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Optimal control for multi-input bilinear systems with an application in cancer chemotherapy.

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Abstract: *In this paper we study the optimal control problem for multi-input bilinear systems. We adopt a method based on rewriting our system in a compartments form, and finding the optimal control which minimizes a given cost function by applying the Pontryagin's maximum principle. Also, we present an iterative process to find a solution of the optimality system.*

Keywords: *Bilinear systems, Optimal control, Pontryagin's principle, Cancer chemotherapy.*

1. INTRODUCTION

Bilinear systems are a special class of nonlinear systems, in which nonlinear terms are constructed by multiplication of control vector and state vector. Through nearly half a century, they have received great attention by researchers. The importance of such systems lies in the fact that many important processes, not only in engineering [1], but also in biology [2], socio-economics [3], and chemistry [4-5], can be modeled by bilinear systems. An overview of the available control strategies for bilinear systems can be found in [6]-[7]. Besides, optimal control is one of the most active subjects in the control theory. It has successful applications is many disciplines, economics, environment, management, engineering etc. As we know optimal control problem for the bilinear systems does not have an analytical solution as linear case so this reason motivates many researchers to try to obtain an approximate solution for this problem. Theory and application of optimal control have been widely used in different fields such as aircraft systems [8], robotic [9], biomedicine [10], etc.

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{i=p} u_i(t)B^i x(t) \tag{1}$$

with the initial conditions $x(t_0) = x_0$. Where $x \in \mathbb{R}^n$, $u = (u_1, u_2, \ldots, u_p) \in \mathbb{R}^p$, A and B are $n \times n$ matrices. We assumed that the process starts from t_0 and ends at fixed time $t_f \succ 0$.

The main objective of this paper is to develop an optimal control design algorithm for a multi-input bilinear systems. We use a method developed by [11] and presented in [12] and [13]. This method is based on the maximum Pontrygin's principle, and a numerical algorithm is proposed to find a solution of the optimality system.

The system (1) can be rewritten in a compartments form.

$$\begin{cases} \dot{x}_1 = \sum_{j=1}^{n} a_{1j}x_j + \sum_{i=1}^{p} u_i \left(\sum_{j=1}^{n} b_{1j}^i x_j \right) \\ \dot{x}_2 = \sum_{j=1}^{n} a_{2j}x_j + \sum_{i=1}^{p} u_i \left(\sum_{j=1}^{n} b_{2j}^i x_j \right) \\ \vdots \\ \dot{x}_n = \sum_{j=1}^{n} a_{nj}x_j + \sum_{i=1}^{p} u_i \left(\sum_{j=1}^{n} b_{nj}^i x_j \right) \end{cases} \tag{2}$$

with the initial $conditions\ x_k(t_0) = x_k^0$, where $x = (x_1, x_2, \dots, x_n)$, $a_{ij} = (A_{ij})_{1 \le i,j \le n}$ and $b_{ij} = (B_{ij})_{1 \le i,j \le n}$.

The x_i is the i-th composents of the state system, which can represent, for example, in a chemotherapeutic model, the average number of cancer cells in the i-th compartment. Also, the a_{ij} and b_{ij} can represent the exchanges between these compartments, and the control u denoting the drug dosage administered.

The paper is organized as follows. Section 2 we present a compartments form for a multi-input bilinear system, and we analyze the optimal control problem. In section 3, we present a numerical algorithm to find a solution of the optimality system. In section 4, we present a study of a optimal control for a cancer chemotherapeutic model and the simulation corresponding results. Finally, the conclusion is summarized in Section 5.

