The Analysis of Fixed Final State Optimal Control in Bilinear System Applied to Bone Marrow by Cell-Cycle Specific (CCS) Chemotherapy

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Abstract. The research conducted by Fister & Panetta shown an optimal control model of bone marrow cells against Cell Cycle Specific chemotherapy drugs. The model used was a bilinear system model. Fister & Panetta research has proved existence, uniqueness, and characteristics of optimal control (the chemotherapy effect). However, by using this model, the amount of bone marrow at the final time could achieve less than 50 percent from the amount of bone marrow before given treatment. This could harm patients because the lack of bone marrow cells made the number of leukocytes declining and patients will experience leukemia. This research would examine the optimal control of a bilinear system that applied to fixed final state. It will be used to determine the length of optimal time in administering chemotherapy and kept bone marrow cells on the allowed level at the same time. Before simulation conducted, this paper shows that the system could be controlled by using a theory of Lie Algebra. Afterward, it shows the characteristics of optimal control. Based on the simulation, it indicates that strong chemotherapy drug given in a short time frame is the most optimal condition to keep bone marrow cells spine on the allowed level but still could put playing an effective treatment. It gives preference of the weight of treatment for keeping bone marrow cells. The result of chemotherapy's effect (u) is not able to reach the maximum value. On the other words, it needs to make adjustments of medicine's dosage to satisfy the final treatment condition e.g. the number of bone marrow cells should be at the allowed level.

1. Introduction

Chemotherapy is the type of medication given to patients with cancer by using medicines [1]. Chemotherapy treatment is given especially for cancer cells with high proliferation ability such as breast cancer or blood cancers [1]. Administering chemotherapy is not only killing cells of cancer but also killing normal cells in the body. One of the normal cells affected during the chemotherapy treatment is bone marrow cells. To minimize the influence of chemotherapy against bone marrow cells then it is given therapeutics that cared for cell growth phase. Type of this medication chemotherapy called chemotherapy Cell Cycle Specific (CCS). The examples of chemotherapy medicine that used are Taxol and Cyclophosphamide [2]. Model of mathematics that discussed the influence of giving chemotherapy (CSS) against to bone marrow cells was a model conducted by Fister and Panetta [2]. It was used the drug effects as a control of bone marrow cells changes. The objective function used was maximizing the number of bone marrow cells and maximizing medicine effects of cancer cells. However, both factors having influence mutual contrary. It means when we want to maximize the number of bone marrow cells then the medicine effect would be lower and vice versa. This research showed that time of treatment with a short interval time and high dosage of a drug continue to be effective in reducing bone marrow cells died that caused of cancer drugs. Ledzewicz et. al used this mathematical model and added objective of Bolza type in representing the effect of drug dosage [3]. The other research, they combined this model by adding with pharmacokinetics equation which

models the time-evolution of the drug's concentration in the body [4]. Alamir M. et. al design optimal control to maximize the quantity of drug injected over treatment period while continuously restricted the value of states [5]. Skandari et. al used a new linear quadratics function to describe the effect of drug dosage in CCS chemotherapy [6].

The research uses the model of Fister & Panetta and adds a requirement at the end of treatment, some bone marrow cells at the level of allowed. The certain dosages of drugs must be able to keep the number of cells not less than 50 % of normal circumstances [1], [2]. The results would be simulated to get the optimal time in administering CCS chemotherapy drugs, so it would be known whether short time intervals of treatment and continue dosage of a drug to be effective in this case. Before simulated done, it would be shown the system controllable using Lie Algebra and analyzed the characteristics optimal control of bilinear system model using Hamilton equation.

2. Model Of Fixed Final State Optimal Control Applied To Bone Marrow By Cell-Cycle Specific (CSS) Chemotherapy

By Fister & Panetta were made a model describe the state of bone marrow cells with the influence of giving chemotherapy medicine in it [2]. Figure 1 showed the dynamic model of bone marrow by administering chemotherapy drugs. In this model, the cells divide into two phases which are *P* and *Q*. *P* is a proliferating phase, *Q* is a quiescent phase. At *P* phase, some of the cells died naturally or died because of administering medication, and there are cells in *P* who moved to quiescent phase *Q*. Furthermore, cells in *P* phase can grow due to proliferating phase. The cell on *Q* phase partially transformed into blood cells and get into the blood stream. Besides of that, the cell in *Q* can increase or reduce as a result of the cells coming from *P* and out of *Q*. Transition cells can be seen more details in Figure 1. As a control, it uses the effect of chemotherapy where compensation of less dose of medicine in the patient body resulting the number of bone marrow cells died would increase.

