Int. J. Sensing, Computing & Control
Vol. 2, No. 1, pp. 27-37, 2012

IJSCC
ISSN 2185-0763
www.ijsc2.org

Optimal Control for General n-Compartmental Models in Cancer Chemotherapy Using Measure Theoretical Approach

Mohammad Hadi Noori Skandari* **and Mohammad Hadi Farahi**

Faculty of Mathematical Sciences, Ferdowsi University of Mashhad, Mashhad, Iran.

* Corresponding author: hadinoori344@yahoo.com

Abstract: In this paper we consider the general compartmental models for cancer chemotherapy as an optimal control problems over a fix therapy interval with drug dosages as controls and with arbitrary objectives (linear, quadratic or nonlinear). These models are based on cell-cycle kinetics. Here we use the measure theoretical approach for obtaining the optimal solutions of these problems. In this approach, the optimal control problems are converted to the corresponding linear programming problems. Using optimal solutions of these linear programming problems, we can construct the approximate optimal control and optimal state for original problem.

Keywords: Optimal control, Cancer Chemotherapy, Compartmental Models, Measure theory, Linear programming.

1. Introduction

Mathematical models for cancer chemotherapy have a long history [1,2,3,4]. In this paper we consider the general form of mathematical models based on cell-cycle dynamics which was firstly introduced by Kimmel and Swiernaik [5,6,7] and has been analyzed in some papers [8,9,10,11,12,13]. Different phases of the cell-cycle are modeled as compartments and the average numbers of cancer cells and various drug dosages form the state variables and control variables respectively in these models. The papers [6,14,15,16] explain cell-cycle dynamic and here we do not repeat it. The numerical and theoretical methods in the above papers are usually based on the Pontryagin maximum principle and bang bang controls which give the necessary conditions for optimality. But, in this paper we use a different approach based on measure theory and obtain the approximate optimal solutions of the problem.
An optimal control problem for General n-Compartmental Models in Cancer Chemotherapy can be stated as follows:

$$Minimize \quad I(N(\cdot), u(\cdot)) = rN(t_f) + \int_{t_0}^{t_f} f(t, N(t), u(t)) \tag{1}$$

$$subject\ to \quad \dot{N}(t) = (A + \sum_{i=1}^{m} u_i B_i(t))N(t), \quad N(t_0) = N_0 \tag{2}$$

where the components of the state vector $N(\cdot) = (N_1(\cdot), N_2(\cdot), \cdots, N_n(\cdot))$ and control variable $u(\cdot) = (u_1(\cdot), u_2(\cdot), \cdots, u_m(\cdot))$ denote the average numbers of cancer cells and various drug dosages, respectively. In the dynamics (2) matrices A and B_i , $i = 1, 2, \cdots, m$ are constant $n \times n$ matrices such that all of matrices $A + \sum_{i=1}^{m} u_i B_i(t)$ have negative diagonal and nonnegative off-diagonal entries. The objective function (cost function) $I(N(\cdot), u(\cdot))$ can be considered as different forms. In some papers (see [9, 10,12, 16]), $I(N(\cdot), u(\cdot))$ is considered as linear functional

$$I(N(\cdot), u(\cdot)) = rN(t_f) + \int_{t_0}^{t_f} (qN(t) + su(t))\ dt$$

where $r = (r_1, r_2, \cdots, r_n)$, $q = (q_1, q_2, \cdots, q_n)$ and $s = (s_1, s_2, \cdots, s_m)$ are row vectors of weights where components of r are positive and components of vectors q and s are non-negative. In addition, the objective function in problem (1)-(2) may be as the following quadratic functional

$$I(N(.), u(.)) = rN(t_f) + \int_{t_0}^{t_f} \big(qN^2(t) + su^2(t) + pN(t) + hu(t)\big)\ dt.$$

However, in this paper one consider the general objective function of (1) where function $f(., ., .)$ may be linear, quadratic or nonlinear.

