturity of all the follicles through a global control $U(t, M)$ which can be interpreted as the FSH plasma level. One can refer to [13, 14, 33] for more details on the model.

The aging velocity controls the duration of the cell division cycle. Once the cell age has reached a critical age, the mitosis event is triggered and a mother cell gives birth to two daughter cells. The two daughter cells enter a new cell cycle, which results in a local doubling of the flux. Hence, there are local singularities in the subpart of the domain where $y \leq y_s$, that correspond to the flux doubling due to the successive mitosis events. The maturation velocity controls the time needed to reach a threshold maturity y_s , when the cell exits the division cycle definitively. After the exit time, the cell is no more able to contribute to the increase in the follicular cell mass.

Ovulation is triggered when the ovarian maturity reaches a threshold value M_s . The stopping time T_s is defined as

$$T_s := \min \{T \mid M(T) = M_s\}, \quad (4)$$

and corresponds on the biological ground to the triggering of a massive secretion of the hypothalamic gonadotropin releasing hormone (GnRH).

As a whole, system (1)-(3) combined with stopping condition (4) defines a multiscale reachability problem. It can be associated to an optimal control problem that consists in minimizing T_s for a given target maturity M_s .

Some related control problems have already been investigated on a mathematical ground. In [13], the authors studied the characteristics associated with a follicle as an open-loop control problem. They described the sets of microscopic initial conditions compatible with either ovulation or atresia in the framework of backwards reachable set theory. Since these sets were largely overlapping, their results illustrate the prominent impact of cell dynamics control in the model. In [30], the author focused on the issue of the selection process in a game theory approach, where one follicle plays against all the other ones. Whether the follicle becomes atretic (doomed) or ovulatory (saved) depends on the follicular cell mass reached at the time when all cells stop proliferating.

The aim of this paper is to investigate whether there exists an optimal way for a follicle to reach ovulation. On the one hand, the follicle can benefit from a strong and quick enlargement of its cell population. On the other hand, this enlargement occurs at the expense

of the maturation of individual cells. This compromise was instanced here as a problem of composition of velocities. A concept central to the understanding of these entangled processes is that of the management of follicular cell resources. There is indeed a finely tuned balance between the production of new cells through proliferation, that increases the whole cell mass, and the maturation of cells, that increases their contribution to hormone secretion.

The controllability of nonlinear hyperbolic equations (or systems) have been widely studied for a long time; for the 1D case, see, for instance [7, 9, 11, 17, 21, 26, 27, 28, 38] for smooth solutions and [1, 3, 16, 23] for bounded variation entropic solutions. In particular, [8] provides a comprehensive survey of controllability of partial differential equations including nonlinear hyperbolic systems. As far as optimal control problems for hyperbolic systems are concerned, one can refer to [18, 19, 20, 34]. However, most of these monographs study the case where the controls are either applied inside the domain or on the boundary. Our control problem is quite different from the problems already studied in the literature, since the control terms appear in the flux. To solve the problem, we make use both of analytical methods based on Hybrid Maximum Principle (HMP) and numerical computations.

The paper is organized as follows. In section 2, we set the optimal control problem, together with our assumptions, and we enunciate the main result. In section 3, we give necessary optimality conditions from HMP in the case where Dirac masses are used as a rough approximation of the density. An alternative sketch of the proof based on an approximation method is given in appendix. Using the optimality conditions, we show that for finite Dirac masses, every measurable optimal control is a bang-bang control with one single switching time. In addition to the theoretical results, we give some numerical illustrations. In section 4, we go back to the original PDE formulation of the model, and we show that there exists at least one optimal bang-bang control with one single switching time.

2 Problem statement and introductory results

2.1 Simplifications with respect to the original model

To make the initial problem tractable, we have made several simplifications on the model dynamics.

- S_1 . We consider only one developing follicle, i.e. $f = 1$;
- S_2 . There is no loss term anymore, i.e. $\lambda = 0$;
- S_3 . The age velocity is uncontrolled, i.e. $g_f \equiv 1$;
- S_4 . The cell division is represented by a new gain term, i.e. $c(y)$ defined by (7);
- S_5 . The target maturity M_s can always be reached in finite time.

(S_1) means that, in this problem, we are specially interested in the control of the follicular cell resources for each follicle, in the sense that we ignore the influence of the other growing

follicles. The goal is to find the optimal balance between the production of new cells and the maturation of cells.

In (S_2) , we neglect the cell death, which is quite natural when considering only ovulatory trajectories, while, in (S_3) , we consider that the cell age evolves as time. Moreover, the cell division process is distributed over ages with (S_4) , so that there is a new gain term in the model instead of the former mitosis transfer condition.

Even if it is simplified, the problem studied here still captures the essential question of the compromise between proliferation and differentiation that characterizes terminal follicular development. A relatively high aging velocity tends to favor cell mass production, while a relatively high maturation velocity tends to favor an increase in the average cell maturity.

As shown in section 2.4, assumptions (S_2) and (S_5) allow us to replace a minimal time criterion by a criterion that consists in maximizing the final maturity. Hence, from the initial, minimal time criterion, we have shifted, for sake of technical simplicity, to an equivalent problem where the final time is fixed and the optimality criterion is the follicular maturity at final time. On the biological ground, this means that for any chosen final time t_1 , the resulting maturity at final time $M_f(t_1)$ can be chosen in turn as a maturity target which would be reached in minimal time at time t_1 . It can be noticed that in the initial problem (4), there might be no optimal solution without assumption (S_5) , if the target maturity is higher than the maximal asymptotic maturity.

2.2 Optimal control problem

Under these assumptions, we arrived to consider the following conservation law on a fixed time horizon:

$$\begin{cases} \rho_t + \rho_x + ((a(y) + b(y)u)\rho)_y = c(y)\rho, & t \in (t_0, t_1), x > 0, y > 0, \\ \rho(t, 0, y) = \rho(t, x, 0) = 0, & t \in (t_0, t_1), x > 0, y > 0, \\ \rho(0, x, y) = \rho_0(x, y), & x > 0, y > 0, \end{cases} \quad (5)$$

where

$$a(y) := -y^2, \quad b(y) := c_1 y + c_2, \quad (6)$$

and

$$c(y) := \begin{cases} c_s, & \text{if } y \in [0, y_s), \\ 0, & \text{if } y \in [y_s, \infty), \end{cases} \quad (7)$$

with y_s , c_s , c_1 and c_2 being given strictly positive constants. We assume that

$$\frac{y_s^2}{c_1 y_s + c_2} < 1. \quad (8)$$

Let us denote by w a positive constant such that

$$w \in \left(\frac{y_s^2}{c_1 y_s + c_2}, 1 \right). \quad (9)$$

From (6) and (9), we have

$$a(y) + b(y)u > 0, \forall y \in [0, y_s], \forall u \in [w, 1]. \quad (10)$$

Throughout this paper the control u is assumed to satisfy the constraint

$$u \in [w, 1]. \quad (11)$$

The left constraint w in (11) ensures that the maturation velocity is always positive in the proliferation phase. The right constraint in (11) is natural since FSH plasma levels are bounded. The maximal bound can be scaled to 1 for sake of restricting the number of parameters in the model.

By (11), there is a maximal asymptotic maturity \bar{y} on the cell scale, i.e. the positive root y of $a(y) + b(y)u = 0$ with control $u = 1$. From (6), we have

$$\bar{y} = \frac{c_1 + \sqrt{c_1^2 + 4c_2}}{2}. \quad (12)$$

Let $u \in L^\infty((t_0, t_1); [w, 1])$. Let us define the map

$$\begin{aligned} \Psi : [t_0, t_1] \times [0, y_s] \times L^\infty((t_0, t_1); [w, 1]) &\rightarrow [0, \bar{y}] \\ (t, y_0, u) &\mapsto \Psi(t, y_0, u) \end{aligned}$$

by requiring

$$\begin{cases} \frac{\partial \Psi}{\partial t}(t, y_0, u) = a(\Psi(t, y_0, u)) + b(\Psi(t, y_0, u))u(t), \\ \Psi(t_0, y_0, u) = y_0. \end{cases} \quad (13)$$

Let us now define the exit time \hat{t}_0 as

$$\Psi(\hat{t}_0, 0, w) = y_s. \quad (14)$$

Let us point out that, by (10), there exists one and only one \hat{t}_0 satisfying (14). Note that it is not guaranteed that the exit time \hat{t}_0 occurs before the final time t_1 , so that we may have $\hat{t}_0 > t_1$. When $t > \hat{t}_0$, all the cells are in Phase 3, i.e. their maturity is larger than the threshold y_s . After time \hat{t}_0 the mass will not increase any more due to (7). The maximal cell mass that can be reached at \hat{t}_0 is obtained when applying $u = w$ from the initial time.

