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Optimal Control of Bone Marrow in Cancer Chemotherapy

M. H. Noori Skandari[1], H. R. Erfanian[2], A. V. Kamyad[1] and S. Mohammadi[3*]

[1]*School of Mathematical Sciences, Ferdowsi University of Mashhad, Mashhad, Iran*
[2]*Department of Applied Mathematics, University of Science &Culture, Tehran, Iran*
[3]*Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran*

ABSTRACT

We introduce an optimal method for controlling the bone marrow dynamics in cell-cycle-specific cancer chemotherapy. This method is based on measure theory and gives us the strategy applying drug where both bone marrow mass and the dose be maximized over the treatment interval. Using measure theory, the corresponding optimal control problem be transfer into a modified problem which is a type of an infinite dimensional linear programming problem whose its optimal solution can be approximated by optimal solution of finite dimensional problem.

Keywords: Optimal control, Cancer chemotherapy, Bone Marrow, Measure theory.

INTRODUCTION

In the last two decades there has been growing interest in developing and analyzing models for cancer chemotherapy [1,2,3,4]. In these models, finding optimal way to administer drugs is very important. Since, drugs kill both healthy and cancer cells. Some of these models be called cell-cycle-specific which drugs act on cells that are in a specific phase of the cell cycle [5,6,7,8]. However, the bone marrow is one of the main factors in cell-cycle-specific cancer chemotherapy. Since the bone marrows cells produces the blood cells and by blood cell count from a patient, clinicians determine the doses of chemotherapy. At first, Panetta [9] and, Fister and Panetta [7] introduce and analyze a bone marrow model. They use dynamical control systems which include both the active and resting phases of the cell-cycle to analyze the effect of cell-cycle-specific chemotherapy. This system is as

$$\begin{cases} \dot{p}(t) = \big(\gamma - \delta - \alpha - su(t)\big)P(t) + \beta Q(t), \\ \dot{Q}(t) = \alpha P(t) - (\lambda + \beta)Q(t), \end{cases} \qquad (1)$$

where $P(.)$ and $Q(.)$ are the proliferating and quiescent cells mass in the bone marrow respectively, and bounded measurable function $u(.)$ shows the drugs treatment which takes values in interval $[0,1]$ and acts only on the proliferating cells. Moreover, the parameters are all considered constant, positive, and are defined as follows. γ, cycling cells' growth rate; α, transition rate from proliferating to resting; δ, natural cell death; β, transition rate from resting to proliferating; λ, cell differentiation-mature bone marrow cell leaving the bone marrow and entering the blood stream as various types of blood cells; and s, the strength or effectiveness of the treatment. Note that $u(.)$ is control function and $u(t) = 0$ means no drug is injected at time t while $u(t) = 1$ means maximum rate is used. Usually for dynamical control system (1) be defined an objective function which form an optimal control problem that by solving it we can determine the value of drug as possible such that at the same time keep the bone marrow high[5,7,10,11]. Alamir and Chareyron[5] suggest a good constraint on the bone marrow cells which is as follows:

$$P(t)+Q(t)\geq\rho,\quad t\in[0,T] \qquad (2)$$

where T is the treatment duration and ρ is a positive constant. By (2), we can only use drug $u(.)$ which functions $P(.)$ and $Q(.)$ of system (1) satisfy constraint (2). The purpose of all considered optimal control problems for bone marrow in papers [5,7,10,11] is maximizing both bone marrow mass and the drug over the treatment interval. Here, we consider an optimal control problem which is including and covering all suggested problems by Alamir and Chareyron [5], Fister and Panetta [7], and Ledzewicz and Schattler[10,11].

By system (1) and constraint (2), we define and suggest the following optimal control problem for bone marrow cells in cancer chemotherapy which has a linear-quadratic objective function:

$$\begin{aligned}
&\textit{maximize}\\
&\quad I(P,Q,u)=r_1P(T)+r_2Q(T)\\
&\qquad\qquad +\int_0^T\left(r_3P^2(t)+r_4Q^2(t)+r_5P(t)+r_6Q(t)-r_7\left(1-u(t)\right)^2+r_8u(t)\right)dt\\
&\textit{subject to}\quad \dot{p}(t)=\left(\gamma-\delta-\alpha-su(t)\right)P(t)+\beta Q(t), \qquad (3)\\
&\qquad\qquad \dot{Q}(t)=\alpha P(t)-(\lambda+\beta)Q(t),\\
&\qquad\qquad P(t)+Q(t)\geq\rho,\ 0\leq u(t)\leq 1,\ t\in[0,T]\\
&\qquad\qquad P(0)=P_0,\ Q(0)=Q_0.
\end{aligned}$$