Note that we can write the final state $N(t_f)$as follows:

$$\begin{aligned} N(t_f) &= N(t_0) + \int_{t_0}^{t_f} \dot{N}(t)\, dt \\ &= N(t_0) + \int_{t_0}^{t_f} (\, A + \sum_{i=1}^{m} u_i B_i(t)\,)N(t)\, dt \end{aligned} \tag{3}$$

Thus if the final state $N(t_f)$ is unknown, we may replace the objective function of (1) with the following equivalent objective function:

$$I(N(\cdot), u(\cdot)) = \int_{t_0}^{t_f} (r(\, A + \sum_{i=1}^{m} u_i B_i(t)\,)N(t) + f(t, N(t), u(t)))\, dt \tag{4}$$

The above result is used in the simulation in Section 3 of this paper.

The structure of this paper is as follows: in Section 2, the measure theoretical approach is introduced for approximation optimal solutions of an optimal control problem. In Section 3, we use the approach of Section 2 for obtaining the approximate optimal solution of problem (1)-(2). In addition, the results for some compartmental models which are discussed in paper [17] are simulated and compared. The conclusions of this paper are stated in Section 4.

2. Measure theoretical approach

In this section, we are going to introduce the measure theoretical approach (see [18]) for solving an optimal control problem. Consider the following optimal control problem:

$$Minimize \quad I(x(.), u(.)) = \int_{t_0}^{t_f} f(t, x, u)dt \tag{5}$$

$$subject\ to \quad \dot{x}(t) = g(t, x, u), \quad t \in [t_0, t_f] \tag{6}$$

$$x(t_0) = x_0, \quad x(t_0) = x_f$$

where $x(\cdots)$ and $u(\cdots)$ are the state and control variables, respectively. We assume $J = [t_0, t_f]$ is a fixed interval. Measure theory approach is successfully used in the many research and has gave good results (see [19,20,21,22]).

Definition 1 *We call $p = (x(\cdot), u(\cdot))$ is an admissible pair if the following conditions hold:*

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

ii) The m-vector function $u(\cdot)$ be Lebesgue measurable function on $J$and takes its values in $U \subset \mathbb{R}^m$.

iii) The n-vector function $x(\cdot)$ satisfies boundary conditions $x(t_0) = x_0$and $x(t_0) = x_f$.

iv) The pair $p = (x(\cdot), u(\cdot))$ satisfies equation $\dot{x}(t) = g(t, x, u)$.

We suppose that the set of all admissible pairs is nonempty and denote it by W. Let $p \in W$and $\Omega = J \times A \times U$. We consider the following map:

$$\Lambda_p : F \in C(\Omega) \mapsto \int_J F(t, x, u)\, dt, \tag{7}$$

where $C(\Omega)$is the space of all continuous function on Ω.

Proposition 1 *The transformation $p \to \Lambda_p$of the admissible pairs $p = (x(\cdot), u(\cdot)) \in W$into mappings $\Lambda_p$defined in* (7) *is injection.*

Proof. See [18]. ■

By the Riesz representation theorem there exists a positive Radon measure μ on Ω such that

$$\Lambda_p(F) = \int_J F(t, x, u)\, dt = \int_\Omega F\, d\mu = F(\mu), \qquad F \in C(\Omega) \tag{8}$$

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 problem (5)-(6) a measure $\mu^* \in M^+(\Omega)$ is identified such that be equal to functional Λ_{p^*} where $p^* = (x^*(\cdot), u^*(\cdot))$ is an optimal admissible pair for problem (5)-(6).

Let B be an open ball in $\mathbb{R}^{n+1}$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 $\varphi^g$for all $\varphi \in C'(B)$as follows:

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

We have

$$\int_J \varphi^g(t, x(t), u(t))\, dt = \varphi(t_f, x(t_f)) - \varphi(t_0, x(t_0)) = \Delta\varphi \tag{10}$$

Now, let $J_0 = (t_0, t_f)$, we denote the space of all infinity differentiable functions on $J_0$with compact support by $D(J_0)$ and define

$$\begin{aligned} &\psi_j(t, x(t), u(t)) = x_j(t)\psi'(t) + g(t, x(t), u(t))\psi(t) \\ &\psi \in D(J_0), \quad j = 1, 2, \cdots, n. \end{aligned} \tag{11}$$

Thus

$$\int_J \psi_j(t, x(t), u(t))\, dt = 0 \tag{12}$$

since $\psi(t_0) = \psi(t_f) = 0$. Moreover, if $C_1(\Omega)$be space of all function in $C(\Omega)$that depends only on time, then