For any admissible control $u \in L^\infty((t_0, t_1); [w, 1])$, we define the cost function

$$J(u) := - \int_0^{+\infty} \int_0^{+\infty} y \, d\rho(t_1, x, y), \quad (15)$$

and we want to study the following optimal control problem:

$$\text{minimize } J(u) \text{ for } u \in L^\infty((t_0, t_1); [w, 1]). \quad (16)$$

A similar minimal time problem was investigated in another ODE framework [6], where the proliferating and differentiated cells were respectively pooled in a proliferating and a

differentiated compartment. The author proved by Pontryagin Maximum Principle (PMP) that the optimal strategy is a bang-bang control, which consists in applying permanently the minimal apoptosis rate and in switching once the cell cycle exit rate from its minimal bound to its maximal one. In contrast, due to the fact that c is discontinuous, we cannot apply PMP directly here. The idea is to first consider optimal control problems for Dirac masses (see section 3), and then to pass to the limit to get optimal control results for the PDE case (see section 4).

For “discontinuous” optimal control problems of finite dimension, one cannot derive necessary optimality conditions by applying directly the standard apparatus of the theory of extremal problems [4, 24, 32]. The first problem where the cost function was an integral functional with discontinuous integrand was dealt in [2]. Later, in [35], the author studied the case of a more general functional that includes both the discontinuous characteristic function and continuous terms. There, the author used approximation methods to prove necessary optimality conditions in the form of PMP. One of the difficulties of our problem is that both the integrand of the cost function and the dynamics are discontinuous.

However, our problem can be classified as a hybrid optimal control problem, since the problem has a discontinuous dynamics ruled by a partition of the state space. One of the most important results in the study of such problems is the HMP proved in [15, 31, 36, 37]. There, the authors followed the standard line of the full procedure for the direct proof of PMP, based on the introduction of a special class of control variations, and the computation of the increments of the cost and all constraints. In [12], the authors formulated the hybrid problem as a classical optimal control problem. They then proved the HMP using the classical PMP. Later, in [22], the authors regularized the hybrid problems to standard smooth optimal control problems, to which they can apply the usual PMP. They also derived jump conditions appropriate to our problem.

The main result of this paper is the following theorem.

Theorem 2.1. *Let us assume that*

$$t_1 > \hat{t}_0, \tag{17}$$

$$2y_s - c_1 > 0 \quad \text{and} \quad c_s > \frac{a(y_s) + b(y_s)}{y_s}. \tag{18}$$

Then, among all admissible controls $u \in L^\infty((t_0, t_1); [w, 1])$, there exists an optimal control u_ for the minimization problem (16) such that*

$$\exists t_* \in [t_0, t_1] \text{ such that } u_* = w \text{ in } (t_0, t_*) \text{ and } u_* = 1 \text{ in } (t_*, t_1). \tag{19}$$

Remark 2.1. *From the mathematical viewpoint, assumptions (17) and (18) arise naturally from the computations (see section 3.2.1). Condition (17) means that we consider a target time large enough so that all the cells have gone to the differentiation phase. Condition (18) gives specific relations between the proliferation rate and the parameters of the maturation*

velocity. Together, these relations are related to the transit time within the proliferation phase.

Remark 2.2. In our case, the dynamics of ρ is essentially one-dimensional, since there is a transport with constant velocity along variable x and we have just to deal with variable y . Hence our results can be generalized to n -spatial dimensional problem like

$$\rho_t + m \cdot \nabla_x \rho + (h(y, u)\rho)_y = c(y)\rho, \quad (20)$$

where m is a constant vector. Generalization to n -spatial dimensional dynamics with both velocities controlled should also be feasible.

2.3 Solution to Cauchy problem (5)

In this section, we give the definition of a (weak) solution to Cauchy problem (5).

Let ρ_0 be a Borel measure on $\mathbb{R} \times \mathbb{R}$ such that

$$\rho_0 \geq 0, \quad (21)$$

$$\text{and the support of } \rho_0 \text{ is included in } [0, 1] \times [0, y_s]. \quad (22)$$

Let $K := [0, t_1 - t_0 + 1] \times [0, y]$. Let $M(K)$ be the set of Borel measures on K , i.e. the set of continuous linear maps from $C^0(K)$ into \mathbb{R} . The solution to Cauchy problem (5) is the function $\rho : [t_0, t_1] \rightarrow M(K)$ such that, for every $\varphi \in C^0(K)$,

$$\iint_K \varphi(\alpha, \beta) d\rho(t, \alpha, \beta) = \iint_K \varphi(x_0 + t - t_0, \Psi(t, y_0, u)) e^{\int_{t_0}^t c(\Psi(s, y_0, u)) ds} d\rho_0(x_0, y_0). \quad (23)$$

We take expression (23) as a definition. This expression is also justified by the fact that if ρ_0 is a L^∞ function, one recovers the usual notion of weak solutions to Cauchy problem (5) studied in [8, 10, 33, 34], as well as by the characteristics method used to solve hyperbolic equations (see figure 2).

Remark 2.3. From (23), if ρ_0 is a positive Borel measure, then solution ρ is also a positive Borel measure. If $\rho_0 \in C^0$ or if ρ_0 is Lipschitz continuous, then $\rho \in C^0$ or ρ is Lipschitz continuous, but if $\rho_0 \in C^1$, it may happen that ρ is not in C^1 due to the fact that $c(y)$ is discontinuous.

2.4 Minimal time versus maximal maturity

In this section, we show that the two optimal control problems enunciate either as: “minimize the time to achieve a given maturity” or “achieve a maximal maturity at a given time” are equivalent when S_2 and S_5 hold. The threshold target maturity \bar{M}_5 in S_5 can be computed

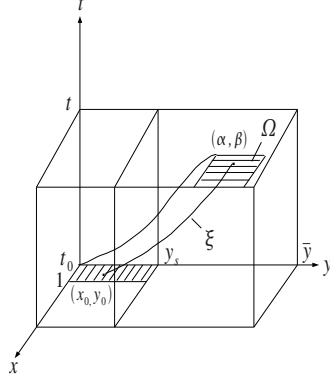


Figure 2: Construction of a weak solution by backward tracking of the characteristics. Variables x and y respectively denote the age and maturity, y_s is the threshold maturity and \bar{y} is the maximal asymptotic maturity. The initial mass concentrates in the shaded area $[0, 1] \times [0, y_s]$. The curve $\xi = (x, y)$ is the characteristic curve passing through (t, α, β) that intersects the initial plane $t = t_0$ at (t_0, x_0, y_0) .

from the maximal cell mass combined with the maximal asymptotic maturity \bar{y} when applying $u = w$ from the initial time until \hat{t}_0 and $u = 1$ thereafter, so that S_5 can be formulated as:

$$M_s < \bar{M}_s := \bar{y} \int_0^\infty \int_0^\infty d\rho(\hat{t}_0, x, y). \quad (24)$$

Let ρ_0 be a nonzero Borel measure on $\mathbb{R} \times \mathbb{R}$ satisfying (21) and (22). Let us denote by $M^u(t)$ the maturity at time t for the control $u \in L^\infty((t_0, t_1); [w, 1])$ (and the initial data ρ_0).

