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

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Abstract : In this paper we study the optimal control problem for a multi-input bilinear system. 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. Finally we applying this method to cancer chemotherapeutic model.

Keywords : Bilinear discrete-time systems, Optimal control, Pontryagin's Maximum Principle, Cancer chemotherapy.

AMS Subject Classification:

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 [11], but also in biology [20], socio-economics [12], and chemistry [3-1], can be modeled by bilinear systems. An overview of the available control strategies for bilinear systems can be found in [18]-[5]. Besides, optimal control is one of the most active subjects in the control theory. It has successful applications is many disciplines, economics, environement, 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 [9], robotic [19], biomedicine [6], etc.

In this paper, we consider the bilinear discrete time system described as follow

$$x_{k+1} = Ax_k + \sum_{i=1}^{i=p} u_i(k) B^i x_k \tag{1.1}$$

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for $k = 0, 1, ..., T-1$. where k is the index for the time steps, with the initial conditions $x(0) = x_0$. Where $x_k \in \mathbb{R}^n$, $u(k) = (u_1(k), ..., u_p(k)) \in \mathbb{R}^p$, A and B are $n \times n$ matrices. We assumed that the process starts from $k = 0$ and ends at fixed time $T \succ 0$.

In the theory of systems, there are two kinds of mathematical dynamic systems: the continuous-time models described by differential equations and the discrete-time models described by difference equations. The continuous-time models have been widely investigated in many articles (for example, [16–21] and the references cited therein). In recent years, for several reasons, we have seen more attention being given to the discrete-time models (see, [22–13] and the references cited therein). First, a number of systems are discrete in nature. Whenever a computer is part of control system, sampling this system becomes a necessary step. Also, analysis and control of a system in its discrete version is often appreciated by the engineer because it spares him some mathematical complications such as the choice of space and regularity of the soulution.

we suppose that the system (1) is positive[7]. The main objective of this paper is to present an optimal control design algorithm for a discrete time multi-input bilinear systems. We applying the discrete version of Pontryagin's Maximum Principle[15], The key idea is introducing the adjoint function to attach the system of difference 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 difference equations with initial condition to finding the control to optimize Hamiltonian pointwise with respect to the control.

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

2 The optimal control problem

Now, the comparment form of the system (1.1) is given as follow :

$$\begin{cases} x_1(k+1) = \sum_{j=1}^{n} a_{1j}x_j(k) + \sum_{i=1}^{p} u_i(k)\left(\sum_{j=1}^{n} b_{1j}^i x_j(k)\right) \\ x_2(k+1) = \sum_{j=1}^{n} a_{2j}x_j(k) + \sum_{i=1}^{p} u_i(k)\left(\sum_{j=1}^{n} b_{2j}^i x_j(k)\right) \\ \vdots \\ x_n(k+1) = \sum_{j=1}^{n} a_{nj}x_j(k) + \sum_{i=1}^{p} u_i(k)\left(\sum_{j=1}^{n} b_{nj}^i x_j(k)\right) \end{cases} \tag{2.1}$$

with the initial conditions $x_i(0) = x_i^0$ for $i \in \{1, 2, ..., n\}$. Where $a_{ij} = (A_{ij})_{1\leq i,j\leq n}$, $b_{ij}^k = \left(B_{ij}^k\right)_{1\leq i,j\leq n}$. The x_i is the i-th components 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.

We define the objective functional as

$$J(u) = \phi(x_1(T), ..., x_n(T)) + \sum_{k=0}^{T-1}\left[\sum_{i=1}^{n} p_i x_i(k) + \sum_{i=1}^{p}\frac{r_i}{2}u_i^2(k)\right] \tag{2.2}$$

where the parameters $p_i \geq 0$ and $r_i > 0$ are the cost coefficients, they are selected to weigh the relative importance of x_i and u_i. and 0 and T are the initial and final times. The term, $\phi(x_1(T), ..., x_n(T))$, 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 $[0, T]$.

Our goal is to minimize this objective functional. In other words, we seek the optimal control u^* such that

$$J(u^*) = \min\{J(u) : u \in U\} \tag{2.3}$$

where U is the set of admissible controls defined by

$$U = \{u(k) = (u_1(k), ..., u_p(k)) : u_i \text{ is Lebesgue mesurable, } a \leq u_i(k) \leq b,\ k \in [0, T-1],\ i = 1, ..., p\} \tag{2.4}$$

Where a_i, for $i = 1, ..., p$, and b_i, for $i = 1, ..., p$, are given real numbers. Note that U is compact and convex subset of $\mathbb{R}^p$.