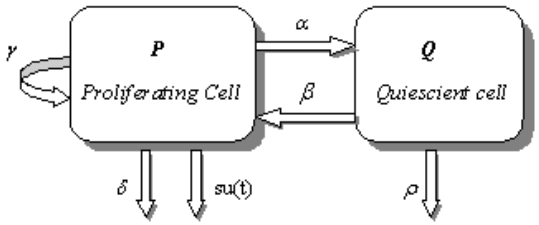


Figure 1. Model of Bone Marrow Cells with Chemotherapy CCS

Let, $\alpha =$ the rate of displacement cells from *P* to *Q*, $\beta =$ the rate of displacement cells from *Q* to *P*, $\gamma =$ cell growing rate, $\delta =$ natural death rate, $\rho =$ the rate of cell that entering into blood stream, $s =$ the strength of treatment/the strength of chemotherapy drugs, $u =$ the effect of chemotherapy treatment. All the parameter applies to a unit of the day. The values of those parameters were given in Table 1 [2]. For control of *u*, was defined admissible space that given by equation (1)

$$U = \{u \text{ admissible function} | 0 \le u(t) \le 1, t \in [0,T]\} \tag{1}$$

$u(t) = 1$ Shows maximal chemotherapy. On the other word, at time t the state of bone marrow was at the maximal influence of the drug. $u(t) = 0$ Shows no chemotherapy drug in bone marrow cells. Based on Figure 1, it could be shown by equation (2) and (3).

$$\dot{P} = (\gamma - \delta - \alpha - su(t))P + \beta Q, P(0) = P_0 \tag{2}$$

$$\dot{Q} = \alpha P - (\rho + \beta)Q, \; Q(0) = Q_0 \tag{3}$$

The objective function used in this model is maximizing the effect of chemotherapy treatment without incurring excessive damage of cells. The function uses equation (4).

$$J(u)=\int_0^T\left[a\left(P(t)+Q(t)-\frac{b}{2}(1-u(t))^2\right)\right]dt \tag{4}$$

Parameter *a* was weight to maximize the number of bone marrow cells $P(t)+Q(t)$ and parameter b was weight to maximize the chemotherapy effect $u(t)$. Part of $\frac{1}{2}(1-u(t))^2$ was the reduction of the number of bone marrow cells. $1-u(t)$ The amount of chemotherapy drug given to the patient. Weights of a and b would affect the damage of cells. If the number of patient's blood cells was below the desired level, then $\frac{a}{b}>1$ was chosen. The aim was maximizing the number of bone marrow cells. Conversely, if we want to maximize drug given, then the value of weight b would become greater, so $\frac{a}{b}<1$.

Table 1. The Value of Parameters

Value (Range)/Day	
$\gamma=1{,}47;(0{,}6667-2)$	$\delta=0$
$\alpha=5{,}643;(4{,}94-6{,}12)$	$\beta=0{,}48$
$\rho=0{,}164$	

In this research, the model would complete by adding a final state condition based on the fact that the number of bone marrow cells are not more than 50 % of the total cell before treatment, so in this model is added a limit and we have equation (5)

$$P(t)+Q(t)=0.5(P_0+Q_0), \tag{5}$$

By this equation, it would be a guarantee that total bone marrow cells at the final time would equal to a half of total cells before treatment. P_0 Indicated the number of proliferating cells at the beginning of treatment and Q_0 indicated the number of quiescent cells at the beginning of treatment.