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

where $a_\theta$is the integral of function θon J. By relations (8),(10),(12) and (13), we can change problem (5)-(6) as follows:

$$\underset{\mu \in M^+(\Omega)}{Minimize} \quad \mu(f) \tag{14}$$

$$subject\ to \quad \mu(\varphi^g) = \Delta\varphi, \quad \varphi \in C'(B) \tag{15}$$

$$\mu(\psi_j) = 0, \quad \psi \in D(J_0), \quad j = 1, 2, \cdots \tag{16}$$

$$\mu(\theta) = a_\theta, \quad \theta \in C_1(\Omega) \tag{17}$$

Now, we topologize the space $M^+(\Omega)$ by the weak$^*-$topology (see [**?**]) and define the set $Q \subset M^+(\Omega)$ of measure satisfying equations (15), (16) and (17).

Proposition 2 *(i)The functional $I : \mu \in Q \mapsto \mu(F) \in \mathbb{R}$ is continuous. (ii) In the topology induced by weak$^*-$ topology on $M^+(\Omega)$, set Q is compact. (iii) There is an optimal measure $\mu \in Q$ such that.*

$$\mu^*(F) = \inf_{\mu \in Q} \ \mu(F)$$

Proof. See [18]. ■

Now, the minimizing problem (14)-(17) is an infinite dimensional problem. We are interested in approximation of this infinite dimensional problem by a finite dimensional problem. Let $\{\varphi_i \in C'(B) : i \in \mathbb{N}\}$be total set in $C'(B)$. In addition, assume$\{\chi_h \in D(J_0) : h \in \mathbb{N}\}$total set in $D(J_0)$. Define the set $Q(M_1, M_2) \subset M^+(\Omega)$of measures satisfying

$$\mu(\varphi_i^g) = \Delta\varphi_i, \quad i = 1, 2, \cdots, M_1 \tag{18}$$

$$\mu(\chi_h) = 0, \quad h = 1, 2, \cdots, M_2 \tag{19}$$

here without less of generality, we ignore function $\theta \in C_1(\Omega)$, however we will used this function latter.

Proposition 3 *Let $\eta(M_1, M_2) = \inf_{\mu \in Q(M_1, M_2)} \mu(f)$. Then $\eta(M_1, M_2)$ tends to $\inf_{\mu \in Q} \ \mu(f)$ while M_1 and M_2 tend to infinity.*

Proof. See page 25 of [18]. ■

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:

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

Proposition 4 *let* $\mu^*(f) = \inf_{\mu \in Q(M_1,M_2)} \mu(f)$*. Then there exist coefficients* $\alpha_k^* \geq 0$ *and points*$z_k^* \in \Omega$ *for* $k = 1, 2, ..., M_1 + M_2$ *such that*

$$\mu^* = \sum_{k=1}^{M_1+M_2} \alpha_k^* \, \delta(z_k^*) \tag{20}$$

Proof: As a result of Rosenbloom [24], where can be seen the proof in Appendix A.5 in [18].

Thus using (18)*,* (19) *and* (20) *we can approximate problem* (14)-(17) *as the following nonlinear optimization problem with unknown variables* α_k*and* z_k *for* $k = 1, 2, ..., M_1 + M_2$*:*

$$\begin{aligned}
&Minimize \quad \sum_{k=1}^{M_1+M_2} \alpha_k \, f(z_k) \\
&subject\ to \quad \sum_{k=1}^{M_1+M_2} \alpha_k \, \varphi_i^g(z_k) = \Delta\varphi_i \ , \quad i = 1, 2, \cdots, M_1 \\
&\qquad\qquad\quad \sum_{k=1}^{M_1+M_2} \alpha_k \, \chi_h(z_k) = 0 \ , \quad h = 1, 2, \cdots, M_2 \\
&\qquad\qquad\quad \alpha_k \ \geq 0, \quad k = 1, 2, \cdots, M_1 + M_2
\end{aligned} \tag{21}$$

The following proposition helps us to convert the nonlinear problem (21) *to the linear programming problem.*