2. THE OPTIMAL CONTROL PROBLEM

We consider the system of differential equations

$$\begin{cases} \dot{x}_1 = \sum_{j=1}^{n} a_{1j}x_j + \sum_{i=1}^{p} u_i \left(\sum_{j=1}^{n} b_{1j}^i x_j \right) \\ \dot{x}_2 = \sum_{j=1}^{n} a_{2j}x_j + \sum_{i=1}^{p} u_i \left(\sum_{j=1}^{n} b_{2j}^i x_j \right) \\ \vdots \\ \dot{x}_n = \sum_{j=1}^{n} a_{nj}x_j + \sum_{i=1}^{p} u_i \left(\sum_{j=1}^{n} b_{nj}^i x_j \right) \end{cases} \tag{2}$$

with the initial conditions $x_k(t^0) = x_k^0$ for $k \in \{1,2,\dots,n\}$. Where $x = (x_1, x_2, \dots, x_n)^T$, $a_{ij} = (A_{ij})_{1 \le i,j \le n}$, $b_{ij} = (B_{ij})_{1 \le i,j \le n}$ and $u_i \in \mathbb{R}$ for $i \in \{1,2,\dots,p\}$.

We define the objective functional as

$$J(u) = \phi(x_1(t_f), \dots, x_n(t_f)) + \int_{t_0}^{t_f} \sum_{i=1}^{n} p_i x_i + \sum_{i=1}^{p} \frac{r_i}{2} u_i^2 ds \tag{3}$$

where the parameters $p_i \ge 0$ and $r_i > 0$ are the cost coefficients, they are selected to weigh the relative importance of x_i and u_i. And t_0 and t_f are the initial and final times. The term, $\varphi(x_1(t_f), \dots, x_n(t_f))$, represents a type of `salvage' term; for example, in a cancer model this term can represent a weighted average of the total number of cancer cells at the end of the therapy interval $[t_0, t_f]$.

Our goal is to minimize this objective functional. In other words, we seek the optimal control $u^* = (u_1^*, u_2^*, \dots, u_p^*)^T$ such that

$$J(u^*) = \min\{J(u) : u \in U\} \tag{4}$$

where U is the set of admissible controls defined by

$$U = \{u(t) = (u_1(t),\ldots,u_p(t)) \ : u_i \text{ is Lebesgue mesurable, } a \le u_i(t) \le b,\ t \in [t_0,t_f],\ i = 1,\ldots,p\ \} \tag{5}$$

Returning to the general model (1), we also make the assumption that the control system is internally positive [14]: i.e. For any admissible control u, if $x_i(0)\succ 0$ for all $i = 1,\ldots,n$, then $x_i(t)\succ 0$for all $i = 1,\ldots,n$, and all times $t > 0$.

A simple sufficient condition for this assumption to hold (for example, see [14]) is that all the matrices $A + \sum_{i=1}^{i=p} u_i(t)B_i$, they have negative diagonal entries, but non-negative off-diagonal entries.

This condition is natural and will be satisfied for any compartmental model whose dynamics are given by balance equations where the diagonal entries correspond to the outflows from the $i-$th compartments and the off-diagonal entries represent the inflows from the $i-$th into the $j-$th compartment, $i \neq j$.

Positive systems play an important role in systems and control theory because in many physical systems the state-variables represent quantities that can never attain negative values (e.g. population sizes or protein concentrations) [15,16,17].

The solution of (1) is bounded. Indeed, the solution of (1) is

$$\forall t \in [t_0,t_f],\ \ x(t) = x_0 + \int_{t_0}^{t} Ax(s) + \sum_{i=1}^{p} u_i(s)B_i x(s)ds \tag{6}$$

where $x = (x_1, x_2, \ldots, x_n)^T$ and $x_0 = x(t_0)$.

So, $\forall t \in [t_0, t_f]$,

$$\begin{aligned} \|x(t)\| &\le \|x_0\| + \int_{t_0}^{t} \left\| A + \sum_{i=1}^{p} u_i(s)B_i \right\| \|x(s)\| ds \\ &\le \|x_0\| + \int_{t_0}^{t} \left(\|A\| + \sum_{i=1}^{p} |u_i(s)| \|B_i\| \right) \|x(s)\| ds \\ &\le \|x_0\| + \int_{t_0}^{t} \left(\|A\| + c \sum_{i=1}^{p} \|B_i\| \right) \|x(s)\| ds \\ &\le C_1 + \int_{t_0}^{t} C_2 \|x(s)\| ds \end{aligned} \tag{7}$$

where $c = sup(|a|, |b|)$, $C_1 = \ \|x_0\|$ and $C_2 = \ \|A\| + c \sum_{i=1}^{i=p} \|B_i\|$.