Theorem 2.1. *(Weierstrass Extreme Value Theorem) Every continuous function on a compact set attains its extreme values on that set.*

Note that the $J(u)$ is continuous for all u in the control set U. Since U is compact subset of $\mathbb{R}^p$, so there exists an optimal control $u^* \in U$, with corresponding states from (2.1) such that $J(u^*) = \underset{u \in U}{max}\ J(u)$.

Returning to the general model (1.1), we also make the assumption that the control system is internally positive [7]: i.e. For any admissible control u, if $x_i(0) \succ 0$ for all $i = 1, ..., n$, then $x_i(k) > 0$ for all $i = 1, ..., n$, and all times $k \in \{0, 1, ..., T\}$.

A simple sufficient condition for this assumption to hold is that all the matrices $A + \sum_{i=1}^{i=p} u_i(k)B^i$, they have non-negative entries. Using the hypothesis by recurrence, this condition is satisfied.

This condition is natural and will be satisfied for many compartmental model in discrete time, whose dynamics are given by equations of equilibrium where the diagonal elements have the form $\alpha_{ii} + \sum_{j=1}^{j=p} u_j(k)b_{ii}^j$, with $\alpha_{ii} = 1 - a_{ii}$. The a_{ii} and b_{ii}^j represent the proportion of outflows from i-th compartments. And the off-diagonal entries represent the inflows from the i-th into the j-th compartment, $i \neq j$. An example of this case is given in the section (4).

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) [2,4,8].

2.1 Characterization of the Optimal Control.

We applying the discrete version of Pontryagin's Maximum Principle[15], The key idea is introducing the adjoint function to attach the system of difference equation 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 difference equation with initial condition to finding the control to optimize Hamiltonian pointwise (with respect to the control).

Now we have the Hamiltonian H_k at time step k, defined by

$$H_k = \sum_{i=1}^{n} p_i x_i + \sum_{i=1}^{p} \frac{r_i}{2} u_i^2 + \sum_{j=1}^{n} \lambda_{j,k+1} f_{j,k}(x, u, k) \tag{2.5}$$

where $f_{j,k+1}$ is the right side of the difference equation of the j^{th} state variable at time step k. By applying the discrete version of Pontryagin's maximum principle [15], we obtain the following theorem:

Theorem 2.2. *For $k = 0, 1, ..., T$, there exists an optimal control $u^*(k)$, and corresponding solution $x_1^*(k)$,..., $x_n^*(k)$, that minimizes $J(u)$ over U. Moreover, there exists adjoint functions, $\lambda_1(k)$,...,$\lambda_n(k)$ verifying*

$$\left\{ \lambda_i(k) = p_k + \sum_{j=1}^{n} \lambda_j(k+1) \left(a_{ji} + \sum_{i=1}^{p} u_i(k) b_{ji}^i \right), \quad \text{for } i \in \{1, 2, ..., n\} \right. \tag{2.6}$$

with the transversality conditions at time T

$$\lambda_i(T) = \frac{\partial \phi}{x_i(T)}(x_1(T), ..., x_n(T)), \quad \text{for } i \in \{1, 2, ..., n\}$$

Futhermore, for $k = 0, 1, ..., T-1$, the optimal control u_i^* is given by

$$u_i^*(k) = \min\left[b, \max(a, -\frac{1}{r_i}\sum_{l=1}^{n}\lambda_l(k+1)\left(\sum_{j=1}^{n} b_{lj}^i x_j(k)\right))\right], \quad i \in \{1, 2, ..., p\} \tag{2.7}$$

Proof. The Hamiltonian at time step k is

$$H(k) = \sum_{i=1}^{n} p_i x_i + \sum_{i=1}^{p}\frac{r_i}{2}u_i^2 + \sum_{j=1}^{n}\lambda_{j,k+1} f_{j,k}(x, u, k) \tag{2.8}$$

