

On the Analysis of a Biological System: Compartment Model Approach

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Abstract

In this paper, we are interested in control of a substance which circulate among organs in leaving being. We determine, under certain conditions, the optimal control which steers such systems from an initial state to a desired one. The linear quadratic optimal control problem of such systems is analyzed using the Hilbert Uniqueness Method (HUM). To illustrate our approach, some examples and numerical simulations are given.

Keywords: Compartment models, controllability, optimal control, impulsive commands

1 Introduction

There is no exact definition in the literature of a compartment model. For Jacquez [6]: "a compartment system is a system which is made of a finite number of macroscopic sub-systems called compartments exchanging material". According to Legay [12]: "a compartment system is a set of two or more compartments communicating and among which one or more determined elements circulate. The number of compartments and circulation rules make up the system rules".

Different biological systems are modelled as compartment systems: in "cancer chemotherapy" (see, for instance [10], [14], [18]), in "pharmacokinetics" and "computer-assisted clinical pharmacokinetics" (see, for instance [4], [5]), in "blood glucose control for diabetic patients" [15],

In this work, we adopt a compartmental model to determine the optimal manoeuvre which allows a biological system to reach a predefined profile. More precisely, we consider a system made of n compartments exchanging a given

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substance. It is known (see [3], [7], [17]) that if we allocate a number from 1 to n and if $x_{ji}(t)$ is the amount of substance transferred from compartment i to compartment j and $x_i(t)$ the amount of substance contained in compartment i at time t , then the evolution in time of the vector $x(t) = (x_1(t), x_2(t), \dots, x_n(t))^T$, is described by the differential equation

$$\begin{cases} \dot{x}(t) = Ax(t) + BU(t) \\ x(0) \text{ is given} \end{cases} \quad (1)$$

where $A = (k_{ij})_{1 \leq i, j \leq n}$ is an $n \times n$ square matrix; k_{ij} is the proportionality ratio between $\frac{d}{dt}x_{ji}(t)$ and $x_i(t)$ (the model we adopt is based on the fact that k_{ij} is constant).

$U(t) = (U^1(t), U^2(t), \dots, U^n(t))^T$ where $U^i(t)$ is the rate of external input of the substance to compartment i at time t ; $U(t)$ represent then the control variable.

B is the $n \times n$ diagonal matrix given by

$$B = \begin{pmatrix} b_1 & 0 & 0 & \cdots & 0 \\ 0 & b_2 & 0 & \cdots & \vdots \\ 0 & 0 & \ddots & 0 & \vdots \\ \vdots & \vdots & 0 & \ddots & 0 \\ 0 & \cdots & \cdots & 0 & b_n \end{pmatrix}$$

where $b_i = 1$ when compartment i receives the substance from outside and $b_i = 0$ when it doesn't. (for example: for cancer chemotherapy, in the 2-compartment model made of different phases of the cell-cycle; blocking agents like Cyclophosphamide act during synthesis (compartment 1) and killing agents like Taxol act during mitosis (compartment 2) (see [9]).

In order for the mathematical model to be representative of various situations, it is incorrect to assume that the control $U(t)$ is a continuous function in time. Therefore we take into consideration both impulsive and continuous controls: For example, in the case of treating a patient, an injection can be interpreted as impulsive control and a perfusion is the continuous one. We assume that the control $U(t) = (u(t), v(t))$ where $v(t)$ is continuous in time, and $u(t) = (u^1(t), u^2(t), \dots, u^n(t))^T$ with $u^i(t)$ is a sequence of impulsive controls $(u_k^i)_k$, where every action u_k^i has a time support $[t_k^i, t_k^i + \varepsilon_k^i[$ (for example, in case of treating a patient, $t_k^i \in [0, T]$ means time of taking medicine meant to compartment i and ε_k^i means the necessary time for compartment i to absorb the medicine).

In other words, we consider the system described by

$$\begin{cases} \dot{x}(t) = Ax(t) + B_1u(t) + B_2v(t) & 0 \leq t \leq T \\ x(0) \text{ is given} \end{cases} \quad (2)$$

where $A, B_1, B_2 \in \mathcal{L}(\mathbb{R}^n)$; B_1 and B_2 are diagonal matrices; $u \in \mathcal{E}$ and $v \in L^2(0, T; \mathbb{R}^n)$; \mathcal{E} is the set of impulsive controls (the set \mathcal{E} will be highlighted in section 2).

we investigate the optimal control $(u^*, v^*) \in \mathcal{E} \times L^2(0, T; \mathbb{R}^n)$ such that

$$\begin{cases} 1) & x_{(u^*, v^*)}^{x_0}(T) = x_d \\ 2) & \|(u^*, v^*)\| = \min\{\|(u, v)\| / x_{(u, v)}^{x_0}(T) = x_d\} \end{cases}$$

where $x_{(u^*, v^*)}^{x_0}(T)$ is the solution of system (2) corresponding to the control (u^*, v^*) at time T and $\|\cdot\|$ is the usual norm of $L^2(0, T; \mathbb{R}^n) \times L^2(0, T; \mathbb{R}^n)$. To illustrate this work, some examples are given.

The section 3 of this paper is devoted to the study of the problem of linear quadratic optimal control for such systems, i.e, we investigate the control $u =$

$$\sum_{i=0}^{N-1} u_i \chi_{[t_i, t_i + \varepsilon_i[} \in \mathcal{E}_N \text{ which minimizes the cost functional}$$

$$J(u) = \langle x(T), Gx(T) \rangle + \sum_{i=0}^{N-1} \langle x(t_i), Mx(t_i) \rangle + \int_0^T \langle u(t), Ru(t) \rangle dt$$

where $x(t_i)$ is the solution of system (1) corresponding to the control u at time t_i , G, M and R are self-adjoint and non-negative with $\langle Ru, u \rangle \geq \alpha \|u\|^2$ for some $\alpha > 0$ and all $u \in \mathcal{E}_N$.

The technic used for this is similar to HUM method (see [1], [2], [8], [13]), we adapt the technic of [16] to our system, the optimal control is given by inversion of some isomorphism in an adequate Hilbert space.

2 Mathematical Modelling of the problem

Let's consider the system

$$\begin{cases} \dot{x}(t) = Ax(t) + B_1u(t) + B_2v(t) & 0 \leq t \leq T \\ x(0) \text{ is given} \end{cases} \tag{3}$$

where $A = (k_{ij})_{1 \leq i, j \leq n}$ is an $n \times n$ square matrix; B_1 and B_2 are $n \times n$ diagonal matrix.