where P_0 and Q_0 are initial values of the proliferating and quiescent cells mass in the bone marrow respectively. Moreover, the proliferating and quiescent cells mass in final time T is $P(T)$ and $Q(T)$, respectively . Here, parameters $r_1,r_2,...,r_7$ and r_8 are given nonnegative weights which describing the importance of each term in objective function of problem (3) and satisfying the following relations:

$$r_3\times r_5=0,\ r_4\times r_6=0,\ r_7\times r_8=0.$$

In optimal control problem (3), we maximize the both bone marrow cells and drug over treatment interval $[0,T]$. The problem (3) for $r_i=0, i=1,2,...6$ and $r_7=\frac{1}{T}$, $r_8=0$ is discussed in paper [5]. Indeed problem (3) for $r_i=0, i=1,2,3,4,8$ and $r_i>0, i=5,6,7$ is analyzed and discussed in paper [7] Moreover, optimal control problem (3) is considered in paper [10,11] where $r_i=0, i=3,4,7$ and $r_i>0, i=1,2,5,6,8$. Thus, the suggested optimal control problem (3) is including and covering the considered problems in all paper [5,7,10,11]. However, there are many well known works in dealing with cancer chemotherapy [12,13,14].

In this paper, we use the measure theory approach to solving optimal control problem (3). The structure of paper is as follows: In Section 2, we transform optimal control problem (3) to the corresponding variational form. In Section 3, an optimization problem in measure space be suggested which appear to have good properties in some aspect. In Section 4, be introduced a finite linear programming problem which by solving it we can approximate optimal measure. Section 5 is including a numerical example and the conclusion of approach is given in Section 6 of paper.

2. VARIATIONAL FROM OF THE PROBLEM

In this paper, we assume $x(.)=\left(x_1(.),x_2(.)\right)=\left(P(.),Q(.)\right)$, $J=[0,T]$ and $U=[0,1]$. Moreover, assume the proliferating and quiescent cells mass are bounded by compact set A in $\mathbb{R}^2$. Now we have:

$$P(T)=\int_0^T\left(\frac{P_0}{T}+\dot{P}(t)\right)dt=\int_0^T\left(\frac{P_0}{T}+\left(\gamma-\delta-\alpha-su(t)\right)P(t)+\beta Q(t)\right)dt, \quad (4)$$

$$Q(T)=\int_0^T\left(\frac{Q_0}{T}+\dot{Q}(t)\right)dt=\int_0^T\left(\frac{Q_0}{T}+\alpha P(t)-(\lambda+\beta)Q(t)\right)dt \qquad (5)$$

.

We define the following functions on $\Omega = J\times A\times U$:

$$g_1(t,x,u)=\left(\gamma-\delta-\alpha-su(t)\right)x_1(t)+\beta x_2(t),$$
$$g_2(t,x,u)=\alpha x_1(t)-(\lambda+\beta)x_2(t). \qquad (6)$$

By (4), (5) and (6) we can write objective function of problem (3) as follows:

$$I(t,x,u)=\int_0^T f(t,x,u)dt$$

where for all $(t,x,u)\in\Omega$

$$f(t,x,u)=\left(\frac{r_1P_0+r_2Q_0}{T}\right)+r_1g_1(t,x,u)+r_2g_1(t,x,u)+r_3x_1^2(t)+r_4x_2^2(t)$$
$$+r_5x_1(t)+r_6x_2(t)-r_7\left(1-u(t)\right)^2+r_8u(t) \qquad (7)$$

Definition 2.1: We call $y=(x(.),u(.))$ is an admissible pair if the following conditions hold:

I) The two-vector function $x(.)$ satisfies $x(t)\in A$, $t\in J$ and be absolutely continuous on J .

II) The function $u(.)$ be Lebesgue measurable function on J and takes its values in U .

III) The two -vector function $x(.)$ satisfies boundary conditions $x(0)=(P_0,Q_0)$ and $x(T)=(P(T),Q(T))$.