Using Gronwall inequality, see [18], we obtain $\forall t \in [t_0, t_f]$,

$$\begin{aligned} \|x(t)\| &\le C_1 + \int_{t_0}^{t} C_2 \|x(s)\| ds \\ &\le C_1 \exp(\int_{t_0}^{t} C_2 ds) \\ &\le C_1 \exp(C_2(t_f - t_0)). \end{aligned} \tag{8}$$

Then, the boundedness of the solution (1).

2.1 Existence of an Optimal Control.

The existence of the optimal control can be obtained using a result by Fleming and Rishel in [19] (see Corollary 4.1).

Theorem.1: Consider the control problem with system (2). There exists an optimal control $u^* \in U$ such that

$$J(u^*) = min\{J(u): u \in U\},$$

if the following conditions are met:
(1) The set of controls and corresponding state variables is nonempty.
(2) The control set U is convex and closed.
(3) The right-hand side of the state system is bounded by a linear function in the state and control variables.
(4) The integrand of the objective functional is convex on U.
(5) There exist constants $c_1, c_2 \succ 0$ and $\beta \succ 1$ such that the integrand $L(x_1, x_2, \ldots, x_n, u)$ of the objective functional satisfies

$$L(x_1, x_2, \ldots, x_n, u) \geq c_1 + c_2(|u_1|^2 + \ldots + |u_p|^2)^{\beta/2}. \quad (9)$$

To prove that the set of controls and corresponding state variables is nonempty, we will use a simplified version of an existence result in Boyce and DiPrima ([20], Theorem 7.1.1):

Theorem.2: Let $\dot{x}_i = F_i(t; x_1, \ldots, x_n)$ for $i \in \{1, \ldots, n\}$ be a system of n differential equations with initial conditions $x_i(t_0) = x_i^0$ for $i \in \{1, \ldots, n\}$. If each of the functions $F_1, \ldots, F_n$ and the partial derivatives $\partial F_1/\partial x_1, \ldots, \partial F_1/\partial x_n, \partial F_2/\partial x_1, \ldots, \partial F_2/\partial x_n, \ldots, \partial F_n/\partial x_1, \ldots, \partial F_n/\partial x_n$, are continuous in $\mathbb{R}^{n+1}$ space, then there exists a unique solution $x_1, \ldots, x_n$ that satisfies the initial conditions.

Proof: (Theorem.1) We use Theorem.2 to prove that the set of controls and corresponding state variables is nonempty. Let $\dot{x}_1 = F_1(t; x_1, \ldots, x_n), \ldots, \dot{x}_n = F_n(t; x_1, \ldots, x_n)$, where the $F_1, \ldots, F_n$ form the right hand side of the system of equations (2). Let $u(t) = c$, for some constant, and since all parameters are constants, $F_1, \ldots, F_n$ are linear. Thus, they are continuous everywhere. Additionally, the partial derivatives $\partial F_1/\partial x_1, \ldots, \partial F_1/\partial x_n$, $\partial F_2/\partial x_1, \ldots, \partial F_2/\partial x_n, \ldots, \partial F_n/\partial x_1, \ldots, \partial F_n/\partial x_n$ are all constants, and so they are also continuous everywhere.

Therefore, there exists a unique solution $x_1, \ldots, x_n$ that satisfies the initial conditions. Therefore, the set of controls and corresponding state variables is nonempty, and condition 1 is satisfied.