The controllability problem as it was defined in the previous section, may be, mathematically interpreted by the determination of a control (u^*, v^*) which allows to steer the system from the initial state x_0 to a desired one x_d at time T and with minimal-costs. In others words, we investigate u^* and v^* such that

$$(P) \left\{ \begin{array}{l} i) u^* \in \mathcal{E} = \{u \in L^2(0, T; \mathbb{R}^n) / u = \sum_{k=0}^{N-1} u_k \chi_{[t_k, t_k + \varepsilon_k[}, u_k \in \mathbb{R}^n\} ; v^* \in L^2(0, T; \mathbb{R}^n) \\ \quad t_k = k \frac{T}{N}, N \in \mathbb{N}^*, t_k + \varepsilon_k < t_{k+1}. \\ ii) x_{(u^*, v^*)}^{x_0}(T) = x_d \\ iii) \|(u^*, v^*)\| = \min\{\|(u, v)\| / (u, v) \in \mathcal{E} \times L^2(0, T; \mathbb{R}^n) \text{ and } x_{(u, v)}^{x_0}(T) = x_d\} \end{array} \right.$$

where $x_{(u, v)}^{x_0}(T)$ is the solution of the system (2), corresponding to control (u, v) at time T and initialization x_0 and $\|\cdot\|$ is the usual norm on $L^2(0, T; \mathbb{R}^n) \times L^2(0, T; \mathbb{R}^n)$.

Remark 2.1 *i) The choice of \mathcal{E} as a control space, suppose that the absorption ratios $(\varepsilon_k)_{0 \leq k \leq N-1}$ are the same for every compartment.*

$$ii) \text{ For every } u = \sum_{k=0}^{N-1} u_k \chi_{[t_k, t_k + \varepsilon_k[}, v = \sum_{k=0}^{N-1} v_k \chi_{[t_k, t_k + \varepsilon_k[} \in \mathcal{E}$$

$$\langle u, v \rangle_{L^2(0, T; \mathbb{R}^n)} = \sum_{k=0}^{N-1} \varepsilon_k \langle u_k, v_k \rangle_{\mathbb{R}^n}$$

$$iii) \|u\|_{L^2(0, T; \mathbb{R}^n)}^2 = \sum_{k=0}^{N-1} \varepsilon_k \|u_k\|^2$$

iv) \mathcal{E} endowed with $L^2(0, T; \mathbb{R}^n)$ topology is a Hilbert space.

The solution of the system (3) is

$$x(t) = e^{tA} x_0 + \int_0^t e^{(t-s)A} B_1 u(s) ds + \int_0^t e^{(t-s)A} B_2 v(s) ds, \quad t \in [0, T].$$

We deduce that for $u = \sum_{k=0}^{N-1} u_k \chi_{[t_k, t_k + \varepsilon_k[}$; we have

$$\begin{aligned} x(T) &= e^{TA} x_0 + \sum_{k=0}^{N-1} \int_{t_k}^{t_k + \varepsilon_k} e^{(T-s)A} B_1 u_k ds + \int_0^T e^{(T-s)A} B_2 v(s) ds \\ &= e^{TA} x_0 + \mathcal{H}(u, v) \end{aligned}$$

where \mathcal{H} is an operator defined from $\mathcal{E} \times L^2(0, T; \mathbb{R}^n)$ to \mathbb{R}^n by

$$\mathcal{H}(u, v) = \sum_{k=0}^{N-1} \int_{t_k}^{t_k + \varepsilon_k} e^{(T-s)A} B_1 u_k ds + \int_0^T e^{(T-s)A} B_2 v(s) ds.$$

Lemma 2.1 \mathcal{H} is a linear continuous operator, and if we consider the inner product defined on $L^2(0, T; \mathbb{R}^n) \times L^2(0, T; \mathbb{R}^n)$; \mathcal{H}^* the adjoint operator of \mathcal{H} is defined, for all $x \in \mathbb{R}^n$, by

$$\mathcal{H}^* x = (\mathcal{H}_1^* x, \mathcal{H}_2^* x)$$

where

$$(\mathcal{H}_1^* x)(\theta) = \begin{cases} \frac{1}{\varepsilon_k} (\int_{t_k}^{t_k + \varepsilon_k} B_1 e^{(T-s)A^T} u_k ds) x, & \theta \in [t_k, t_k + \varepsilon_k[, \quad k \in \{0, 1, \dots, N-1\} \\ 0 & \text{elsewhere} \end{cases}$$

$$(\mathcal{H}_2^* x)(\theta) = B_2 e^{(T-\theta)A^T} x , \quad \theta \in [0, T]$$

Proof

The linearity is obvious, moreover

$$\begin{aligned} \|\mathcal{H}(u, v)\|_{\mathbb{R}^n} &\leq \sum_{k=0}^{N-1} \int_{t_k}^{t_k + \varepsilon_k} \|e^{(T-s)A} B_1\| \|u_k\| ds + (\int_0^T \|e^{(T-s)A} B_2\|^2 ds)^{\frac{1}{2}} (\int_0^T \|v(s)\|^2 ds)^{\frac{1}{2}} \\ &\leq \sum_{k=0}^{N-1} \int_0^T \|e^{(T-s)A} B_1\| ds \|u_k\| + (\int_0^T \|e^{(T-s)A} B_2\|^2 ds)^{\frac{1}{2}} \|v\|_{L^2(0, T; \mathbb{R}^n)} \\ &\leq (\int_0^T \|e^{(T-s)A} B_1\| ds) \sum_{k=0}^{N-1} \|u_k\| + (\int_0^T \|e^{(T-s)A} B_2\|^2 ds)^{\frac{1}{2}} \|v\|_{L^2(0, T; \mathbb{R}^n)} \\ &\leq (\int_0^T \|e^{(T-s)A} B_1\| ds) (\sum_{k=0}^{N-1} 1^2)^{\frac{1}{2}} (\sum_{k=0}^{N-1} \|u_k\|^2)^{\frac{1}{2}} + (\int_0^T \|e^{(T-s)A} B_2\|^2 ds)^{\frac{1}{2}} \|v\| \\ &\leq (\int_0^T \|e^{(T-s)A} B_1\| ds) \sqrt{N} (\sum_{k=0}^{N-1} \alpha \varepsilon_k \|u_k\|^2)^{\frac{1}{2}} + (\int_0^T \|e^{(T-s)A} B_2\|^2 ds)^{\frac{1}{2}} \|v\| \end{aligned}$$

where α is a constant verifying $1 \leq \alpha \varepsilon_k$ for every k (for example $\alpha = \sup_{0 \leq k \leq N-1} (\frac{1}{\varepsilon_k})$).
Hence

$$\|\mathcal{H}(u, v)\| \leq (\int_0^T \|e^{(T-s)A} B_1\| ds) \cdot \sqrt{N\alpha} \|u\| + (\int_0^T \|e^{(T-s)A} B_2\|^2 ds)^{\frac{1}{2}} \|v\|$$

That establishes the continuity of \mathcal{H} .