IV) The pair $y=(x(.),u(.))$ satisfies equation $\dot{x}(t)=g(t,x,u)$ which $g=(g_1,g_2)$ satisfies (6).

We suppose that the set of all admissible pairs is nonempty and denote it by W . We are going to find an optimal pair $y^*=(x^*(.),u^*(.))\in W$. Consider the following map:

$$\Lambda_y : F\in C(\Omega)\longrightarrow\int_J F(t,x,u)dt, \qquad (8)$$

where $C(\Omega)$ is the space of all continuous function on Ω. The transformation $y\to\Lambda_y$ of the admissible pairs $y=(x(.),u(.))\in W$ into mappings Λ_y defined in (8) is injection [15]. Now, let B be an open ball in $\mathbb{R}^3$ containing $J\times A$ and $C'(B)$ be the space of all bounded real-valued continuously differentiable functions on B such that the first derivative is also bounded. We define function φ^g for all $\varphi\in C'(B)$ as follows:

$$\varphi^g(t,x(t),u(t))=\frac{\partial\varphi}{\partial t}+g(t,x(t),u(t))\frac{\partial\varphi}{\partial x}, \quad t\in J. \qquad (9)$$

We have

$$\int_J\varphi^g(t,x(t),u(t))dt=\varphi(T,x(T))-\varphi(t_0,x(t_0))=\Delta\varphi. \qquad (10)$$

Now, let $J_0=(0,T)$, we denote the space of all infinity differentiable functions on J_0 with compact support by $D(J_0)$ and define

$$\psi_j(t,x(t),u(t))=x_j(t)\psi'(t)+g(t,x(t),u(t))\psi(t), \quad \psi\in D(J_0), \quad j=1,2. \qquad (11)$$

Thus

$$\int_J\psi_j(t,x(t),u(t))dt=0, \qquad (12)$$

since $\psi(0)=\psi(T)=0$. Moreover, if $C_1(\Omega)$ be space of all function in $C(\Omega)$ that depends only on time, then

$$\int_J\theta(t,x(t),u(t))dt=a_\theta, \quad \theta\in C_1(\Omega), \qquad (13)$$

where a_θ is the integral of function θ on J .

We need to convert the inequality constraints $x_1(t)+x_2(t)\ge\rho, t\in[0,T]$ to integral form. For this purpose we define

$$h(x_1(t),x_2(t)) = \left|\rho - x_1(t) - x_2(t) + \left|\rho - x_1(t) - x_2(t)\right|\right| \qquad (14)$$

By (14), we can show the inequality constraint $x_1(t)+x_2(t) \geq \rho, t \in [0,T]$ is equivalent to the following equality: $\int_J h\left(x_1(t),x_2(t)\right) dt = 0.$

Thus, the corresponding varitional form (or functional form) of the problem (3) is as follows:

$$\begin{aligned}
&maximize \quad \Lambda(f) && (15)\\
&subject\ to \quad \Lambda(\varphi^g) = \Delta\varphi,\ \ \varphi \in C'(B) && (16)\\
&\Lambda(\psi_j) = 0,\ \ \psi \in D(J_0),\ \ j = 1,2 && (17)\\
&\Lambda(\theta) = a_\theta,\ \ \theta \in C_1(\Omega) && (18)\\
&\Lambda(h) = 0 && (19)
\end{aligned}$$

where $\Lambda_y(F) = \int_J F(t,x,u)dt$, $F \in C(\Omega)$.

3. OPTIMIZATION IN THE MEASURE SPACE

In this section, we introduce an equivalent optimization problem to optimal control problem (15)-(19) in measure space. By the Riesz representation theorem [16] there exists a positive Radon measure μ on Ω such that

$$\Lambda_y(F) = \int_J F(t,x,u)dt = \int_\Omega F\, d\mu = \mu(F), \qquad F \in C(\Omega) \qquad (20)$$

Here, the space of all positive Radon measures on Ω will be denoted by $M^+(\Omega)$. In measure theoretical approach for obtaining optimal state and control of the problem (15)-(19) a measure $\mu^* \in M^+(\Omega)$ is identified such that be equal to functional Λ_{y^*} where $y^* = (x^*(.),u^*(.))$ is an optimal admissible pair for problem (15)-(19). We topologize the space $M^+(\Omega)$ by the weak $^*-$topology [16]. By relation (20) we can change problem (15)-(19) as follows:

$$\underset{\mu\in S}{maximize} \quad \mu(f) \qquad (21)$$

where the $S \subset M^+(\Omega)$ is set of measures satisfying

$$\mu(\varphi^g) = \Delta\varphi,\ \ \mu(\psi_j) = 0,\ \mu(\theta) = a_\theta,\ \ \mu(h) = 0,$$
$$\varphi \in C'(B),\ \ \psi \in D(J_0),\ \ \theta \in C_1(\Omega),\ \ j = 1,2.$$