The control set is convex and closed by definition. Since the state system is bilinear in u, the right side of (2) satisfies condition 3, using the boundedness of the solution. The integrand in the objective functional (4) is convex on U. It rest to show that there exists constants $c_1, c_2 \succ 0$ and $\beta \succ 1$ such that the integrand $L(x_1, \ldots, x_n, u_1, \ldots, u_p)$ of the objective functional satisfies

$$L(x_1, x_2, \ldots, x_n, u) \geq c_1 + c_2\left(|u_1|^2 + \ldots + |u_p|^2\right)^{\beta/2}.$$

The state variables being bounded, let $c_1 = \frac{1}{n} inf(p_1 x_1, \ldots, p_n x_n)$, $c_2 = \frac{1}{p} inf(\frac{r_1}{2}, \ldots, \frac{r_p}{2})$ and $\beta = 2$. Then it follows that : $\sum_{i=1}^{n} p_i x_i + \sum_{i=1}^{n} \frac{r_i}{2} u_i^2 \geq c_1 + c_2(|u_1|^2 + \ldots + |u_p|^2)$.

2.2 Characterization of the Optimal Control.

We are applying the Pontryagin's Maximum Principle [21]; the key idea is introducing the adjoint function to attach the system of differential equations to the objective functional, resulting in the formation of a function called the Hamiltonian. This principle converts the problem of finding the control to optimize the objective functional subject to the state differential equations with initial condition, to find the control to optimize Hamiltonian pointwise (with respect to the control).

Now we have the Hamiltonian in time t,

$$H(t) = \sum_{i=1}^{n} p_i x_i + \sum_{i=1}^{p} \frac{r_i}{2} u_i^2 + \sum_{j=1}^{n} \lambda_j f_j(x_1, \ldots, x_n, u, t) \quad (10)$$

Where λ_j for $j = 0,1, \ldots, n$, is the adjoint function, where f_j is the right hand side of the system of differential equations of $j - th$ equation for $j = 0,1, \ldots, n$.

Theorem.3: There exists an optimal control u^* and corresponding solutions $x_1^*, x_2^*, \dots, x_n^*$ that minimize $J(u)$ over U. Furthermore, there exists adjoint functions, $\lambda_1, \lambda_2, \dots, \lambda_n$, satisfying the equations

$$\left\{ \dot{\lambda}_k = -p_k - \sum_{j=1}^{n} \lambda_j \left(a_{jk} + \sum_{i=1}^{p} u_i b_{jk}^i \right), \quad k \in \{1,2,\dots,n\} \right. \tag{11}$$

with the transversality conditions

$$\lambda_i(t_f) = \frac{\partial \phi}{x_i(t_f)}(x_1(t_f),\dots,x_n(t_f)), \ \ for \ i \in \{1,2,\dots,n\} \tag{12}$$

Furthermore, the optimal control u^* is given by

$$u_k^* = \min\left[b; \max\left(a; -\frac{1}{r_k} \sum_{i=1}^{n} \lambda_i \left(\sum_{i=1}^{n} b_{ij}^k x_j \right) \right) \right], \quad k \in \{1,2,\dots,p\} \tag{13}$$

Proof: The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that

$$\left\{ \begin{array}{l} \dot{\lambda}_1 = -\frac{\partial H}{\partial x_1}, \quad \lambda_1(t_f) = \frac{\partial \phi}{x_1(t_f)}(x_1(t_f),\dots,x_n(t_f)) \\ \dot{\lambda}_n = -\frac{\partial H}{\partial x_2}, \quad \lambda_2(t_f) = \frac{\partial \phi}{x_2(t_f)}(x_1(t_f),\dots,x_n(t_f)) \\ \qquad\qquad \vdots \\ \dot{\lambda}_n = -\frac{\partial H}{\partial x_n}, \quad \lambda_n(t_f) = \frac{\partial \phi}{x_n(t_f)}(x_1(t_f),\dots,x_n(t_f)) \end{array} \right. \tag{14}$$

The optimal control u^* can be solved from the optimality condition,

$$\frac{\partial H}{\partial u_k} = 0, \quad k \in \{1,2,\dots,p\} \tag{15}$$

that is

$$\frac{\partial H}{\partial u_k} = r_k u_k + \sum_{i=1}^{n} \lambda_i \left(\sum_{i=1}^{n} b_{ij}^k x_j \right) = 0, \quad k \in \{1,2,\dots,p\} \tag{16}$$

By the bounds in U of the controls, we obtain u^* in the form of (13).

