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Optimization of an Amplification Protocol for Misfolded Proteins by using Relaxed Control

Jean-Michel Coron*

Pierre Gabriel[†]

Peipei Shang[‡]

Abstract

We investigate an optimal control problem which arises in the optimization of an amplification technique for misfolded proteins. The improvement of this technique may play a role in the detection of prion diseases. The model consists in a linear system of differential equations with a nonlinear control. The appearance of oscillations in the numerical simulations is understood by using the Perron and Floquet eigenvalue theory for nonnegative irreducible matrices. Then to overcome the unsolvability of the optimal control, we relax the problem. In the two dimensional case we solve explicitly the optimal relaxed control problem when the final time is large enough.

Keywords: optimal control, relaxed control, Perron eigenvalue, Floquet eigenvalue, structured populations.

2010 Mathematics Subject Classification. 49J15, 35Q92, 37N25.

1 Introduction

Transmissible Spongiform Encephalopathies (TSE) are fatal, infectious, neurodegenerative diseases. They include bovine spongiform encephalopathies (BSE) in cattle, scrapie in sheep and Creutzfeldt-Jakob disease (CJD) in human. During the so-called “mad-cow crisis” in the 90’s, people were infected by a variant of BSE by ingesting contaminated pieces of beef. More recently, CJD was transmitted between humans via blood or growth hormones. Because of the long incubation times (some decades), TSE still represent an important public health risk. Indeed, there is no *ante mortem* diagnosis currently available to detect infected individuals and prevent possible contaminations. A promising tool to design a diagnosis test is the protein misfolded cyclic amplification (PMCA) technique [5, 27, 28].

The PMCA principle is based on the “protein-only hypothesis” [14, 25]. According to this widely accepted hypothesis, the infectious agent of TSE, known as prions, may consist in misfolded proteins called PrP^{sc} (for Prion Protein scrapie). The PrP^{sc} replicates in a self-propagating process, by converting the normal form of PrP (called PrP^c for Prion Protein cellular) into PrP^{sc}. The PMCA

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enabled to consolidate the idea of an autocatalytic replication of PrPsc by nucleated polymerization. In this model originally proposed by Landsbury [15], PrPsc is considered to be a polymeric form of PrPc. Polymers can lengthen by addition of PrPc monomers, and they can replicate by splitting into smaller fragments. The PrPc is mainly expressed by the cells of the central nervous system, so PrPsc concentrates in this zone. The amount of PrPsc in tissues such as blood is very small and this is why it is very difficult to diagnose an infected individual.

The PMCA mimics *in vitro* the nucleation/polymerization mechanism occurring *in vivo* with the aim to quickly amplify the polymers present in minute amount in an infected sample. It is a cyclic process, where each cycle consists in two phases: the *incubation* phase during which the polymerization is favored due to the presence of a large quantity of PrPc monomers, and the *sonication* phase when the PrPsc polymers are broken down with ultrasounds. The *incubation* phase is expected to increase the size of the polymers, while the ultrasounds are known to increase the fragmentation of the polymers and so increase their number. This technique could allow us to detect PrPsc in the samples of blood for instance. But for now, it is not efficient enough to do so. Mathematical modelling and optimization tools can help to optimize the PMCA protocol.

The mathematical modeling of prion proliferation with ordinary or partial differential equation (PDE) produced a large literature since the first model of Griffith [14]. Today, the most widely studied nucleation/polymerization model is the one of Masel [22]. A PDE version of this model has been introduced by Greer *et al.* [13] and studied by many authors including [3, 4, 8, 10, 11, 16, 26, 30, 33]. Starting from it, we propose to model the PMCA with the following controlled size-structured PDE

$$\partial_t f(t, \xi) + r(u(t)) \partial_\xi (\tau(\xi) f(t, \xi)) = u(t) \left(\int_\xi^\infty \beta(\zeta) \kappa(\xi, \zeta) f(t, \zeta) d\zeta - \beta(\xi) f(t, \xi) \right) \quad (1.1)$$

with the boundary condition $f(t, 0) = 0$ for every time $t \geq 0$. The unknown $f(t, \xi)$ is the number, or density of polymers of size $\xi > 0$ at time t . The size of the polymers increases by polymerization with respect to the growth rate $\tau(\xi)$. The terms in the large brackets on the right hand side of (1.1) form the fragmentation operator, with $\beta(\xi)$ the global fragmentation rate and $\kappa(\xi, \zeta)$ the fragmentation kernel. The conservation of the quantity of polymerized proteins during the fragmentation process requires that this kernel satisfies the following standard condition (see [7] for instance)

$$\int_0^\zeta \xi \kappa(\xi, \zeta) d\xi = \zeta. \quad (1.2)$$

The fragmentation is modulated by a multiplicative factor $u(t) \in [u_{\min}, u_{\max}]$ which represents the *sonication* intensity. The control $u(t) \equiv u_{\min} = 1$ corresponds to the absence of *sonication*, while $u(t) \equiv u_{\max} > 1$ represents the maximal power of the *sonicator*. We assume that the *sonication* does not only increase the fragmentation but also influence the polymerization process. This is taken into account by the positive term $r(u(t))$ where the function r should be decreasing if we consider that the ultrasounds have a negative effect on the growth of the polymers. The optimal control problem we are interested in is, starting with a given initial size distribution $f(t = 0, \xi) = f^0(\xi) \geq 0$, to maximize the objective

$$J(u) = \int_0^\infty \xi f(T, \xi) d\xi, \quad (1.3)$$

which represents the total quantity of polymerized proteins at a given final time T .

For the mathematical study in this paper, we consider a n -compartment approximation of (1.1)

$$\frac{dx_i}{dt} + r(u(t))(\tau_i x_i - \tau_{i-1} x_{i-1}) = u(t) \left(\sum_{j=i+1}^n \beta_j \kappa_{i,j} x_j - \beta_i x_i \right), \quad \text{for } 1 \leq i \leq n,$$

with $\beta_1 = 0$ and $\tau_n = 0$. This is a finite dimensional ordinary differential system, linear in $x = (x_1, \dots, x_n)^T$, which can be written under a matrix form

$$\begin{cases} \dot{x} = uFx + r(u)Gx, & t \in [0, T], \\ x(t=0) = x^0 > 0, \end{cases} \quad (1.4)$$

where G is the growth matrix

$$G = \begin{pmatrix} -\tau_1 & & & & & \\ \tau_1 & -\tau_2 & & & & \\ & \ddots & \ddots & & & \\ & & & \ddots & & \\ & & 0 & \tau_{n-2} & -\tau_{n-1} & \\ & & & & \tau_{n-1} & 0 \end{pmatrix}, \quad (1.5)$$

and F is the fragmentation matrix

$$F = \begin{pmatrix} 0 & & & & \\ & -\beta_2 & & (\kappa_{ij}\beta_j)_{i<j} & \\ & & \ddots & & \\ & 0 & & & \\ & & & & -\beta_n \end{pmatrix}. \quad (1.6)$$

In (1.4) and in the following, if $x = (x_1, \dots, x_n)^T$, by $x > 0$ (and we also write x is positive) we mean that $x_i > 0$ for every $i \in \{1, \dots, n\}$. We use the same notation for row vectors.

We assume that

$$\tau_i > 0 \quad \text{and} \quad \beta_{i+1} > 0, \quad \forall i \in [1, n-1]. \quad (1.7)$$

The mass conservation assumption (1.2) on κ becomes

$$\sum_{i=1}^{j-1} i \kappa_{ij} = j, \quad j = 2, \dots, n. \quad (1.8)$$

The quantity (1.3) we want to maximize writes

$$J(u) = \sum_{i=1}^n i x_i(T). \quad (1.9)$$

Such n -compartment optimal control problems have been widely studied in cancer chemotherapy and the conclusion is usually that the optimal control is bang-bang since singular controls are not optimal [17, 18, 19, 20, 31]. In contrast with these results, we show that, for our problem, the optimal control is essentially singular.

The organization of the paper is the following. In Section 2, we investigate eigenvalue optimization problems related to the optimal control problem (1.9). More precisely, we aim to maximize the Perron and Floquet eigenvalues with respect to constant or periodic control parameters. Starting from information on these eigenvalue problems, we analyze in Section 3 a relaxed control problem. In Section 4, we treat the case where $n = 2$ and give explicitly the optimal relaxed control. Finally, in the Appendix, we give the details of the proofs for the results of Section 2.

2 Eigenvalue problems

For a fixed parameter $u > 0$ and for $r(u) > 0$, the matrix $uF + r(u)G$ is irreducible (see, for instance, [29, Section 2.8] for a definition of irreducible) and has nonnegative extra-diagonal entries. So the Perron-Frobenius theorem (see, for instance, [29, Section 5.3]) applies and ensures the existence of a simple dominant eigenvalue λ_P . In our case, this eigenvalue is positive and it provides the exponential growth rate of the solutions to the equation $\dot{x} = (uF + r(u)G)x$ (see, for instance, [24, Section 6.3.1]). A first question is to investigate the dependence of the first eigenvalue on the parameter u . Indeed, maximizing the Perron eigenvalue is related to our optimal control problem (1.9). It can be regarded as the limit when $T \rightarrow +\infty$ of our optimization problem when we restrict to constant controls. A remarkable fact is that for some coefficients, the dependence $u \mapsto \lambda_P(u)$ can be non monotonic and there may exist an optimal value u_{opt} for which λ_P admits a global maximum on \mathbb{R}^+ . Theorem 1, which is proved in Appendix A, gives sufficient conditions for the existence of such a global optimum.

Theorem 1. *Assume that $r : \mathbb{R}^+ \rightarrow \mathbb{R}^{+*}$ is continuous and admits an expansion of the form*

$$\exists l > 0, r_l \geq 0, \quad r(u) = r_0 + r_l u^{-l} + \underset{u \rightarrow +\infty}{o} \left(u^{-l} \right). \quad (2.1)$$

Consider also that $(\tau_i)_{1 \leq i \leq n}$ satisfies the discrete convexity condition

$$\exists k \in \mathbb{N}^* \quad \text{such that} \quad \forall i \leq k, \tau_i = i \tau_1 \quad \text{and} \quad \tau_{k+1} > (k+1) \tau_1. \quad (2.2)$$

Then there exists an optimal value $u_{\text{opt}} > 0$ which satisfies

$$\forall u \geq 0, \quad \lambda_P(u) \leq \lambda_P(u_{\text{opt}}).$$

The interpretation is that in this case, there is a compromise between too much sonication which forms many small polymers but may have a small growth rate, and too high sonication which forms large polymers but in small quantity.

The theory of Perron-Frobenius can be extended to periodic controls: this is the Floquet theory. It ensures that for time periodic matrices which are monotonic and irreducible for any time, there exists a dominant eigenvalue. It allows one to define for a periodic control $u(t)$ a Floquet eigenvalue $\lambda_F[u] > 0$ which prescribes, as in the case of the Perron eigenvalue, the asymptotic exponential growth rate of the solutions to the equation $\dot{x} = (u(t)F + r(u(t))G)x$ (see [24, Section 6.3.2] for instance). A natural question is then to compare these periodic eigenvalues to the best constant one $\lambda_P(u_{\text{opt}})$. Theorem 2, which is proved in Appendix B, ensures that if r satisfies the condition

$$\frac{r''(u_{\text{opt}})}{r(u_{\text{opt}}) - u_{\text{opt}} r'(u_{\text{opt}})} > 0, \quad (2.3)$$

then the value u_{opt} is a saddle point in the set of periodic controls. This means that there exist periodic controls which provide a larger growth rate than $\lambda_P(u_{\text{opt}})$.

Theorem 2. *Assume that there exists an optimal value u_{opt} for the Perron eigenvalue and that $u_{\text{opt}}F + r(u_{\text{opt}})G$ is diagonalisable. Define for a frequency $\omega > 0$ and a perturbation $\varepsilon > 0$ the Floquet eigenvalue $\lambda_F(\varepsilon, \omega) := \lambda_F[u_{\text{opt}} + \varepsilon \cos(\omega t)]$. Then we have*

$$\lim_{\omega \rightarrow +\infty} \frac{\partial^2}{\partial \varepsilon^2} \lambda_F(0, \omega) = \frac{1}{2} \frac{r''(u_{\text{opt}})}{r(u_{\text{opt}}) - u_{\text{opt}} r'(u_{\text{opt}})} \lambda_P(u_{\text{opt}}).$$

The link between the eigenvalue problem and the optimal control problem (1.9) is investigated in [2] when the function r is a constant. In this case, there exists an optimal control $u^*(t)$ which is essentially equal to the best constant u_{opt} of the Perron optimization problem (see Chapter 5 in [10] for numerical simulations). Under condition (2.3) and the assumptions of Theorem 2, such a behavior is not expected since we can find oscillating controls which provide a better eigenvalue than u_{opt} . The aim of this paper is to investigate the optimal control problem (1.9) in the case where there exists an optimal constant $u_{\text{opt}} \in (u_{\text{min}}, u_{\text{max}})$ and the function r satisfies Assumption (2.3). The first question is the existence of an optimal control since the numerical simulations in Figure 1 show oscillations. These questions are investigated in the following section by using the relaxed control theory.

