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A Tumor anti-angiogenesis Treatment by Using Optimal Control in Minimum Time of Remedy Process

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ABSTRACT

One of the most important goals of tumor remedy is the minimum duration of treatment time, especially, when the patient is in an emergency situation. Based on the advantages of anti-angiogenesis treatment, the researchers, first, defined the treatment region for tumors as an optimal time problem. Then, by applying an embedding procedure and using the Fibonacci search technique, the optimal time and treatment strategy are obtained. The method is friendly used for physician in comparison with the others, since the solution is obtained via solving a finite linear programming. A numerical simulation is also given.

KEYWORDS: optimal time control, tumor, Angiogenesis inhibitors, linear programming, Fibonacci search

1. INTRODUCTION AND BACKGROUND

Despite all genetic abnormalities, the tumor diameter or thickness cannot be more than one or two millimetres. Since the tumor cannot supply the required oxygen and food relying on its host's blood vessel, it has to do angiogenesis and expands its system of capillaries. Angiogenesis is a normal and vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, it is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer[3]. So, naturally the tumor starts angiogenesis for its growth. As a natural reaction, one of the best practical opinions in tumor treatments is trying to stop this action by using angiogenic inhibitors. As a result, not only the tumor would fade away due to the lack of oxygen and food ingredients [3] but also the other cells would not harm so much.

As a matter of fact, some cancer cells are simply not affected by current drugs and others easily generate resistant mutations. Even if the chemotherapy in cancer treatments shows success initially, the medics are faced with the drug resistance problem. Hence, there is a strong interest in alternative treatments that would not be prone to drug resistance. Anti-angiogenesis treatment has been studied since the mid-nineties and is used in clinical trials. It is a mechanism that offers such a hope for the treatment of tumor cancers [9].

Although tumor angiogenesis process has properly been described by partial differential equations, low-order approximations have also been developed in terms of ordinary differential equations that are easier to analyse. One of the earliest mathematical models of this type, that has been medically validated, was formulated by Hahnfeldt et al. in 1999 [7]. In this model, the primary tumor cells volume and the vascular endothelial cells volume are estimated and their interactive growth is modelled. Then, some extensions have been given by Onofrio and Gandolfi in 2004 [1]. The model also in [4] was mathematically simplified by Ergun et al. as a problem of optimal scheduling of anti-angiogenic therapy within an optimal control framework; however, their analysis left several questions open. An almost complete solution to the problem was given by Ledzewicz and Schattler in 2006 [6] based on the Principle Maximal Pontryagin. But no study has been done to obtain the shortest time of this remedy especially, in emergency cases.

In this paper, based on the optimal control model of tumor angiogenesis and its inhibitors given by Ergun et al. and revised by Ledzewicz et al., the researchers presented an almost linear solution method for determining the optimal tumor treatment in shortest time. The method has many advantages. Numerical result shows the efficiency of this work.

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2. TUMOR TREATMENT

The researchers introduced some of prominent ways of tumor treatment in this section.

- **Chemotherapy** is the treatment of cancer with one or more cytotoxic antineoplastic drugs ("chemotherapeutic agents") as part of a standardized regimen. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.
- **Radiation Therapy** is the medical use of ionizing radiation, generally as part of cancer treatment to control or kill malignant cells. Radiation therapy may be curative in a number of types of cancer if they are localized to one area of the body.
- **Surgery** is one the ways that used for treatment of tumor which does not have metastasis.
- **Targeted therapy** or **Molecularly targeted therapy** is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth.
- An **angiogenesis inhibitor** is a substance that inhibits the growth of new blood vessels (angiogenesis). Some angiogenesis inhibitors are a normal part of the body's control, some are administered as drugs, and some come from diet.

3. DYNAMIC TUMOR ANTI-ANGIOGENESIS MATHEMATICAL MODEL

It is assumed that the tumor growth is Gompertzian (a pattern of cell growth in tumors in which there is increased doubling time and decreased growth fraction as a function of time) with a variable carrying capacity. To introduce the underlying diffusion of the dynamic tumor, first the researchers determined the variables and parameters as below;

$p(t)$: The primary tumor cells volume (a trajectory function of the system),

$e(t)$: The vascular endothelial cells volume (a trajectory function of the system),

ξ : Tumor growth parameter,

G: Anti-angiogenic killing parameter,

b: Endothelial stimulation (birth),

d: Inhibition parameters (death),

$u(t)$: Angiogenic dose rate (control function of the system).