3. Numerical algorithm.

In this section we present an iterative method for the numerical solution of the optimality system. The numerical algorithm presented below is a semi-implicit finite difference method.

We discretize the interval $[t_0, t_f]$ at the points $t_i = t_0 + ih, (i = 0,1,\dots,n)$, where h is the time step such that $t_n = t_f$, [22]. Next, we define the state and adjoint variables $x_1(t), x_2(t), \dots, x_n(t)$, $\lambda_1(t), \lambda_2(t), \dots, \lambda_n(t)$ and the control $u(t)$ in terms of nodal points $x_1^i, \dots, x_n^i$, $\lambda_1^i, \dots, \lambda_n^i$ and u^i. Now a combination of forward and backward difference approximation is used as follows:

The method, developed by [11] and presented in [12] and [13], is then read as:

$$\left\{ \begin{array}{l} \frac{x_1^{k+1} - x_1^k}{h} = a_{11} x_1^{k+1} + \sum_{j=2}^{n} a_{1j} x_j^k + \sum_{i=1}^{p} u_i^k (b_{11}^i x_1^{k+1}) + \sum_{i=1}^{p} u_i^k \left(\sum_{j=2}^{n} b_{1j}^i x_j^k \right) \\ \qquad\qquad \vdots \\ \frac{x_n^{k+1} - x_n^k}{h} = \sum_{j=1}^{n} a_{nj} x_j^{k+1} + \sum_{i=1}^{p} u_i^k \left(\sum_{j=1}^{n} b_{nj}^i x_j^{k+1} \right) + \sum_{j=1}^{p} d_{nj} u_j^k \end{array} \right. \tag{17}$$

By using a similar technique, we approximate the time derivative of the adjoint variables by their first-order backward-difference and we use the appropriated scheme as follows

$$\begin{cases} \frac{\lambda_1^{n-1}-\lambda_1^{n-l-1}}{h} = -p_1 - \lambda_1^{n-l-1}\left(a_{11}+\sum_{i=1}^{p} u_i^l b_{11}^i\right) - \sum_{j=2}^{n} \lambda_j^{n-l}\left(a_{j1}+\sum_{i=1}^{p} u_i^l b_{j1}^i\right) \\ \vdots \\ \frac{\lambda_n^{n-1}-\lambda_n^{n-l-1}}{h} = -p_n - \sum_{j=n}^{n-1} \lambda_j^{n-l-1}\left(a_{jn}+\sum_{i=1}^{p} u_i^l b_{jn}^i\right) \end{cases} \tag{18}$$

The algorithm describing the approximation method for obtaining the optimal control is the following

Algorithm:

Step 1:

$x_1(0) = x_1^0,\ x_2(0) = x_2^0, \ldots, x_n(0) = x_n^0,\ \lambda_i(t_f) = \frac{\partial \phi}{x_i(t_f)}(x_1(t_f), \ldots, x_n(t_f))\ (i = 1, \ldots, n),\ u(0) = u_0.$

Step 2: for $i = 1, \ldots, n-1$, do :