On the other hand, since $B_i^T = B_i$ for $i = 1, 2$; we have

$$\begin{aligned}
\langle \mathcal{H}(u, v), x \rangle &= \sum_{k=0}^{N-1} \langle \int_{t_k}^{t_k+\varepsilon_k} e^{(T-s)A} B_1 u_k ds, x \rangle + \langle \int_0^T e^{(T-s)A} B_2 v(s) ds, x \rangle \\
&= \sum_{k=0}^{N-1} \int_{t_k}^{t_k+\varepsilon_k} \langle u_k, B_1 e^{(T-s)A^T} x \rangle ds + \int_0^T \langle v(s), B_2 e^{(T-s)A^T} x \rangle ds \\
&= \sum_{k=0}^{N-1} \langle u_k, \int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} x ds \rangle + \langle v, \mathcal{H}_2^* x \rangle_{L^2(0, T; \mathbb{R}^n)} \\
&= \sum_{k=0}^{N-1} \varepsilon_k \langle u_k, \frac{1}{\varepsilon_k} \int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} x ds \rangle + \langle v, \mathcal{H}_2^* x \rangle \\
&= \langle u, \mathcal{H}_1^* x \rangle + \langle v, \mathcal{H}_2^* x \rangle \\
&= \langle (u, v), \mathcal{H}^* x \rangle.
\end{aligned}$$

Thus, the adjoint of \mathcal{H} is

$$\mathcal{H}^* x = (\mathcal{H}_1^* x, \mathcal{H}_2^* x)$$

where

$$\begin{aligned}
(\mathcal{H}_1^* x)(\theta) &= \begin{cases} \frac{1}{\varepsilon_k} (\int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} u_k ds) x, & \theta \in [t_k, t_k + \varepsilon_k[, \quad k \in \{0, 1, \dots, N-1\} \\ 0 & \text{elsewhere} \end{cases} \\
(\mathcal{H}_2^* x)(\theta) &= B_2 e^{(T-\theta)A^T} x, \quad \theta \in [0, T]
\end{aligned}$$

■

Definition 2.1 *The system (3) is said to be controllable on $[0, T]$ if the operator \mathcal{H} is surjective.*

Proposition 2.1 *\mathcal{H} is surjective if and only if for all $x_0, x_d \in \mathbb{R}^n$ it exists a control $u \in \mathcal{E}$ and a control $v \in L^2(0, T; \mathbb{R}^n)$ such that $x_{(u,v)}^{x_0}(T) = x_d$, where $x_{(u,v)}^{x_0}(T)$ is the solution of the system (3) corresponding to control (u, v) .*

Proof

If \mathcal{H} is surjective then $\exists u \in \mathcal{E}, v \in L^2(0, T; \mathbb{R}^n)$ such that $\mathcal{H}(u, v) = x_d - e^{TA} x_0$ hence $x_d = x_{(u,v)}^{x_0}(T)$.

Conversely, if for $x_0 = 0$ and any x_d in \mathbb{R}^n , there exists $u \in \mathcal{E}, v \in L^2(0, T; \mathbb{R}^n)$ such that $x_{(u,v)}^{x_0}(T) = x_d$, then $\mathcal{H}(u, v) = x_d$ that establishes that \mathcal{H} is surjective.

■

Remark 2.2 *It follows from the previous proposition that*

The system (3) is controllable on $[0, T] \Leftrightarrow \text{Im}\mathcal{H} = \mathbb{R}^n \Leftrightarrow \text{Ker}\mathcal{H}^* = \{0\}$.

Proposition 2.2 *The system (3) is controllable on $[0, T]$ if and only if*

$$\text{Ker} \begin{pmatrix} \int_{t_0}^{t_0+\varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1+\varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1}+\varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix} = \{0\}$$

Proof

It is an immediate consequence of the definition of \mathcal{H}^* and the remark 2.2 .

■

In order to lighten the matrix condition in the previous proposition, we give the following necessary condition

Proposition 2.3

$$\begin{aligned} & \text{Ker} \begin{pmatrix} \int_{t_0}^{t_0+\varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1+\varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1}+\varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix} = \{0\} \\ \Rightarrow & \text{Ker} \begin{pmatrix} B_1 \\ B_1 A^T \\ \vdots \\ B_1 (A^T)^{n-1} \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix} = \{0\} \\ \Leftrightarrow & \text{rank} \left[B_1 \mid B_1 A^T \mid \dots \mid B_1 (A^T)^{n-1} \mid B_2 \mid B_2 A^T \mid \dots \mid B_2 (A^T)^{n-1} \right] = n \end{aligned}$$

Proof

If we suppose that

$$x \in Ker \begin{pmatrix} B_1 \\ B_1 A^T \\ \vdots \\ B_1 (A^T)^{n-1} \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix}$$

then

$$B_1 x = B_1 A^T x = \dots = B_1 (A^T)^{n-1} x = 0$$

by the Cayley-Hamilton theorem, there exist reals a_0, a_1, \dots, a_{n-1} such that

$$A^n = a_0 I + a_1 A + \dots + a_{n-1} A^{n-1}$$

we deduce by immediate recurrence that, for any integer k ,

$$B_1 (A^T)^k x = 0$$

thus for any $t \in [0, T]$,

$$B_1 e^{tA^T} x = 0$$

consequently, for any $k = 0, 1, \dots, N-1$

$$\left(\int_{t_k}^{t_k + \varepsilon_k} B_1 e^{(T-s)A^T} ds \right) x = 0$$

therefore

$$x \in Ker \begin{pmatrix} \int_{t_0}^{t_0 + \varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1 + \varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1} + \varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix}$$

■

Remark 2.3 *The reciprocal of proposition 2.3 is false. Indeed for $A^T = \begin{pmatrix} 1 & 1 \\ 0 & 0 \end{pmatrix}$, $B_1 = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}$, $B_2 = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}$; we have $\text{rank}[B_1|B_1A^T|B_2|B_2A^T] = 2$ and*

$$\text{Ker} \begin{pmatrix} M_0 \\ M_1 \\ \vdots \\ M_{N-1} \\ B_2 \\ B_2A^T \end{pmatrix} \neq \{0\} \text{ where } M_k = \int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} ds$$

Indeed, we have

$$A^T = \begin{pmatrix} 1 & 1 \\ -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} 0 & -1 \\ 1 & 1 \end{pmatrix}$$

$$M_k = \begin{pmatrix} [-e^{(T-s)A^T}]_{t_k}^{t_k+\varepsilon_k} & [-e^{(T-s)A^T}]_{t_k}^{t_k+\varepsilon_k} \\ 0 & 0 \end{pmatrix}$$

then

$$\begin{pmatrix} 1 \\ -1 \end{pmatrix} \in \text{Ker} \begin{pmatrix} M_0 \\ M_1 \\ \vdots \\ M_{N-1} \\ B_2 \\ B_2A^T \end{pmatrix}.$$

■

Consider Λ the $n * n$ matrix defined by

$$\Lambda = \mathcal{H}\mathcal{H}^*$$

we have then

$$\begin{aligned} \Lambda x &= \mathcal{H}(\mathcal{H}^* x) \\ &= \mathcal{H}(\mathcal{H}_1^* x, \mathcal{H}_2^* x) \\ &= \sum_{k=0}^{N-1} \left(\int_{t_k}^{t_k+\varepsilon_k} e^{(T-s)A} B_1 \left(\frac{1}{\varepsilon_k} \int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} ds \right) x \right) ds \\ &\quad + \int_0^T e^{(T-s)A} B_2 (B_2 e^{(T-s)A^T}) x ds \\ &= \sum_{k=0}^{N-1} \frac{1}{\varepsilon_k} \left(\int_{t_k}^{t_k+\varepsilon_k} e^{(T-s)A} B_1 ds \right) \left(\int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} ds \right) x \\ &\quad + \left(\int_0^T e^{(T-s)A} B_2^2 e^{(T-s)A^T} ds \right) x \end{aligned}$$

It's easy to show that Λ is a bounded self-adjoint operator.