3 Relaxed Control and the Pontryagin maximum principle

Let u_{min} and u_{max} be two positive real numbers such that $u_{\text{min}} < u_{\text{max}}$. We consider in this section a function $r \in \mathcal{C}^2([u_{\text{min}}, u_{\text{max}}])$ satisfying

$$r(u) > 0, \quad \forall u \in [u_{\text{min}}, u_{\text{max}}], \quad (3.1)$$

$$r''(u) > 0, \quad \forall u \in (u_{\text{min}}, u_{\text{max}}), \quad (3.2)$$

$$r(u) - ur'(u) > 0, \quad \forall u \in (u_{\text{min}}, u_{\text{max}}), \quad (3.3)$$

and we assume that there exists a strict optimum $u_{\text{opt}} \in (u_{\text{min}}, u_{\text{max}})$ for the Perron eigenvalue. Under these assumptions, condition (2.3) is automatically fulfilled. Remark that condition (3.3) is satisfied when r is decreasing and satisfies (3.1), which are relevant conditions from view point of biology. To study this case, it will be convenient to use the equivalent alternative statement of (1.4) where x is solution to

$$\begin{cases} \dot{x}(t) = u(t)Fx(t) + v(t)Gx(t), & t \in [0, T], \\ x(t=0) = x^0 > 0, \end{cases} \quad (3.4)$$

with the two dimensional control (u, v) which belongs to the graph of the function r , *i.e.*,

$$\forall t \in [0, T], \quad (u(t), v(t)) \in \Omega := \text{Graph}(r) = \{(u, r(u)), u_{\text{min}} \leq u \leq u_{\text{max}}\}.$$

Let

$$\psi := (1, 2, \dots, n) \in \mathbb{R}^n \quad (3.5)$$

be the *mass vector*. Note that, from (1.6), the mass conservation assumption (1.8) and (3.5), one has

$$\psi F = 0. \quad (3.6)$$

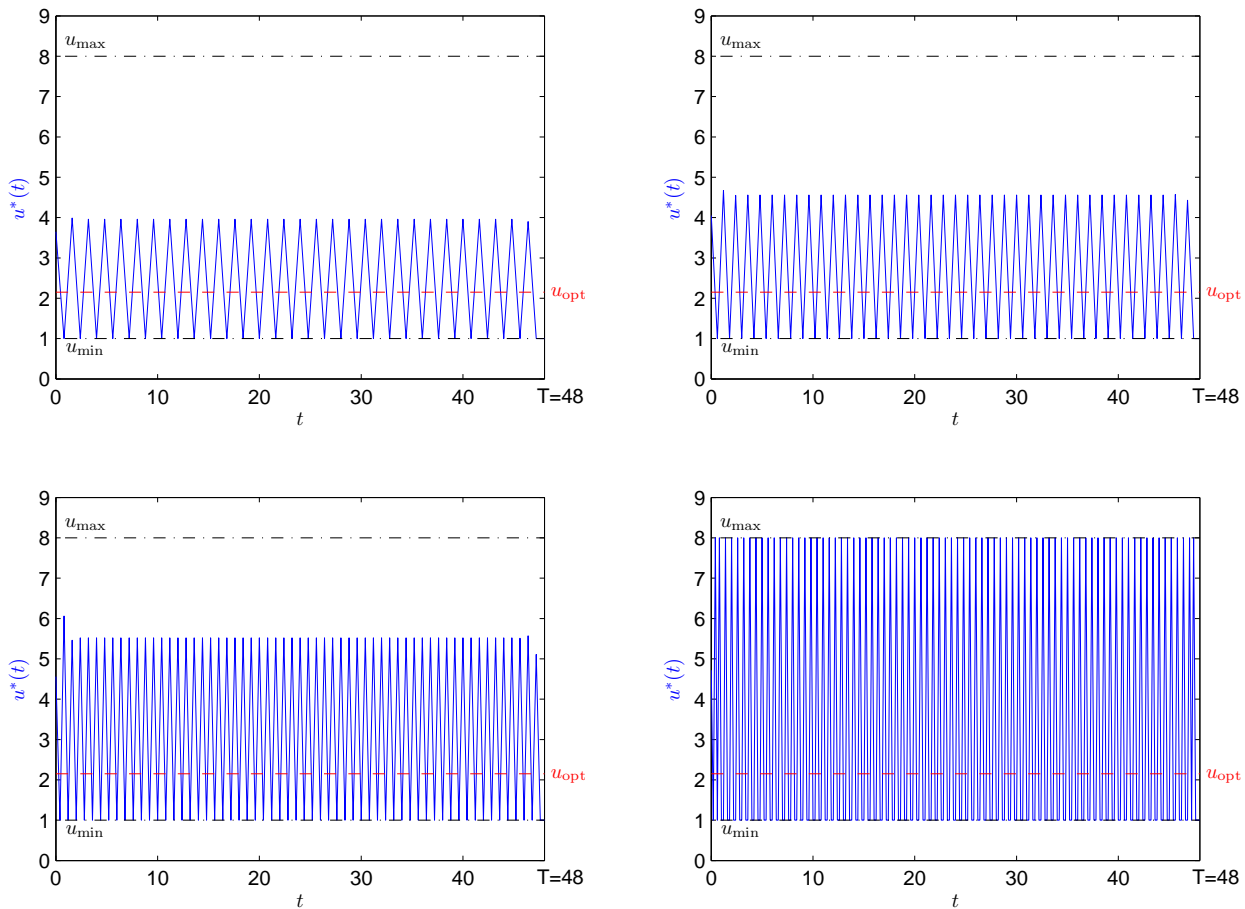


Figure 1: Piecewise optimal controls $u^*(t)$ obtained for different values of Δt with the decreasing convex function $r(u) = \frac{2}{1+u}$. The control varies between $u_{\min} = 1$ and $u_{\max} = 8$ and the final time is $T = 48$. The dimension of the model is $n = 3$ and the coefficients are $\tau_1 = 1$, $\tau_2 = 10$, $\beta_2 = 0.5$, $\beta_3 = 1$, $\kappa_{1,2} = 2$ and $\kappa_{1,3} = \kappa_{2,3} = 1$. The time step varies as follows: $\Delta t = 0.8$ (top left), $\Delta t = 0.6$ (top right), $\Delta t = 0.4$ (bottom left) and $\Delta t = 0.2$ (bottom right).

The optimal control problem (1.9) now becomes

$$\text{maximize } J(u, v) = \psi x(T), \quad (u, v) : [0, T] \rightarrow \Omega \text{ is a Lebesgue measurable function,} \quad (3.7)$$

subject to dynamics (3.4). Since the function r is strictly convex, the graph Ω is not a convex subset of \mathbb{R}^2 and, since the kernel of G is not reduced to $\{0\}$, for any $x > 0$, the velocity set

$$\mathcal{V}(x) = \{(uF + vG)x, (u, v) \in \Omega\}$$

is also not convex. For this kind of situation, the existence of an optimal control for (3.7) cannot be ensured and it is standard to relax the problem by replacing the control set Ω by its convex hull $H(\Omega)$ (see, for instance, [21, Section 4.2]): One replaces problem (3.7) by the following optimal control problem

$$\text{maximize } J(u, v) = \psi x(T), \quad (u, v) : [0, T] \rightarrow H(\Omega) \text{ is a Lebesgue measurable function,} \quad (3.8)$$

subject to dynamics (3.4). For this problem, the velocity set is the convex hull of $\mathcal{V}(x)$, so it is convex and the existence of an optimal control is ensured by classical results (see [21, Theorem 5 p. 271] for instance). Moreover,

- The supremum in problem (3.7) is equal to the maximum in problem (3.8).
- Let $(u^*, v^*) : [0, T] \rightarrow H(\Omega)$ be a measurable function which is optimal for problem (3.8). Then one can easily construct a sequence of piecewise constant functions $(u^n, v^n)_{n \in \mathbb{N}} \rightarrow \Omega$ such that, as n tends to $+\infty$,

$$u^n \rightharpoonup u^* \text{ weakly in } \sigma(L^1, L^\infty) \text{ and } v^n \rightharpoonup v^* \text{ weakly in } \sigma(L^1, L^\infty). \quad (3.9)$$

Let us emphasize that (3.9) implies that

$$J(u^n, v^n) \rightarrow J(u^*, v^*) \text{ as } n \rightarrow +\infty.$$

In particular, $(u^n, v^n)_{n \in \mathbb{N}}$ is a maximizing sequence for problem (3.7).

Now we want to obtain informations on the optimal controls for (3.8) by using the Pontryagin maximum principle. This principle in our case gives the following theorem.

Theorem 3 (Pontryagin Maximum Principle (PMP)). *Let (u^*, v^*) be an optimal control for problem (3.8) and let x^* be the corresponding trajectory (i.e., the solution of (3.4) with $(u, v) := (u^*, v^*)$). Call $p^* : [0, T] \rightarrow \mathbb{R}^n$ the row vector solution of the adjoint linear equation*

$$\dot{p}^*(t) = -p^*(t)(u^*F + v^*G), \quad (3.10)$$

with the transversality condition

$$p^*(T) = \psi. \quad (3.11)$$

Let us define the Hamiltonian as

$$H(x, p, u, v) := p(uF + vG)x. \quad (3.12)$$

Then the maximality condition

$$H(x^*(t), p^*(t), u^*(t), v^*(t)) = \max_{(u, v) \in H(\Omega)} H(x^*(t), p^*(t), u, v). \quad (3.13)$$

holds for almost every time $t \in [0, T]$ and there exists a constant $H^* \in \mathbb{R}$ such that

$$H(x^*(t), p^*(t), u^*(t), v^*(t)) = H^*, \text{ for almost every } t \in [0, T]. \quad (3.14)$$

Remark 4. *Since, for any positive u and v , the matrix $uF + vG$ has nonnegative extra-diagonal entries and is irreducible, we have, using (3.4), (3.5), (3.10) and (3.11),*

$$x^*(t) > 0 \text{ and } p^*(t) > 0, \text{ for every time } t \in [0, T]. \quad (3.15)$$

The Pontryagin maximum principle is useful to obtain information on the optimal control. It allows us to prove (Corollary 6 below) that the optimal control lies on the line Σ defined by (see Figure 2)

$$\Sigma := \text{Graph}(\sigma) = \{(u, \sigma(u)), u_{\min} \leq u \leq u_{\max}\},$$

where σ is the affine function defined by

$$\sigma(u) = \theta u + \zeta$$

with

$$\theta := \frac{r(u_{\max}) - r(u_{\min})}{u_{\max} - u_{\min}}, \quad (3.16)$$

$$\zeta := \frac{u_{\max}r(u_{\min}) - u_{\min}r(u_{\max})}{u_{\max} - u_{\min}}. \quad (3.17)$$

The set Σ is the string which links $(u_{\min}, r(u_{\min}))$ to $(u_{\max}, r(u_{\max}))$. Since r is convex, the boundary of the control set $H(\Omega)$ is $\partial H(\Omega) = \Omega \cup \Sigma$.

One has the following lemma which is illustrated by the incoming arrows in Figure 2.

Lemma 5. *Let $(u, v) \in H(\Omega) \setminus \Sigma$. Then, for $\varepsilon > 0$ small enough,*

$$((1 + \varepsilon)u, (1 + \varepsilon)v) \in H(\Omega).$$

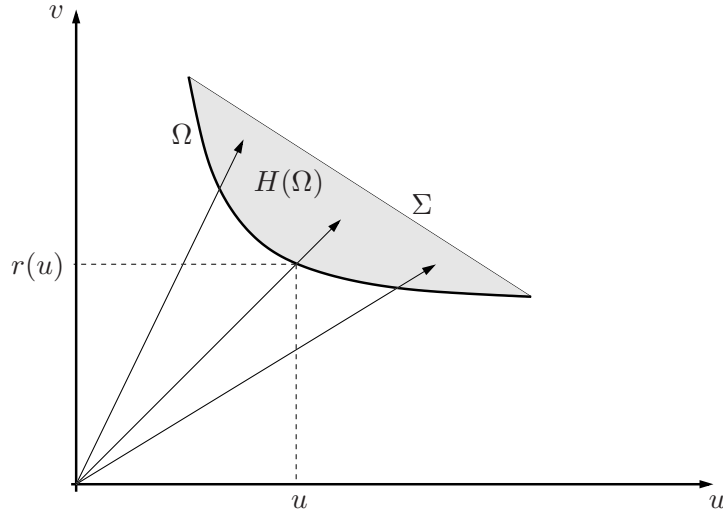


Figure 2: The set Ω , the string Σ and the convex hull $H(\Omega)$ for r a decreasing and convex function. The arrows oriented along the vectors $(u, r(u))$ point inside $H(\Omega)$ on the lower boundary Ω .