Proposition 5 *Let* ω *be a countable dense subset of* Ω*. For given* $\varepsilon > 0$ *there exists a measure* $\nu \in M^+(\Omega)$ *such that*

$$|(\mu^* - \nu)(f)| < \varepsilon, \ |(\mu^* - \nu)(\varphi_i^g)| < \varepsilon, \ |(\mu^* - \nu)(\chi_h)| < \varepsilon$$
$$i = 1, 2, \cdots, M_1, \quad h = 1, 2, \cdots, M_2$$

and measure ν *has the form* $\nu = \sum_{k=1}^{M_1+M_2} \alpha_k^* \, \delta(z_k)$ *where the coefficient* α_k^* *for* $k = 1, 2, ..., M_1 + M_2$ *are the same as in the optimal measure* (20) *and* $z_k \in \omega$*,* $k = 1, 2, \cdots, M_1 + M_2$.

Proof. See page 29 of [18]. ■

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

$$
\begin{aligned}
Minimize \quad & \sum_{k=1}^{N} \alpha_k \; f(z_k) \\
subject\ to \quad & \sum_{k=1}^{N} \alpha_k \; \varphi_i^g(z_k) = \Delta\varphi_i \;, \quad i = 1, 2, \cdots, M_1 \\
& \sum_{k=1}^{N} \alpha_k \; \chi_h(z_k) = 0 \;, \quad h = 1, 2, \cdots, M_2 \\
& \sum_{k=1}^{N} \alpha_k \theta_s(z_k) = a_s, \quad s = 1, 2, \cdots, L \\
& \alpha_k \; \geq 0, \quad k = 1, 2, \cdots, M_1 + M_2
\end{aligned} \tag{22}
$$

where $N \gg M_1 + M_2$ and z_k, $k = 1, 2, \cdots, M_1 + M_2$ is chosen fix point in the k^{th}grid of ω. Note that in problem (22) the set $\{\theta_s : \; s = 1, 2, \cdots\}$is a total set for the space $C_1(\Omega)$ which $\theta_s$for all $s = 1, 2, \cdots$ satisfies equation (17).

By solving the problem (20), we gain coefficients $\alpha_1^*, \alpha_2^*, \cdots, \alpha_N^*$ of measure μ^*which is as

$$\mu^* \simeq \sum_{k=1}^{N} \alpha_k^* \; \delta(z_k)$$

Now, we may construct a constant piecewise optimal control using coefficient $\alpha_1^*, \alpha_2^*, ..., \alpha_N^*$based on given analysis in Section 5 of the Rubio ([18]). 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 $\{\varphi_i : i = 1, 2, \cdots, M_1\}$, $\{\chi_h : h = 1, 2, \cdots, M_2\}$and $\{\theta_s : s = 1, 2, \cdots, L\}$ as follows:

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

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

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 a even number.

Remark 1 *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 $z_k = (t_k, x_k, u_k),\ k = 1, 2, ..., N$.*

3. Simulation results

In the current section, we apply the measure theoretical approach on the following example.

Example 1 *Consider the following compartmental problem in cancer chemotherapy:*

$$\begin{aligned} Minimize \quad & r_1N_1(t_f) + r_2N_2(t_f) + r_3N_3(t_f) + \int_0^{t_f} u_1(t)\,dt \\ subject\ to \quad & \dot{N}_1(t) = -a_1N_1(t) + 2a_3(1-u_1)N_3(t), \\ & \dot{N}_2(t) = a_1N_1(t) - a_2(1-u_2)N_2(t), \\ & \dot{N}_3(t) = a_2(1-u_2)N_2(t) - a_3N_3(t) \\ & N_1(0) = 15.45,\ N_2(0) = 0.85,\ N_3(0) = 3.85 \end{aligned} \tag{23}$$