Lemma 2.2 *the system (3) is controllable on $[0, T]$ if and only if $\text{Ker}\Lambda = \{0\}$.*

Proof

It is sufficient to show the equality

$$\text{Ker}\Lambda = \text{Ker} \begin{pmatrix} \int_{t_0}^{t_0+\varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1+\varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1}+\varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix}.$$

Let's consider

$$x \in \text{Ker} \begin{pmatrix} \int_{t_0}^{t_0+\varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1+\varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1}+\varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix}$$

that implies that

$$\int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} x ds = 0, \quad \forall k \in \{0, 1, \dots, N-1\}$$

and

$$B_2 x = B_2 A^T x = \dots = B_2 (A^T)^{n-1} x = 0$$

thus

$$\left(\int_{t_k}^{t_k+\varepsilon_k} e^{(T-s)A} B_1 ds \right) \left(\int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} x ds \right) = 0, \quad \forall k \in \{0, 1, \dots, N-1\}$$

and

$$\int_0^T e^{(T-s)A} B_2 (B_2 e^{(T-s)A^T} x) ds = 0$$

hence

$$\Lambda x = 0$$

which means

$$x \in Ker \Lambda.$$

Conversely, if we suppose that $\Lambda x = 0$ then $\langle \Lambda x, x \rangle = 0$ and $\langle \mathcal{H}\mathcal{H}^* x, x \rangle = 0$, which implies that $\|\mathcal{H}^* x\| = 0$ ie $\mathcal{H}^* x = 0$. Consequently,

$$x \in Ker \begin{pmatrix} \int_{t_0}^{t_0+\varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1+\varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1}+\varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix}.$$

■

Now, we establish the fundamental result of this section.

Theorem 2.1 *If we suppose that the system (3) is controllable on $[0, T]$,*

$$i.e., Ker \begin{pmatrix} \int_{t_0}^{t_0+\varepsilon_0} B_1 e^{(T-s)A^T} ds \\ \int_{t_1}^{t_1+\varepsilon_1} B_1 e^{(T-s)A^T} ds \\ \vdots \\ \int_{t_{N-1}}^{t_{N-1}+\varepsilon_{N-1}} B_1 e^{(T-s)A^T} ds \\ B_2 \\ B_2 A^T \\ \vdots \\ B_2 (A^T)^{n-1} \end{pmatrix} = \{0\}$$

then the unique control solution (u^*, v^*) of the problem (P) is given by

$$(u^*(\theta), v^*(\theta)) = \left(\sum_{k=0}^{N-1} \frac{1}{\varepsilon_k} \left(\int_{t_k}^{t_k+\varepsilon_k} B_1 e^{(T-s)A^T} ds \right) \chi_{[t_k, t_k+\varepsilon_k]}(\theta) f, B_2 e^{(T-\theta)A^T} f \right)$$

where f is the unique solution of the linear system

$$\Lambda f = x_d - e^{TA} x_0.$$

Proof

If the system (3) is controllable, by lemma 2.2, we have

$$\text{Ker}\Lambda = \{0\}$$

$\Lambda \in \mathcal{L}(\mathbb{R}^n)$, then Λ is bijective, hence there exists $f \in \mathbb{R}^n$, unique solution of the equation

$$\Lambda f = x_d - e^{TA}x_0.$$

Observe that the control (u^*, v^*) may be written as follows

$$(u^*, v^*) = \mathcal{H}^* f \in \mathcal{E} \times L^2(0, T; \mathbb{R}^n)$$

we have

$$\begin{aligned} x_{(u^*, v^*)}^{x_0}(T) &= e^{TA}x_0 + \mathcal{H}(u^*, v^*) \\ &= e^{TA}x_0 + \mathcal{H}\mathcal{H}^* f \\ &= e^{TA}x_0 + \Lambda f \\ &= x_d \end{aligned}$$

then the control (u^*, v^*) allows to steer the system from the initial state x_0 to the desired one x_d at instant T.

Let $(u, v) \in \mathcal{E} \times L^2(0, T; \mathbb{R}^n)$ another control such that $x_{(u, v)}^{x_0}(T) = x_d$, then

$$\begin{aligned} \mathcal{H}(u^*, v^*) = \mathcal{H}(u, v) &\Rightarrow \langle \mathcal{H}((u^*, v^*) - (u, v)), f \rangle = 0 \\ &\Rightarrow \langle (u^*, v^*) - (u, v), \mathcal{H}^* f \rangle = 0 \\ &\Rightarrow \langle (u^*, v^*) - (u, v), (u^*, v^*) \rangle = 0 \\ &\Rightarrow \|(u^*, v^*)\|^2 = \langle (u, v), (u^*, v^*) \rangle \leq \|(u, v)\| \|(u^*, v^*)\|. \end{aligned}$$

Consequently

$$\|(u^*, v^*)\| \leq \|(u, v)\|$$

that establishes the optimality of (u^*, v^*) . ■

Example : Let us consider a 2-compartment model, then A is a 2×2 square matrix which supposed diagonalisable, so we can write

$$A^T = PDP^{-1}$$

where

$$P = \begin{pmatrix} a & b \\ c & d \end{pmatrix}; P^{-1} = \frac{1}{\det P} \begin{pmatrix} d & -b \\ -c & a \end{pmatrix}; D = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}$$

λ_1, λ_2 are the eigenvalues of A. Therefore

$$e^{(T-s)A^T} = \frac{1}{\det P} \begin{pmatrix} ade^{\lambda_1(T-s)} - bce^{\lambda_2(T-s)} & -abe^{\lambda_1(T-s)} + abe^{\lambda_2(T-s)} \\ cde^{\lambda_1(T-s)} - cde^{\lambda_2(T-s)} & -bce^{\lambda_1(T-s)} + ade^{\lambda_2(T-s)} \end{pmatrix}$$

If we take

$$B_1 = B_2 = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}$$

which means that the impulsive control (for example injection) and the continuous control (for example perfusion) act only on compartment 1. Let we call

$$M = \begin{pmatrix} M_0 \\ M_1 \\ \vdots \\ M_{N-1} \\ B_2 \\ B_2 A^T \end{pmatrix} \quad \text{where } M_k = \int_{t_k}^{t_k + \varepsilon_k} B_1 e^{(T-s)A^T} ds$$

then

$$M_k = \frac{1}{\det P} \begin{pmatrix} y_k & z_k \\ 0 & 0 \end{pmatrix}$$

where

$$\begin{aligned} y_k &= ad\alpha_k e^{\lambda_1(T-t_k)} - bc\beta_k e^{\lambda_2(T-t_k)} \\ z_k &= ab[-\alpha_k e^{\lambda_1(T-t_k)} + \beta_k e^{\lambda_2(T-t_k)}] \end{aligned}$$

with

$$\alpha_k = \begin{cases} \frac{1}{\lambda_1}(1 - e^{-\lambda_1 \varepsilon_k}) & \text{if } \lambda_1 \neq 0 \\ \varepsilon_k & \text{if } \lambda_1 = 0 \end{cases} ; \quad \beta_k = \begin{cases} \frac{1}{\lambda_2}(1 - e^{-\lambda_2 \varepsilon_k}) & \text{if } \lambda_2 \neq 0 \\ \varepsilon_k & \text{if } \lambda_2 = 0 \end{cases}$$

Using proposition 2.2, the system is controllable if and only if $Ker M = \{0\}$. For $N = 1$ and $B_2 = 0$; $M = M_0$ then $\det M = 0$, i.e., $Ker M \neq \{0\}$; the system is not controllable, it means that if the control acts on only one compartment, taking medicine (for example) only one time is not sufficient to lead the system to the desired state.