Proof of Lemma 5. Let $\text{Int}(H(\Omega))$ be the interior of $H(\Omega)$. If $(u, v) \in \text{Int}(H(\Omega))$, then the result follows from the fact that $\text{Int}(H(\Omega))$ is an open set by definition. It remains to study the case where $(u, v) \in \Omega \setminus \{(u_{\min}, r(u_{\min}))\} \cup \{(u_{\max}, r(u_{\max}))\}$, i.e., $v = r(u)$ with $u \in (u_{\min}, u_{\max})$. We have, using (3.3),

$$\begin{aligned} (1 + \varepsilon)r(u) - r((1 + \varepsilon)u) &= (1 + \varepsilon)r(u) - r(u) - \varepsilon ur'(u) + \underset{\varepsilon \rightarrow 0^+}{o}(\varepsilon) \\ &= \varepsilon(r(u) - ur'(u) + \underset{\varepsilon \rightarrow 0^+}{o}(1)) \geq 0, \quad \text{for } \varepsilon \text{ small and positive.} \end{aligned}$$

Hence, if $\varepsilon > 0$ is small enough, $r((1 + \varepsilon)u) \leq (1 + \varepsilon)r(u)$. Moreover, by (3.2), we have $r(u) < \sigma(u)$ and, therefore, if ε is small enough, $(1 + \varepsilon)r(u) \leq \sigma((1 + \varepsilon)u)$.

The proof is complete. \square

As a consequence of Theorem 3 and Lemma 5, we have the following corollary.

Corollary 6. *Let (u^*, v^*) be an optimal control for problem (3.8). Then, for almost every time $t \in [0, T]$, the optimal control $(u^*(t), v^*(t)) \in \Sigma$.*

Proof of Corollary 6. Indeed, by (3.14), there exists a sequence $(t_n)_{n \in \mathbb{N}}$ of elements in $[0, T]$ such that

$$H(x^*(t_n), p^*(t_n), u^*(t_n), v^*(t_n)) = H^*, \quad (3.18)$$

$$t_n \rightarrow T \quad \text{as} \quad n \rightarrow +\infty. \quad (3.19)$$

Extracting a subsequence if necessary we may assume, without loss of generality, that there exists $\tilde{v} \in \mathbb{R}$ such that

$$\tilde{v} \in [r(u_{\max}), r(u_{\min})] \subset (0, +\infty), \quad (3.20)$$

$$v^*(t_n) \rightarrow \tilde{v} \quad \text{as} \quad n \rightarrow +\infty. \quad (3.21)$$

Letting $n \rightarrow +\infty$ in (3.18), and using (3.6), (3.11), (3.12), (3.19) and (3.21), one gets that

$$H^* = \tilde{v}\psi Gx(T). \quad (3.22)$$

From (1.5), (1.7) and (3.5), one gets that

$$\psi G > 0, \quad (3.23)$$

which, together with (3.15), implies that

$$\psi Gx(T) > 0. \quad (3.24)$$

From (3.20), (3.22) and (3.24), one obtains

$$H^* > 0.$$

Let $t \in [0, T]$ be such that

$$(u^*(t), v^*(t)) \in H(\Omega) \setminus \Sigma, \quad (3.25)$$

$$H(x^*(t), p^*(t), u^*(t), v^*(t)) = H^*. \quad (3.26)$$

From Lemma 5 and (3.25), there exists $\varepsilon > 0$ such that $((1 + \varepsilon)u^*(t), (1 + \varepsilon)v^*(t)) \in H(\Omega)$. Using (3.26), one has

$$\begin{aligned} H(x^*(t), p^*(t), (1 + \varepsilon)u^*(t), (1 + \varepsilon)v^*(t)) &= (1 + \varepsilon)H(x^*(t), p^*(t), u^*(t), v^*(t)) \\ &= (1 + \varepsilon)H^* \\ &> H^* = H(x^*(t), p^*(t), u^*(t), v^*(t)), \end{aligned}$$

which shows that (3.13) does not hold. Since, by Theorem 3, (3.13) holds for almost every $t \in [0, T]$, this, together with (3.14), concludes the proof of Corollary 6. \square

Now we look for controls and corresponding trajectories which satisfy the optimality condition (3.13). To that end, we take advantage of our analysis of the Perron eigenvalue problem. For $(u, v) \in H(\Omega)$, define the Perron eigenvalue $\lambda_P = \lambda_P(u, v)$ of the matrix $uF + vG$ and the corresponding right and left eigenvectors $X > 0$ and $\phi > 0$ normalized as follows

$$\lambda_P X = (uF + vG)X, \quad \|X\|_1 = 1, \quad (3.27)$$

$$\lambda_P \phi = \phi(uF + vG), \quad \phi X = 1, \quad (3.28)$$

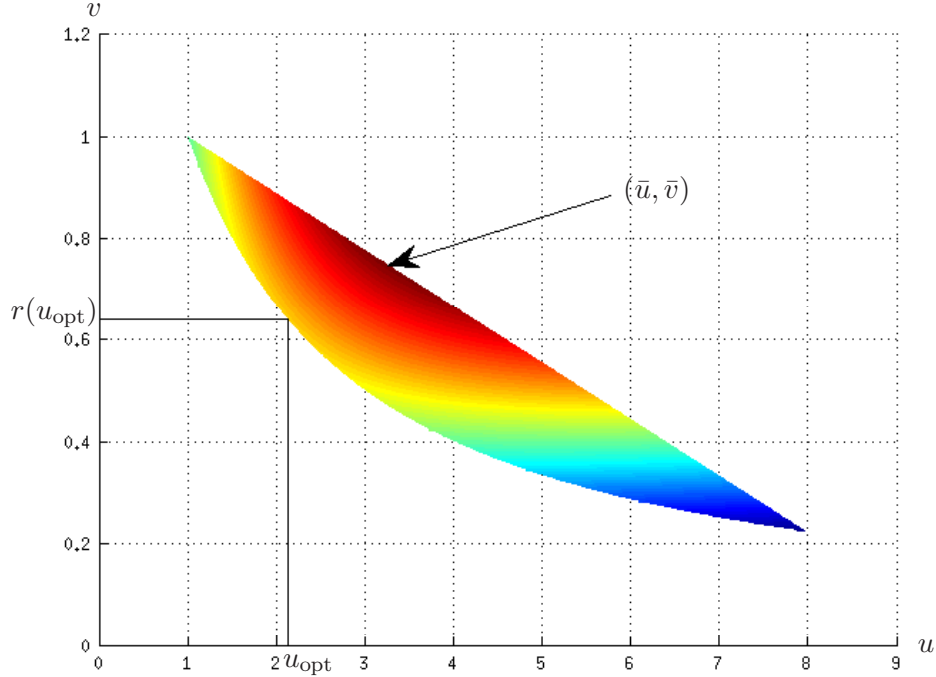


Figure 3: The eigenvalue function $\lambda_P(u, v)$ on the convex hull $H(\Omega)$ for $r(u) = \frac{2}{1+u}$, $u_{\min} = 1$, $u_{\max} = 8$, $n = 3$, $\tau_1 = 1$, $\tau_2 = 10$, $\beta_2 = 0.5$, $\beta_3 = 1$, $\kappa_{1,2} = 2$ and $\kappa_{1,3} = \kappa_{2,3} = 1$.

where, for $x = (x_1, \dots, x_n)^T$, $\|x\|_1 := \sum_{i=1}^n |x_i|$. The function $(u, v) \mapsto \lambda_P(u, v)$ admits an optimum (\bar{u}, \bar{v}) on the compact set $H(\Omega)$ (See Figure 3 for the numerical simulations). We denote by $\bar{\lambda}_P$, \bar{X} and $\bar{\phi}$ the corresponding optimal eigenelements. First, we notice that Lemma 5 implies that, as for the optimal control, the optimum (\bar{u}, \bar{v}) of λ_P lies on Σ .

Corollary 7. *We have $(\bar{u}, \bar{v}) \in \Sigma \setminus \{(u_{\min}, r(u_{\min})), (u_{\max}, r(u_{\max}))\}$.*

Proof of Corollary 7. Multiplying (3.27) on the left by ψ and using (3.6), one gets

$$\lambda_P(u, v)\psi X = v\psi GX, \quad \forall (u, v) \in H(\Omega). \quad (3.29)$$

From $\psi > 0$ (see (3.5)), $X > 0$, (3.23) and (3.29), one gets

$$\lambda_P(u, v) > 0, \quad \forall (u, v) \in H(\Omega). \quad (3.30)$$

(For a different proof of (3.30), see the proof of Lemma 20.) Corollary 7 follows from Lemma 5, (3.30) and from the following linearity of the eigenvalue

$$\forall \alpha, u, v > 0, \quad \lambda_P(\alpha u, \alpha v) = \alpha \lambda_P(u, v).$$

□

We now build a solution to the relaxed control problem (3.4) which satisfies the optimality condition (3.13).

Proposition 8. *Let $R > 0$ and $S > 0$. Then the constant control (\bar{u}, \bar{v}) and the following corresponding direct and adjoint trajectories*

$$\begin{cases} \bar{x}(t) = R\bar{X} e^{\bar{\lambda}_P t}, \\ \bar{p}(t) = S\bar{\phi} e^{-\bar{\lambda}_P t}, \end{cases} \quad (3.31)$$

satisfy the maximality condition

$$H(\bar{x}(t), \bar{p}(t), \bar{u}, \bar{v}) = \max_{(u,v) \in H(\Omega)} H(\bar{x}(t), \bar{p}(t), u, v), \quad \forall t \in [0, T]. \quad (3.32)$$

Proof of Proposition 8. Without loss of generality, we may assume that $R = S = 1$. From (3.12), (3.27), (3.28) and (3.31), we obtain, for every $t \in [0, T]$,

$$H(\bar{x}(t), \bar{p}(t), \bar{u}, \bar{v}) = \lambda_P(\bar{u}, \bar{v}). \quad (3.33)$$

For any $(u, v) \in H(\Omega)$, we have, for every $t \in [0, T]$,

$$\begin{aligned} H(\bar{x}(t), \bar{p}(t), u, v) &= \bar{p}(t)(uF + vG)\bar{x}(t) \\ &= \bar{p}(t)(\bar{u}F + \bar{v}G)\bar{x}(t) + \bar{p}(t)((u - \bar{u})F + (v - \bar{v})G)\bar{x}(t) \\ &= H(\bar{x}(t), \bar{p}(t), \bar{u}, \bar{v}) + \bar{\phi}((u - \bar{u})F + (v - \bar{v})G)\bar{X}. \end{aligned} \quad (3.34)$$

Testing (3.27) against the adjoint eigenvector ϕ and using the normalization $\phi X = 1$ (see (3.28)), we obtain

$$\lambda_P(u, v) = \phi(uF + vG)X. \quad (3.35)$$

Differentiating (3.35) with respect to u and using (3.27) together with (3.28), we get

$$\begin{aligned} \frac{\partial \lambda_P}{\partial u} &= \frac{\partial \phi}{\partial u}(uF + vG)X + \phi FX + \phi(uF + vG)\frac{\partial X}{\partial u} \\ &= \lambda_P(u, v)\frac{\partial \phi}{\partial u}X + \phi FX + \lambda_P(u, v)\phi\frac{\partial X}{\partial u} \\ &= \lambda_P(u, v)\frac{\partial(\phi X)}{\partial u} + \phi FX \\ &= \phi FX. \end{aligned} \quad (3.36)$$

We obtain in the same way that

$$\frac{\partial \lambda_P}{\partial v} = \phi GX. \quad (3.37)$$

From (3.33), (3.34), (3.36) and (3.37), we obtain

$$H(\bar{x}(t), \bar{p}(t), u, v) = \lambda_P(\bar{u}, \bar{v}) + \begin{pmatrix} u - \bar{u} \\ v - \bar{v} \end{pmatrix} \cdot \nabla \lambda_P(\bar{u}, \bar{v}). \quad (3.38)$$

Moreover, since $H(\Omega)$ is convex and λ_P is maximal in $H(\Omega)$ at (\bar{u}, \bar{v}) ,

$$\begin{pmatrix} u - \bar{u} \\ v - \bar{v} \end{pmatrix} \cdot \nabla \lambda_P(\bar{u}, \bar{v}) \leq 0, \quad \forall (u, v) \in H(\Omega). \quad (3.39)$$

From (3.38) and (3.39), we get that (\bar{u}, \bar{v}) satisfies the maximality condition (3.32).

The proof is complete. \square

Remark 9. For the trajectories (3.31) to satisfy additionally the initial condition of (3.4) and the terminal condition (3.11), the initial distribution $x^0 > 0$ has to be taken collinear to $\bar{X} > 0$ and the objective we want to maximize has to be modified by replacing in (3.8) the vector ψ by a positive vector and collinear to $\bar{\phi}$.

All the results of this section give indications that the optimal relaxed controls do not lie on Ω , which would explain the oscillations that we observed numerically in Figure 1. In the next section, we precise these indications in the case of a two compartments model.

4 Dimension $n = 2$

As in the previous sections, u_{\min} and u_{\max} are two positive real numbers such that $u_{\min} < u_{\max}$ and $r \in \mathcal{C}^2([u_{\min}, u_{\max}])$. We still assume that (3.1) and (3.2) holds. However, we no longer assume that (3.3) holds. We precise what has been done in the two previous sections in the two dimensional case.