A. For fixed target time t_1 , suppose that the maximum of the maturity M is achieved with an optimal control $u \in L^\infty((t_0, t_1); [w, 1])$

$$M^u(t_1) = M. \quad (25)$$

Then we conclude that for this fixed M , the minimal time needed to reach M is t_1 with the same control u . We prove it by contradiction. We assume that there exists another control $\tilde{u} \in L^\infty((t_0, \tilde{t}_1); [w, 1])$ such that

$$M^{\tilde{u}}(\tilde{t}_1) = M, \quad \tilde{t}_1 < t_1. \quad (26)$$

We extend \tilde{u} to $[t_0, t_1]$ by requiring $\tilde{u} = 1$ in $(\tilde{t}_1, t_1]$. Let us prove that

$$t \in [\tilde{t}_1, t_1] \rightarrow M^{\tilde{u}}(t) \text{ is strictly increasing.} \quad (27)$$

Let $\tilde{\rho} : [t_0, t_1] \rightarrow M(K)$ be the solution to Cauchy problem (5) (see section 2.3). Note that $a(y) + b(y) > 0$ for every $y \in [0, \bar{y})$ and that, for every $t \in [t_0, t_1]$, the support of $\tilde{\rho}(t)$ is included in $[0, t_1 - t_0 + 1] \times [0, y_s]$. Together with (23) for $\rho = \tilde{\rho}$ and $\varphi(\alpha, \beta) = \beta$, this proves (27). From (27) it follows that

$$M^{\tilde{u}}(t_1) > M^{\tilde{u}}(\tilde{t}_1) = M, \quad (28)$$

which is a contradiction with the optimality of u .

B. For any fixed target maturity M , suppose that the minimal time needed to reach M is t_1 with control $u \in L^\infty((t_0, t_1); [w, 1])$. Then we conclude that for this fixed target time t_1 , the maximal maturity at time t_1 is M with the same control u . We prove it again by contradiction. We assume that there exists another control $\tilde{u} \in L^\infty((t_0, t_1); [w, 1])$ such that

$$M^{\tilde{u}}(t_1) > M. \quad (29)$$

Then by the continuity of $M^{\tilde{u}}(t)$ with respect to time t , there exists a time $\tilde{t}_1 < t_1$ such that

$$M^{\tilde{u}}(\tilde{t}_1) = M, \quad (30)$$

which is a contradiction with the minimal property of t_1 . This concludes the proof of the equivalence between the two optimal control problems. \blacksquare

3 Results on optimal control for finite Dirac masses

In this section, we give results on the optimal control problem (16) when the initial data $\rho_0 \geq 0$ is a linear combination of a finite number of Dirac masses. For $(\alpha, \beta)^{\text{tr}} \in \mathbb{R}^2$, we denote by $\delta_{\alpha, \beta}$ the Dirac mass at $(\alpha, \beta)^{\text{tr}}$. We assume that, for some positive integer N , there exist N elements $((x_1^{k0}, x_2^{k0}))_{k \in \{1, \dots, N\}}$ of $[0, 1] \times [0, y_s]$ and N strictly positive real numbers $(x_3^{k0})_{k \in \{1, \dots, N\}}$ such that

$$\rho_0 := \sum_{k=1}^N x_3^{k0} \delta_{x_1^{k0}, x_2^{k0}}. \quad (31)$$

First, we formulate our problem within a hybrid framework. Let us denote by X_α and X_β two disjoint and open subsets of \mathbb{R}^3 , where

$$\begin{aligned} X_\alpha &:= \left\{ (x_1, x_2, x_3) \in \mathbb{R}^3 \mid x_2 < y_s \right\}, \\ X_\beta &:= \left\{ (x_1, x_2, x_3) \in \mathbb{R}^3 \mid x_2 > y_s \right\}. \end{aligned}$$

The boundary between the two domains $X_\alpha(t)$ and $X_\beta(t)$ can be written as

$$\left\{ (x_1, x_2, x_3) \in \mathbb{R}^3 \mid F(x) = 0 \right\},$$

where

$$F(x) := x_2 - y_s. \quad (32)$$

We consider the following Cauchy problem:

$$\begin{cases} \dot{x}^k = f(x^k, u), & u \in L^\infty((t_0, t_1); [w, 1]), \quad t \in [t_0, t_1], \\ x^k(t_0) = x^{k0}, \end{cases} \quad (33)$$

where

$$f(x^k, u) := \begin{cases} f_\alpha(x^k, u), & x^k \in X_\alpha, \\ f_\beta(x^k, u), & x^k \in X_\beta, \end{cases} \quad x^k = \begin{pmatrix} x_1^k \\ x_2^k \\ x_3^k \end{pmatrix}, \quad x^{k0} = \begin{pmatrix} x_1^{k0} \\ x_2^{k0} \\ x_3^{k0} \end{pmatrix}, \quad (34)$$

with

$$f_\alpha(x^k, u) := \begin{pmatrix} 1 \\ a(x_2^k) + b(x_2^k)u \\ c_s x_3^k \end{pmatrix}, \quad f_\beta(x^k, u) := \begin{pmatrix} 1 \\ a(x_2^k) + b(x_2^k)u \\ 0 \end{pmatrix}.$$

It is easy to check that the maximal solution to Cauchy problem (33) is defined on $[t_0, t_1]$.

One can also easily check that the solution to Cauchy problem (5), as defined in section 2.3, is

$$\rho(t) = \sum_{k=1}^N x_3^k(t) \delta_{x_1^k(t), x_2^k(t)}. \quad (35)$$

The cost function J defined in (15) now becomes

$$J(u) = \sum_{k=1}^N -x_2^k(t_1) x_3^k(t_1). \quad (36)$$

We define

$$f^0(x^k, u) := \begin{cases} f_\alpha^0(x^k, u), & x^k \in X_\alpha, \\ f_\beta^0(x^k, u), & x^k \in X_\beta, \end{cases}$$

where

$$\begin{aligned} f_\alpha^0(x^k, u) &= -(a(x_2^k) + b(x_2^k)u) + c_s x_2^k x_3^k, \\ f_\beta^0(x^k, u) &= -(a(x_2^k) + b(x_2^k)u) x_3^k. \end{aligned}$$

Hence, to minimize (36) is equivalent to minimize

$$J(u) = \sum_{k=1}^N \int_{t_0}^{t_1} f^0(x^k, u) dt - \sum_{k=1}^N x_2^{k0} x_3^{k0}. \quad (37)$$

One of the goals of this section is to prove that there exists an optimal control for this optimal control problem and that, if (17) and (18) hold, every optimal control is bang-bang with only one switching time. More precisely, we prove the following Theorem 3.1 and Theorem 3.2.

Using (10), we can easily check the continuity of the exit time with respect to the weak- L^∞ topology for the control. From the standard Arzelà-Ascoli theorem, we then get the following theorem (see also [31, Theorem 1])

Theorem 3.1. *The optimal control problem (16) has a solution, i.e., there exists $u_* \in L^\infty((t_0, t_1); [w, 1])$ such that*

$$J(u_*) = \inf_{u \in L^\infty((t_0, t_1); [w, 1])} J(u).$$

Theorem 3.2. *Let us assume that (17) and (18) hold. Then, for every optimal control u_* for the optimal control problem (16), there exists $t_* \in (t_0, t_1)$ such that*

$$u_* = w \text{ in } (t_0, t_*) \text{ and } u_* = 1 \text{ in } (t_*, t_1). \quad (38)$$

This section is organized as follows. In subsection 3.1 we prove a HMP (Theorem 3.3) for our optimal control problem. In subsection 3.2 we show how to deduce Theorem 3.2 from Theorem 3.3.