The adjoint equations for $k = 0, 1, ..., T-1$ and transversality conditions can be obtained by using Pontryagin Maximum Principle such that

$$\begin{cases} \lambda_1(k) = \frac{\partial H_k}{\partial x_1(k)}, & \lambda_1(T) = \frac{\partial \phi}{x_1(T)}(x_1(T), ..., x_n(T)) \\ \lambda_2(k) = \frac{\partial H_k}{\partial x_2(k)}, & \lambda_2(T) = \frac{\partial \phi}{x_2(T)}(x_1(T), ..., x_n(T)) \\ & \vdots \\ \lambda_n(k) = \frac{\partial H_k}{\partial x_n(k)}, & \lambda_n(T) = \frac{\partial \phi}{x_n(T)}(x_1(T), ..., x_n(T)) \end{cases}$$

For $k = 0, 1, ..., T-1$, the optimal control $u_i^*(k)$ can be solve from the optimality condition,

$$\frac{\partial H_k}{\partial u_i(k)} = 0, \quad i \in \{1, 2, ..., p\}$$

that is

$$\frac{\partial H_k}{\partial u_i(k)} = r_i u_i + \sum_{l=1}^{n}\lambda_l(k+1)\left(\sum_{j=1}^{n} b_{lj}^i x_j(k)\right)) = 0, \quad i \in \{1, 2, ..., p\}$$

By the bounds in U of the controls, we obtain u_i^* in the form of (2.7). □

3 Numerical algorithm

In this section we present the results obtained by solving numerically the optimality system. This system consists of the state system, adjoint system, initial and final time conditions, and the control characterization. So the optimality system is given by

$$\begin{cases} x_1(k+1) = \sum_{j=1}^{n} a_{1j}x_j(k) + \sum_{i=1}^{p}\min\left[b; \max\left(a; T_i(k)\right)\right]\left(\sum_{j=1}^{n} b_{1j}^i x_j(k)\right) \\ x_2(k+1) = \sum_{j=1}^{n} a_{2j}x_j(k) + \sum_{i=1}^{p}\min\left[b; \max\left(a; T_i(k)\right)\right]\left(\sum_{j=1}^{n} b_{2j}^i x_j(k)\right) \\ \quad \vdots \\ x_n(k+1) = \sum_{j=1}^{n} a_{nj}x_j(k) + \sum_{i=1}^{p}\min\left[b; \max\left(a; T_i(k)\right)\right]\left(\sum_{j=1}^{n} b_{nj}^i x_j(k)\right) \\ \\ \lambda_1(k) = p_1 + \sum_{j=1}^{n}\lambda_j(k+1)\left(a_{j1} + \sum_{i=1}^{p}\min\left[b; \max\left(a; T_i(k)\right)\right] b_{j1}^i\right) \\ \lambda_2(k) = p_2 + \sum_{j=1}^{n}\lambda_j(k+1)\left(a_{j2} + \sum_{i=1}^{p}\min\left[b; \max\left(a; T_i(k)\right)\right] b_{j2}^i\right) \\ \\ \lambda_n(k) = p_n + \sum_{j=1}^{n}\lambda_j(k+1)\left(a_{jn} + \sum_{i=1}^{p}\min\left[b; \max\left(a; T_i(k)\right)\right] b_{jn}^i\right) \\ \\ \text{With } T_i(k) = \frac{1}{r_i}\sum_{j=1}^{n}\lambda_j(k+1)\left(\sum_{j=1}^{n} b_{1j}^i x_j(k)\right), \quad i \in \{1, ..., p\} \end{cases}$$

with $x_i(0) = x_i^0$ and $\lambda_i(T) = \frac{\partial \phi}{x_i(T)}(x_1(T), ..., x_n(T))$, for $i = 1, ..., n$. In this formulation, there were initial conditions for the state variables and terminal conditions for the adjoints. That is, the optimality system is a two-point boundary value problem, with separated boundary conditions at times step $k = 0$ and $k = T$. We solve the optimality system by an iterative method with forward solving of the state system followed by backward solving of the adjoint system. We start with an initial guess for the control at the first iteration and then before the next iteration, we update the control by using the characterization. We continued until convergence of successive iterates is achieved. Thus, we obtain the following algorithm

Step 1 : $x_i(0) = x_i^0$ and $\lambda_i(T) = \frac{\partial \phi}{x_i(T)}(x_1(T), ..., x_n(T))$, for $i = 1, ..., n$. $u_i(0) = u_i^0$ for $i = 1, ..., p$.