Proposition 3.1 (i) The functional $I: \mu \in S \longrightarrow \mu(F) \in \mathbb{R}$ is continuous. (ii) In the topology induced by weak*- topology on $M^+(\Omega)$, set S is compact. (iii) There is an optimal measure $\mu \in S$ such that

$$\mu^*(F) = \sup_{\mu\in S} \mu(F)$$

Proof: see [15].

Now, the maximizing problem (21) is an infinite dimensional problem. We are interested in approximation of this infinite dimensional problem by a finite dimensional problem. Let $\{\varphi_i \in C'(B): i \in \mathbb{N}\}$, $\{\chi_h \in D(J_0): h \in \mathbb{N}\}$ and $\{\theta_s \in C_1(\Omega): s \in \mathbb{N}\}$ are total sets in $C'(B)$, $D(J_0)$ and $C_1(\Omega)$, respectively. Define the set $S(M_1,M_2,L) \subset M^+(\Omega)$ of measures satisfying

$$\begin{aligned}
&\mu(\varphi_i^g) = \Delta\varphi_i,\ \ \mu(\chi_h) = 0,\ \ \mu(\theta_s) = a_s,\ \ \mu(h) = 0\\
&i = 1,2,...,M_1,\ \ h = 1,2,...,M_2,\ \ s = 1,2,...,L
\end{aligned} \qquad (22)$$

Now, let $\eta(M_1,M_2,L) = \sup_{\mu\in S(M_1,M_2,L)} \mu(f)$. Then one can prove that $\eta(M_1,M_2,L)$ tends to $\sup_{\mu\in S} \mu(f)$ while M_1, M_2 and L tend to infinity (see page 25 of book [15]).

4. OPTIMAL MEASURE

Now, for triple $z=(t,x,u)\in\Omega$, consider unitary atomic measure $\delta(z)\in M^{+}(\Omega)$ with support the singleton set $\{z\}$ as follows:

$$\delta(z)F=F(z),\ \ F\in C(\Omega) \qquad (23)$$

As a result of Rosenbloom [17], if $\mu^{*}(f)=\sup\limits_{\mu\in S(M_1,M_2,L)}\mu(f)$ Then there exist coefficients $\alpha_k^{*}\geq 0$ and points $z_k^{*}\in\Omega$ for $k=1,2,...,M$ such that

$$\mu^{*}=\sum_{k=1}^{M}\alpha_k^{*}\ \delta(z_k^{*}) \qquad (24)$$

where $M=M_1+M_2+L$. Thus using (22) and (24), we can approximate problem (21) as the following nonlinear optimization problem with decision variables α_k and z_k for $k=1,2,...,M$:

$$maximize\ \ \sum_{k=1}^{M}\alpha_k\ f(z_k) \qquad (25)$$

$$subject\ to$$

$$\sum_{k=1}^{M}\alpha_k\ \varphi_i^{g}(z_k)=\Delta\varphi_i\ ,\ \ \sum_{k=1}^{M}\alpha_k\ \chi_h(z_k)=0\ ,$$

$$\sum_{k=1}^{M}\alpha_k\ \theta_S(z_k)=0,\sum_{k=1}^{M}\alpha_k\ h(z_k)=0,\alpha_k\geq 0,$$

$$h=1,2,...,M_2,\ \ s=1,2,...,L,\ \ k=1,2,...,M$$

where $M=M_1+M_2+L$. The following proposition helps us to convert the nonlinear problem (25) to the linear programming problem.