For $N = 2$, $t_0 = 0$, $t_1 = \frac{T}{2}$

$$\det \begin{pmatrix} y_0 & z_0 \\ y_1 & z_1 \end{pmatrix} = ab(\det P) e^{\frac{\lambda_1 + \lambda_2}{2} T} (-\alpha_1 \beta_0 e^{\frac{\lambda_2}{2} T} + \alpha_0 \beta_1 e^{\frac{\lambda_1}{2} T})$$

if we suppose $ab \neq 0$; $\varepsilon_0 = \varepsilon_1 = \varepsilon$ and $\lambda_1 \neq \lambda_2$ (i.e. $\alpha_0 = \alpha_1$, $\beta_0 = \beta_1$) then

$\det \begin{pmatrix} y_0 & z_0 \\ y_1 & z_1 \end{pmatrix} \neq 0$; in which case the system is controllable.

Using theorem 2.1, if $\lambda_1 \neq 0$, $\lambda_2 \neq 0$ and $\lambda_1 + \lambda_2 \neq 0$ and when the system is controllable, the optimal control (u^*, v^*) which allows the system to be leads from a state x_0 to a desired final state x_d at time T is given by

$$u^*(\theta) = \begin{cases} \frac{1}{\varepsilon_k(\det P)} \begin{pmatrix} y_k & z_k \\ 0 & 0 \end{pmatrix} f & \text{if } \theta \in [t_k, t_k + \varepsilon_k[\\ 0 & \text{elsewhere} \end{cases}$$

$$v^*(\theta) = \frac{1}{\det P} \begin{pmatrix} ad e^{\lambda_1(T-\theta)} - bc e^{\lambda_2(T-\theta)} & -ab (e^{\lambda_1(T-\theta)} - e^{\lambda_2(T-\theta)}) \\ 0 & 0 \end{pmatrix} f$$

where

$$f = (\det P)^2 \begin{pmatrix} \sum_{k=0}^{N-1} \frac{1}{\varepsilon_k} y_k^2 + y & \sum_{k=0}^{N-1} \frac{1}{\varepsilon_k} y_k z_k + z \\ \sum_{k=0}^{N-1} \frac{1}{\varepsilon_k} y_k z_k + z & \sum_{k=0}^{N-1} \frac{1}{\varepsilon_k} z_k^2 + w \end{pmatrix}^{-1} (x_d - e^{TA} x_0)$$

$$\begin{aligned} y_k &= ad\alpha_k e^{\lambda_1(T-t_k)} - bc\beta_k e^{\lambda_2(T-t_k)} & \alpha_k &= \frac{1}{\lambda_1}(1 - e^{-\lambda_1 \varepsilon_k}) \\ z_k &= ab [-\alpha_k e^{\lambda_1(T-t_k)} + \beta_k e^{\lambda_2(T-t_k)}] & \beta_k &= \frac{1}{\lambda_2}(1 - e^{-\lambda_2 \varepsilon_k}) \\ y &= -a^2 d^2 \gamma_1 + 2abcd\gamma - b^2 c^2 \gamma_2 & \gamma_1 &= \frac{1}{2\lambda_1}(1 - e^{2T\lambda_1}) \\ z &= ab [ad\gamma_1 - (bc + ad)\gamma + bc\gamma_2] & \gamma_2 &= \frac{1}{2\lambda_2}(1 - e^{2T\lambda_2}) \\ w &= -a^2 b^2 (\gamma_1 - 2\gamma + \gamma_2) & \gamma &= \frac{1}{\lambda_1 + \lambda_2}(1 - e^{T(\lambda_1 + \lambda_2)}) \end{aligned}$$

Numerical simulation

The parameter values chosen for the model are taken from [5] and are $\begin{pmatrix} -0.15 - 0.081 & 0.56 \\ 0.081 & -0.56 \end{pmatrix}$ the unit is h^{-1} , $x_d = \begin{pmatrix} 1.1 \times 10^{-4} \\ 0 \end{pmatrix}$ the unit is g and

$Ka = 2.3 h^{-1}$ the absorption constance.

Then , in the case when there is only an impulsive control,

for $B_2 = 0$; $x_0 = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$; $\varepsilon_k = \varepsilon = \frac{1}{2.3}h^{-1}$, $k = 0, 1, \dots, N-1$; and for $T = 120$

h and

$N = 5$, we have

$a = 1$; $b = 1$; $c = -3.31838022$; $d = 1.125046886$; $\det P = 4.443427106$; $\lambda_1 = -0.728757033$; $\lambda_2 = -0.0622429671$; $\alpha_k = 0.5118514633$ and $\beta_k = 0.4409424737$, $k = 0, 1, \dots, N-1$.

The parameters y_k and z_k are given in table 1.

k	0	1	2	3	4
$y_k \times 10^4$	8.346315978	37.175556	165.584669	737.535242	3285.076055
$z_k \times 10^4$	2.515177714	11.202922	49.899246	222.257605	989.963728

Table 1. The parameters y_k and z_k .

$$f = \begin{pmatrix} -0.1081830018 \times 10^9 \\ 0.3589923336 \times 10^9 \end{pmatrix}$$

and the optimal control u^* is given in table 2; $u^*(\theta) = \begin{pmatrix} u_1^*(\theta) \\ 0 \end{pmatrix}$

θ	[0 ; 0.435[[24 ; 24.435[[48 ; 48.435[[72 ; 72.435[[96 ; 96.435[
$u_1^*(\theta) \times 10^4$	0.2567294553	-67.1249512	114.823352	-69.0944365	63.57317267

Table 2. The evolution of the control u_1^* .

3 Linear quadratic optimal control

In this section, we consider the problem of linear quadratic optimal control related to the system described by

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) & 0 \leq t \leq T \\ x(0) \text{ is given} \end{cases} \quad (4)$$

where $A \in \mathcal{L}(\mathbb{R}^n)$; B is an $n \times n$ diagonal matrix;

$$u \in \mathcal{E}_N = \left\{ u = \sum_{k=0}^{N-1} u_k \chi_{[t_k, t_k + \varepsilon_k[}, \quad u_k \in \mathbb{R}^n, \quad t_k = k \frac{T}{N}, \quad t_k + \varepsilon_k < t_{k+1} \right\}$$

Our control problem is to determine the control $u \in \mathcal{E}_N$ which minimizes the cost functional

$$J(u) = \langle x(T), Gx(T) \rangle + \sum_{i=0}^{N-1} \langle x(t_i), Mx(t_i) \rangle + \int_0^T \langle u(t), Ru(t) \rangle dt$$

where G , M and R are self-adjoint and non-negative operators of $\mathcal{L}(\mathbb{R}^n)$ with $\langle Ru, u \rangle \geq \alpha \|u\|^2$ for some $\alpha > 0$ and all $u \in \mathcal{E}_N$.