3. Result and Discussion

Based on equation (2) and (3), a model of this system was model control of a bilinear system. The bilinear system is part of the nonlinear system [7]. One of the advantages of using bilinear system can linearize around equilibrium point as a linear system. There are some discussions about solving the optimal control of bilinear system especially using indirect method, there are Hamilton–Jacobi–Bellman (HJB) equation [8] or transform optimal control problem into a nonlinear two-point boundary value (TPBVP)[9]. In this part, we will use TPBVP to find the optimal solution, but first, it would be shown controllability of bilinear system and continue with discussing about characteristics of optimal control. At the end of this part, it would be shown the result of the simulation.

3.1. Controllability System

To ensure that systems could be controllable, it was used control theory of Lie Algebra [10], [11]. From the equation (2) and (3) it can be rewritten by equation (6).

$$A=\begin{bmatrix}a_{11} & a_{12}\\ a_{21} & -a_{22}\end{bmatrix},\ B=\begin{bmatrix}-s & 0\\ 0 & 0\end{bmatrix},\ x=\begin{bmatrix}x_1\\ x_2\end{bmatrix}=\begin{bmatrix}P\\ Q\end{bmatrix} \tag{6}$$

where are $a_{11}=\gamma-\delta-\alpha,\ a_{12}=\beta,\ a_{21}=\alpha,\ a_{22}=\rho+\beta$?

So, we have two vector fields $f(x)$ and $g(x)$ where are shown by equation (7),

$$f(x)=Ax=\begin{bmatrix}a_{11} & a_{12}\\ a_{21} & -a_{22}\end{bmatrix}\begin{bmatrix}x_1\\ x_2\end{bmatrix}=\begin{bmatrix}a_{11}x_1+a_{12}x_2\\ a_{21}x_1-a_{22}x_2\end{bmatrix},\ g(x)=Bx=\begin{bmatrix}-s & 0\\ 0 & 0\end{bmatrix}\begin{bmatrix}x_1\\ x_2\end{bmatrix}=\begin{bmatrix}-sx_1\\ 0\end{bmatrix} \tag{7}$$

Because of $f(x)=Ax$ and $g(x)=Bx$, it is clear that A and B are Jacobian matrices that can be written into equation (8)

$$\frac{\partial f}{\partial x}=\begin{bmatrix} a_{11} & a_{12} \\ a_{21} & -a_{22} \end{bmatrix}=A,\ \frac{\partial g}{\partial x}=\begin{bmatrix} -s & 0 \\ 0 & 0 \end{bmatrix}=B \tag{8}$$

It could be built a distribution Δ that has characteristics of the maximal integral manifold to ensure that system is weakly controllable [10]. Next, it would be shown that the controllability rank condition was fulfilled, e.g. $\dim \Delta_c(x)=n$.

Proof:

Using Lie Bracket definition, we could determine $[A,B],[A,[A,B]],[A,[A,[A,B]]],[A,[A,[A,[A,B]]]]$ in equation (9), (10), (11) and (12)

$$[A,B]=BA-AB=s\begin{bmatrix} 0 & -a_{12} \\ a_{21} & 0 \end{bmatrix} \tag{9}$$

$$[A,[A,B]]=s\begin{bmatrix} -2a_{12}a_{21} & (a_{11}+a_{22})a_{12} \\ (a_{11}+a_{22})a_{21} & 2a_{12}a_{21} \end{bmatrix} \tag{10}$$

$$[A,[A,[A,B]]]=\left\{(a_{11}+a_{22})^2+4a_{12}a_{21}\right\}[A,B] \tag{11}$$

$$[A,[A,[A,[A,B]]]]=\left\{(a_{11}+a_{22})^2+4a_{12}a_{21}\right\}[A,[A,B]] \tag{12}$$

It could be shown new vector fields that are made by vector fields $f(x)$ and $g(x)$ using Lie bracket [10],

$$[f,g](x)=\frac{\partial g}{\partial x}f(x)-\frac{\partial f}{\partial x}g(x)=\begin{bmatrix} -sa_{12}x_2 \\ sa_{21}x_1 \end{bmatrix}=[A,B]x, etc. \tag{13}$$

Then based on equation (13) it will be constructed distribution $\Delta_c=span\{[A,B]x,[A,[A,B]]x\}$, where are

$$C=\left\{\tau\in V(R^2):\tau(x)=Tx, T\in span\{[A,B],[A,[A,B]]\}\right\}. \tag{14}$$