First we give the form of the matrices F and G in dimension 2 (see (1.5)-(1.8)):

$$F = \begin{pmatrix} 0 & 2\beta \\ 0 & -\beta \end{pmatrix}, \quad G = \begin{pmatrix} -\tau & 0 \\ \tau & 0 \end{pmatrix},$$

with $\beta > 0$ and $\tau > 0$. Notice that, for the sake of clarity, we have skipped the indices of the coefficients: the coefficient β stands for β_2 and τ stands for τ_1 .

In dimension 2, the optimal control still lies on Σ even if (3.3) is no longer assumed to hold. This is a consequence of the following lemma.

Lemma 10. For any control $(u, v) \in (L^\infty((0, T); (0, +\infty)))^2$, the solution $p = (p_1, p_2)$ to the adjoint equation

$$\dot{p} = -p(uF + vG), \quad p(T) = \psi = (1, 2),$$

satisfies

$$(2p_1 - p_2)(t) > 0 \quad \text{and} \quad (p_2 - p_1)(t) > 0, \quad \forall t \in [0, T]. \quad (4.1)$$

Proof of Lemma 10. Denote by \tilde{p} the vector

$$\tilde{p} := \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \end{pmatrix} := \begin{pmatrix} p_2 - p_1 \\ 2p_1 - p_2 \end{pmatrix}.$$

It satisfies the equation

$$\dot{\tilde{p}} = - \begin{pmatrix} -v\tau & u\beta \\ 2v\tau & -u\beta \end{pmatrix} \tilde{p}, \quad \tilde{p}(T) = \begin{pmatrix} 1 \\ 0 \end{pmatrix},$$

the result of the lemma follows. \square

Corollary 11. Let (u^*, v^*) be an optimal control for problem (3.8). Then $(u^*(t), v^*(t))$ lies on Σ for almost every $t \in [0, T]$.

Proof of Corollary 11. Let x^* be the trajectory corresponding to the control (u^*, v^*) . Let $p^* : [0, T] \rightarrow \mathbb{R}^2$ be the row vector solution of (3.10)-(3.11). Since Σ is a string of the convex (see (3.2)) function r , we have that $v \leq \sigma(u)$ for every $(u, v) \in H(\Omega)$. From Lemma 10, we deduce that, for every time $t \in [0, T]$,

$$p^*(t)Gx^*(t) = \tau(p_2^*(t) - p_1^*(t))x_1^*(t) > 0.$$

Then, using the maximality property (3.13), we conclude that $v^*(t) = \sigma(u^*(t))$ for almost every $t \in [0, T]$. \square

Corollary 12. *If r is such that $r(u_{\min}) \leq r(u_{\max})$, then the optimal control is, for almost every $t \in [0, T]$,*

$$(u^*, v^*) \equiv (u_{\max}, r(u_{\max})).$$

Proof of Corollary 12. We use the same notations as in the proof of Corollary 11. When $r(u_{\min}) \leq r(u_{\max})$, we have, for every $(u, v) \in H(\Omega)$, $u \leq u_{\max}$ and $v \leq r(u_{\max})$. From Lemma 10, we know that, for every time $t \in [0, T]$,

$$p^*(t)Gx^*(t) = \tau(p_2^*(t) - p_1^*(t))x_1^*(t) > 0 \quad \text{and} \quad p^*(t)Fx^*(t) = \beta(2p_1^*(t) - p_2^*(t))x_2^*(t) > 0.$$

We conclude by using the maximality property (3.13). \square

The result in Corollary 12 solves very simply the optimal control problem in the case $r(u_{\min}) \leq r(u_{\max})$. The case when

$$r(u_{\min}) > r(u_{\max}) \tag{4.2}$$

is more delicate and we investigate it now. From now on, we assume that (4.2) holds. Using Corollary 11, we can reduce the optimal control problem (3.8) to the control set Σ . Then $v = \sigma(u) = \theta u + \zeta$ with θ defined in (3.16) and ζ defined in (3.17). The dynamic equation (3.4) and the adjoint equation (3.10) become respectively

$$\dot{x} = u(F + \theta G)x + \zeta Gx, \tag{4.3}$$

$$\dot{p} = -up(F + \theta G) - \zeta pG. \tag{4.4}$$

The assumption $r(u_{\max}) < r(u_{\min})$, together with (3.16) and (3.17), ensures that

$$\theta < 0 \quad \text{and} \quad \zeta > 0.$$

Call

$$H_{\Sigma}(x, p, u) = up(F + \theta G)x + \zeta pGx$$

the Hamiltonian for dynamics (4.3)-(4.4) and define by

$$\Phi(x, p) := \frac{\partial H_{\Sigma}(x, p, u)}{\partial u} = p(F + \theta G)x$$

the switching function. First we look for singular trajectories on open intervals I , *i.e.*, (x, p, u) with $x \in \mathcal{C}^0(I; (0, +\infty)^2)$, $p^T \in \mathcal{C}^0(I; (0, +\infty)^2)$, $u \in L^{\infty}(I; [u_{\min}, u_{\max}])$ solutions of (4.3)-(4.4) such that

$$\Phi(t) := \Phi(x(t), p(t)) = 0, \quad \text{for almost every } t \in I.$$

Theorem 13. *For a nonempty open interval I , $t \in I \mapsto (x(t), p(t), u(t))$ is a singular trajectory if and only if*

$$u(t) = u_{\text{sing}} := \frac{\zeta \tau}{\sqrt{-2\theta\tau\beta}} \frac{2\beta + \sqrt{-2\theta\tau\beta}}{\beta + 2\sqrt{-2\theta\tau\beta} - \theta\tau}, \quad \text{for almost every } t \in I, \tag{4.5}$$

and there exist two positive real numbers R and S such that

$$x(t) = RXe^{\lambda t} \quad \text{and} \quad p(t) = S\phi e^{-\lambda t}, \quad \forall t \in I, \tag{4.6}$$

where

- λ is the Perron eigenvalue of the matrix $u_{\text{sing}}(F + \theta G) + \zeta G$ and

$$\lambda = \frac{\zeta\tau\beta}{\beta + 2\sqrt{-2\theta\tau\beta} - \theta\tau}, \quad (4.7)$$

- X and ϕ are respectively direct and adjoint positive eigenvectors of the matrix $u_{\text{sing}}(F + \theta G) + \zeta G$ associated to the Perron eigenvalue λ .

Proof of Theorem 13.

Let us first remark that u_{sing} defined by (4.5) satisfies

$$u_{\text{sing}} = \frac{\zeta}{-\theta} \frac{\sqrt{-2\theta\tau\beta} - \theta\tau}{\beta + 2\sqrt{-2\theta\tau\beta} - \theta\tau} \in \left(0, \frac{\zeta}{-\theta}\right).$$

thus, $u_{\text{sing}}\theta + \zeta > 0$ and the matrix $u_{\text{sing}}F + (u_{\text{sing}}\theta + \zeta)G$ satisfies the assumptions of the Perron-Frobenius theorem.

First step: "If" part. Simple computations prove that

$$X = (2\sqrt{\beta}, \sqrt{-2\theta\tau})^T, \quad (4.8)$$

$$\phi = (\sqrt{\beta} + \sqrt{-2\theta\tau}, 2\sqrt{\beta} + \sqrt{-2\theta\tau}) \quad (4.9)$$

are, respectively, right and left eigenvectors of the matrix $u_{\text{sing}}(F + \theta G) + \zeta G$ associated to the eigenvalue λ defined by (4.7). Since $X > 0$ and $\phi > 0$ are positive, they are necessarily Perron eigenvectors of this matrix and λ is its Perron eigenvalue $\lambda_P(u_{\text{sing}})$.

Let $\bar{x} : I \rightarrow \mathbb{R}^2$, $\bar{p} : I \rightarrow \mathbb{R}^2$, $\bar{u} : I \rightarrow \mathbb{R}$ be defined by

$$\bar{x}(t) := e^{\lambda t} X, \quad \bar{p}(t) := e^{-\lambda t} \phi \quad \text{and} \quad \bar{u}(t) = u_{\text{sing}}, \quad \forall t \in I. \quad (4.10)$$

As already used in the previous section, $(\bar{x}, \bar{p}, \bar{u})$ are solutions of (4.3)-(4.4). It remains only to check, along this trajectory $(\bar{x}, \bar{p}, \bar{u})$, $\Phi = 0$, which indeed holds since $\Phi = \phi(F + \theta G)X = 0$ (and because $\phi(F + \theta G)X = \lambda'_P(u_{\text{sing}})\phi X$, we also get that u_{sing} is a critical point of λ_P .)

Second step: "Only if" part. Suppose that (x, p, u) is a singular trajectory on an open interval I . We have $\Phi(t) = p(t)(F + \theta G)x(t) = 0$ on I . This gives the relation

$$-\theta\tau x_1(p_1 - p_2) + \beta x_2(2p_1 - p_2) = 0. \quad (4.11)$$

Differentiating Φ with respect to t on I , we get

$$\dot{\Phi} = \zeta p[F, G]x = 0,$$

where $[F, G] := FG - GF$ is the Lie bracket of F and G . It provides a second identity

$$x_1(2p_1 - p_2) + 2x_2(p_1 - p_2) = 0. \quad (4.12)$$

If we differentiate Φ a second time, we get

$$\ddot{\Phi} = \zeta up([F, G], F) + \theta([F, G], G)x + \zeta^2 p[[F, G], G]x = 0. \quad (4.13)$$

Using (4.12), we obtain

$$\begin{aligned} p([F, G], F)x &= 4\tau\beta^2 p_1 x_2, \\ p([F, G], G)x &= -2\tau^2\beta p_2 x_1. \end{aligned}$$

We remark that

$$p([F, G], F) + \theta([F, G], G)x = \frac{\zeta p}{u}([F, G], G)x = -\frac{2\zeta}{u}\tau^2\beta p_2 x_1$$

cannot vanish because $x > 0$ and $p > 0$. So we can divide (4.13) by this term and we get

$$u = \frac{-\zeta p([F, G], G)x}{p([F, G], F)x + \theta p([F, G], G)x} = \frac{\zeta \tau p_2 x_1}{2\beta p_1 x_2 - \theta \tau p_2 x_1}. \quad (4.14)$$

Consider now (4.11)-(4.12) as a system of equations for the unknown (x_1, x_2) . Since x is positive, this system must have a vanishing determinant and it gives the relation

$$\beta(2p_1 - p_2)^2 + 2\theta\tau(p_1 - p_2)^2 = 0.$$

Using (4.1) in Lemma 10, we can write

$$2p_1 - p_2 = \sqrt{\frac{-2\theta\tau}{\beta}}(p_2 - p_1),$$

and finally we get

$$\frac{p_1}{p_2} = \frac{\sqrt{\beta} + \sqrt{-2\theta\tau}}{2\sqrt{\beta} + \sqrt{-2\theta\tau}}. \quad (4.15)$$

Similarly, if we consider (4.11)-(4.12) as a system of equations for the positive unknown (p_1, p_2) , from the fact that the determinant vanishes, we obtain

$$\theta\tau x_1^2 + 2\beta x_2^2 = 0.$$

Since $x > 0$, $\theta < 0$ and $\tau > 0$, we deduce that

$$x_1 = \sqrt{\frac{2\beta}{-\theta\tau}}x_2. \quad (4.16)$$

Plugging (4.15) and (4.16) into (4.14), we get (4.5). From (4.8), (4.9), (4.10), (4.15) and (4.16), one gets the existence of $R : I \rightarrow (0, +\infty)$ and $S : I \rightarrow (0, +\infty)$ such that

$$x = R\bar{x} \quad \text{and} \quad p = S\bar{p}.$$

Using the fact that (x, p, u_{sing}) and $(\bar{x}, \bar{p}, u_{\text{sing}})$ are both solutions of (4.3)-(4.4), one readily gets that $\dot{R} = \dot{S} = 0$.

The proof is complete. \square

In the proof of Theorem 13, we have pointed out a link between the singular trajectories and the critical points of the Perron eigenvalue. In Theorem 14, we prove that u_{sing} is actually the unique maximum of λ_P .