Step 2 : for $k = 0, ..., T-1$, do :

$$\begin{cases} x_1(k+1) = \sum_{j=1}^{n} a_{1j}x_j(k) + \sum_{i=1}^{p} u_i(k)\left(\sum_{j=1}^{n} b_{1j}^i x_j(k)\right) \\ \quad \vdots \\ x_n(k+1) = \sum_{j=1}^{n} a_{nj}x_j(k) + \sum_{i=1}^{p} u_i(k)\left(\sum_{j=1}^{n} b_{nj}^i x_j(k)\right) \\ \\ \lambda_1(T-k) = p_1 + \sum_{j=1}^{n} \lambda_j(T-k+1)\left(a_{j1} + \sum_{i=1}^{p} u_i(k) b_{j1}^i\right) \\ \quad \vdots \\ \lambda_n(T-k) = p_n + \sum_{j=1}^{n} \lambda_j(T-k+1)\left(a_{jn} + \sum_{i=1}^{p} u_i(k) b_{jn}^i\right) \\ \\ T_i(T-k) = -\frac{1}{r_i}\sum_{l=1}^{n} \lambda_l(T-k+1)\left(\sum_{j=1}^{n} b_{lj}^i x_j(k)\right), \quad i \in \{1, ..., p\} \\ u_i^*(k+1) = \min\left[b; \max\left(a; T_i(T-k)\right)\right], \quad i \in \{1, ..., p\} \end{cases}$$

End for

Step 3 : For $k = 0, 1, ..., T$, write

$x_1^*(k) = x_k^*$,..., $x_n^*(k) = x_k^*$ and $u_1^*(k) = u_k^*$,..., $u_n^*(k) = u_k^*$

End for.

4 Application : Optimal controls for a cancer chemotherapeutic model.

In this section we formulate a general n-compartment model in discrete time for cancer chemotherapy as an optimal control problem over a fixed therapy interval with dynamics described by a bilinear system[10].

Let $N = (N_1, ..., N_n)^T$ denote the state-vector with N_i denoting the number of cancer cells in the i-th compartment, $i = 1, ..., n$. The control is a vector $u = (u_1, ..., u_m)^T$ 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, $i = 1, ..., m$, be constant $n \times n$ matrices, let $r = (r_1, ..., r_n)$ be a row-vector of positive numbers and let $s = (s_1, ..., s_m)$ 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

$$J(u) = \phi(N_1(T), ..., N_n(T)) + \sum_{k=0}^{T-1}\left[\sum_{i=1}^{n} p_i N_i + \sum_{i=1}^{p} \frac{r_i}{2} u_i^2\right] \tag{4.1}$$

subject to the dynamics

$$N(k+1) = (I - A)\,N(k) + \sum_{i=1}^{i=p} u_i(k) B_i N(k), \qquad N(0) = N_0 \tag{4.2}$$

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 is the final time. The term $\phi(N_1(T), ..., N_n(T))$ represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy period $\{0, 1, ..., T\}$.

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

$$J(u^*) = \min\{J(u) : u \in U\} \tag{4.3}$$

where U is the set of admissible controls defined by

$$U = \{u(k) = (u_1(k), ..., u_p(k)) : u_i \text{ is Lebesgue mesurable}, a \leq u_i(k) \leq b,\ k = 0, ..., T \text{ and } i = 1, ..., p\} \tag{4.4}$$

We also make the assumption that the control system is internally positive [7]: i.e. For any admissible control u, if $N_i(0) \succ 0$ for all $i = 1, ..., n$, then $N_i(k) > 0$ for all $i = 1, ..., n$, and all times $k \in \{0, 1, ..., T\}$.

Before introducing a 4-compartment discrete-time model for cancer chemotherapy, we give a brief biological background on the cell cycle and chemotherapy agents[10]. 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 [17], 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.

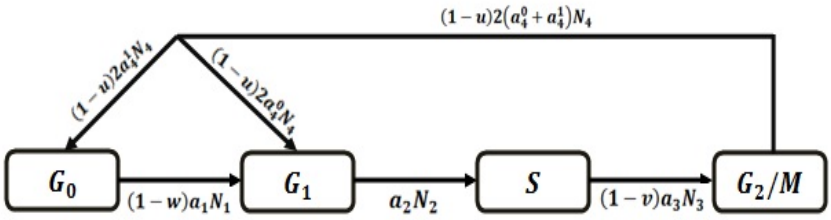

Figure 1: A discrete time model of cancer chemotherapy.