So, using equation (14) we had matrix

$$[[f(x),g(x)][f(x),[f(x),g(x)]]]=[[A,B]x,[A,[A,B]x]]=\begin{bmatrix} -sa_{12}x_2 & -2sa_{12}a_{21}x_1+s(a_{11}+a_{22})a_{12}x_2 \\ sa_{21}x_1 & s(a_{11}+a_{22})a_{21}x_1+2sa_{12}a_{21}x_2 \end{bmatrix} \tag{15}$$

Form the equation (15) we had that $\dim \Delta_c=2$, for each x in maximal integral manifold, and it is applied equation (16)

$$U^*=\left\{x\in R^2:(a_{11}+a_{22})x_1+a_{12}x_2\neq 0\right\} \tag{16}$$

So, the system was weakly controllable for each x is defined in U^*.

3.2. Characteristics of Optimal Control

To know the characteristic of optimal control then it was used Hamiltonian equation. Lewis discusses how to solve optimal control for fixed final state [12]. Based on that, so from equation (2) and (3) we could build a Hamiltonian equation (17)

$$H=a(P+Q)-\frac{b}{2}(1-u)^2+\lambda_1(\gamma-\delta-\alpha-su)P+\lambda_1\beta Q+\lambda_2\alpha P-\lambda_2(\rho+\beta)Q+w_1(t)u+w_2(t)(1-u) \tag{17}$$

where $w_1(t)\geq 0,\ w_2(t)\geq 0$ are penalty multiplications that were the full field

$$w_1(t)u=0\ w_2(t)(1-u)=0 \text{ so (18)}$$

when u^* is optimal.

$$u^*(t) = \frac{b - \lambda_1 sP + w_1(t) - w_2(t)}{b} \tag{19}$$

Using Maximum Pontryagin Principle, to get optimal control without w_1 and w_2 explicitly then the equation (19) will be divided into three cases:

1. For $\{t | 0 < u^*(t) < 1\}$, to satisfy equation (18), then it should be $w_1(t) = 0 = w_2(t)$ so the equation (19) could be written into

$$u^*(t) = \frac{b - \lambda_1 sP}{b} \tag{20}$$

2. For $\{t | u^*(t) = 1\}$, $w_1(t) = 0$ and $w_2(t) \neq 0$, so it must be

$$u^*(t) = 1 \leq \frac{b - \lambda_1 sP}{b} \tag{21}$$

3. For $\{t | u^*(t) = 0\}$, , it should be $w_2(t) = 0$ and $w_1(t) \neq 0$, so

$$\frac{b - \lambda_1 sP}{b} \leq 0 = u^*(t) \tag{22}$$

Based on the equation (20), (21), and (22) then the optimal control can be written as equation (23)

$$u^*(t) = \min\left(1, \left(\frac{b - \lambda_1 sP}{b}\right)^+\right), \tag{24}$$

With boundary condition $P(0) = P_0, Q(0) = Q_0$ and $P(T) + Q(T) = 0.5(P_0 + Q_0)$. Because of the initial state and final state are given then $dx_T = 0, dT \neq 0$ and to full fill, that condition is given in Lewis then it should be $H|_T = 0$ [12].