where $a_1 = 0.197,\ a_2 = 0.395,\ a_3 = 0.107$ *and* $t_f = 7$. *The problem* (23) *is discussed in paper [17] where it is assumed that* $0 \le u_1 \le 1$ *and* $0 \le u_2 \le 0.3$. *Now we apply the measure theoretical approach to obtaining approximate optimal states* $N_1^*(\cdot),\ N_2^*(\cdot),\ N_3^*(\cdot)$ *and optimal control* $u_1^*(\cdot),\ u_2^*(\cdot)$. *Note that for objective function, we may use of the relation* (4). *Here, we assume that* $x(\cdot) = (x_1(\cdot), x_2(\cdot), x_3(\cdots)) = (N_1(\cdot), N_2(\cdot), N_3(\cdot))$ *and* $M_1 = 3, M_2 = 4,\ L = 14$. *Choose function* $\varphi_i(\cdot,\cdot),\ i = 1,2,3$ *and* $\chi_h(\cdot,\cdot),\ h = 1,2,3,4$ *as follows:*

$$\varphi_1(t,x) = x_1, \quad \varphi_2(t,x) = x_2, \quad \varphi_3(t,x) = x_3 \tag{24}$$

$$\chi_1(t) = \sin(\tfrac{2\pi t}{7}), \quad \chi_2(t) = \sin(\tfrac{4\pi t}{7}), \quad \chi_3(t) = 1 - \cos(\tfrac{2\pi t}{7}), \quad \chi_4(t) = 1 - \cos(\tfrac{4\pi t}{7}) \tag{25}$$

Moreover, we suppose that $0 \le x_j \le 20,\ j = 1,2,3$ *and* $\Omega = [0,7] \times [0,20] \times [0,20] \times [0,20] \times [0,1] \times [0,0.3]$, *and divide intervals* $[0,7], [0,20], [0,1]$ *and* $[0,0.3]$ *to the 14, 10, 4, and 3 equidistance subintervals, respectively. By these assumptions we have N=168000. From above subintervals, we may divide the set* Ω *to the 168000 grid. By solving linear programming* (22) *and applying analysis in Section 5 of the Rubio ([18]) we obtain optimal states and controls which is illustrated in Figures 1-3. Also, in Tables 1 and 2, are illustrated the switching times of optimal controls of problem* (23) *on interval [0,7]. In addition, we compare the obtained results of measure approach with results appeared in [17] for problem* (23) *in Table 3. By this comparison, we reach to this fact which obtained optimal control of measure theoretical approach for problem* (23) *is better from obtained local optimal control in [17].*

4. Conclusions

In this article, we proposed the measure theoretical approach which allows us to approximate optimal control and optimal states corresponding compartmental models in cancer chemotherapy. We showed that solving an optimal control problem can be converted to the linear programming problem which its optimal solutions help us to construct a constant piecewise optimal control. This obtained control and dynamical equation of optimal control problem gave the optimal state by numerical methods (such as Runge Kutta method). The efficiency of measure approach in optimal control of cancer chemotherapy was stated in numerical simulations. In all papers [9,10,11,17] in order to facilitate the computations , final states are considered as a fixed numbers. In fact, minimum principle, which is used in these papers, unable solves the mentioned optimal control problems which have the unknown final states. But, by measure theory approach we could solve optimal control problems with unknown final states. In addition, measure approximate approach can be applied to optimal control of cancer chemotherapy with objective functions linear, quadratic or nonlinear.

Figure 1. Obtained optimal states corresponding to the example 3.1

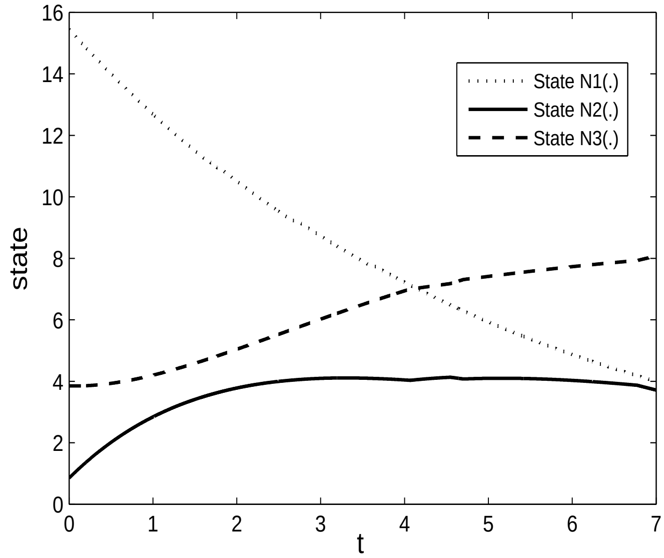

Figure 2. Optimal control $u_1^*(.)$ of example 3.