Theorem 14. *The Perron eigenvalue $\lambda_P(u)$ of the matrix $u(F + \theta G) + \zeta G$ is well defined on $(0, \frac{\zeta}{-\theta})$ and it reaches its unique maximum at $\bar{u} = u_{\text{sing}}$.*

Proof of Theorem 14. The function $u \mapsto \theta u + \zeta$ is positive on $(0, \frac{\zeta}{-\theta})$, so the matrix $uF + (\theta u + \zeta)G$ satisfies the hypotheses of the Perron-Frobenius theorem on this interval. Notice that $\lambda_P(u)$ tends to zero as u tends to 0 or to $\frac{\zeta}{-\theta}$, so λ_P necessarily has a maximum on $(0, \frac{\zeta}{-\theta})$. The characteristic polynomial is

$$X^2 + ((\theta u + \zeta)\tau + u\beta)X - u(\theta u + \zeta)\beta\tau.$$

The discriminant of this polynomial is

$$\begin{aligned} \Delta &= (\theta u + \zeta)^2\tau^2 + u^2\beta^2 + 6u(\theta u + \zeta)\beta\tau \\ &= (\theta^2\tau^2 + \beta^2 + 6\theta\beta\tau)u^2 + 2\zeta\tau(\theta\tau + 3\beta)u + \zeta^2\tau^2. \end{aligned} \quad (4.17)$$

Since $0 < u < \frac{\zeta}{-\theta}$, we have $\Delta > 0$. Define new relevant parameters

$$A := \theta\tau + \beta, \quad B := \sqrt{-2\theta\beta\tau}, \quad C := \theta\tau + 3\beta \quad \text{and} \quad D := \zeta\tau.$$

With these notations, discriminant (4.17) writes

$$\Delta = (A^2 - 2B^2)u^2 + 2CDu + D^2,$$

and the first eigenvalue of $uF + (u\theta + \zeta)G$ is

$$\lambda_P(u) = \frac{1}{2}(-Au - D + \sqrt{\Delta}) > 0.$$

The optimal value \bar{u} satisfies $\lambda'_P(\bar{u}) = 0$, with

$$\lambda'_P(u) = \frac{1}{2} \left(\frac{\Delta'}{2\sqrt{\Delta}} - A \right).$$

To obtain \bar{u} , we solve the equation

$$(\Delta')^2 = 4A^2\Delta, \quad (4.18)$$

which writes

$$-2B^2(A^2 - 2B^2)u^2 - 4B^2CDu + D^2(C^2 - A^2) = 0.$$

The discriminant of this binomial is

$$\mathfrak{D} = 8A^2B^2D^2(C^2 + 2B^2 - A^2) = 64A^2B^2D^2\beta^2,$$

and the roots are

$$u^\pm = \frac{D}{B} \frac{BC \pm 2\beta A}{2B^2 - A^2}.$$

A solution to $\lambda'_P(u) = 0$ is a solution to (4.18) which satisfies $\frac{\Delta'}{A} > 0$. The computations give

$$\frac{\Delta'(u^-)}{A} = 4\beta \frac{D}{B} > 0 \quad \text{and} \quad \frac{\Delta'(u^+)}{A} = -4\beta \frac{D}{B} < 0,$$

so $\lambda'_P(u) = 0$ has a unique solution which is

$$\bar{u} = u^- = \frac{D}{B} \frac{BC - 2\beta A}{2B^2 - A^2}.$$

Since u_{sing} is also a critical point of λ_P , we have that $\bar{u} = u_{\text{sing}}$. This identity can also be checked by computation, from (4.5),

$$\begin{aligned} u_{\text{sing}} &= \frac{D}{B} \frac{2\beta + B}{C - 2A + 2B} \\ &= \frac{D}{B} \frac{(2\beta + B)(C - 2A - 2B)}{(C - 2A)^2 - 4B^2} \\ &= \frac{D}{B} \frac{2\beta A - BC}{A^2 - 2B^2} \\ &= u^- = \bar{u}. \end{aligned}$$

□

As an immediate consequence of the proofs of Theorems 13 and 14, we have explicit expressions of the optimal eigenlements.

Corollary 15. *The maximal Perron eigenvalue is*

$$\lambda_P(\bar{u}) = \frac{\zeta\tau\beta}{\beta + 2\sqrt{-2\theta\tau\beta} - \theta\tau}$$

and the associated right and left eigenvectors are given by

$$X = (2\beta, \sqrt{-2\theta\tau\beta})^T \quad \text{and} \quad \phi = (\beta + \sqrt{-2\theta\tau\beta}, 2\beta + \sqrt{-2\theta\tau\beta}).$$

Remark 16. *Theorem 13 can also be proved without computation by noticing that every critical point of λ_P provides with (4.6) a singular trajectory. Since there exists a singular trajectory (up to multiplicative constants for x and p), this gives the uniqueness of the critical point of λ_P and, therefore, this critical point realizes the maximum of λ_P on $(0, \frac{\zeta}{-\theta})$. One can even prove Theorem 13 and Theorem 14 together by showing that there exists at most a singular trajectory (up to multiplicative constants for x and p) and that every critical point of λ_P provides with (4.6) a singular trajectory.*

We are now ready to exhibit the unique optimal control when the horizon T is large enough. It consists mainly in the singular control u_{sing} , except in the regions close to the endpoints of $[0, T]$. For small time, the optimal control depends on the initial data x^0 and it consists in reaching as fast as possible the singular trajectory. Then the control remains constant equal to the value which maximizes the Perron eigenvalue (see Figure 4). At the end of the experiment, the control is u_{min} due to the transversality condition induced by the objective function. This kind of strategy is known as *turnpike properties* (see [34] for instance), the “turnpike” is the singular trajectory which corresponds to the Perron eigenvector X with an exponential growth of maximal rate $\lambda_P(\bar{u})$.

We divide the construction of the optimal control in two steps. First, we build a control such that the PMP is satisfied. Then, with an analysis of the switching function $\Phi(t)$, we prove that this is the only possible one.

Before stating the results, let us give some notations. For $x = (x_1, x_2)^T$ and $p = (p_1, p_2)$, where x_1, x_2, p_1 and p_2 are positive real numbers, we define the projected variables

$$y := \frac{x_1}{x_1 + x_2} \in [0, 1] \quad \text{and} \quad q := \frac{p_1}{p_1 + p_2} \in [0, 1]. \quad (4.19)$$

For $(x(t), p(t))$ a solution to (4.3)-(4.4), the projections $y(t)$ and $q(t)$ satisfy the dynamics

$$\dot{y} = \mathcal{Y}(y, u) := 2u\beta - (3u\beta + (u\theta + \zeta)\tau)y + u\beta y^2, \quad (4.20)$$

$$\dot{q} = \mathcal{Q}(q, u) := -[(\theta u + \zeta)\tau - (3(\theta u + \zeta)\tau - u\beta)q + (2(\theta u + \zeta)\tau - 3u\beta)q^2]. \quad (4.21)$$

For u in $[u_{\min}, u_{\max}]$, let $Y(u) \in (0, 1)$ be the projection of the Perron eigenvector $X(u)$ of the matrix $uF + (\theta u + \zeta)G$ and let $\pi(u)$ be the projection of the adjoint Perron eigenvector $\phi(u)$. Note that, for every u in $[u_{\min}, u_{\max}]$,

$$(y - Y(u))\mathcal{Y}(y, u) < 0, \quad \forall y \in [0, 1] \setminus \{Y(u)\}, \quad (4.22)$$

$$(q - \pi(u))\mathcal{Q}(q, u) > 0, \quad \forall q \in [0, 1] \setminus \{\pi(u)\}. \quad (4.23)$$

In particular, for u fixed in $[u_{\min}, u_{\max}]$,

- Every solution y of (4.20) with $y(0)$ in $[0, 1]$ lies in $[0, 1]$ for every $t \in [0, +\infty)$ and converges to $Y(u)$ as $t \rightarrow +\infty$.
- Every solution of (4.21) with $q(0)$ in $[0, 1]$ stays in $[0, 1]$ for every $t \in (-\infty, 0]$ and converges to $\pi(u)$ as $t \rightarrow -\infty$.

In our problem, denote by $x^0 = (x_1^0, x_2^0)^T$, then y and q satisfy the initial and terminal conditions

$$y(0) = \frac{x_1^0}{x_1^0 + x_2^0}, \quad q(T) = \frac{1}{3},$$

which belong to $[0, 1]$, so $y(t)$ and $q(t)$ lie in $[0, 1]$ for every time $t \in [0, T]$.

Lemma 17. *There exist a time $T_\psi > 0$ and a function T_0 defined on $[0, 1]$, satisfying*

$$\forall y \in [0, 1] \setminus \{Y(\bar{u})\}, \quad T_0(y) > 0, \quad T_0(Y(\bar{u})) = 0, \quad \sup_{[0,1]} T_0 < +\infty,$$

such that, for $T > T_0(y(0)) + T_\psi$, the control defined by

$$u^*(t) = \begin{cases} \begin{cases} u_{\min} & \text{if } y(0) > Y(\bar{u}) \\ u_{\max} & \text{if } y(0) < Y(\bar{u}) \end{cases} & \text{for } t \in [0, T_0(y(0))], \\ \bar{u} & \text{for } t \in (T_0(y(0)), T - T_\psi], \\ u_{\min} & \text{for } t \in (T - T_\psi, T], \end{cases} \quad (4.24)$$

satisfies the PMP. Moreover, we have $y = Y(\bar{u})$ and $q = \pi(\bar{u})$ on $[T_0(y(0)), T - T_\psi]$.

Based on Lemma 17, we have the following theorem

Theorem 18. *There exists a time $T_c > T_\psi + \sup_{[0,1]} T_0$ such that, for every final time $T > T_c$, the control defined by (4.24) is the unique optimal control of the problem*

$$\begin{cases} \dot{x} = u(F + \theta G)x + \zeta Gx, \\ x(0) = x^0 > 0, \\ J(u) = \psi x(T) \rightarrow \max. \end{cases}$$

For the optimal relaxed control $(u^*, \sigma(u^*)) \rightarrow \Sigma$ given by (4.24), we can easily build a sequence of piecewise constant functions $(u^n, v^n)_{n \in \mathbb{N}} \rightarrow \Omega$ such that $(u^n, v^n) \rightarrow (u^*, \sigma(u^*))$ weakly in $\sigma(L^1, L^\infty)$. It suffices to replace $u^* = \bar{u}$ on the interval $(T_0, T - T_\psi]$ by

$$u^n(t) = \begin{cases} u_{\min} & \text{if } t \in (T_0 + (k-1)\Delta t, T_0 + (k-1)\Delta t + \Delta_{\min}] \\ u_{\max} & \text{if } t \in (T_0 + (k-1)\Delta t + \Delta_{\min}, T_0 + k\Delta t] \end{cases}, \quad \text{for } k = 1, \dots, n,$$

where we have defined

$$\Delta t = \frac{T - (T_0 + T_\psi)}{n}, \quad \Delta_{\min} := \frac{u_{\max} - \bar{u}}{u_{\max} - u_{\min}} \Delta t \quad \text{and} \quad \Delta_{\max} := \frac{\bar{u} - u_{\min}}{u_{\max} - u_{\min}} \Delta t, \quad (4.25)$$

and to set $v^n = r(u^n)$.

Proof of Lemma 17. For $y(0) \in [0, Y(\bar{u})]$, we want to check that the solution y of (4.20) with $u = u_{\max}$ reaches $Y(\bar{u})$ in finite time $T_0(y(0)) > 0$. By (4.22), this is true if and only if $Y(u_{\max}) > Y(\bar{u})$. In the same way for the case $y(0) \in (Y(\bar{u}), 1]$, we need to check that $Y(u_{\min}) < Y(\bar{u})$. To that end, we study the variations of the function $u \mapsto Y(u)$. Starting from the computations in the proof of Theorem 14, we get

$$Y(u) = \frac{\lambda_P(u) + u\beta}{\lambda_P(u) + u\beta + (u\theta + \zeta)\tau} = \frac{u\beta - (u\theta + \zeta)\tau + \sqrt{\Delta}}{u\beta + (u\theta + \zeta)\tau + \sqrt{\Delta}},$$

and by differentiation

$$Y'(u) = \frac{2h(u)}{(u\beta + (u\theta + \zeta)\tau + \sqrt{\Delta})^2} \quad \text{with} \quad h(u) := \beta\zeta\tau - \theta\tau\sqrt{\Delta} + \frac{\Delta'}{2\sqrt{\Delta}}(u\theta + \zeta)\tau.$$

To have the sign of h on $[0, \frac{\zeta}{-\theta}]$, we differentiate h :

$$h'(u) = \frac{(u\theta + \zeta)\tau}{4\Delta\sqrt{\Delta}} (2\Delta\Delta'' - (\Delta')^2)$$

and we have with the notations in the proof of Theorem 14

$$2\Delta\Delta'' - (\Delta')^2 = 4D^2(A^2 - 2B^2 - C^2) = -32D^2\beta^2 < 0.$$

So h is decreasing and since $h(\frac{\zeta}{-\theta}) = 2\zeta\beta\tau > 0$, we get that $h > 0$ on $[0, \frac{\zeta}{-\theta}]$. Then Y is increasing and

$$Y(u_{\min}) < Y(\bar{u}) < Y(u_{\max}). \quad (4.26)$$

In the time interval $[T - T_\psi, T]$, we consider the projection q of the adjoint function p (see (4.19)). We need to prove that, starting from $q(T) = \frac{1}{3}$, the (backward) solution q of (4.21) with $u = u_{\min}$ reaches $\pi(\bar{u})$ in a finite time $T_\psi < T$. We proceed as for the direct equation. We compute

$$\pi(u) = \frac{\lambda_P(u) + u\beta}{\lambda_P(u) + 3u\beta} = \frac{u\beta - (u\theta + \zeta)\tau + \sqrt{\Delta}}{5u\beta - (u\theta + \zeta)\tau + \sqrt{\Delta}}$$

and

$$\pi'(u) = \frac{4g(u)}{(5u\beta - (u\theta + \zeta)\tau + \sqrt{\Delta})^2} \quad \text{with} \quad g(u) = \beta \left(\zeta\tau - \sqrt{\Delta} + \frac{u\Delta'}{2\sqrt{\Delta}} \right).$$

We have

$$g'(u) = \frac{\beta}{4\Delta\sqrt{\Delta}} (2\Delta\Delta'' - (\Delta')^2) < 0.$$

Hence $g < 0$ since $g(0) = 0$. We obtain

$$\pi(u_{\min}) > \pi(\bar{u}) > \pi(u_{\max}) > \pi\left(\frac{\zeta}{-\theta}\right) = \frac{1}{3}, \quad (4.27)$$

which, together with (4.23) gives the conclusion.