3.1 Hybrid Maximum Principle

Let us define the Hamiltonian

$$\begin{aligned} \mathcal{H} : (\mathbb{R}^3)^N \times \mathbb{R} \times (\mathbb{R}^3)^N &\rightarrow \mathbb{R} \\ (x, u, \psi) = ((x^1, x^2, \dots, x^N), u, (\psi^1, \psi^2, \dots, \psi^N)) &\mapsto \mathcal{H}(x, u, \psi) \end{aligned}$$

by

$$\mathcal{H}(x, u, \psi) := \sum_{k=1}^N \langle f(x^k, u), \psi^k \rangle - \sum_{k=1}^N f^0(x^k, u). \quad (39)$$

In (39) and in the following, $\langle a, b \rangle$ denotes the usual scalar product of $a \in \mathbb{R}^3$ and $b \in \mathbb{R}^3$. Let us also define the Hamilton-Pontryagin function $H : (\mathbb{R}^3)^N \times (\mathbb{R}^3)^N \rightarrow \mathbb{R}$ by

$$H(x, \psi) := \max_{u \in [w, 1]} \mathcal{H}(x, u, \psi). \quad (40)$$

It follows from [12, 15, 22, 31, 36, 37] that we have the following theorem:

Theorem 3.3. *Let $u_* \in L^\infty((t_0, t_1); [w, 1])$ be an optimal control for the optimal control problem (16). Let $x_*^k = (x_{*1}^k, x_{*2}^k, x_{*3}^k)^{tr}$, $k = 1, \dots, N$, be the corresponding optimal trajectory, i.e. $x_*^k \in (W^{1,\infty}(t_0, t_1))^3$ are solutions to the following Cauchy problems*

$$\dot{x}_{*1}^k = 1, \quad x_{*1}^k(t_0) = x_1^{k0}, \quad (41)$$

$$\dot{x}_{*2}^k = a(x_{*2}^k) + b(x_{*2}^k) u_*, \quad x_{*2}^k(t_0) = x_2^{k0}, \quad (42)$$

$$\dot{x}_{*3}^k = c(x_{*2}^k) x_{*3}^k, \quad x_{*3}^k(t_0) = x_3^{k0}. \quad (43)$$

*If $y_s \in \{x_{*2}^k(t); t \in [t_0, t_1]\}$, let $\hat{t}_k \in [t_0, t_1]$ be the exit time for the k -th Dirac mass, i.e. the unique time $\hat{t}_k \in [t_0, t_1]$ such that $x_{*2}^k(\hat{t}_k) = y_s$.*

*If $y_s \notin \{x_{*2}^k(t); t \in (t_0, t_1]\}$, let $\hat{t}_k = t_1 + 1$. Then, there exists N vector functions $\psi^k = (\psi_1^k, \psi_2^k, \psi_3^k)^{tr} \in (W^{1,\infty}(((t_0, \hat{t}_k) \cup (\hat{t}_k, t_1)) \cap (t_0, t_1)))^3$, such that*

$$\psi_1^k = 0, \quad (44)$$

$$\begin{aligned} \psi_2^k &= -(a'(x_{*2}^k) + b'(x_{*2}^k)u_*)\psi_2^k - (a'(x_{*2}^k) + b'(x_{*2}^k)u_*)x_{*3}^k \\ &\quad - c(x_{*2}^k)x_{*3}^k \quad \text{in } ((t_0, \hat{t}_k) \cup (\hat{t}_k, t_1)) \cap (t_0, t_1), \end{aligned} \quad (45)$$

$$\psi_3^k = -c(x_{*2}^k)\psi_3^k - (a(x_{*2}^k) + b(x_{*2}^k)u_*) - c(x_{*2}^k)x_{*2}^k, \quad (46)$$

$$\psi_1^k(t_1) = \psi_3^k(t_1) = 0, \quad (47)$$

and

$$\psi_1^k(\hat{t}_k - 0) = \psi_1^k(\hat{t}_k + 0), \quad (48)$$

$$\psi_3^k(\hat{t}_k - 0) = \psi_3^k(\hat{t}_k + 0), \quad (49)$$

- if $\hat{t}_k < t_1$,

$$\psi_2^k(\hat{t}_k + 0) - \psi_2^k(\hat{t}_k - 0) \in \left[\frac{c_s x_{*3}^k(\hat{t}_k)(y_s + \psi_3^k(\hat{t}_k))}{a(y_s) + b(y_s)}, \frac{c_s x_{*3}^k(\hat{t}_k)(y_s + \psi_3^k(\hat{t}_k))}{a(y_s) + b(y_s)w} \right], \quad (50)$$

$$\psi_2^k(t_1) = 0, \quad (51)$$

- if $\hat{t}_k = t_1$,

$$-\psi_2^k(t_1) \in \left[0, \frac{c_s x_{*3}^k(t_1)y_s}{a(y_s) + b(y_s)w} \right]. \quad (52)$$

Moreover, there exists a constant h such that the following condition holds

$$\mathcal{H}(x_*^k(t), u_*(t), \psi^k(t)) = H(x_*^k(t), \psi^k(t)) = h, \quad a.e. \quad t \in (t_0, t_1). \quad (53)$$

Proof of Theorem 3.3. For sake of simplicity, we give the proof only for one Dirac mass ($N = 1$). To simplify the notations we also delete the $k = 1$ index. For more than one Dirac mass, the proof is similar.

Applying the HMPs given in [12, 15, 22, 31, 36, 37], we get the existence of $\psi = (\psi_1, \psi_2, \psi_3)^{\text{tr}} \in (W^{1,\infty}(((t_0, \hat{t}) \cup (\hat{t}, t_1)) \cap (t_0, t_1)))^3$ such that (44) to (49) and, if $\hat{t} < t_1$, (51) hold, together with the existence of $h \in \mathbb{R}$ such that (53) is satisfied. Let us finally deal with (50) and (52). Let us treat only the case where $\hat{t} < t_1$ (the case $\hat{t} = t_1$ being similar). We follow [22]. From (53), there exist $v_1 \in [w, 1]$ and $v_2 \in [w, 1]$ such that

$$\begin{aligned} H(\hat{t} - 0) &= \max_{v \in [w, 1]} \mathcal{H}(x(\hat{t} - 0), v, \psi(\hat{t} - 0)) = H(x(\hat{t} - 0), v_1, \psi(\hat{t} - 0)) \\ &= \langle f(x(\hat{t} - 0), v_1), \psi(\hat{t} - 0) \rangle - f^0(x(\hat{t} - 0), v_1), \end{aligned} \quad (54)$$

$$\begin{aligned} H(\hat{t} + 0) &= \max_{v \in [w, 1]} \mathcal{H}(x(\hat{t} + 0), v, \psi(\hat{t} + 0)) = H(x(\hat{t} + 0), v_2, \psi(\hat{t} + 0)) \\ &= \langle f(x(\hat{t} + 0), v_2), \psi(\hat{t} + 0) \rangle - f^0(x(\hat{t} + 0), v_2). \end{aligned} \quad (55)$$

From (53), (54) and (55), we obtain

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) = \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t})) + b(y_s)(x_3(\hat{t}) + \psi_2(\hat{t} - 0))(v_1 - v_2)}{a(y_s) + b(y_s)v_2}, \quad (56)$$

and

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) = \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t})) + b(y_s)(x_3(\hat{t}) + \psi_2(\hat{t} + 0))(v_1 - v_2)}{a(y_s) + b(y_s)v_1}. \quad (57)$$

The Hamiltonian (39) becomes

$$\begin{aligned} \mathcal{H}(x, u, \psi) &= (a(x_2) + c(x_2)x_2)x_3 + \psi_1 + a(x_2)\psi_2 + c(x_2)x_3\psi_3 \\ &\quad + b(x_2)(x_3 + \psi_2)u, \quad t \in [t_0, t_1]. \end{aligned} \quad (58)$$

Let us denote

$$\Phi := x_3 + \psi_2. \quad (59)$$

When $t \neq \hat{t}$, from (7), (43) and (45), we obtain

$$\frac{d\Phi}{dt} = -(a'(x_2) + b'(x_2)u) \Phi. \quad (60)$$

Noting that

$$\Phi(t_1) > 0. \quad (61)$$

Combining (60) and (61), we get

$$\Phi(t) > 0, \quad \forall t \in (\hat{t}, t_1]. \quad (62)$$

Next, we analyze different cases:

1. When $\Phi(\hat{t} - 0) > 0$ and $\Phi(\hat{t} + 0) > 0$, we have $v_1 = v_2 = 1$. From (56) or (57), we get

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) = \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t}))}{a(y_s) + b(y_s)}. \quad (63)$$

2. When $\Phi(\hat{t} - 0) < 0$ and $\Phi(\hat{t} + 0) > 0$, we have $v_1 = w$ and $v_2 = 1$. From (56), we get

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) = \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t})) + b(y_s)\Phi(\hat{t} - 0)(w - 1)}{a(y_s) + b(y_s)}. \quad (64)$$

Since $\Phi(\hat{t} - 0) < 0$, from (64), we obtain

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) > \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t}))}{a(y_s) + b(y_s)}. \quad (65)$$