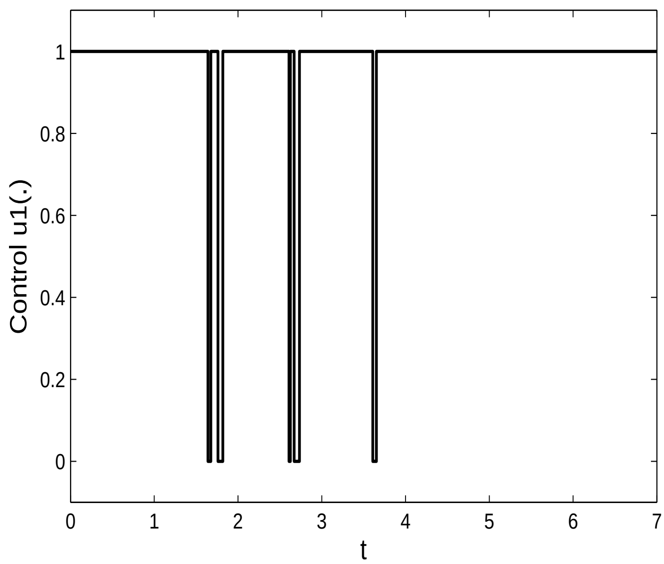

Figure 3. Optimal control $u_2^*(.)$ of example 3.1

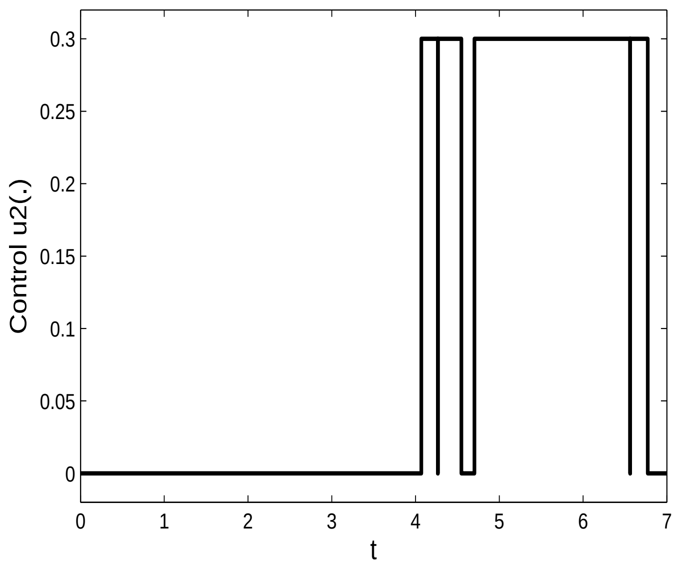

Table 1. Switching times in control $u_1^*(.)$ on time interval [0,7]

1.676	1.761	1.819	2.608	2.625	2.670	2.734	3.609	3.653

Table 2. Switching times in control $u_2^*(.)$ on time interval [0,7]

4.069	4.266	4.547	4.703	6.563	6.773

Table 3. Comparison of obtained results of optimal control of compartmental problem (23) by applying two approaches

Comparison obtained results	Measure approach	Presented approachin [17]
Optimal value ofobjective function	20.7058	20.7200
Final state of $N_1^*(.)$	3.9988	5.0000
Final state of $N_2^*(.)$	8.0712	8.5000
Final state of $N_3^*(.)$	3.7137	5.0000

References

[1] Eisen, M., Mathematical Models in Cell Biology and Cancer Chemotherapy, *Lecture Notes in Biomathematics*, Springer Verlag, 1979, Vol. 30.

[2] Martin, R. B. , Optimal control drugs scheduling of cancer chemotherapy, *Automatica*, 1992, Vol. 28, pp. 1113–1123.

[3] Swan, G.W., Role of optimal control in cancer chemotherapy. *Math. Biosci.*, 1990, Vol.101, pp. 237–284.

[4] Swierniak, A. and Duda, Z., Some control problems related to optimal chemotherapy - singular solutions. *Appl. Math. and Comp. Sci.,* 1992, Vol. 2, pp. 293-302.