$$\begin{cases} x_1^{k+1} = \frac{x_1^k + h\left(\sum_{j=2}^{n} a_{1j}x_j^k + \sum_{i=1}^{p} u_i^k\left(\sum_{j=2}^{n} b_{1j}^i x_j^k\right)\right)}{1-h\left(a_{11}+\sum_{i=1}^{p} u_i^k b_{11}^i\right)} \\ x_2^{k+1} = \frac{x_2^k + h\left(a_{21}x_1^{k+1} + \sum_{j=3}^{n} a_{2j}x_j^k + \sum_{i=1}^{p} u_i^k b_{21}^i x_1^{k+1} + \sum_{i=1}^{p} u_i^k\left(\sum_{j=3}^{n} b_{2j}^i x_j^k\right)\right)}{1-h\left(a_{22}+\sum_{i=1}^{p} u_i^k b_{22}^i\right)} \\ \vdots \\ x_n^{k+1} = \frac{x_n^k + h\left(\sum_{j=1}^{n-1} a_{nj}x_j^{i+1} + \sum_{i=1}^{p} u_i^k\left(\sum_{j=1}^{n-1} b_{nj}^i x_j^{i+1}\right)\right)}{1-h\left(a_{nn}+\sum_{i=1}^{p} u_i^k b_{nn}\right)} \\ \lambda_1^{n-k-1} = \frac{\lambda_1^{n-k} + h\left(p_1 + \sum_{j=2}^{n} \lambda_j^{n-k}\left(a_{j1}+\sum_{i=1}^{p} u_i^k b_{j1}^i\right)\right)}{1-h\left(a_{11}+\sum_{i=1}^{p} u_i^k b_{11}^i\right)} \\ \lambda_2^{n-k-1} = \frac{\lambda_2^{n-k} + h\left(p_2 + \lambda_1^{n-k-1}\left(a_{12}+\sum_{i=1}^{p} u_i^k b_{12}^i\right) + \sum_{j=3}^{n} \lambda_j^{n-k}\left(a_{j2}+\sum_{i=1}^{p} u_i^k b_{j2}^i\right)\right)}{1-h\left(a_{22}+\sum_{i=1}^{p} u_i^k b_{22}^i\right)} \\ \vdots \\ \lambda_n^{n-k-1} = \frac{\lambda_n^{n-k} + h\left(p_n + \sum_{j=1}^{n-1} \lambda_j^{n-k-1}\left(a_{jn}+\sum_{i=1}^{p} u_i^k b_{jn}^i\right)\right)}{1-h\left(a_{nn}+\sum_{i=1}^{p} u_i^k b_{nn}^i\right)} \\ T_l^{k+1} = -\frac{1}{r}\sum_{i=1}^{n} \lambda_i^{n-k-1}\left(\sum_{j=1}^{n} b_{ij}^l x_j^{k+1}\right), \quad l \in \{1, \ldots, p\} \\ u_l^* = \min[b; \max(a; T_l^{i+1})], \quad l \in \{1, \ldots, p\} \end{cases} \tag{19}$$

end for

Step 3: for $i = 0,\dots,n$, write

$$x_1^*(t_i) = x_1^i,\ x_2^*(t_i) = x_2^i,\dots,\ x_n^*(t_i) = x_n^i,\ u^*(t_i) = u^i.$$

end for.

4. Application: Optimal controls for a cancer chemotherapeutic model.

In this section we formulate a general n-compartment model for cancer chemotherapy as an optimal control problem over a fixed therapy interval with dynamics described by a bilinear system [23].

Let $N = (N_1,\dots,N_n)^T$ denote the state-vector with N_i denoting the number of cancer cells in the i-th compartment, $i = 1,\dots,n$. The control is a vector $u = (u_1,\dots,u_m)^T$ with u_i denoting the drug dosage administered. The control set U is a compact m-dimensional interval of the form $[\alpha_1,\beta_1]\times\cdots\times[\alpha_m,\beta_m]$ with each interval $[\alpha_i,\beta_i]\in[0,\infty)$. Let A and B_i, $i = 1,\dots,m$, be constant $n\times n$ matrices, let $r = (r_1,\dots,r_n)$ be a row-vector of positive numbers and let $s = (s_1,\dots,s_m)$ be a row-vector of non-negative numbers. The vectors r and s represent subjective weights in the objective. We then consider the following optimal control problem:

Minimize the objective

$$J(u) = \phi(N_1(t_f),\dots,N_n(t_f)) + \int_{t_0}^{t_f} \sum_{i=1}^{n} p_i N_i + \sum_{i=1}^{p} \frac{r_i}{2} u_i^2 ds \tag{20}$$

Subject to the dynamic

$$\dot{N}(t) = AN(t) + \sum_{i=1}^{i=p} u_i(t) B_i N(t), \quad N(0) = N_0 \tag{21}$$

where the parameters $p_i \geq 0$ and $r_i > 0$ are the cost coefficients, they are selected to weigh the relative importance of N_i and u_i. and t_0 and t_f are the initial and final times. The term $\varphi(N_1(t_f),\dots,N_n(t_f))$ represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[t_0,t_f]$.