From (57), we have

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) = \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t})) + b(y_s)\Phi(\hat{t} + 0)(w - 1)}{a(y_s) + b(y_s)w}. \quad (66)$$

Since $\Phi(\hat{t} + 0) > 0$, from (66), we obtain

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) < \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t}))}{a(y_s) + b(y_s)w}. \quad (67)$$

3. When $\Phi(\hat{t} - 0) = 0$ and $\Phi(\hat{t} + 0) > 0$, from (56), we obtain

$$\psi_2(\hat{t} + 0) - \psi_2(\hat{t} - 0) = \frac{c_s x_3(\hat{t})(y_s + \psi_3(\hat{t}))}{a(y_s) + b(y_s)}. \quad (68)$$

In the three cases, we have proved that jump condition (50) holds. This concludes the proof of Theorem 3.3. ■

3.2 Proof of Theorem 3.2

In this section, we use the necessary optimality conditions given in Theorem 3.3 to prove Theorem 3.2. From now on, we assume that the target time t_1 satisfies $t_1 > \hat{t}_0$ so that all the cells will exit from Phase 1 into Phase 3 before time t_1 . We give a proof of Theorem 3.2 in the case where $N = 1$ in section 3.2.1. In section 3.2.3, we study the case where $N > 1$; in this case we need additionally to analyze the dynamics between different exit times \hat{t}_k , $k = 1, 2, \dots, N$, to obtain that there exists one and only one switching time and that the optimal switching direction is from $u = w$ to $u = 1$. In both cases $N = 1$ or $N > 1$, we give some numerical illustrations, respectively in section 3.2.2 and section 3.2.4.

3.2.1 Proof of Theorem 3.2 in the case $N = 1$

Let u be an optimal control for the optimal control problem (16) and let $x = (x_1, x_2, x_3)^{\text{tr}}$ be the corresponding trajectory. Note that, by (6), $b(x_2) > 0$. Then, by (40), (53), (58) and (59), one has, for almost every $t \in (t_0, t_1)$,

$$u(t) = 1 \quad \text{if} \quad \Phi(t) > 0, \quad (69)$$

$$u(t) = w \quad \text{if} \quad \Phi(t) < 0. \quad (70)$$

Let us recall that, under assumption (17) of Theorem 3.2, there exists one and only one $\hat{t} \in [t_0, t_1)$ such that

$$x_2(\hat{t}) = y_s. \quad (71)$$

Then

$$x_2(t) > y_s, \quad \forall t \in (\hat{t}, t_1]. \quad (72)$$

We study the case where $\hat{t} > t_0$, the case $\hat{t} = t_0$ being obvious. Thanks to (50), we get

$$\Phi(\hat{t} + 0) - \Phi(\hat{t} - 0) \geq c_s x_3(\hat{t}) \frac{y_s + \psi_3(\hat{t})}{a(y_s) + b(y_s)}. \quad (73)$$

By (42) and (46), we get

$$\frac{d(x_2 + \psi_3)}{dt} = -(x_2 + \psi_3) c(x_2), \quad (74)$$

and then, using also (7), (47), (71), (72) and (74), we obtain

$$y_s + \psi_3(\hat{t}) = (x_2 + \psi_3)(\hat{t}) = (x_2 + \psi_3)(t_1) \geq y_s. \quad (75)$$

Combining (73) with (75), we get

$$\Phi(\hat{t} - 0) \leq \Phi(\hat{t} + 0) - c_s x_3(\hat{t}) \frac{y_s}{a(y_s) + b(y_s)}. \quad (76)$$

By (6) and (60), we obtain

$$\Phi(\hat{t} + 0) = \Phi(t_1) e^{-\int_{\hat{t}}^{t_1} (2x_2(s) - c_1 u(s)) ds}. \quad (77)$$

Using the first inequality of (18), (51), (72) and (77), we get

$$\Phi(\hat{t} + 0) \leq x_3(t_1). \quad (78)$$

Noticing that $x_3(\hat{t} + 0) = x_3(t_1)$ and using (76) and (78), we get

$$\Phi(\hat{t} - 0) \leq x_3(t_1) \left(1 - c_s \frac{y_s}{a(y_s) + b(y_s)}\right). \quad (79)$$

From the second inequality of (18) and (79), we get

$$\Phi(\hat{t} - 0) < 0. \quad (80)$$

which, together with (60), gives us

$$\Phi(t) < 0, \quad t \in [t_0, \hat{t}). \quad (81)$$

Moreover, by (51), we have

$$\Phi(t) = (x_3 + \psi_2)(t_1) = x_3(t_1) > 0,$$

which together with (60), gives

$$\Phi(t) > 0, \quad t \in (\hat{t}, t_1]. \quad (82)$$

Taking $t_* = \hat{t}$ and combining (81) and (82), with (69) and (70), we conclude the proof of Theorem 3.2 in the case where $N = 1$. ■

3.2.2 Numerical illustration in the case $N = 1$

For one Dirac mass, the optimal switching time is unique. Assumption (18) is not necessary to guarantee that the optimal control is a bang-bang control with only one switching time. It is just used to guarantee that the optimal switching time coincides with the exit time. We give a numerical example to show that when c_s is “small”, there is no switch at all and the optimal control is constant ($u = 1$), while when c_s is “large”, there is a switch occurring at the exit time (see figure 3).

The default parameter values are specified in Table 1 for the numerical studies.

3.2.3 Proof of Theorem 3.2 in the case $N > 1$

Now, the Hamiltonian (39) becomes

$$\begin{aligned} \mathcal{H}(x, u, \psi) = \sum_{k=1}^N & \left((a(x_2^k) + c(x_2^k)x_2^k)x_3^k + \psi_1^k + a(x_2^k)\psi_2^k + c(x_2^k)x_3^k\psi_3^k \right. \\ & \left. + b(x_2^k)(x_3^k + \psi_2^k)u \right), \quad t \in [t_0, t_1]. \end{aligned} \quad (83)$$

t_0	initial time	0.0
t_1	final time	17.0
c_1	slope in the $b(y)$ function	11.892
c_2	origin ordinate in the $b(y)$ function	2.288
y_s	threshold maturity	6.0
w	minimal bound of the control	0.5

Table 1: Default parameter values

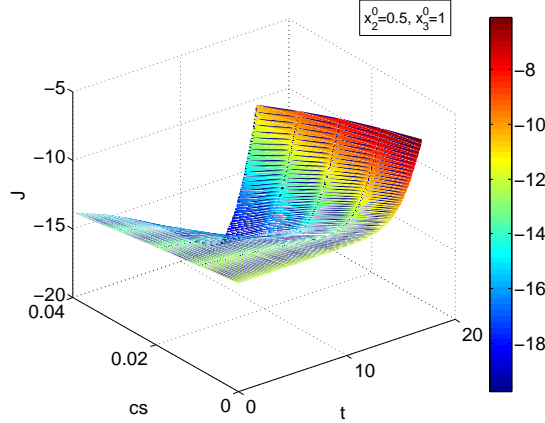


Figure 3: Value of the cost function J with respect to the switching time (t) and c_s parameter in the case of one Dirac mass. When c_s is “small”, there is no switching time ($t = 0$) and the optimal control is constant ($u = 1$), while, when c_s is “large”, the optimal control strategy consists in switching from $u = w$ to $u = 1$ at a time coinciding with the exit time. The initial values are specified in the insert.