The last point to prove Lemma 17 is to verify that the control we have built by (4.24) satisfies the maximality condition, *i.e.*,

$$H_{\Sigma}(x(t), p(t), u^*(t)) = \max_{u \in [u_{\min}, u_{\max}]} H_{\Sigma}(x(t), p(t), u), \quad \forall t \in [0, T],$$

where (x, p) is the solution of (4.3)-(4.4) satisfying the boundary condition $x(0) = (x_1^0, x_2^0)^T > 0$ and $p(T) = (1, 2)$. For this, it suffices to check that the switching function $\Phi(t) = \Phi(x(t), p(t))$ is positive when $u^*(t) = u_{\max}$, negative when $u^*(t) = u_{\min}$, and null when $u^*(t) = \bar{u}$ (see Figure 4 for a numerical illustration). In the interval $[T_0(y(0)), T - T_{\psi}]$, we have $u^* = \bar{u}$, but we also have $y = Y(\bar{u})$ and $p = \pi(\bar{u})$. Thus, by Theorem 13 and Theorem 14, $\Phi = 0$. For the endpoints intervals, the key point is to notice that Φ satisfies the equation

$$\dot{\Phi} = \Lambda_1 \Phi + \Lambda_2, \quad (4.28)$$

with

$$\begin{aligned} \Lambda_1 &:= \zeta\tau \frac{x_1}{x_2}, \\ \Lambda_2 &:= \zeta\tau(p_2 - p_1) \left(-\theta\tau \left(\frac{x_1}{x_2} \right)^2 - 2\beta \right) x_2. \end{aligned}$$

Let us point out that

$$\text{sign}(\Lambda_2(t)) = \text{sign}(y(t) - Y(\bar{u})), \quad \forall t \in [0, T], \quad (4.29)$$

where, for every real number a , $\text{sign}(a) = 1$ if $a > 0$, $\text{sign}(a) = -1$ if $a < 0$ and $\text{sign}(a) = 0$ if $a = 0$. Indeed, using Corollary 15, we can write

$$\begin{aligned} \Lambda_2 &= \frac{\zeta\tau}{2\beta} \frac{p_2 - p_1}{x_2} (\sqrt{-2\theta\tau\beta}x_1 + 2\beta x_2) (\sqrt{-2\theta\tau\beta}x_1 - 2\beta x_2) \\ &= \frac{\zeta\tau}{2\beta} (2\beta + \sqrt{-2\theta\tau\beta}) \frac{x_1 + x_2}{x_2} (p_2 - p_1) (\sqrt{-2\theta\tau\beta}x_1 + 2\beta x_2) (y - Y(\bar{u})) \end{aligned}$$

and, from Lemma 10, we know that $p_2 - p_1 > 0$. It is noteworthy that the sign of Λ_2 does not depend on p . In the interval $[0, T_0(y(0))]$, if $y(0) > Y(\bar{u})$, we have $u^*(t) \equiv u_{\min}$ and $y(t) > Y(\bar{u})$. We deduce that, in this case, $\Lambda_2(t) > 0$ and, since $\Phi(T_0(y(0))) = 0$, we have $\Phi(t) < 0$ in the interval $[0, T_0(y(0))]$. The same argument proves that, if $y(0) < Y(\bar{u})$, then $u^*(t) \equiv u_{\max}$ and $\Phi(t) > 0$ in the interval $[0, T_0(y(0))]$. In the interval $(T - T_{\psi}, T]$, we have $u^*(t) \equiv u_{\min}$, since $y(T - T_{\psi}) = Y(\bar{u})$, we have $y(t) < Y(\bar{u})$. It follows that $\Lambda_2(t) < 0$, then $\Phi(t) < 0$ since $\Phi(T - T_{\psi}) = 0$.

The proof of Lemma 17 is complete. \square

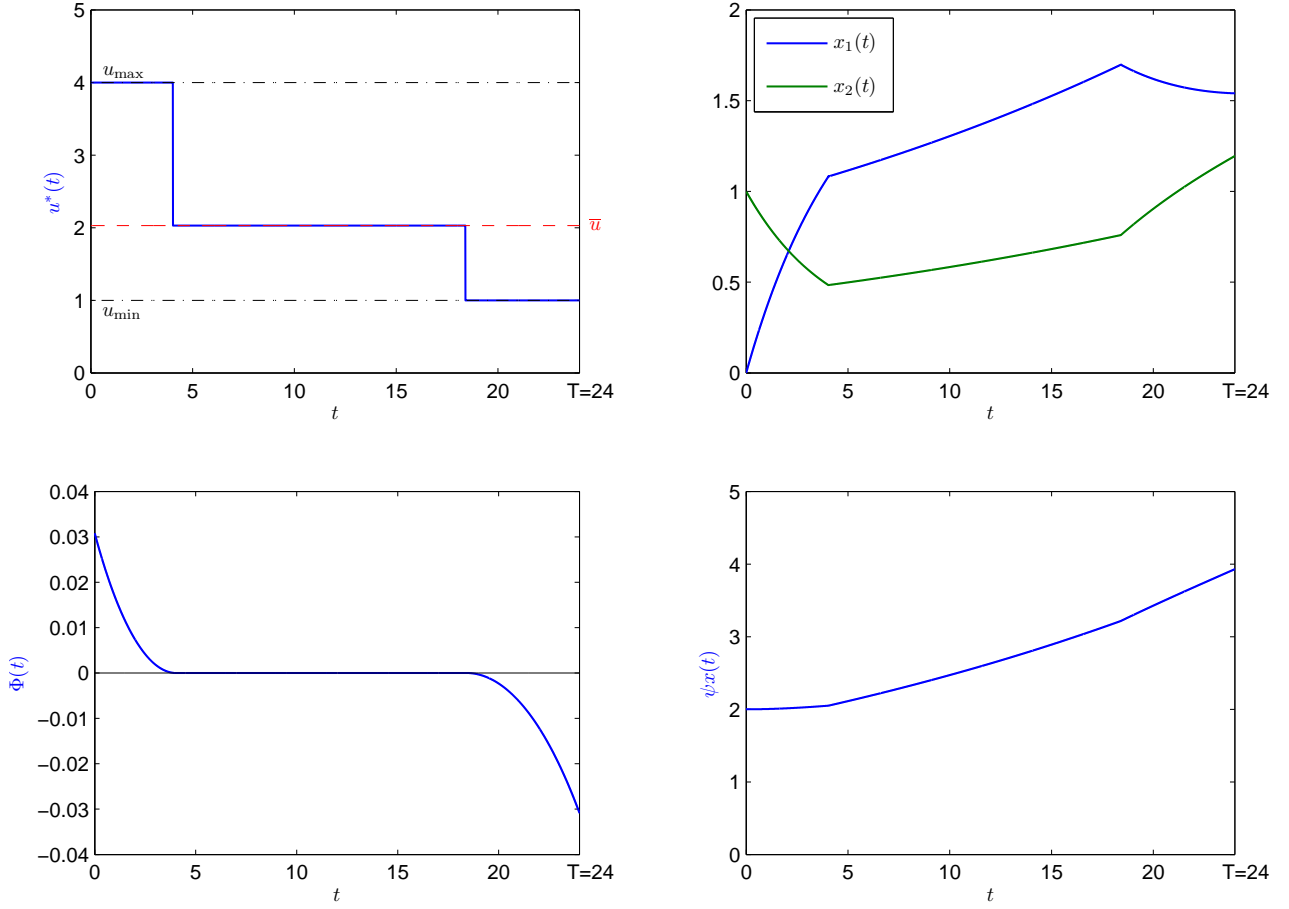


Figure 4: Top left: the optimal control for $T = 24$, $n = 2$, $\theta = -0.2$, $\zeta = 1$, $\tau = 0.1$, $\beta = 0.05$ and the initial data $x^0 = (0, 1)^T$. Top right: the corresponding trajectories $x_1(t)$ and $x_2(t)$. Bottom left: the switching function $\Phi(t)$. Bottom right: the evolution of the objective $\psi x(t) = x_1(t) + 2x_2(t)$.

Proof of Theorem 18. Let $t \in [0, T] \mapsto u^*(t)$ be a control such that the PMP is satisfied. Let x^* , p^* , y^* , q^* and Φ^* be the corresponding functions. Since $\Phi^*(T) = \theta \tau x_1^*(T) < 0$, necessarily, $u^* = u_{\min}$ in a neighborhood of T . We start from time T and analyze the optimal control backward in time.

First we prove by contradiction that there exist $\eta > 0$ and $T_1 > 0$ (both independent of x^0) such that, if $T > T_1$, $y^*(T)$ cannot belong to $[Y(u_{\min}) - \eta, Y(u_{\min}) + \eta]$. We start from the fact that

$$\phi(u_{\min})(F + \theta G)X(u_{\min}) = \lambda'_P(u_{\min}) > 0. \quad (4.30)$$

(The first equality of (4.30) can be obtained by differentiating $(u(F + \theta G) + \zeta G)X(u) = \lambda_P(u)X(u)$ with respect to u and by using $\phi(u)(u(F + \theta G) + \zeta G) = \lambda_P(u)\phi(u)$.) Property (4.30) ensures that there exists $\varepsilon > 0$ such that

$$\max\{|y - Y(u_{\min})|, |q - \pi(u_{\min})|\} \leq \varepsilon \implies \Phi(x, p) > 0. \quad (4.31)$$

Using (4.27) and decreasing $\varepsilon > 0$ if necessary, we may assume that $\pi(u_{\min}) - \varepsilon > 1/3$. Then there exists $T_{1,1} > 0$ such that, if q is the solution of (4.21) with $u = u_{\min}$ and $q(0) = 1/3$, one

has $q(-T_{1,1}) = \pi(u_{\min}) - \varepsilon$. Consider now $\eta > 0$ such that, every solution y of (4.20) with control $u = u_{\min}$ satisfying $y(0) \in [Y(u_{\min}) - \eta, Y(u_{\min}) + \eta]$ remains in $[Y(u_{\min}) - \varepsilon, Y(u_{\min}) + \varepsilon]$ during the interval of time $[-T_{1,1}, 0]$. (This $\eta > 0$ exists since $(y, u) := (Y(u_{\min}), u_{\min})$ is a solution of (4.20).) Still decreasing $\varepsilon > 0$ if necessary and using (4.26), we may assume that

$$Y(u_{\min}) + \varepsilon < Y(\bar{u}). \quad (4.32)$$

By (4.22), (4.26) and (4.32), there exists (a unique) $T_{1,2} > 0$ such that the solution y of (4.20) with control $u = u_{\max}$ and such that $y(0) = Y(u_{\min}) + \varepsilon$, satisfies $y(-T_{1,2}) = 0$. Let $T_1 := T_{1,1} + T_{1,2}$ and $T > T_1$. Let us assume that $y^*(T)$ belongs to $[Y(u_{\min}) - \eta, Y(u_{\min}) + \eta]$. If $\Phi^* < 0$ in $[T - T_{1,1}, T]$, then $u^* = u_{\min}$ in $[T - T_{1,1}, T]$, and, by the property of η , $y^*(T - T_{1,1}) \in [Y(u_{\min}) - \varepsilon, Y(u_{\min}) + \varepsilon]$, which, together with (4.31) gives $\Phi^*(T - T_{1,1}) > 0$. Hence $\Phi^* < 0$ on $[T - T_{1,1}, T]$ does not hold and there exists $t' \in [T - T_{1,1}, T]$ such that $\Phi^*(t') = 0$ and $\Phi^* < 0$ in $(t', T]$. Then $y^*(t') \leq Y(u_{\min}) + \varepsilon < Y(\bar{u})$, which, with (4.28) and (4.29), gives $(\Phi^*)'(t') < 0$. Hence, for $t < t'$ close to t' , $\Phi^* > 0$ in $[t, t')$ and $u^* = u_{\max}$ almost every where in $[t, t')$. Then, from (4.22), (4.26), (4.28) and (4.29), one gets that, for every $t \in [0, t')$, $\Phi^*(t) > 0$ and $y^*(t) < Y(\bar{u})$. In particular, $u^* = u_{\max}$ almost every where in $[0, t']$. Then, using the definition of $T_{1,2} > 0$, we get that $y^*(T - t' - T_{1,2}) \leq 0$, which is not possible since $x^* > 0$ in $[0, T]$. Hence $y^*(T)$ cannot belong to $[Y(u_{\min}) - \eta, Y(u_{\min}) + \eta]$.