Based on the studies in [4] and [7], the following equation gives the change rate in the volume of primary tumor cells

$$\dot{p} = -\xi p \ln(\frac{p}{e})$$

Moreover, the volume changing rate of vascular endothelial cells is taken by:

$$\dot{e} = be^{\frac{2}{3}} - de^{\frac{4}{3}} - Gue$$

By assuming $e = x^3$ and $y = \int_0^T u(t)dt$, Ergun et al. model [4] was converted to the following form:

$$Min: \ p(T)$$

$$s.t.: \quad \dot{p} = -\xi p \ln(\frac{p}{x^3}) \qquad (1)$$

$$\dot{x} = \frac{1}{3}(b - dx^2 - Gux)$$

$$\dot{y} = u.$$

Over the set of all Lebesgue measureable functions $u:[0,T] \to [0,a]$ which represents the inhibitor's dose of the given drugs in term of time. Moreover, it is proved that the terminal condition is $y(T) = A$ and $p(T) = e(T)$ that T can be found by these equations [8]. A complete solution to the problem was given by U. Ledzewicz and H. Schattler in [8] based on the Principle Maximal Pontryagin and using the property of singular and bang optimal control. The researchers suppose that the time duration of remedy, T, is unknown and look for the minimum one. The researchers, also, present a computational method which is able to compute the shortest time and the optimal control easier in comparison with the others.

4. LINEARIZATION BY MEASURES

Embedding method is an efficient method that has been used for solving different types of optimal control problem in two recent decades. The method is based on the linearization properties of measurement and has many advantages like an automatic existence theorem, converting the strong non-linear problems into a linear one, a known and easily applicable method for determining the optimal control as a piecewise constant function. The historical background of this method and also its applications can be found in many literatures like [5, 11 and 12]. For better understanding, the researchers introduce some related mathematical concepts of analysis and topology of famous text books like [13].

First, let $J=[0,T]$, be the interval time in which the controlled system will be evolved; the interior of interval is denoted by J^0. For $X(t)=(p(t),x(t),y(t));\ X:J\to A$ is an absolutely continuous bounded function, say trajectory, where $\wp=[a_1,b_1]\times[a_2,b_2]\times[a_3,b_3]$ is a bounded, closed and path wise-connected set in $\mathbb{R}^4$ such that the trajectory of the controlled system is constrained to stay in $\wp$ for all $t\in J$. Initial and final states of trajectory are $X_0\in\wp$ and $X_T\in\wp$, respectively.

The function $u:J\to U$, is the control function which is a Lebesgue measurement where $U=[0,a]$. The state equation of the system is expressed as $\dot{X}(t)=g(t,p(t),x(t),y(t),u(t))$, where g is a function on $\Omega=J\times\wp\times U$ and defined as:

$$g(t,p(t),x(t),y(t),u(t))=\left(-\xi p\ln(\frac{p}{x^3}),\frac{1}{3}\left(b-dx^2-Gux\right),u)\right) \qquad (3)$$

Definition: The researchers believe that a trajectory-control pair $P=\left(X(.),u(.)\right)$ is admissible if it satisfies in these and the boundary conditions.

The set of all admissible pairs is shown by **W**. The target function of problem is the final time of treatment duration, i.e. $f_0=T=\int_0^T dt$. The researchers must note that although T is unknown, the set $J=[0,T]$ is bounded and closed, so the set $\Omega=J\times\wp\times U$ is compact.

The researchers try to overcome the difficulties they confront in this and similar problems. For example:

a) The set W may be empty. Even if the set W is nonempty, the infimum (In mathematics, the infimum (plural infima) of a subset S of a partially ordered set T is the greatest element of T that is less than or equal to all elements of S) of f_0 over W may not be achieved at its element.
b) Even if the set W is nonempty and an optimal pair exists in W, it may be difficult to characterize the optimal pair or impossible to be estimated numerically; there aren't any comprehensive computational methods for this purpose.

Regarding these difficulties, the researchers transformed the problem into another appropriate space that can guide them to conquest these problems. First of all, the researchers represent their main problem as a variation form. Therefore, they follow Robio in [11], characterize the properties of admissible pairs as some integral relations.