Reordering if necessary the x^k 's, we may assume, without loss of generality, that

$$x_2^{10} < x_2^{20} < \dots < x_2^{k0} < \dots < x_2^{N0}. \quad (84)$$

Let u be an optimal control for the optimal control problem (16) and let $x = (x^1, \dots, x^k, \dots, x^N)$, with $x^k = (x_1^k, x_2^k, x_3^k)^{\text{tr}}$, be the corresponding trajectory. From (84), we have

$$\hat{t}_N < \hat{t}_{N-1} < \dots < \hat{t}_k < \dots < \hat{t}_1. \quad (85)$$

Let $\Phi_N : [t_0, t_1] \rightarrow \mathbb{R}$ be defined by

$$\Phi_N(t) := \sum_{k=1}^N b(x_2^k(t))(x_3^k(t) + \psi_2^k(t)). \quad (86)$$

Noticing that $b(x_2^k) > 0$, by (40), (53), (83) and (86), one has, for almost every $t \in (t_0, t_1)$,

$$u = w, \quad \text{if } \Phi_N(t) < 0, \quad (87)$$

$$u = 1, \quad \text{if } \Phi_N(t) > 0. \quad (88)$$

We take the time-derivative of (86) when $t \neq \hat{t}_k, k = 1, \dots, N$. From (6), we obtain

$$\dot{\Phi}_N(t) = \sum_{k=1}^N (c_1(x_2^k)^2 + 2c_2x_2^k)(x_3^k + \psi_2^k). \quad (89)$$

Similarly to the above proof for one Dirac mass, we can prove that, under assumption (18), we have, for each $k = 1, \dots, N$,

$$(x_3^k + \psi_2^k)(t) < 0, \quad \text{when } t \in (t_0, \hat{t}_k), \quad (90)$$

$$(x_3^k + \psi_2^k)(t) > 0, \quad \text{when } t \in (\hat{t}_k, t_1). \quad (91)$$

By (85), (86), (90) and (91), and note that $b(x_2^k) > 0$, we get

$$\Phi_N(t) < 0, \quad \text{when } t \in (t_0, \hat{t}_N), \quad (92)$$

$$\Phi_N(t) > 0, \quad \text{when } t \in (\hat{t}_1, t_1). \quad (93)$$

The key point now is to study the dynamics of Φ_N between different exit times \hat{t}_k . Let $k \in \{1, \dots, N-1\}$ and let us assume that

$$\Phi_N(t) = 0, \quad \text{for some } t \in (\hat{t}_{k+1}, \hat{t}_k). \quad (94)$$

From (86) and (94), we get

$$x_3^k(t) + \psi_2^k(t) = - \sum_{i \neq k} \frac{b(x_2^i(t))}{b(x_2^k(t))} (x_3^i(t) + \psi_2^i(t)). \quad (95)$$

From (90) and (91), for every $t \in (\hat{t}_{k+1}, \hat{t}_k)$,

$$x_3^i(t) + \psi_2^i(t) < 0, \quad \text{when } i \leq k-1, \quad (96)$$

$$x_3^i(t) + \psi_2^i(t) > 0, \quad \text{when } i \geq k+1. \quad (97)$$

From (6), (89) and (95), we get

$$\begin{aligned} \dot{\Phi}_N(t) &= \sum_{i \leq k-1} \frac{x_3^i + \psi_2^i}{b(x_2^k)} (c_1^2 x_2^i x_2^k + 2c_2^2 + c_1 c_2 (x_2^i + x_2^k)) (x_2^i - x_2^k) \\ &+ \sum_{i \geq k+1} \frac{x_3^i + \psi_2^i}{b(x_2^k)} (c_1^2 x_2^i x_2^k + 2c_2^2 + c_1 c_2 (x_2^i + x_2^k)) (x_2^i - x_2^k). \end{aligned} \quad (98)$$

From (84), we get

$$x_2^i(t) - x_2^k(t) < 0, \quad \text{when } i \leq k-1, \quad (99)$$

$$x_2^i(t) - x_2^k(t) > 0, \quad \text{when } i \geq k+1. \quad (100)$$

Using (96) to (100), we get

$$\dot{\Phi}_N(t) > 0 \quad \text{whenever} \quad \Phi_N(t) = 0, \quad \forall t \in (\hat{t}_{k+1}, \hat{t}_k). \quad (101)$$

Combining (87), (88), (92), (93) and (101) together, we get the existence of $t_* \in (t_0, t_1)$ such that

$$u_* = w \quad \text{in} \quad (t_0, t_*) \quad \text{and} \quad u_* = 1 \quad \text{in} \quad (t_*, t_1).$$

This concludes the proof of Theorem 3.2. ■

3.2.4 Numerical illustration in the case $N > 1$

The optimal control can in some cases be not unique for more than one Dirac mass. Let us consider the case of two Dirac masses as an example. The optimal switching time may happen either at the first exit time or at the second exit time (see figure 4), or between the two exit times (see figure 5).

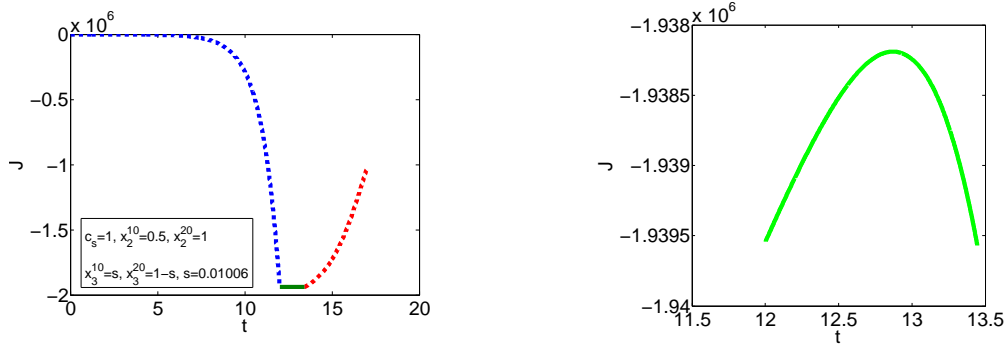


Figure 4: Value of the cost function J with respect to the switching time (t) in the case of two Dirac masses and a “large” value of c_s ($c_s = 1.0$). In the left panel, the three-part curve represents the value of the cost function obtained after switching from $u = w$ to $u = 1$ at time t . Blue dashed curve: switching time occurring before the first exit time; green solid curve: switching time occurring in between the two exit times; red dashed curve: switching time occurring after the second exit time. The initial values are specified in the insert. The right panel is a zoom on the green solid curve displayed on the left panel. There are two optimal switching times which coincide with the two exit times.

Remark 3.1. *The values of the cost function J in Fig 3 and Fig 4, Fig 5 have different orders. This is due to differences in the value of the proliferation rate c_s . There is a great contribution of the cell mass to the criterion when c_s is “large” in Fig 4 and Fig 5.*

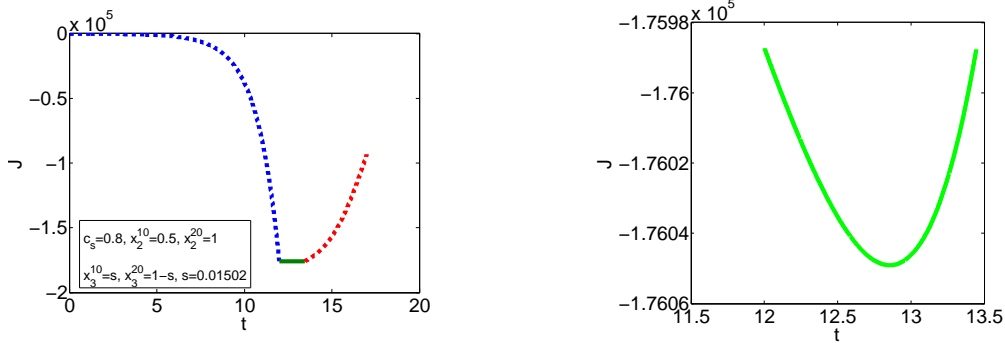


Figure 5: Value of the cost function J with respect to the switching time (t) in the case of two Dirac masses and a “large” value of c_s ($c_s = 0.8$). In the left panel, the three-part curve represents the value of the cost function obtained after switching from $u = w$ to $u = 1$ at time t . Blue dashed curve: switching time occurring before the first exit time; green solid curve: switching time occurring in between the two exit times; red dashed curve: switching time occurring after the second exit time. The initial values are specified in the insert. The right panel is a zoom on the green solid curve displayed on the left panel. There is one single optimal switching time, which occurs in between the two exit times.

4 Optimal control in the PDE case

In this section, we study the optimal control in the PDE case. We give the proof of Theorem 2.1. We first give an explicit expression for the cost function J defined in (15).