By (4.22), there exists (a unique) $T_2 > 0$ such that, if y is the solution of (4.20) with $u = u_{\min}$ and $y(0) = Y(u_{\min}) - \eta$, then $y(-T_2) = 0$. For $T > T_2$, the terminal value $y^*(T)$ cannot be in $[0, Y(u_{\min}) - \eta]$. Indeed, if $y^*(T)$ is in $[0, Y(u_{\min}) - \eta]$, using (4.22), (4.26), (4.28) and (4.29), one gets that $y^* < Y(u_{\min}) < Y(\bar{u})$ in $[0, T]$, $\Phi^* < 0$ in $[0, T]$, $u^* = u_{\min}$ almost every where in $[0, T]$. With the definition of T_2 , this leads to $y^*(T - T_2) \leq 0$, which, again, is not possible since $x^* > 0$ on $[0, T]$.

By (4.22), there exists $T_{3,1} > 0$ such that, if y is the solution of (4.20) with $u = u_{\min}$ and $y(0) = Y(u_{\min}) + \eta$, then $y(-T_{3,1}) = 1$. Let us assume that $T > T_{3,1}$. If $y^*(T) \in (Y(u_{\min}) + \eta, 1]$, then there exists a time $t_0 > T - T_{3,1}$ such that $\Phi^*(t_0) = 0$ because $y^*(t)$ has to be less than 1 for every time in $[0, T]$. Increasing t_0 if necessary, we may also impose that $\Phi^* < 0$ in $(t_0, T]$. It is not possible to have $y^*(t_0) > Y(\bar{u})$ because in this case, by (4.28) and (4.29), we would have $\Phi^*(t_0) = 0$ with $(\Phi^*)'(t_0) = \Lambda_2(t_0) > 0$, which cannot hold since $\Phi^* < 0$ in $(t_0, T]$. So we necessarily have $y^*(t_0) \leq Y(\bar{u})$. If $y^*(t_0) < Y(\bar{u})$, then, by (4.29), $\Lambda_2(t_0) < 0$, $\Phi^*(t) > 0$ for $t < t_0$ close to t_0 , which implies that $u^*(t) = u_{\max}$ for almost every $t < t_0$ close to t_0 . From (4.28) and (4.29), we get that Φ^* remains positive for every time in $[0, t_0)$ because y^* remains less than $Y(\bar{u})$ and thus $\Lambda_2 < 0$. By (4.22) and (4.26), there exists (a unique) $T_{3,2} > 0$ such that, if y is the solution of (4.20) with $u = u_{\max}$ and $y(0) = Y(\bar{u})$, then $y(-T_{3,2}) = 0$. We get that $y^*(t_0)$ cannot be less than $Y(\bar{u})$ if $T > T_3 := T_{3,1} + T_{3,2}$. Hence, for $T > T_3$, we have $y^*(t_0) = Y(\bar{u})$. We deduce from this identity, together with $\Phi^*(t_0) = 0$, that $q^*(t_0) = \pi(\bar{u})$ and it implies that $t_0 = T - T_\psi$, where, T_ψ is defined in the proof of Lemma 17. As a consequence, the only possible value for $y^*(T)$ is $y(T_\psi) \in (Y(\bar{u}), 1)$, where y is the solution of (4.20) with $u = u_{\min}$ such that $y(0) = Y(\bar{u})$.

Here, we have proved that, for $T > \max\{T_1, T_2, T_3\}$, the only possible control which satisfies the PMP takes the value u_{\min} in $[T - T_\psi, T]$. Moreover, the associated trajectories satisfy $y^*(T - T_\psi) = Y(\bar{u})$ and $q^*(T - T_\psi) = \pi(\bar{u})$. Then, using (4.28) with the same kind of arguments as above, it is straightforward to check that the control defined by (4.24) is the only control which satisfies the PMP for $T > T_c := \max\{T_1, T_2, T_3\}$. Since any optimal control satisfies the PMP (see Theorem 3), we conclude that this is the only optimal control. \square

Corollary 19. *Asymptotically in T we have the convergence*

$$\lim_{T \rightarrow +\infty} \frac{\ln(J(u^*))}{T} = \lambda_P(\bar{u}).$$

A similar ergodic result is proved in [2] in the case of dimension $n = 3$ but without proving that the limit is $\lambda_P(\bar{u})$.

5 Conclusion and perspectives

We have modeled the PMCA protocol by a system of differential equations with a control term. The analysis of the optimal control problem which aims to maximize the efficiency of the PMCA makes appear strong relations with the optimization of the Perron eigenvalue for constant controls. In dimension 2 the explicit solution indicates that, for the efficiency of the technique to be almost maximal, the ratio between the length of the sonication phases and the duration of the incubation phases has to be close to $\frac{\Delta_{\max}}{\Delta_{\min}} = \frac{\bar{u} - u_{\min}}{u_{\max} - \bar{u}}$ (see (4.25)) where $\bar{u} \in (u_{\min}, u_{\max})$ is the constant which maximizes the Perron eigenvalue.

However many works remain to do before applying our results for the optimization of real PMCA experiments. First the cases of dimensions higher than two should be investigated. But it appears that even for the dimension three the situation is much more delicate than in dimension two. Then to use the mathematical results in practice, the parameters of the model have to be estimated from experiments. This requires precise measurements of the size distribution of the polymers and inverse problem methods as the one detailed in [9] (see also the references therein).

Appendix

A Perron eigenvalue

For $u > 0$ fixed and $r(u) > 0$, denote by $(\lambda_P(u), X_P(u), \phi_P(u))$ the Perron eigenlements of the matrix $M(u) := uF + r(u)G$ defined by

$$\begin{cases} \lambda_P X_P = M(u) X_P, & X_P > 0, & \|X_P\|_1 = 1, \\ \lambda_P \phi_P = \phi_P M(u), & \phi_P > 0, & \phi_P X_P = 1. \end{cases}$$

In the current section we investigate the dependence of these elements on the control parameter u . Such eigenlements also exist for the continuous growth-fragmentation equation (1.1) (see [7] for instance), and their dependence on parameters is investigated in [1, 11].

The function $r : \mathbb{R}^+ \rightarrow \mathbb{R}^{+*}$ is assumed to be continuous and bounded. Theorem 1 is an immediate consequence of the following Lemma 20 and Theorem 21.

Lemma 20. *The eigenlements λ_P , X_P and ϕ_P are continuous functions of u on \mathbb{R}^+ . Moreover, we have*

$$\lambda_P(u) > 0 \text{ for } u > 0 \quad \text{and} \quad \lim_{u \rightarrow 0} \lambda_P(u) = 0.$$

Proof. Since the function r is continuous, the coefficients of the matrix $M(u)$ depend continuously on u . As a consequence, the characteristic polynomial of $M(u)$ varies continuously with u . The first eigenvalue λ_P is the largest root of this characteristic polynomial and the Perron-Frobenius theorem ensures that the multiplicity of this root is 1. So λ_P is a continuous function of u .

Let $u \geq 0$ and $(u_k)_{k \in \mathbb{N}}$ be a positive sequence which converges to u . Since $\|X_P(u_k)\|_1 = 1$ there exists a subsequence of $(X_P(u_k))_k$ which converges to a limit X_∞ . By continuity of $\lambda_P(u)$ and $M(u)$, this limit satisfies $M(u)X_\infty = \lambda_P(u)X_\infty$ and $\|X_\infty\|_1 = 1$. By uniqueness of the first eigenvector, we conclude that the whole sequence $(X_P(u_k))_k$ converges to $X_\infty = X_P(u)$ and so X_P is a continuous function of u . Since $(X_P(u_k))_k$ is a positive convergent sequence, it is lower bounded and we deduce from the normalization $\phi_P X_P = 1$ that the sequence $(\phi_P(u_k))_k$ is bounded. The same as for X_P , we conclude from the uniqueness of the adjoint eigenvector that ϕ_P is a continuous function of u .

Define $\Theta := (1, 1, \dots, 1)$ and, for $j = 2, \dots, n$, $K_j := \sum_{i=1}^{j-1} \kappa_{ij} > 0$. We have: $\Theta X_P = \|X_P\|_1 = 1$ since $X_P > 0$, $\Theta G = 0$ from (1.5), and $\Theta F = (0, K_2 \beta_2, \dots, K_n \beta_n)^T$ from (1.6). So multiplying the identity $\lambda_P X_P = M(u)X_P$ by Θ we get

$$\lambda_P(u) = u \Theta F X_P \leq u \max_{2 \leq j \leq n} K_j \beta_j$$

which ensures that $\lambda_P(u)$ is positive for u positive and tends to zero when $u \rightarrow 0$. □

Theorem 21. *Under Assumptions (2.1) and (2.2), we have the expansions*

$$\begin{aligned} k < l, \quad &\implies \quad \lambda_P(u) = r_0 \tau_1 + \left[r_0^{k+1} (\tau_{k+1} - (k+1) \tau_1) \prod_{i=1}^k \frac{\tau_i}{\beta_{i+1}} \right] u^{-k} + o_{u \rightarrow +\infty}(u^{-k}), \\ k = l, \quad &\implies \quad \lambda_P(u) = r_0 \tau_1 + \left[r_0^{k+1} (\tau_{k+1} - (k+1) \tau_1) \prod_{i=1}^k \frac{\tau_i}{\beta_{i+1}} + r_k \tau_1 \right] u^{-k} + o_{u \rightarrow +\infty}(u^{-k}), \\ k > l, \quad &\implies \quad \lambda_P(u) = r_0 \tau_1 + r_l \tau_1 u^{-l} + o_{u \rightarrow +\infty}(u^{-l}). \end{aligned}$$

This result can be related to Corollary 1 in [1] which provides an expansion of the first eigenvalue for the continuous growth-fragmentation model. The proof of Theorem 21 uses the following lemma which gives the asymptotic behavior of the eigenvector $X_P = (x_1, x_2, \dots, x_n)^T$.

Lemma 22. *Assume that $r(u)$ admits a limit $r_0 > 0$ when u tends to $+\infty$, then*

$$\forall i \in [1, n], \quad x_i(u) \underset{u \rightarrow +\infty}{\sim} r_0^{i-1} \prod_{j=1}^{i-1} \frac{\tau_j}{\beta_{j+1}} u^{1-i}. \quad (\text{A.1})$$

Proof of Lemma 22. We prove by induction on i that

$$u^i x_{i+1}(u) \xrightarrow{u \rightarrow +\infty} r_0^i \prod_{j=1}^i \frac{\tau_j}{\beta_{j+1}} \quad \text{and} \quad u^i x_j(u) \xrightarrow{u \rightarrow +\infty} 0, \quad \forall j > i+1. \quad (\text{IH})$$

$i = 0$: We have by definition

$$(r(u)G + uF)X_P(u) = \lambda_P(u)X_P(u) \quad \text{with} \quad \|X_P(u)\|_1 = 1. \quad (\text{A.2})$$

We use $\psi = (1, 2, \dots, n)$, which satisfies $\psi F = 0$ (see (3.6)). Testing (A.2) against ψ on the left, we obtain

$$r(u)\psi G X_P(u) = \lambda_P(u)\psi X_P(u) \quad (\text{A.3})$$

and so $\lambda_P(u)$ is bounded since $\|X_P(u)\|_1 = 1$ and r is bounded. Dividing by u in (A.2), we get

$$\left(\frac{r(u)}{u}G + F\right)X_P(u) = \frac{\lambda_P(u)}{u}X_P(u). \quad (\text{A.4})$$

The sequence $X_P(u)$ is bounded and thus convergence occurs when $u \rightarrow +\infty$ for a subsequence. But from (A.4) the limit X_P^∞ must satisfy $FX_P^\infty = 0$ so the whole sequence converges to

$$X_P^\infty = \delta := (1, 0 \cdots, 0)^T.$$

$i \rightarrow i+1$: ($i+2 \leq n$) We have

$$u^{i+1}FX_P(u) = u^i\lambda_P(u)X_P(u) - u^i r(u)GX_P(u).$$

We consider the $n-i-1$ last lines of this matrix identity and find

$$\begin{pmatrix} -\beta_{i+2} & & & \\ & (2\kappa_{kj}\beta_j) & & \\ & \ddots & & \\ 0 & & & -\beta_n \end{pmatrix} \begin{pmatrix} u^{i+1}x_{i+2}(u) \\ \vdots \\ u^{i+1}x_n(u) \end{pmatrix} = \begin{pmatrix} (\lambda_P(u) + r(u)\tau_{i+2})u^i x_{i+2}(u) - r(u)\tau_{i+1}u^i x_{i+1}(u) \\ \vdots \\ \lambda_P(u)u^i x_n(u) - r(u)\tau_{n-1}u^i x_{n-1}(u) \end{pmatrix} \\ \xrightarrow[u \rightarrow +\infty]{\text{by (IH)}} \begin{pmatrix} -r_0\tau_{i+1} \cdot r_0^i \prod_{j=1}^i \frac{\tau_j}{\beta_{j+1}} \\ 0 \end{pmatrix},$$

which concludes the proof of Lemma 22. \square

Proof of Theorem 21. Notice that $k < n$ since $\tau_n = 0$ and $\tau_1 > 0$. Using (A.3), the convergence of X_P to $\delta = (1, 0 \cdots, 0)^T$ and the convergence of r to r_0 , we obtain that $\lambda_P(u)$ converges when $u \rightarrow +\infty$ and that the limit λ_P^∞ satisfies

$$r_0\psi G\delta = \lambda_P^\infty\psi\delta, \quad (\text{A.5})$$

which gives

$$\lambda_P^\infty = r_0\tau_1. \quad (\text{A.6})$$

We make the difference between (A.3) and (A.5). By (A.6), we obtain

$$(\lambda_P(u) - r_0\tau_1)\psi X_P(u) + r_0\tau_1\psi(X_P(u) - \delta) = r(u)\psi G(X_P(u) - \delta) + (r(u) - r_0)\psi G\delta. \quad (\text{A.7})$$