Let $B\subseteq\mathbb{R}^4$ be an open ball containing $J\times\wp$; the researchers denote the space of real-valued continuously differentiable functions on B by $C'(B)$ such that they and their derivatives are bounded to B . Let $\phi\in C'(B)$, and defined as:

$$\phi^g(t,p,x,y,u)=\phi_x(t,p,x,y)g(t,p,x,y,u)+\phi_t(t,p,x,y), \qquad (3)$$

Note that both $\phi_x(t,p,x,y)$ and $g(t,p,x,y,u)$ are n-vector, and the first term in the right-hand side of (3) is their inner product. It is easy to show:

$$\int_J \phi^g(t,p,x,y,u)dt=\phi(T)-\phi(0)\equiv\Delta\phi. \qquad (4)$$

The researchers denoted $D(J^0)$ as the space of infinitely differentiable real-valued functions with compact support in J^0. For j=1,2,3 and all $\psi\in D(J^0)$ define:

$$\psi(t,X,u)=X_j\dot{\psi}(t)+g_j(t,X,u)\psi(t),(t,X,u)\in\Omega, (5)$$

where X_j and g_j are the component of the vectors X and g, respectively. Since the trajectory and control functions are an admissible pair that satisfy (5) on J^0; also the function ψ has compact support in J^0, one can show that $\psi(t_a) = \psi(t_b) = 0$; therefore:

$$\int_J \psi_j(t, p, x, y, u)dt = 0. \qquad (6)$$

For some applications, let consider a subspace of $C(\Omega)$, denoted by $C_1(\Omega)$, containing all the functions which are only depended on the variable *t*. Thus, for each $f \in C_1(\Omega)$, the researchers have:

$$\int_J f(t)dt = a_f \qquad (7)$$

where a_f is the Lebesgue integral of $f(t)$ on J. Now, the researchers can rewrite the problem (1) by considering these relations as the following:

$$\begin{aligned} Min: \quad & \frac{1}{T}\int_0^T p(T)dt \\ S.to: \quad & \int_J \phi^g(t,p,x,y,u)dt = \Delta\phi, \ \ \phi \in \acute{C}(B); \\ & \int_J \psi_j(t,p,x,y,u)dt = 0, \ \ \psi_j \in \mathfrak{D}(J^0); \quad (8) \\ & \int_J f(t,p,x,y,u)dt = a_f, \ \ f \in C_1(\Omega). \end{aligned}$$

The basis of embedding process is to convert the solution space into a measure space; this would be achieved by defining a linear, bounded and positive function, Λ_w for every admissible pair, w=(X,u) such that:

$$\Lambda_w : F \in C(\Omega) \to \int_J F(t, p, x, y, u)dt \in \square \qquad (9)$$

According to the Riesz Representation Theorem, for each functional Λ_w, there is a unique positive Borel measure, μ_w, on Ω such that:

$$\Lambda_w(F) = \int_\Omega F(t, X, u)d\mu \equiv \mu_w(F), \ F \in C(\Omega) \qquad (10)$$

Therefore, the problem can be transferred into the space of measures. So, the researchers achieved something deep; since the measures are linear, by applying (10), their problem will be changed into a linear one with respect to the unknown measure, μ_w. But, since the mapping $w \to \Lambda_w$ is injection, and induced measure μ_w from Riesz Representation Theorem is unique, the mentioned difficulties still remain. To overcome these difficulties, the researchers extended the solution space and considered the set of all positive radon measures like μ (not only the measures resulted from Riesz Representation Theorem) satisfying the conditions of the following problem:

$$\begin{aligned} Min: \quad & \mu(f_0) && \mu \in M^+(\Omega); \\ S.to: \quad & \mu(\phi^g) = \Delta\phi, && \phi \in \acute{C}(B); \qquad (11) \\ & \mu(\psi_j) = 0, && \psi_j \in \mathfrak{D}(J^0); \\ & \mu(f) = a_f, && f \in C_1(\Omega), \end{aligned}$$

Where $M^+(\Omega)$ is the set of all positive radon measures on Ω.

Assume *Q* is the set of all positive radon measures in $M^+(\Omega)$ which satisfies equations of system (11). By equipping *Q* with $weak^*$ topology ([12]); according to the following theorem, existence of optimum measure, μ^*, for (11) is guaranteed.