In other words, we seek the optimal control u^* such that

$$J(u^*) = \min\{J(u) : u \in U\} \tag{22}$$

where U is the set of admissible controls defined by

$$U = \{u(t) = (u_1(t),\dots,u_p(t)) \ : u_i \text{ is Lebesgue mesurable, } a \leq u_i(t) \leq b,\ t \in [t_0,t_f],\ i = 1,\dots,p\ \}$$

We also make the assumption that the control system is internally positive [14]: i.e. For any admissible control u, if $N_i(0) > 0$ for all $i = 1,\dots,n$, then $N_i(t) > 0$ for all $i = 1,\dots,n$, and all times $t > 0$.

Before introducing a 4-compartment model for cancer chemotherapy, we give a brief biological background on the cell cycle and chemotherapy agents[23]. Each cell passes through a sequence of phases from cell birth to cell division. After an initial growth phase G_1, the cell enters a phase S where DNA synthesis occurs. Following a second growth phase G_2, the cell prepares for mitosis or phase M that leads to cell division. Each of the two daughter cells can either reenter phase G_1 or for some time may simply lie dormant in a separate phase G_0 until reentering G_1, thus starting the entire process all over again. Multi-compartment models combine phases of the cell cycle into clusters [24], with the purpose of effectively modeling the different types of chemotherapeutic agents used: cytotoxic (killing), cytostatic (blocking) and recruiting agents.

The dynamics of this cell cycle and the chemotherapy agents may be represented by the following compartmental model.

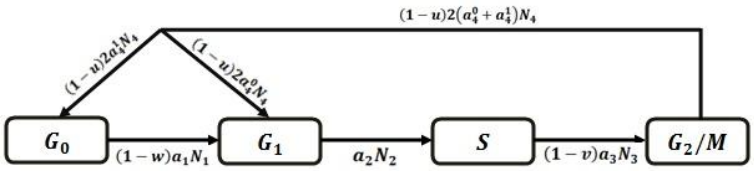

Figure 1: 4-compartment model.

Where the a_i are positive coefficients related to the mean transit times of cells through the i-th compartment. The total number of cancer cells at time t in the phases of the cell cycle G_0, G_1, S and G_2/M, is given by N_1, N_2, N_3 and N_4, respectively. The killing agent u act in the G_2/M phase which makes sense from a biological standpoint for a couple of reasons[23]. First, in mitosis M the cell becomes very thin and porous. Hence, the cell is more vulnerable to an attack while there will be a minimal effect on the normal cells. Second, chemotherapy during mitosis will prevent the creation of daughter cells. It is assumed that the dose rate stands in direct relation to the fraction of cells which are being killed in the G_2/M phase. Therefore only the fraction $1-u$ of the outflow of cells from the last compartment, $-a_4N_4$, undergoes cell division and reenters the first and second compartment. As a result the flow of cancer cells from the fourth into the first and the second compartment, $2({a_4}^0+{a_4}^1)N_2$, is reduced to $(1-u)2({a_4}^0+{a_4}^1)N_2$. However, all cells leave compartment G_2/M. The blocking agent v is applied to slow the transit times of cancer cells during the synthesis phase S. As a result the flow of cancer cells from the third into the fourth compartment, a_2N_2, is reduced by a factor $1-v$ to $(1-v)a_2N_2$. The recruiting agent w is applied to reduce the average sejour time in the quiescent phase. As a result the average transit time through the compartment G_0 is reduced resulting in the outflow being increased by a factor $1+w$. The chemotherapy agents can vary between 0 (no chemotherapy) and 1 (maximal chemotherapy). (Note: Maximal chemotherapy is essentially a sub-lethal dose, or the maximum that can be given that will not kill the patient).