Denoting $m := \min(k, l)$ and using (A.7), we obtain

$$\begin{aligned} u^m(\lambda_P(u) - r_0\tau_1)\psi X_P(u) &= u^m r(u)\psi G(X_P(u) - \delta) + u^m(r(u) - r_0)\psi G\delta - u^m r_0\tau_1\psi(X_P(u) - \delta) \\ &= u^m r_0\psi(G - \tau_1 Id)(X_P(u) - \delta) + u^m(r(u) - r_0)\psi GX_P(u) \\ &= u^m r_0 \sum_{j=1}^{n-1} (\tau_j - j\tau_1)(x_j(u) - \delta_{1,j}) + u^m(r(u) - r_0)\psi GX_P(u) \\ &= r_0 \sum_{j=k+1}^{n-1} (\tau_j - j\tau_1)u^m x_j(u) + u^m(r(u) - r_0)\psi GX_P(u) \\ &\xrightarrow[u \rightarrow +\infty]{(\text{A.1})} \mathbb{1}_{\{k \leq l\}} r_0^{k+1} (\tau_{k+1} - (k+1)\tau_1) \prod_{i=1}^k \frac{\tau_i}{\beta_{i+1}} + \mathbb{1}_{\{k \geq l\}} r_l \tau_1, \end{aligned}$$

where $\delta_{1,j} = 1$ if $j = 1$ and $\delta_{1,j} = 0$ otherwise. □

B Floquet eigenvalue

For a T -periodic control $u(t)$, the Floquet theorem ensures that there is a Floquet eigenvalue $\lambda_F[u(\cdot)]$ and a T -periodic function $X_F[u(\cdot)](t)$ solution to

$$\frac{d}{dt}X_F(t) = [M(u(t)) - \lambda_F]X_F(t).$$

The Floquet eigenvalues can sometimes be compared to the Perron eigenvalues [6, 12]. Here we make periodic variations around the optimal constant control u_{opt} to find whether or not periodic controls can provide a better eigenvalue than $\lambda_P(u_{\text{opt}})$.

Consider directional perturbations $u(t) = u_{\text{opt}} + \varepsilon\gamma(t)$, where γ is a fixed T -periodic function and ε a varying parameter. For the sake of clarity, we denote by $\lambda_F(\varepsilon) := \lambda_F[u_{\text{opt}} + \varepsilon\gamma(\cdot)]$ the Floquet eigenvalue associated to ε , $V_F(\varepsilon; t) := V_F[u_{\text{opt}} + \varepsilon\gamma(\cdot)](t)$ the eigenfunction and $V'_F(\varepsilon; t) := \partial_\varepsilon V_F(\varepsilon; t)$ its derivative with respect to ε . We also use the notation

$$\langle f \rangle := \frac{1}{T} \int_0^T f(t) dt$$

for the time average of any T -periodic function $f(t)$.

Now we compute the derivatives of $\lambda_F(\varepsilon)$ which correspond to the directional derivatives of the Floquet eigenvalue at the point u_{opt} . This kind of differentiation technique is used in [23] to prove the results about the optimization of the Perron eigenvalue in the case of the continuous cell division problem. A formula which involves only the coefficients of the equation and the first eigenvectors is obtained for the first and second derivatives. Here, the computation of the second derivative requires a basis of eigenvectors, and so cannot be extended to continuous models. For $M(u_{\text{opt}})$ diagonalizable, we choose two bases (X_1, X_2, \dots, X_n) and $(\phi_1, \phi_2, \dots, \phi_n)$ of direct and adjoint eigenvectors associated to the eigenvalues $\lambda_1 = \lambda_P(u_{\text{opt}}) = \lambda_F(0) \in \mathbb{R}$, $\lambda_2 \in \mathbb{C}, \dots, \lambda_n \in \mathbb{C}$ such that $\phi_i X_i = 1$. Moreover, we choose X_1 positive and normalized to have $X_1 = X_P(u_{\text{opt}}) = X_F(\varepsilon = 0)$.

Proposition 23 (First order condition). *We have*

$$\frac{d\lambda_F}{d\varepsilon}(0) = \langle \gamma \rangle \frac{d\lambda_P}{du}(u_{\text{opt}}) = 0.$$

Hence, u_{opt} is a critical point also in the class of periodic control.

We need to go to the following order.

Proposition 24 (Second order condition). *If $M(u_{\text{opt}})$ is diagonalizable, we have*

$$\frac{d^2\lambda_F}{d\varepsilon^2}(0) = \langle \gamma^2 \rangle \phi_1 M''(u_{\text{opt}}) X_1 + 2 \sum_{i=2}^n \langle \gamma_i^2 \rangle (\lambda_1 - \lambda_i) (\phi_1 M'(u_{\text{opt}}) X_i) (\phi_i M'(u_{\text{opt}}) X_1),$$

where $\gamma_i(t) := \phi_i X'_F(0; t) (\phi_i M'(u_{\text{opt}}) X_1)^{-1}$ is the unique T -periodic solution to the ODE

$$\dot{\gamma}_i(t) + \lambda_1 \gamma_i(t) = \gamma(t) + \lambda_i \gamma_i(t). \tag{B.1}$$

Remark 25. For $\gamma \equiv 1$, we obtain the second derivative of the Perron eigenvalue

$$\frac{d^2 \lambda_1}{du^2}(u_{\text{opt}}) = \phi_1 M''(u_{\text{opt}}) X_1 + 2 \sum_{i=2}^n \frac{(\phi_1 M' X_i)(\phi_i M' X_1)}{\lambda_1 - \lambda_i},$$

which is negative since u_{opt} is a maximum. This formula appears in [32]. There exists a physical interpretation in terms of repulsive/attractive forces among the eigenvalues.

Proof of Proposition 23. First we give an expression of the first derivative for the Perron eigenvalue. By definition, we have

$$M(u)X_P = \lambda_P X_P,$$

which provides by differentiation

$$\lambda'_P X_P + \lambda_P X'_P = M'(u)X_P + M(u)X'_P.$$

Testing against the adjoint eigenvector ϕ_P , we obtain

$$\lambda'_P + \lambda_P \phi_P X'_P = \phi_P M'(u)X_P + \phi_P M(u)X'_P.$$

Since

$$\phi_P M(u) = \lambda_P \phi_P, \tag{B.2}$$

we have

$$\lambda'_P = \phi_P M'(u)X_P = \phi_P (r'(u)G + F)X_P.$$

Now, starting from the Floquet eigenvalue problem, we have

$$\partial_t X_F + \lambda_F(\varepsilon)X_F = M(u_{\text{opt}} + \varepsilon\gamma)X_F,$$

which provides by differentiation with respect to ε that

$$\partial_t X'_F + \lambda'_F(\varepsilon)X_F + \lambda_F(\varepsilon)X'_F = \gamma(t)M'(u_{\text{opt}} + \varepsilon\gamma)X_F + M(u_{\text{opt}} + \varepsilon\gamma)X'_F. \tag{B.3}$$

We test the preceding equation against ϕ_1 and we evaluate at $\varepsilon = 0$. We obtain, using (B.2),

$$\partial_t(\phi_1 X'_F) + \lambda'_F = \gamma\phi_1 M'(u_{\text{opt}})X_1,$$

and, after integration in time,

$$\lambda'_F = \left(\frac{1}{T} \int_0^T \gamma(t) dt \right) \phi_1 M'(u_{\text{opt}})X_1 = \left(\frac{1}{T} \int_0^T \gamma(t) dt \right) \frac{d\lambda_P}{du}(u_{\text{opt}}) = 0.$$

It proves the first order condition. \square

Proof of Proposition 24. We test (B.3) against another adjoint eigenvector ϕ_i and we evaluate at $\varepsilon = 0$. Using Proposition 23 and denoting $\gamma_i(t) := \phi_i X'_F(t)(\phi_i M'(u_{\text{opt}})X_1)^{-1}$, we obtain

$$\dot{\gamma}_i(t) + \lambda_1 \gamma_i(t) = \gamma(t) + \lambda_i \gamma_i(t). \tag{B.4}$$

Next, we differentiate (B.3) with respect to ε and we get

$$\begin{aligned} & \partial_t X''_F + \lambda''_F(\varepsilon)X_F + 2\lambda'_F(\varepsilon)X'_F + \lambda_F X''_F \\ & = \gamma^2 M''(u_{\text{opt}} + \varepsilon\gamma)X_F + 2\gamma M'(u_{\text{opt}} + \varepsilon\gamma)X'_F + M(u_{\text{opt}} + \varepsilon\gamma)X''_F. \end{aligned}$$

We evaluate at $\varepsilon = 0$ and we test against ϕ_1 to find, using once more Proposition 23,

$$\partial_t(\phi_1 X_F'') + \lambda_F''(0) = \gamma^2 \phi_1 M''(u_{\text{opt}})X_1 + 2\gamma(t)\phi_1 M'(u_{\text{opt}})X_F'. \quad (\text{B.5})$$

We decompose the unknown X_F' along the basis (X_1, \dots, X_n)

$$X_F' = \sum_{i=1}^n \gamma_i(t)(\phi_i M'(u_{\text{opt}})X_1)X_i.$$

We have in particular

$$\phi_1 M'(u_{\text{opt}})X_F' = \sum_{i=2}^n \gamma_i(t)(\phi_i M'(u_{\text{opt}})X_1)(\phi_1 M'(u_{\text{opt}})X_i).$$

To conclude, we integrate (B.5) on $[0, T]$ to obtain

$$\lambda_F''(0) = \langle \gamma^2 \rangle \phi_1 M''(u_{\text{opt}})X_1 + 2 \sum_{i=2}^n \langle \gamma \gamma_i \rangle (\phi_i M'(u_{\text{opt}})X_1)(\phi_1 M'(u_{\text{opt}})X_i)$$

and use the identity

$$(\lambda_1 - \lambda_i) \left(\int_0^T \gamma_i^2(t) dt \right) = \int_0^T \gamma(t) \gamma_i(t) dt,$$

which can be checked by multiplying (B.4) by γ_i and by integrating the result on $[0, T]$. \square

Now we can prove Theorem 2 stated in Section 2 by using the result of Proposition 24.

Proof of Theorem 2. We consider the periodic function

$$\gamma(t) = \cos(\omega t)$$

and we denote by $\lambda_F(\varepsilon, \omega)$ the Floquet eigenvalue corresponding to the periodic control $u_{\text{opt}} + \varepsilon \cos(\omega t)$. We compute the $2\pi/\omega$ -periodic solution $\gamma_i(t)$ to (B.1)

$$\gamma_i(t) = \frac{\lambda_1 - \lambda_i}{\omega^2 + (\lambda_1 - \lambda_i)^2} \cos(\omega t) + \frac{\omega}{\omega^2 + (\lambda_1 - \lambda_i)^2} \sin(\omega t)$$

and then we obtain the formula

$$\lambda_F''(0, \omega) = \frac{1}{2} \phi_1 M''(u_{\text{opt}})X_1 + \sum_{i=2}^n \frac{\lambda_1 - \lambda_i}{\omega^2 + (\lambda_1 - \lambda_i)^2} (\phi_1 F X_i)(\phi_i F X_1).$$

But we have

$$\phi_1 M''(u_{\text{opt}})X_1 = r''(u_{\text{opt}})\phi_1 G X_1$$

and we can compute $\phi_1 G X_1$ by doing the appropriate combination of

$$\lambda_P(u_{\text{opt}}) = \phi_1 (r(u_{\text{opt}})G + u_{\text{opt}}F)X_1$$

and

$$\lambda_P'(u_{\text{opt}}) = 0 = \phi_1 (r'(u_{\text{opt}})G + F)X_1$$

to obtain

$$\phi_1 M''(u_{\text{opt}}) X_1 = \frac{r''(u_{\text{opt}})}{r(u_{\text{opt}}) - u_{\text{opt}} r'(u_{\text{opt}})} \lambda_P(u_{\text{opt}}).$$

Thus, we have the limit

$$\lim_{\omega \rightarrow +\infty} \lambda_F''(0, \omega) = \frac{1}{2} \frac{r''(u_{\text{opt}})}{r(u_{\text{opt}}) - u_{\text{opt}} r'(u_{\text{opt}})} \lambda_P(u_{\text{opt}}).$$

□

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