Let us define a new map

$$\begin{aligned} e : [0, y_s] \times L^\infty((t_0, t_1); [w, 1]) &\rightarrow [t_0, t_1] \\ (y_0, u) &\mapsto e(y_0, u) \end{aligned}$$

by requiring $\Psi(e(y_0, u), y_0, u) = y_s$, where Ψ is defined by (13). Note that, under assumption (17), one has, for every $y_0 \in [0, y_s]$, the existence of $t \in [t_0, t_1]$ such that

$$\Psi(t, y_0, u) = y_s. \quad (102)$$

Again, (10) implies that there exists at most one $t \in [t_0, t_1]$ such that (102) holds. This shows that e is well defined. Moreover, we have the following lemma

Lemma 4.1. *Let $(y_0^n)_{n \in \mathbb{N}}$ be a sequence of elements in $[0, y_s]$ and $(u^n)_{n \in \mathbb{N}}$ be a sequence of elements in $L^\infty((t_0, t_1); [w, 1])$. Let us assume that, for some $y_0 \in [0, y_s]$ and for some $u \in L^\infty((t_0, t_1); [w, 1])$,*

$$\begin{aligned} y_0^n &\rightarrow y_0 \text{ as } n \rightarrow +\infty, \\ u^n &\overset{*}{\rightharpoonup} u \text{ in } L^\infty(t_0, t_1) \text{ as } n \rightarrow +\infty. \end{aligned}$$

Then

$$e(y_0^n, u^n) \rightarrow e(y_0, u) \text{ as } n \rightarrow +\infty.$$

Let now ρ_0 be a Borel measure on $\mathbb{R} \times \mathbb{R}$ such that (21) and (22) hold. Using (23), (15) becomes

$$J(u) = - \iint_{[0,1] \times [0,y_s]} \Psi(t_1, y_0, u) e^{c_s e(y_0, u)} d\rho_0(x_0, y_0). \quad (103)$$

In order to emphasize the dependence of J on the initial data ρ_0 , from now on we write $J(\rho_0, u)$ for $J(u)$.

It is well known that there exists a sequence $((x_0^{i,n}, y_0^{i,n}, \lambda_0^{i,n}))_{1 \leq i \leq n, n \in \mathbb{N}}$ of elements in $[0, 1] \times [0, y_s] \times (0, +\infty)$ such that, if

$$\rho_0^n := \sum_{i=1}^n \lambda_0^{i,n} \delta_{x_0^{i,n}, y_0^{i,n}}, \quad (104)$$

then

$$\begin{aligned} \lim_{n \rightarrow +\infty} \iint_{[0,1] \times [0,y_s]} \varphi(x_0, y_0) d\rho_0^n(x_0, y_0) = \\ \iint_{[0,1] \times [0,y_s]} \varphi(x_0, y_0) d\rho_0(x_0, y_0), \quad \forall \varphi \in C^0([0, 1] \times [0, y_s]). \end{aligned} \quad (105)$$

From Theorem 3.1 and Theorem 3.2, there exists $t_*^n \in [t_0, t_1]$ such that, if $u_*^n : [t_0, t_1] \rightarrow [w, 1]$ is defined by

$$u_*^n = w \text{ in } [t_0, t_*^n) \text{ and } u_*^n = 1 \text{ in } (t_*^n, t_1], \quad (106)$$

then

$$J(\rho_0^n, u_*^n) \leq J(\rho_0^n, u), \quad \forall u \in L^\infty((t_0, t_1); [w, 1]). \quad (107)$$

Extracting a subsequence if necessary, we may assume without loss of generality the existence of $t_* \in [t_0, t_1]$ such that

$$\lim_{n \rightarrow +\infty} t_*^n = t_*. \quad (108)$$

Let us define $u_* : [t_0, t_1] \rightarrow [w, 1]$ by

$$u_* = w \text{ in } [t_0, t_*) \text{ and } u_* = 1 \text{ in } (t_*, t_1]. \quad (109)$$

Then, using (106), (108) and (109), one gets

$$\Psi(t_1, \cdot, u_*^n) \rightarrow \Psi(t_1, \cdot, u_*) \text{ in } C^0([0, y_s]) \text{ as } n \rightarrow +\infty. \quad (110)$$

Moreover, from (106), (108) and (109), one has

$$u_*^n \xrightarrow{*} u_* \text{ in } L^\infty(t_0, t_1) \text{ as } n \rightarrow +\infty. \quad (111)$$

From Lemma 4.1 and (111), one gets

$$e(\cdot, u_*^n) \rightarrow e(\cdot, u_*) \text{ in } C^0([0, y_s]) \text{ as } n \rightarrow +\infty. \quad (112)$$

From (103), (105), (110) and (112) and a classical theorem on the weak topology (see, e.g., [5, (iv) of Proposition 3.13, p. 63]), one has

$$J(\rho_0^n, u_*^n) \rightarrow J(\rho_0, u_*) \text{ as } n \rightarrow +\infty. \quad (113)$$

Let now $u \in L^\infty((t_0, t_1); [w, 1])$. From Lemma 4.1, (103) and (105), one gets

$$J(\rho_0^n, u) \rightarrow J(\rho_0, u) \text{ as } n \rightarrow +\infty. \quad (114)$$

Finally, letting $n \rightarrow +\infty$ in (107) and using (113) together with (114), one has

$$J(\rho_0, u_*) \leq J(\rho_0, u),$$

which concludes the proof of Theorem 2.1. ■

Appendix

Sketch of another proof of Theorem 3.3

In this section, we sketch another proof of Theorem 3.3, using approximation arguments inspired from [35]. The interest of this approach is that it might be more suitable to prove a maximal principle also in the PDE case. For sake of simplicity, we show the proof only for one Dirac mass. The idea is first to construct a smooth optimal control problem. For the smooth optimal control problem, we can apply PMP. By passing to the limit, we then derive necessary optimality conditions for our discontinuous problem.

Step 1. Let us denote by $\chi : \mathbb{R} \rightarrow \mathbb{R}$ the characteristic function of $(-\infty, y_s)$, i.e.

$$\chi(x_2) = \begin{cases} 1, & \forall x_2 \in (-\infty, y_s), \\ 0, & \forall x_2 \in [y_s, +\infty). \end{cases} \quad (115)$$

Let $(w_i)_{i \in \mathbb{N}^*}$ be a sequence of elements in $C^\infty(\mathbb{R})$ such that

$$0 \leq w_i, \quad \int_{\mathbb{R}} w_i(x) dx = 1, \quad \text{support } w_i \subset [-1/i, 0], \quad \forall i \in \mathbb{N}^*, \quad (116)$$

and, for some $C > 0$,

$$|w_i'(x)| \leq Ci^2, \quad \forall x \in \mathbb{R}, \quad \forall i \in \mathbb{N}^*, \quad (117)$$

(clearly such a sequence does exist). Then, we define a sequence of functions $(\chi_i)_{i \in \mathbb{N}^*}$ from \mathbb{R} into \mathbb{R} as follows:

$$\chi_i(x) := \int_{\mathbb{R}} \chi(y) w_i(x-y) dy = \int_{-\infty}^{y_s} w_i(x-y) dy = \int_{x-y_s}^{+\infty} w_i(z) dz, \quad \forall i \in \mathbb{N}^*, \quad \forall x \in \mathbb{R}. \quad (118)$$

Let $f_i : \mathbb{R}^3 \times \mathbb{R} \rightarrow \mathbb{R}^3$ be defined by

$$f_i(x, u) := \begin{pmatrix} 1 \\ a(x_2) + b(x_2)u \\ c_s \chi_i(x_2)x_3 \end{pmatrix}, \quad \forall x = (x_1, x_2, x_3)^{\text{tr}} \in \mathbb{R}^3, \quad \forall u \in \mathbb{R}. \quad (119)$$

Let u_* be an optimal control for the optimal control problem (16) and let x_* be the associated trajectory. Let $(z_i)_{i \in \mathbb{N}^*}$ be a sequence of uniformly bounded elements of $C^1([t_0, t_1])$ such that

$$z_i \rightarrow u_* \text{ in } L^2(t_0, t_1) \text{ as } i \rightarrow +\infty. \quad (120)$$