Proposition 2):

i) The set of measures Q is compact in the topology induced by the $weak^*$ topology on $M^+(\Omega)$.

ii) The function $\mu(f)$, mapping Q into the real line, is continuous.
iii) Problem (11) has an optimal solution.
Proof : (i) and (ii) are proved in [9]; since each lower semi-continuous function gives its infimum on the compact set, by regarding (i) and (ii), (11) has an optimal solution.

To solve the problem (11) over the set Q of all positive Radon measures on Ω satisfying (11), the researchers remind that this is an infinite dimensional linear programming problem and all the functions in (11) are linear with respect to measure μ furthermore the measure μ is required to be positive. But it has infinite number of constrains and the dimension of its solution space is infinite, too. Therefore, it is too hard to solve the problem directly. It is very desirable if one could obtain the solution somehow by solving a finite linear programming problem, even in the approximated form. The researchers will show the applicability of this process by using two steps of approximation. First, they choose countable subsets of functions whose linear combinations are dense in the appropriate spaces of the constraints. Then, they select a finite number of these functions to transform this problem into a semi-infinite linear programming. Let the set $\{\varphi_i, i = 1,2,...\} \subset C'(B)$ be such that the linear combinations of the functions ϕ_i's are uniformly dense (in the topology of uniform convergence) in the space $C'(B)$. For instance, these functions can be taken as polynomials in the variables' components, $p(t), x(t), y(t)$ and t.

The researchers shall consider only finite number M_1 of function ϕ and only finite number M_2 of the second set of equalities defined in (5) as:

$$sin\left(\frac{2\pi j(t-t_0)}{\Delta t}\right), 1-cos\left(\frac{2\pi j(t-t_0)}{\Delta t}\right), j = 1,2,...$$

Finally, the researchers consider a finite number *S* of functions of type:

$$f_s(t) = \begin{cases} 1 & t \in J_s \\ 0 & t \notin J_s \end{cases}, \qquad s = 1,2,...,S$$

where $J_s = \left(\frac{s-1}{S}, \frac{s}{S}\right], s = 2,...,S$ and $J_1 = [0, \frac{1}{s}]$ Even though these functions, $f_s(t)$ are not continuous, their linear combinations can approximate each function in $C_1(\Omega)$ properly well ([11]).

It must be noted that even in this step the number of constraints are finite; although from the variable space viewpoint, the problem is still infinite dimensionally. By assuming $N = M_1 + M_2 + 1$, according to Rosenbloom's theorem in [9], the optimal measure μ^* can be shown as:

$$\mu^* = \sum_{k=1}^{N} \alpha_k^* \delta(z_k), \qquad (12)$$

where $\delta(z_k) \in M^+(\Omega)$ is the unitary atomic measure with the singleton support $\{z_k = (t_k, x_k, u_k) \in \Omega\}$ such that $\delta(z_k)(F) = F(z_k), F \in C(\Omega), z_k \in \Omega$. The researchers remind that by replacing μ^* in the (11), it changes into a nonlinear programming problem with unknown coefficients α_k and z_k which are not suitable for their purpose. This is the reason for applying their second approximation step.

In the second approximation step that is presented in [11], the researchers employ a discretization on space Ω and choose the nodes which belong to a dense subset; then, the problem can be transferred into a finite linear programming with respect to the only unknown coefficients α_k's (see more details in [11]):

$$Min: \frac{1}{T}\sum_{i=1}^{N} \alpha_i p(T)$$

$$S.to: \sum_{i=1}^{N} \alpha_i \phi_i^g(z_i) = \Delta\phi_i, \ \phi_i \in \acute{C}(B), \ i = 1,2,...,M_1 \qquad (13)$$

$$\sum_{i=1}^{N} \alpha_i \psi_i(z_i) = 0, \qquad \psi_j \in \mathfrak{D}(J^0), \ i = 1,2,...,M_2$$

$$\sum_{i=1}^{N} \alpha_i f_i(z_i) = a_f, \qquad f_i \in C_1(\Omega), \ i = 1,2,...,l$$

$$\alpha_j \geq 0 \qquad j = 1,2,\dots,N$$

The procedure of constructing a piecewise constant control function from a solution $\{\alpha_j^* \geq 0,\ j = 1,2,\dots,N\}$ of the above linear programming problem, which approximate the action of the optimal measure, is based on the analysis in [11].