3.3. Simulation

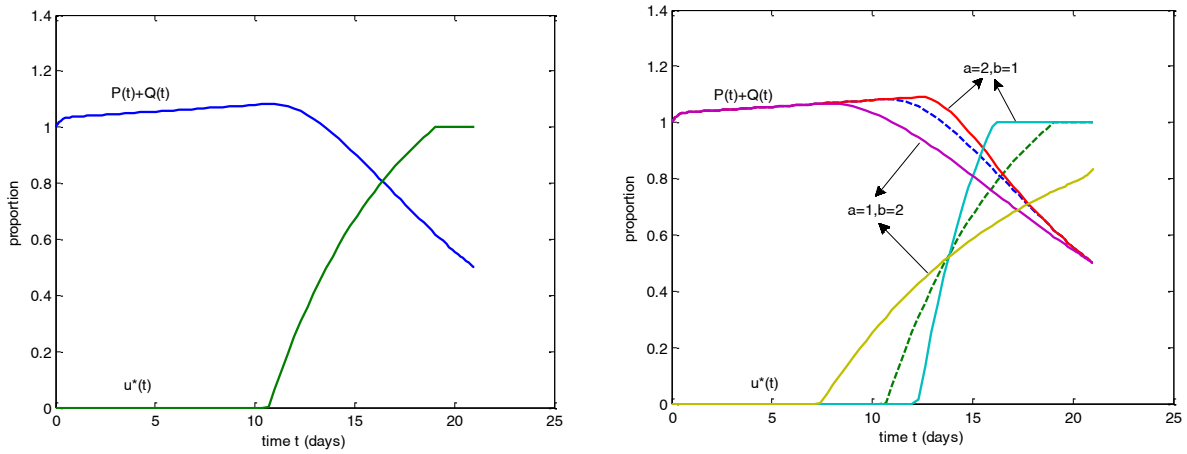
Not only held the analysis on the model but in this research was also did a simulation of optimal control model. To the needs of simulation would be used Matlab, while the completion of model optimal was a form of the solution of boundary value problems for the ordinary differential equation. Some solution of optimal control problems is solved with variation parameter method to optimal control issues were described by Avvakumov [13]. To demonstrate the numerical solution of boundary problem in Matlab, it was used a function of *bp4c* [14]. The use of this function was also described by Wang [15]. Specifically, Wang explains how to solve the optimal control problems uses indirect method especially in the case of fixed state. However, in this simulation was used toolbox Tomlabs for optimization to Matlab [16]. In testing, the parameter value of model was used from Table 1.

From the previous part, it had shown that the system could be controlled and it could be shown the characteristics of optimal control. On this part, it would be discussed the result of model simulation obtained. For the simulations, it would be divided into three cases, e.g.:

1. The influence of changing weights *a* and *b* to the objective function and the length of time treatment.
2. The influence of changing the strength of drugs *s* through objective function and length of time treatment.
3. The influence of changing the time of treatment *T* against objective function and length of time treatment.

Figure 2a-shows the case of the treatment for 21 days with $a = b = 1, s = 1$. The obtained result was that it took waiting time for 10 days before the treatment to be done so, at the end of the treatment process, the condition of bone marrow cells still stayed above 50 percent of the total bone marrow

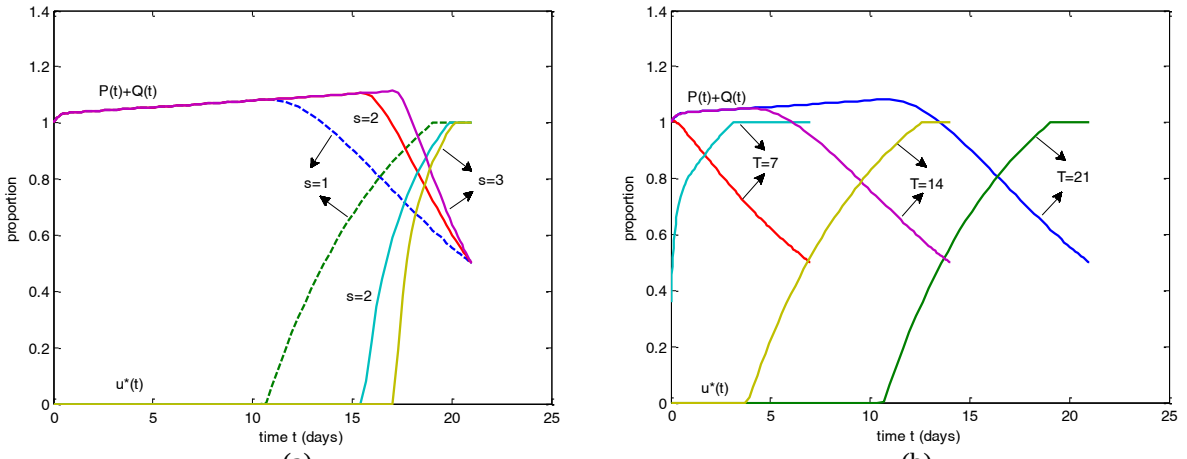
cells at the beginning of treatment. Figure 2b showed the comparing result of simulation to a value of $a > b, a = b$ and $a < b$. When $a > b, a = b,$ both of that condition showed that optimal control u^* could achieve 1. However, $a < b$ is given when we put a higher priority of the patient condition then the effect of chemotherapy drugs. In the other word, our priority was maintaining many bone marrow cells at the final state. We saw that at $a < b,$ the value of u^* could not achieve 1 at the end of treatment. It means that not whole of the quantity of medicine could be given.