Let us then define $J_i : L^\infty((t_0, t_1); [w, 1]) \rightarrow \mathbb{R}$ by

$$J_i(u) := - \int_{t_0}^{t_1} (a(x_2) + b(x_2)u + c_s \chi_i(x_2)x_2)x_3 dt + \frac{1}{\sqrt{i}} \int_{t_0}^{t_1} |u(t) - z_i(t)|^2 dt - x_2^0 x_3^0,$$

where $x : [t_0, t_1] \rightarrow \mathbb{R}^3$ is the solution to the Cauchy problem

$$\dot{x} = f_i(x, u), \quad x(t_0) = x^0. \quad (121)$$

We consider the following optimal control problem

$$\text{minimize } J_i(u) \text{ for } u \in L^\infty((t_0, t_1); [w, 1]). \quad (\mathcal{P}_i)$$

For any $i = 1, 2, \dots$, problem (\mathcal{P}_i) is a “smooth” optimal control problem. By a classical result in optimal control theory (see, e.g., [25, Corollary 2, p. 262]), there exists an optimal control u_i for problem (\mathcal{P}_i) . Let x_i be the optimal trajectory corresponding to the control u_i for dynamics (121). We have the following lemma (compare to [35, Lemma 4]):

Lemma 4.2. *The following holds as $i \rightarrow +\infty$*

$$u_i \rightarrow u_* \text{ in } L^2(t_0, t_1), \quad (122)$$

$$x_i \rightarrow x_* \text{ in } C^0([t_0, t_1]; \mathbb{R}^3), \quad (123)$$

$$\chi_i(x_{i2}) \rightarrow \chi(x_{*2}) \text{ in } L^1(t_0, t_1). \quad (124)$$

Step 2. We now deduce necessary optimality conditions for the optimal control problem (16) in the form of PMP. The Hamiltonian and the Hamilton-Pontryagin function for problem (\mathcal{P}_i) are respectively

$$\mathcal{H}_i(x, u, \psi) = \langle f_i(x, u), \psi \rangle + (a(x_2) + b(x_2)u + c_s \chi_i(x_2)x_2)x_3 - \frac{1}{\sqrt{i}} |u - z_i(t)|^2, \quad (125)$$

$$H_i(x, \psi) = \max_{u \in [w, 1]} \mathcal{H}_i(x, u, \psi). \quad (126)$$

By the PMP -see, e.g., [25, Theorem 2, p. 319] or [4, Section 6.5]-, there exists an absolutely continuous function $\psi_i : [t_0, t_1] \rightarrow \mathbb{R}^3$ such that

$$\dot{\psi}_i \stackrel{\text{a.e.}}{=} - \left[\frac{\partial f_i}{\partial x}(x_i, u_i) \right]^{\text{tr}} \psi_i - \frac{\partial}{\partial x} ((a(x_{i2}) + b(x_{i2})u_i + c_s \chi_i(x_{i2})x_{i2})x_{i3}), \quad (127)$$

$$\psi_i(t_1) = 0, \quad (128)$$

and there exist constants h_i such that

$$\mathcal{H}_i(x_i(t), u_i(t), \psi_i(t)) = H_i(x_i(t), \psi_i(t)) = h_i, \quad a.e. \quad t \in (t_0, t_1). \quad (129)$$

Let us denote $\psi_i = (\psi_{i1}, \psi_{i2}, \psi_{i3})^{\text{tr}}$. From (119), (127) and (128), we have

$$\dot{\psi}_{i1} = 0, \quad (130)$$

$$\begin{aligned} \dot{\psi}_{i2} = & -(a'(x_{i2}) + b'(x_{i2})u_i)\psi_{i2} - c_s \chi'_i(x_{i2})x_{i3}\psi_{i3} - (a'(x_{i2}) + b'(x_{i2})u_i)x_{i3} \\ & - c_s \chi_i(x_{i2})x_{i3} - c_s x_{i2}\chi'_i(x_{i2})x_{i3}, \end{aligned} \quad (131)$$

$$\dot{\psi}_{i3} = -c_s \chi_i(x_{i2})\psi_{i3} - (a(x_{i2}) + b(x_{i2})u_i) - c_s x_{i2}\chi_i(x_{i2}), \quad (132)$$

$$\psi_{i1}(t_1) = \psi_{i2}(t_1) = \psi_{i3}(t_1) = 0. \quad (133)$$

We can prove that

$$\psi_{i1}(t) = \psi_1(t) = 0, \quad \forall t \in [t_0, t_1], \quad (134)$$

and

$$\psi_{i3} \rightarrow \psi_3 \text{ in } C^0([t_0, t_1]) \text{ as } i \rightarrow +\infty. \quad (135)$$

As far as ψ_{i2} is concerned, Theorem 3.3 in the case where $x_{*2}(t_0) = x_2^0 = y_s$ or $x_{*2}(t_1) < y_s$ follows directly from the standard PMP. Hence, we may assume that

$$x_{*2}(t_0) < y_s \leq x_{*2}(t_1). \quad (136)$$

Let us treat the case where

$$x_{*2}(t_0) < y_s < x_{*2}(t_1), \quad (137)$$

(the case $x_{*2}(t_1) = y_s$ being similar). By (10), there exists one and only one $\hat{t} \in (t_0, t_1)$ such that

$$x_{*2}(\hat{t}) = y_s. \quad (138)$$

Using (123) and (138), one also gets that, at least if i is large enough, which, from now on, will always be assumed, there exists one and only one $\hat{t}_i \in (t_0, t_1)$ and one and only one $\bar{t}_i \in (t_0, t_1)$ such that

$$x_{i2}(\hat{t}_i) = y_s, \quad x_{i2}(\bar{t}_i) = y_s - (1/i). \quad (139)$$

Using (122) and (123), we can prove

$$\hat{t}_i \rightarrow \hat{t} \text{ and } \bar{t}_i \rightarrow \hat{t} \text{ as } i \rightarrow +\infty. \quad (140)$$

It is easy to check that

$$\psi_{i2} \rightarrow \psi_2 \text{ in } C^0([t_0, \hat{t} - \varepsilon] \cup [\hat{t} + \varepsilon, t_1]), \quad \forall \varepsilon > 0. \quad (141)$$

We now prove jump condition (50) when $\hat{t} < t_1$, the proof of (52) when $\hat{t} = t_1$ being similar.

Let us integrate (131) from \bar{t}_i to \hat{t}_i , we get

$$\psi_{i2}(\hat{t}_i) - \psi_{i2}(\bar{t}_i) = A(i) + B(i), \quad (142)$$

with

$$A(i) := - \int_{\bar{t}_i}^{\hat{t}_i} ((a'(x_{i2}) + b'(x_{i2}) u_i) (\psi_{i2} + x_{i3}) + c_s \chi_i(x_{i2}) x_{i3}) dt, \quad (143)$$

$$B(i) := - \int_{\bar{t}_i}^{\hat{t}_i} c_s x_{i3} (x_{i2} + \psi_{i3}) \chi_i'(x_{i2}) dt. \quad (144)$$

It is easy to obtain that

$$A(i) \rightarrow 0 \text{ as } i \rightarrow +\infty. \quad (145)$$

For $B(i)$, we perform the change of variable $\tau = x_{i2}(t)$. By (139) and (144), we get

$$B(i) = - \int_{y_s - (1/i)}^{y_s} \frac{c_s x_{i3}(x_{i2}^{-1}(\tau)) (\tau + \psi_{i3}(x_{i2}^{-1}(\tau)))}{a(\tau) + b(\tau)u(x_{i2}^{-1}(\tau))} \chi_i'(\tau) d\tau. \quad (146)$$

Let us point out that, from (116) and (118), one has

$$\int_{y_s - (1/i)}^{y_s} \chi_i'(\tau) d\tau = -1, \quad \chi_i' \leq 0. \quad (147)$$

From (10), (123), (135), (146), (147), one gets that

$$\frac{c_s x_{*3}(\hat{t})(y_s + \psi_3(\hat{t}))}{a(y_s) + b(y_s)} \leq \liminf_{i \rightarrow +\infty} B(i) \leq \limsup_{i \rightarrow +\infty} B(i) \leq \frac{c_s x_{*3}(\hat{t})(y_s + \psi_3(\hat{t}))}{a(y_s) + b(y_s)w},$$

which, together with (140), (141), (142) and (145), gives (50).

Letting $i \rightarrow +\infty$ in (129), we get the existence of h such that (53) holds. This concludes the proof of Theorem 3.3. ■

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