3.1 Preliminary properties

In this subsection, we will develop an optimality system from which derives the optimal control $u^* \in \mathcal{E}_N$. For this, let us call $x_i = x(t_i)$, $0 \leq i \leq N$, so we have

$$\begin{aligned} x_{i+1} &= e^{t_{i+1}A} x_0 + \int_0^{t_{i+1}} e^{(t_{i+1}-s)A} Bu(s) ds \\ &= e^{\delta A} e^{t_i A} x_0 + \int_0^{t_i} e^{\delta A} e^{(t_i-s)A} Bu(s) ds + \int_{t_i}^{t_{i+1}} e^{(t_{i+1}-s)A} Bu(s) ds \\ &= e^{\delta A} x_i + \left(\int_{t_i}^{t_i + \varepsilon_i} e^{(t_{i+1}-s)A} B ds \right) u_i \end{aligned}$$

Then

$$x_{i+1} = Cx_i + B_i u_i$$

where $C = e^{\delta A}$ and $B_i = \int_{t_i}^{t_i + \varepsilon_i} e^{(t_{i+1}-s)A} B ds$.

We can establish easily that

$$\begin{aligned} x_i &= C^i x_0 + \sum_{j=0}^{i-1} C^{i-j-1} B_j u_j & 1 \leq i \leq N \\ x_i &= C^i x_0 + (\mathcal{H}_N(u))_i & 1 \leq i \leq N \end{aligned}$$

Where

$$\begin{aligned} \mathcal{H}_N : \mathcal{E}_N &\longrightarrow l^2(1, 2, \dots, N, \mathbb{R}^n) \\ u = \sum_{i=0}^{N-1} u_i \chi_{[t_i, t_i + \varepsilon_i[} &\longrightarrow ((\mathcal{H}_N(u))_1, (\mathcal{H}_N(u))_2, \dots, (\mathcal{H}_N(u))_N) \end{aligned}$$

with

$$(\mathcal{H}_N(u))_i = \sum_{j=0}^{i-1} C^{i-j-1} B_j u_j \quad 1 \leq i \leq N$$

The adjoint operator \mathcal{H}_N^* is given by

$$\begin{aligned} \mathcal{H}_N^* : l^2(1, 2, \dots, N, \mathbb{R}^n) &\longrightarrow \mathcal{E}_N \\ (x_1, x_2, \dots, x_N) &\longrightarrow \mathcal{H}_N^*(x_1, x_2, \dots, x_N) \end{aligned}$$

such that

$$\mathcal{H}_N^*(x_1, x_2, \dots, x_N)(\theta) = \frac{1}{\varepsilon_i} \sum_{k=i+1}^N B_i^* C^{*k-i-1} x_k \quad \text{if } \theta \in [t_i, t_i + \varepsilon_i[\quad 1 \leq i \leq N-1$$

Indeed, for $u \in \mathcal{E}_N$ and $(x_1, x_2, \dots, x_N) \in l^2(1, 2, \dots, N, \mathbb{R}^n)$; we have

$$\begin{aligned} \langle \mathcal{H}_N u, (x_1, x_2, \dots, x_N) \rangle &= \sum_{k=1}^N \langle (\mathcal{H}_N u)_k, x_k \rangle \\ &= \sum_{k=1}^N \langle \sum_{i=0}^{k-1} C^{k-i-1} B_i u_i, x_k \rangle \\ &= \sum_{k=1}^N \sum_{i=0}^{k-1} \langle u_i, B_i^* C^{*k-i-1} x_k \rangle \\ &= \sum_{i=0}^{N-1} \sum_{k=i+1}^N \langle u_i, B_i^* C^{*k-i-1} x_k \rangle \\ &= \sum_{i=0}^{N-1} \varepsilon_i \langle u_i, \frac{1}{\varepsilon_i} \sum_{k=i+1}^N B_i^* C^{*k-i-1} x_k \rangle \end{aligned}$$

We deduce that

$$\begin{aligned} J(u) &= \langle x_N, Gx_N \rangle + \sum_{i=1}^{N-1} \langle x_i, Mx_i \rangle + \langle u, Ru \rangle_{L^2(0, T, \mathbb{R}^n)} \\ &= \langle C^N x_0 + (\mathcal{H}_N u)_N, G(C^N x_0 + (\mathcal{H}_N u)_N) \rangle \\ &\quad + \sum_{i=1}^{N-1} \langle C^i x_0 + (\mathcal{H}_N u)_i, M(C^i x_0 + (\mathcal{H}_N u)_i) \rangle + \langle u, Ru \rangle \\ &= J_0 + \bar{J}(u) \end{aligned}$$

Where

$$\begin{aligned}
 J_0 &= \langle C^N x_0, GC^N x_0 \rangle + \sum_{i=1}^{N-1} \langle C^i x_0, MC^i x_0 \rangle \\
 \bar{J}(u) &= \langle (\mathcal{H}_N u)_N, G(\mathcal{H}_N u)_N \rangle + \sum_{i=1}^{N-1} \langle (\mathcal{H}_N u)_i, M(\mathcal{H}_N u)_i \rangle \\
 &\quad + 2(\langle (\mathcal{H}_N u)_N, GC^N x_0 \rangle + \sum_{i=1}^{N-1} \langle (\mathcal{H}_N u)_i, MC^i x_0 \rangle) + \langle u, Ru \rangle
 \end{aligned}$$

Let $D_i = M$ if $1 \leq i \leq N - 1$ et $D_N = G$ and consider the linear, auto-adjoint operator \bar{D} defined by

$$\begin{aligned}
 \bar{D} : \quad l^2(1, 2, \dots, N, \mathbb{R}^n) &\longrightarrow l^2(1, 2, \dots, N, \mathbb{R}^n) \\
 (x_1, x_2, \dots, x_N) &\longrightarrow (D_1 x_1, D_2 x_2, \dots, D_N x_N).
 \end{aligned}$$

If we call

$$\begin{cases} a_i = MC^i x_0 & 1 \leq i \leq N - 1 \\ a_N = GC^N x_0 \end{cases} \quad (5)$$

Then

$$\begin{aligned}
 \bar{J}(u) &= \langle \mathcal{H}_N u, \bar{D}\mathcal{H}_N u \rangle + 2 \langle \mathcal{H}_N u, (a_1, a_2, \dots, a_N) \rangle + \langle u, Ru \rangle \\
 &= \langle u, (\mathcal{H}_N^* D \mathcal{H}_N + R)u \rangle + 2 \langle u, \mathcal{H}_N^*(a_1, a_2, \dots, a_N) \rangle
 \end{aligned}$$