This model yields the mathematical system with controls of differential equations

$$\begin{cases} \dot{N}_1 = -(1+w)a_1N_1 + (1-u)2a_4N_4 \\ \dot{N}_2 = (1+w)a_1N_1 - a_2N_2 + (1-u)2a_5N_4 \\ \dot{N}_3 = -(1-v)a_3N_3 + a_2N_2 \\ \dot{N}_4 = -(1-u)2(a_4+a_5)N_4(t) + (1-v)a_3N_3 \end{cases} \tag{23}$$

Our goal is to reduce the number of cancer cells in phases G_0, S and G_2/M of cell cycle and maximize the number of cancer cells in synthesis phase S by slowing the transit times of cancer cells during this phase S. And minimize the cost of chemotherapy. Mathematically, the problem is to minimize the objective functional

$$J(u) = \sum_{\substack{i=1 \\ i\neq 3}}^{4} q_iN_i(t_f) - q_3N_3(t_f) + \int_{t_0}^{t_f} \sum_{\substack{i=1 \\ i\neq 3}}^{4} p_iN_i - p_3N_3 + \frac{r_1}{2}u^2 + \frac{r_1}{2}v^2 + \frac{r_1}{2}w^2 ds \tag{24}$$

Subject to (23).

Using the algorithm proposed in section (3), we have the simulations results presented in the graph below. These graphs, allow us to compare changes in the cancer cell population before and after the introduction of the controls. The part of data for this model are taken from [25], like $a_1 = 0.197$, $a_2 = 0.395$ and $a_3 = 0.107$, $a_4^0 + a_4^1 = 0.107$. But the initial conditions $N_1 = N_3 = N_4 = 1000$ and $N_2 = 9000$ and the parameter $a_4^0 = 0.2$ and $a_4^1 = 0.3$ are arbitrary academic values.

4.1 The numerical simulations.

Figures 2 and 5 show that before chemotherapy, in G_0 and G_2/M phases, the number of cells increase rapidly. Whereas, we notice that after the chemotherapy by using the killing agent and recruiting agent, the number of cells decreases greatly in these phases. Also, figure 3 shows the

effect of the control in decreasing more rapidly the number of cells during the chemotherapy program. In figure 4, we can observe that the blocking agent can, with success, slowing the transit times of cancer cells during this phase S, so, increasing the number of cells in this phase.

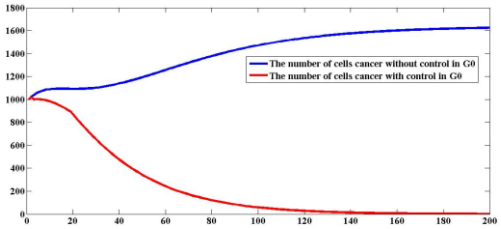

Figure 2: The number of cells cancer with and without control in G_0 phase.

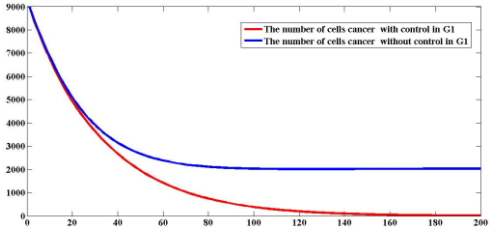

Figure 3: The number of cells cancer with and without control in G_1 phase.

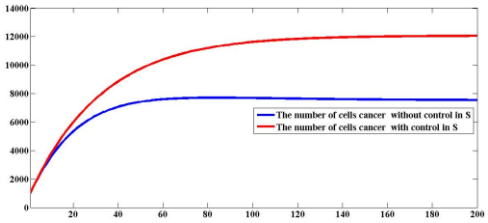

Figure 4: The number of cells cancer with and without control in S phase.

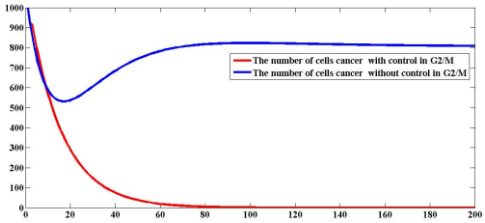

Figure 5: The number of cells cancer with and without control in G_2/M phase.

5. Conclusion

In this paper, we have presented a method for the optimal control problem of a multi-input bilinear system. This method based on the Pontryagin's maximum principle and a numerical algorithm to solve the optimality system. An example of cancer chemotherapy has been proposed to clarify the method.

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