(a) (b)

Figure 2. (a) Comparison value $P(t)+Q(t)$ to $u(t)$ when $a=1, b=1, s=1$, (b) Comparison value $P(t)+Q(t)$ to $u(t)$ when $a=2\&b=1$ $a=1\&b=1$, $a=1\&b=2$

From Figure 3a it shows the effect of s change in value. We saw that when the strength of chemotherapy was increasing then waiting time of medicine given become longer. Whereas in Figure 3b describes the effect of time changing the optimal condition of $P(t)+Q(t)$ and u^*. It shows that in the short time $T = 7$ there was no waiting time in given treatment.



(a) (b)

Figure 3. (a) Comparison value $P(t)+Q(t)$ to $u(t)$ when $s=1, s=2\&s=3$, (b) Comparison value $P(t)+Q(t)$ to $u(t)$ when $a=2\&b=1$, $a=1\&b=1$, $a=1\&b=2$

Further, in Table 2, it shows results of a simulation of three scenarios as delivered above. Based on Table 2, when $a<b$ the value of u^* at the final time only achieved 0,8362 with the longest time treatment. By increasing the strength of chemotherapy medicine (s) with the same observation term, which is 21 days, the values of objective functions are similar. It means that giving a higher dose would be best based on normal condition. In the case of the period of observation change, Table 2 show that the largest value of J happened at time observation 21 days. Table 2 also shows that on 7

days of treatment, there is no waiting time. However, in this conditioning treatment with a short time produce the smallest values of J.

Table 2. The Result of Testing

T	Scenario	$u(T)$	$P(T)+Q(T)$	J	Waiting Time	Time Treatment	Duration of The Influence of Drug
21	a=2, b=1, s=1	1	0,5002	33,5580	12 days	9 days	5 days
	a=1, b=1, s=1	1	0,5002	13,5374	10 days	11 days	3 days
	a=1, b=2, s=1	0,8362	0,5001	7,5180	7 days	14 days	-
21	a=1, b=1, s=1	1	0,5002	13,5374	10 days	11 days	3 days
	a=1, b=1, s=2	1	0,5002	12,9306	15 days	6 days	3 days
	a=1, b=1, s=3	1	0,5004	12,7310	16 days	5 days	2 days
7	a=1, b=1, s=1	1	0,5001	5,1457	-	7 days	4 days
14	a=1, b=1, s=1	1	0,5001	9,3407	2 days	9 days	3 days
21	a=1, b=1, s=1	1	0,5002	13,5374	10 days	11 days	3 days

4. Conclusion and Suggestion

Based on the simulation, it could be concluded that addition of boundary condition e.g. final state of bone marrow cell must comply 50 percent of the initial conditions, then the bilinear system was made by Fister still could be used to determine optimal control of CCS chemotherapy. By using Lie Algebra, it showed that the system was controllable. It was also discussed about the characteristic of optimal control of the system. Giving a strength chemotherapy treatment would be an optimal option in maintaining patient condition. If a dose of medicine was increased then the influence of medicine absorbing not maximal, therefore it would be an indicator that to review the number of given doses.

For the next research, the model could be combined with a model of immunotherapy (immunotherapy, a process to increase the amount of bone marrow at the end of therapy) to see the dynamic interaction between chemotherapy treatment and immunotherapy treatment so then we can decide the appropriate time in giving both therapies. The model could be modified by reexamining factors that affect cell of changes besides naturally death and death caused by administering chemotherapy.

Acknowledgments

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