We deduce that the optimal control u^* of the quadratic function J is such that

$$(\mathcal{H}_N^* D \mathcal{H}_N + R)u^* = -\mathcal{H}_N^*(a_1, a_2, \dots, a_N)$$

Thus, we can establish easily that:

$$\begin{aligned}
 u^* &= -R^{-1} \mathcal{H}_N^*(Mx_1^{u^*}, \dots, Mx_{N-1}^{u^*}, Gx_N^{u^*}) \\
 &= -R^{-1} \mathcal{H}_N^*(D_1 x_1^{u^*}, D_2 x_2^{u^*}, \dots, D_N x_N^{u^*})
 \end{aligned}$$

Therefore

$$u^*(\theta) = -\frac{1}{\varepsilon_i} R^{-1} B_i^* \sum_{k=i+1}^N C^{*k-i-1} D_k x_k^{u^*} \quad \text{if } \theta \in [t_i, t_i + \varepsilon_i[\quad 0 \leq i \leq N - 1$$

Let's consider the signal $(p_i)_{0 \leq i \leq N-1}$ defined by

$$p_i = \sum_{k=i+1}^N C^{*k-i-1} D_k x_k^{u^*} \quad \text{if } \theta \in [t_i, t_i + \varepsilon_i[\quad 0 \leq i \leq N - 1$$

Then the signal p_i verify

$$\begin{cases} p_i = C^* p_{i+1} + M x_{i+1}^{u^*} & 0 \leq i \leq N-2 \\ p_{N-1} = G x_N^{u^*} \end{cases} \quad (6)$$

Finally, we have the following optimality system

$$\begin{cases} u^*(\theta) = -\frac{1}{\varepsilon_i} R^{-1} B_i^* p_i & \text{if } \theta \in [t_i, t_i + \varepsilon_i[& 0 \leq i \leq N-1 \\ p_i = C^* p_{i+1} + M x_{i+1}^{u^*} & 0 \leq i \leq N-2 \\ p_{N-1} = G x_N^{u^*} \\ x_{i+1}^{u^*} = C x_i^{u^*} + B_i u_i & i = 0, \dots, N-1 \end{cases} \quad (7)$$

Where $C = e^{\delta A}$; $B_i = \int_{t_i}^{t_i + \varepsilon_i} e^{(t_{i+1}-s)A} B ds$ and $B_i^* = \int_{t_i}^{t_i + \varepsilon_i} B e^{(t_{i+1}-s)A^T} ds$.

3.2 An adequate topology

The technic developed here is similar to HUM method (see [16]). For $f = (f_1, f_2, \dots, f_N) \in \mathcal{F} = l^2(1, 2, \dots, N, \mathbb{R}^n)$; we define the signal $z^f = (z_0^f, z_0^f, \dots, z_{N-1}^f)$ by the difference equation

$$z_i^f = \sum_{k=i+1}^N C^{*k-i-1} D_k^{\frac{1}{2}} f_k \quad 0 \leq i \leq N-1$$

The following functional defined in \mathcal{F} by

$$\|f\|_N^2 = \|f\|_{\mathcal{F}}^2 + \sum_{i=0}^{N-1} \frac{1}{\varepsilon_i} \|R^{-\frac{1}{2}} B_i^* z_i^f\|^2$$

is a norm in \mathcal{F} equivalent to the norm $\|\cdot\|_{\mathcal{F}}$ de \mathcal{F} . Let's us define the operator Λ_N by

$$\begin{aligned} \Lambda_N : \mathcal{F} &\longrightarrow \mathcal{F} \\ f &\longrightarrow f + \bar{D}^{\frac{1}{2}} \Psi^f. \end{aligned}$$

where $\Psi^f = (\Psi_i^f)_{1 \leq i \leq N}$ is given by

$$\Psi_i^f = (\mathcal{H}_N u_f)_i = \sum_{j=0}^{i-1} C^{i-j-1} B_j u_j^f \quad 1 \leq i \leq N$$

with $u_f = \sum_{i=0}^{N-1} u_i^f \chi_{[t_i, t_i + \varepsilon_i[}$ is described by

$$u_i^f = \frac{1}{\varepsilon_i} R^{-1} B_i^* z_i^f \quad 1 \leq i \leq N-1$$

Lemma 3.1 Λ_N is a bounded, self-adjoint operator satisfying

$$\langle \Lambda_N f, f \rangle = \|f\|_N^2 ; \quad \forall f \in \mathcal{F}$$

Proof: We have

$$\begin{aligned} \langle \Lambda_N f, g \rangle &= \langle f, g \rangle + \sum_{i=1}^N \langle D_i^{\frac{1}{2}} \Psi_i^f, g_i \rangle \\ &= \langle f, g \rangle + \sum_{i=1}^N \langle \Psi_i^f, D_i^{\frac{1}{2}} g_i \rangle \\ &= \langle f, g \rangle + \sum_{i=1}^N \langle \sum_{j=0}^{i-1} C^{i-j-1} B_j (\frac{1}{\varepsilon_j} R^{-1} B_j^* z_j^f), D_i^{\frac{1}{2}} g_i \rangle \\ &= \langle f, g \rangle + \sum_{j=0}^{N-1} \sum_{i=j+1}^N \frac{1}{\varepsilon_j} \langle B_j^* z_j^f, R^{-1} B_j^* C^{*i-j-1} D_i^{\frac{1}{2}} g_i \rangle \\ &= \langle f, g \rangle + \sum_{j=0}^{N-1} \frac{1}{\varepsilon_j} \langle B_j^* z_j^f, R^{-1} B_j^* \sum_{i=j+1}^N C^{*i-j-1} D_i^{\frac{1}{2}} g_i \rangle \\ &= \langle f, g \rangle + \sum_{j=0}^{N-1} \frac{1}{\varepsilon_j} \langle B_j^* z_j^f, R^{-1} B_j^* z_j^g \rangle \\ &= \langle f, g \rangle + \sum_{j=0}^{N-1} \frac{1}{\varepsilon_j} \langle R^{-\frac{1}{2}} B_j^* z_j^f, R^{-\frac{1}{2}} B_j^* z_j^g \rangle \end{aligned}$$

Then

$$\langle \Lambda_N f, g \rangle = \langle f, \Lambda_N g \rangle$$

and

$$\begin{aligned} \langle \Lambda_N f, f \rangle &= \|f\|_{\mathcal{F}}^2 + \sum_{j=0}^{N-1} \frac{1}{\varepsilon_j} \|R^{-\frac{1}{2}} B_j^* z_j^f\|^2 \\ &= \|f\|_N^2 \end{aligned}$$