Proposition 4.1: Let ω be a countable dense subset of Ω and μ^{*} is satisfying (24). For given $\varepsilon>0$ there exists a measure $\nu\in M^{+}(\Omega)$ such that

$$\left|(\mu^{*}-\nu)(f)\right|<\varepsilon,\ \left|(\mu^{*}-\nu)(\varphi_i^{g})\right|<\varepsilon,$$

$$\left|(\mu^{*}-\nu)(\chi_h)\right|<\varepsilon,\left|(\mu^{*}-\nu)(\theta_s)\right|<\varepsilon$$

$$i=1,2,...,M_1,\ \ h=1,2,...,M_2,\ \ s=1,2,...,L$$

and measure ν has the form $\nu=\sum_{k=1}^{M}\alpha_k^{*}\ \delta(z_k)$ where the coefficient α_k^{*} for $k=1,2,...,M$ are the same as in the optimal measure (24) and $z_k\in\omega$, $k=1,2,...,M$.

Proof: see page 29 of [15].

Thus, by attention to the above results, we obtain the following linear programming problem which has decision variables $\alpha_1,\alpha_1,....,\alpha_N$:

$$maximize\ \ \sum_{k=1}^{N}\alpha_k\ f(z_k)$$

$$subject\ to\ \ \sum_{k=1}^{N}\alpha_k\ \varphi_i^{g}(z_k)=\Delta\varphi_i\ ,\sum_{k=1}^{N}\alpha_k\ \chi_h(z_k)=0\ , \qquad (26)$$

$$\sum_{k=1}^{N}\alpha_k\theta_s(z_k)=a_s\ ,\ \ \sum_{k=1}^{N}\alpha_k\ \ h(z_k)=0,\alpha_k\geq 0,$$

$$i=1,2,...,M_1,\ \ h=1,2,...,M_2,\ \ s=1,2,...,L,\ \ k=1,2,...,M$$

where $N \gg M$ and z_k, $k=1,2,...,M$ is chosen fix point in the k^{th} grid of ω. By solving the problem (26), we gain coefficients $\alpha_1^{*},\alpha_2^{*},....,\alpha_N^{*}$ of measure μ^{*} which is as $\mu^{*}\simeq\sum_{k=1}^{N}\alpha_k^{*}\ \delta(z_k)$.

Now, we may construct a piecewise constant optimal control (which is optimal way to administer drug) using

coefficient $\alpha_1^*, \alpha_2^*, ..., \alpha_N^*$ based on given analysis in Section 5 of the Rubio[15]. In addition, for known control we can reach to the optimal state by solving dynamical system $\dot{x} = g(t, x, u)$ using Runge-Kutta method in numerical analysis.
In this paper, we choose functions in total sets $\{\varphi_i : i = 1, 2, ..., M_1\}$, $\{\chi_h : h = 1, 2, ..., M_2\}$ and $\{\theta_s : s = 1, 2, ..., L\}$ as follows:

$$\theta_s(t) = \begin{cases} 1 & t \in J_s \\ 0 & o.w \end{cases} \quad , \quad \varphi_i(t, x) = x^i, \quad i = 1, 2, ..., M_1$$

$$\chi_h(t) = \begin{cases} \sin(\frac{2\pi h t}{t_f - t_0}) & h = 1, 2, ..., \frac{M_2}{2} \\ 1 - \cos(\frac{2\pi (h - \frac{M_2}{2}) t}{t_f - t_0}) & h = \frac{M_2}{2} + 1, \frac{M_2}{2} + 2, ..., M_2 \end{cases}$$

where $J_s = (\frac{(s-1)(t_f - t_0)}{L}, \frac{s(t_f - t_0)}{L})$, $s = 1, 2, ..., L$ and M_2 is an even number.

Remark 4.2: Note that the set $\Omega = J \times A \times U$ must be covered with a grid, where the grid will be defined by taking points in Ω as $z_k = (t_k, x_k, u_k)$, $k = 1, 2, ..., N$.

5. NUMERICAL RESULTS

Consider the following optimal control problem of bone marrow in cell-cycle-specific cancer chemotherapy which is special case of problem (3) and analyzed and discussed by [5,7,11] :

$$\begin{aligned} &maximize \quad I(P, Q, u) = \int_0^T \left(3P(t) + 3Q(t) - (1 - u(t))^2\right) dt \\ &subject\ to \quad \dot{p}(t) = (\gamma - \delta - \alpha - s u(t)) P(t) + \beta Q(t), \qquad (27) \\ &\qquad \dot{Q}(t) = \alpha P(t) - (\lambda + \beta) Q(t), \ 0 \le u(t) \le 1, \\ &\qquad P(0) = P_0, Q(0) = Q_0, t \in [0, T]. \end{aligned}$$