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 k 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[10]. 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, $\left(a_4^0 + a_4^1\right) N_2$, is reduced to $(1-u)a_4N_2$ where $a_4 = a_4^0 + a_4^1$. 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_3N_3, is reduced by a factor $1-v$ to $(1-v)a_3N_3$. 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

$$\begin{cases} N_1(k+1) = (1-a_1+wa_1)N_1(k) + (1-u)a_4^1N_4(k) \\ N_2(k+1) = (1-a_2)N_2 + (1-w)a_1N_1 + (1-u)a_4^0N_4 \\ N_3(k+1) = (1-a_3+va_3)N_3 + a_2N_2 \\ N_4(k+1) = (1-(a_4+a_5)+u(a_4+a_5))N_4(t) + (1-v)a_3N_3 \end{cases} \tag{4.5}$$

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

$$J(u) = \sum_{\substack{i=1 \\ i\neq 3}}^{4} q_iN_i(T) - q_3N_3(T) + \sum_{k=0}^{T-1}\left[\sum_{\substack{i=1 \\ i\neq 3}}^{4} p_iN_i(k) - p_3N_3(k) + \frac{r_1}{2}u^2(k) + \frac{r_1}{2}v^2(k) + \frac{r_1}{2}w^2(k)\right] \tag{4.6}$$

subject to (16).

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 [16], like $a_1 = 0.197$, $a_2 = 0.395$ and $a_3 = 0.107$. But the initial conditions $N_1 = N_3 = N_4 = 1000$ and $N_2 = 9000$ and the parameter $a_4^0 = 0.2$ and $a_4^0 = 0.1$ are arbitrary academic values.

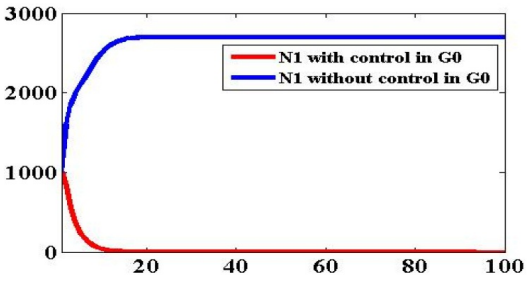

Figure 2: The number of cells cancer with and without control in G0.

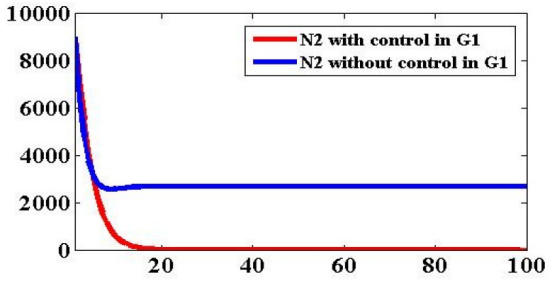

Figure 3: The number of cells cancer with and without control in G1.

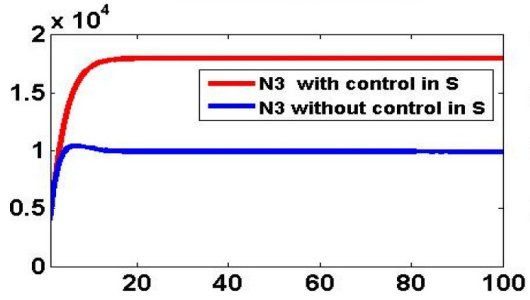

Figure 4: The number of cells cancer with and without control in S.

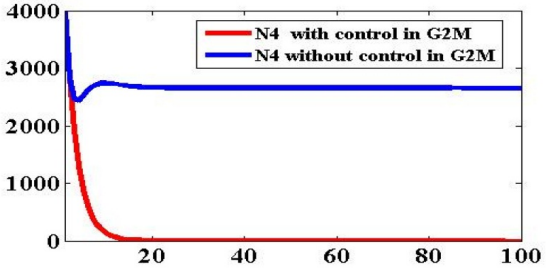

Figure 5: The number of cells cancer with and without control in G2/M.

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 sucess, slowing the transit times of cancer cells during this phase S, so, increasing the number of cells in this phase.

5 Conclusion

In this paper, we have presented a method for the optimal control problem of multi-input bilinear systems. 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 method.

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