■

Finally, we prove the following main result

Theorem 3.1 The optimal control minimizing the functional J in \mathcal{E}_N is given by:

$$u(\theta) = \frac{1}{\varepsilon_i} R^{-1} B_i^* z_i^f ; \quad \theta \in [t_i, t_i + \varepsilon_i[, \quad i = 0, 2, \dots, N-1$$

where z_i^f is the solution of the difference equation

$$\begin{cases} z_i^f = \sum_{k=i+1}^{N-1} C^{*k-i-1} M^{\frac{1}{2}} f_k + C^{*N-i-1} G^{\frac{1}{2}} f_N & 0 \leq i \leq N-2 \\ z_{N-1}^f = G^{\frac{1}{2}} f_N \end{cases} \quad (8)$$

with $C = e^{\delta A}$; $B_i = \int_{t_i}^{t_i+\varepsilon_i} e^{(t_{i+1}-s)A} B ds$
and $f = (f_1, f_2, \dots, f_N)$ is the unique solution of the equation

$$\Lambda_N f = -(M^{\frac{1}{2}} C x_0, \dots, M^{\frac{1}{2}} C^{N-1} x_0, M^{\frac{1}{2}} C^N x_0)$$

Moreover , the optimal cost is

$$J(u) = \|f\|_N^2$$

Proof: From the optimality system (9) ; it is enough to establish that

$$z_i^f = -p_i \quad 0 \leq i \leq N-1$$

i.e.,

$$f_i = -D_i^{\frac{1}{2}} x_i^u \quad 1 \leq i \leq N$$

We have

$$\Lambda_N f = -(M^{\frac{1}{2}} C x_0, \dots, M^{\frac{1}{2}} C^{N-1} x_0, G^{\frac{1}{2}} C^N x_0)$$

Then

$$\begin{aligned} f &= -(M^{\frac{1}{2}}(C x_0 + \Psi_1^f), \dots, M^{\frac{1}{2}}(C^{N-1} x_0 + \Psi_{N-1}^f), G^{\frac{1}{2}}(C^N x_0 + \Psi_N^f)) \\ &= -(M^{\frac{1}{2}}(C x_0 + (\mathcal{H}_N u)_1), \dots, M^{\frac{1}{2}}(C^{N-1} x_0 + (\mathcal{H}_N u)_{N-1}), G^{\frac{1}{2}}(C^N x_0 + (\mathcal{H}_N u)_N)) \\ &= -(M^{\frac{1}{2}} x_1^u, \dots, M^{\frac{1}{2}} x_{N-1}^u, G^{\frac{1}{2}} x_N^u) \end{aligned}$$

Therefore

$$f_i = -D_i^{\frac{1}{2}} x_i^u \quad 1 \leq i \leq N$$

Moreover

$$\begin{aligned} J(u) &= \langle x_N^u, G x_N^u \rangle + \sum_{i=1}^{N-1} \langle x_i^u, M x_i^u \rangle + \langle u, Ru \rangle_{L^2(0,T,\mathbb{R}^n)} \\ &= \langle G^{\frac{1}{2}} x_N^u, G^{\frac{1}{2}} x_N^u \rangle + \sum_{i=1}^{N-1} \langle M^{\frac{1}{2}} x_i^u, M^{\frac{1}{2}} x_i^u \rangle + \int_0^T \langle u(\theta), Ru(\theta) \rangle d\theta \\ &= \langle f_N, f_N \rangle + \sum_{i=1}^{N-1} \langle f_i, f_i \rangle + \sum_{i=1}^{N-1} \int_{t_i}^{t_i+\varepsilon_i} \frac{1}{\varepsilon_i} \langle R^{-1} B_i^* z_i^f, B_i^* z_i^f \rangle d\theta \\ &= \|f\|^2 + \sum_{i=1}^{N-1} \frac{1}{\varepsilon_i} \langle R^{-\frac{1}{2}} B_i^* z_i^f, R^{-\frac{1}{2}} B_i^* z_i^f \rangle \\ &= \|f\|^2 + \sum_{i=1}^{N-1} \frac{1}{\varepsilon_i} \|R^{-\frac{1}{2}} B_i^* z_i^f\|^2 \\ &= \|f\|_N^2 \end{aligned}$$

■

References

- [1] L. Chraïbi, J. Karrakchou, A. Ouansafi and M. Rachik, Exact controllability and optimal control for distributed systems with a discrete delayed control, *Journal of the Franklin Institute*, 337(5) (2000), 499-514.
- [2] A. El Jai and L. Berrahmoune, Controllability of damped flexible systems. IFAC Symposium, Series No. 3, Perpignan, France (1991), 97-102.
- [3] V.Feldmann and R.Schneider, A general approach to multicompartment analysis and models for the pharmaco-dynamics in mathematical models in medicine (Berger et al.,ed.), *Lecture Notes in Biomathematics*, Springer-Verlag, 11 (1976).
- [4] R.Garraffo, A.Iliadis, J.P.Cano, P.Dellamonica and P.Lapalus, Application of Bayesian estimation for prediction of appropriate dosage regimen of amikacin, *J.Pharm.Sci.*, In press, 78(9) (1989).
- [5] A. Iliadis, L'adaptation de posologie assistee par ordinateur en pharmacocinetique clinique, *Informatique et Sante*, Paris, Springer-Verlag, France, 2 (1989), 142-153.
- [6] J. A. Jackez, *Compartmental analysis in Biology and Medicine*, Amsterdam, (1972).
- [7] E.Jolivet, *Introduction aux modeles mathematiques en biologie*, Actualites scientifiques et agronomiques de l'INRA, (Masson.ed.), (1983).
- [8] L. Karrakchou, R. Rabah and M. Rachik, Optimal control of discrete distributed systems with delays in state and control : state space theory and HUM approaches, *SAMS Journal*, 30 (1998), 225-245.
- [9] U. Ledzewicz, T. Brown and H. schattler, A comparaison of optimal controls for a model in cancer chemotherapy with L_1 and L_2 type objectives, *OMS* (2002).
- [10] U. Ledzewicz and H. schattler, Optimal controls for a 2-compartment model for cancer chemotherapy with quadratic objective, *Proceedings of controlo*, Aveiro, Portugal (2002), 241-246.
- [11] E. B. Lee and L. Markus, *Foundations of optimal control theory*, John Wiley, New York (1967).
- [12] J. M. Legay, *Introduction a l'etude des modeles a compartiments*, Informatique et Biosphere, Paris (1973).

- [13] J. L. Lions : Exact controllability, stabilization and perturbation for distributed systems, SIAM Rev. 30 (1988), 71-86.
- [14] R. B. Martin, Optimal control drug scheduling of cancer chemotherapy, Automatica, 28 (1992), 1113-1123.
- [15] R. S. Parker, F. J. Doyle and N. A. Peppas, A model-based algorithm for blood glucose control in type I diabetic patients, IEEE Transactions of biomedical engineering, vol.46(2) (1999).
- [16] M. Rachik, M. Lhous, O. El Kahlaoui, E. Labriji and H. Jourhmane, A quadratic optimal control problem for a class of linear discrete distributed systems, Int. J. Appl. Math. Comput. Sci., 16 (4) (2006), 431-440.
- [17] D. S. Riggs, The mathematical approach to physiological problems, M.I.T, Press.Cambridge, Massachusetts (1972).
- [18] A. Swierniak and Z. Duda, Bilinear models of cancer chemotherapy-singularity of optimal solutions, in:Mathematical Population Dynamics, 2 (1995), 347-358.
- [19] E. Trelat, Controle optimal: theorie et applications, Vuibert, Collection "Mathematiques Concretes", (2005), 246 pages.

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