Where the therapy interval is $T = 3$ and the numerical values of the problem are taken from [7]:
$\gamma = 1.47, \alpha = 5.64, \lambda = 0.16, \delta = 0,$
$\beta = 0.48, P_0 = 1, Q_0 = 1, s = 1.$
Here, we set $x = (x_1, x_2) = (P, Q)$, $M_1 = 2$, $M_2 = 4$, $L = 15$ and choose based function $\varphi_i(.,.), i = 1, 2$ and $\chi_h(.,.), h = 1, 2, 3, 4$ as follows:
$\varphi_1(t, x) = x_1$, $\varphi_1(t, x) = x_2$
$\chi_1(t) = \sin(\frac{2\pi t}{T}), \quad \chi_2(t) = \sin(\frac{4\pi t}{T}),$
$\chi_3(t) = 1 - \cos(\frac{2\pi t}{T}), \quad \chi_4(t) = 1 - \cos(\frac{4\pi t}{T})$

Moreover, we assume that, $0 \le x_j \le 2$, $j = 1, 2$ (by attention to results of papers [5,7,11]) and $\Omega = [0,3] \times [0,2] \times [0,2] \times [0,1]$, and divide intervals $[0,3]$, $[0,2]$ and $[0,1]$ to the 15, 8, and 10 equidistance subintervals, respectively. By these assumptions we have N=9600. From above subintervals, we may divide the set Ω to the 9600 grid. By solving the corresponding linear programming (26) and applying analysis in Section 5 of the Rubio [15] we obtain optimal states (bone marrow mass) and control (drug treatment) which are shown in Figures 1 and 2, respectively.

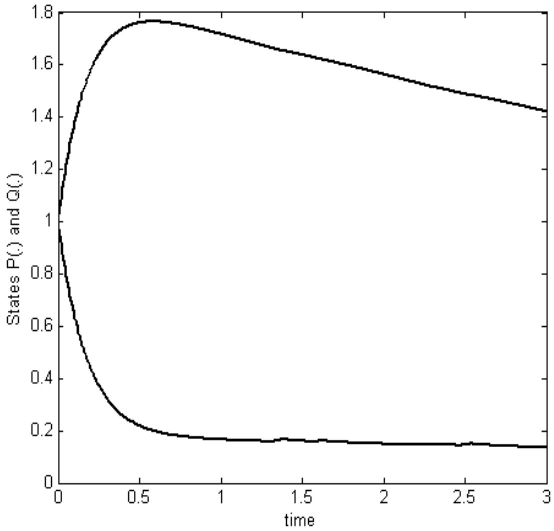

Fig. 1. Optimal states $x_1(.) = P(.)$ (Top) and $x_2(.) = Q(.)$ (Bottom) for problem (27)

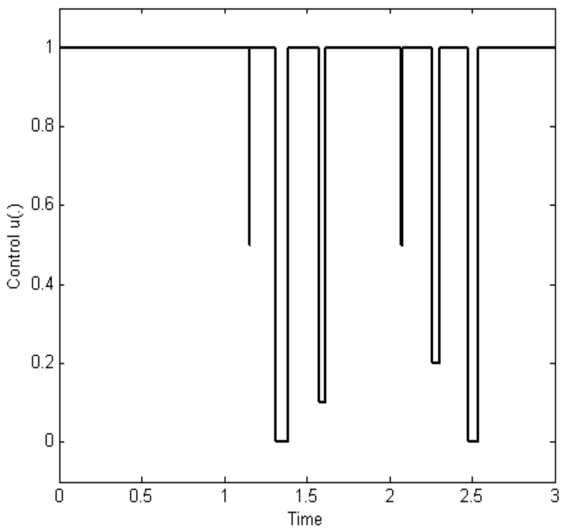

Fig. 2. Optimal control $u(.)$ for problem (27)

CONCLUSION

We introduced measure theoretical approach for controlling the bone marrow dynamics in cell-cycle-specific cancer chemotherapy. By measure theory, we convert the optimal control problem of bone marrow to an optimization problem in measure space. The corresponding optimal control problem be transfer into a modified problem which is a type of an infinite dimensional linear programming problem whose its optimal solution can be approximated by optimal solution of finite dimensional problem. Finally, we give the strategy applying drug where both bone marrow mass and the dose be maximized over the treatment interval.

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