[5] Swierniak, A. and Kimmel, M., Optimal control application to leukemia chemotherapy protocols design. *Sci. Bull. Silesian Tech. Univ*., 1984, Vol. 74, pp. 261–277.

[6] Swierniak, A., Cell cycle as an object of control, *Journal of Biological Systems*, 1995, Vol. 3, pp. 41-54.

[7] Swierniak, A., Polanski, A. and Kimmel, M., Optimal control problems arising in cell-cycle-specific cancer chemotherapy, *Cell prolif.,* 1996, Vol. 29, pp. 117-139.

[8] Fister, K. R. and Panetta, J. C., Optimal control applied to cell-cycle-specific cancer chemotherapy, *SIAM J. Appl. Math*., 2000, Vol. 60, pp. 1059-1072.

[9] Ledzewicz, U. and Schattler, H., Optimal bang-bang controls for a 2-compartment model in cancer chemotherapy, *Journal of Optimization Theory and Applications, JOTA*, 2002, Vol. 114, pp. 609-637.

[10] Ledzewicz, U., and Schattler, H., Optimal Control for a Bilinear Model with Recruiting Agent in Cancer Chemotherapy, *Procceding of the 42nd IEEE conference on decision and control,* 2003, pages 2762-2767.

[11] Ledzewicz, U., Brown, T. and Schattler, H., Comparison of optimal controls for a models in cancer chemotherapy with L_1 and L_2 type objectives, *Optimization methods and software*, 2004, Vol.19, No. 3–4, pp. 339–350.

[12] Ledzewicz, U. and Schattler, H., Application of control theory in modeling cancer chemotherapy, *The Shangri-La Hotel, Bangkok, Thailand, ICCAS*, August 25-27, 2004.

[13] Swierniak, A. , Polanski, A., Duda, Z., and Kimmel, M., Phase-specific chemotherapy of cancer: Optimisation of scheduling and rationale for periodic protocols. *Biocybern. Biomed. Eng*., 1997, Vol. 16, pp. 13-43.

[14] Jansson, B., Simulation of cell cycle kinetics based on a multi-compartmental model. *Simulation*, 1975, Vol. 25, pp. 99-108,

[15] Kimmel, M. and Traganos F., Estimation and prediction of cell cycle specific effects of anticancer drugs. *Math. Biosci.* 1986, Vol. 80, pp. 187-208.

[16] Ledzewicz, U. and Schattler, H., Analysis of a cell-cycle specific model for cancer chemotherapy, *J. of Biological Systems*, 2002, Vol.10, pp. 183-206.

[17] Swierniak, A., Ledzewicz, U. and Schattler, H., Optimal control for a class of compartmental models in cancer chemotherapy, *Int. J. Appl. Math. Comput. Sci*., 2003, Vol.13, no.3, pp. 357–368.

[18] Rubio, J. E., *Control and Optimization: The Linear Treatment of Nonlinear Problems*, Manchester University Press, John Wiely, New York and London, 1986.

[19] Borzabadi, A. H., Kamyad, A.V. and Farahi, M.H., Optimal control of the heat equation in an inhomogeneous body, *J.Appl. Math. Comput.*, 2004, Vol. 15, pp. no.1–2, pp. 127–14.

[20] Borzabadi, A. H., Kamyad, A.V., Farahi, M. H. and Mehne, H. H., Solving some optimal path planning problems using an approach based on measure theory, *Applied mathematics and computation*, 2005,Vol. 170, pp. 1418–1435.

[21] Farahi, M. H., Rubio, J. E. and Wilson, D. A., The optimal control of the linear wave equation, *Int. J. Control*, 1996, Vol. 63, pp. 833–848.

[22] Kamyad, A. V., Keyanpour, M. and Farahi, M. H., A new approach for solving of optimal nonlinear control problems, *Applied Mathematics and Computation*, 2007, Vol.187, pp. 1461–1471.

[23] Rudin, W., *Principles of Mathematical Analysis*, third ed., McGraw-Hill, New York, 1976.

[24] Rosenbloom, P. C., Quelques classes de problemes extermaux, Bulletin de la societe mathematique de France, 1952, Vol. 80, pp. 183-216.