5. FUNCTIONS IN THE CASE OF OPTIMAL TIME PROBLEM

In this section, the researchers will solve the optimal control problem of tumor anti-angiogenesis treatment with the optimal time objective. For this purpose, the researchers will attempt to use an embedding method generalization, while the governing system, the initial and the terminal conditions are satisfied.

Since T is finite but unknown in the time-optimal case, the researchers must redefine their selection of functions and then rewrite the LP problem for using the embedding process (13). The researchers need to remind that in the previous section J is divided to S partitions to construct the functions $f_s(z_i)$ for the third set of equations in (13). But for the optimal time problem, the end part of this partition is unknown; thus the researchers consider a lower bound T_L and an upper bound T_U for optimal time, T, and then divide $[0,T_L]$ to S-1 partition and assume $[T_L,T]$ as the rest of the time interval J in which the researchers seek the optimal time, T. Thus the researchers have to define the functions (4) and (5) in an appropriate form. First, the researcher consider the functions $\psi_j \in (J^0)$ as follows:

$$\psi(t) = \begin{cases} sin\left(\frac{2k\pi t}{T_l}\right) & t\epsilon[0,T_l], \\ 0 & otherwise, \end{cases} \qquad (14)$$

$$\psi(t) = \begin{cases} 1 - cos\left(\frac{2k\pi t}{T_l}\right) & t\epsilon[0,T_l], \\ 0 & otherwise, \end{cases}$$

where $k = 1,2,3,\dots$, second the researchers only consider a finite number of these functions. The researchers, also, define the piecewise constant functions defined in (14) as the following:

$$f_s(t) = \begin{cases} 1 & t \in J_s, \\ 0 & t \notin J_s, \end{cases}$$

where $J_s = \left[\frac{s-1}{S}, \frac{s}{S}\right)$, s=1,2,...,S-1, $J_s = [T_L,T]$

Therefore since a_f is the integral of f_s on J, the researchers have:

$$a_f = \begin{cases} \frac{T_l}{S-1}, & s = 1,2,\dots,S-1, \\ T - T_l, & s = S, \end{cases}$$

where T is considered as an unknown variable. In addition, for the first set of functions ($\varphi_i \in C'(B)$), the researchers consider these functions as before and in the form of polynomials ($\varphi_i = t$ causes that $\Delta\varphi_i = T$, where T is considered as an unknown variable in (13), similarly for each $\varphi_i = t^2, t^3, \dots$).

In the next section, the researchers represent the algorithm of their method and show how the lower bound T_L and finally the optimal time T^* are found.

6. THE ALGORITHM OF COMPUTING METHOD THE LOWER BOUND T_L

For a given value T_L and then solving the related LP (13) for the time optimal problem with use of the above functions, the best time of treatment, which is dependant to T_L, can be obtained The researchers denoted this by $T^*(T_L)$. Therefore, they can look for the best lower bond of time, T_L^*, to be able to find the optimal time for the problem $T^*(T_L^*)$.

To determine the best lower bound T_L^*, the researchers combine the embedding process with the Fibonacci Search Method (FSM). The FSM has been preferred to other search techniques because this method requires the total number of observations, θ, to be taken such that $F_v > \frac{T_l^{b_1} - T_l^{a_1}}{\Upsilon}$ where F_v is v'th Fibonacci number. First, the researchers divide the interval $[0, T_U]$ to n subinterval and then consider $[T_l^{a_1}, T_l^{b_1}] = [T_u - \frac{T_u}{n}, T_u]$ as the initial interval to find the best T_L. Let $\xi_1 = T_l^{a_1} + \frac{F_{v-2}}{F_v}(T_l^{b_1} - T_l^{a_1})$ and $\eta_1 = T_l^{a_1} + \frac{F_{v-1}}{F_v}(T_l^{b_1} - T_l^{a_1})$.
Compute $T^*(\xi_1)$ and $T^*(\eta_1)$; take $k = 1$, and go to the main steps.

Main steps:
Step 1: If $T^*(\xi_1) > T^*(\eta_1)$, go to step 2; otherwise go to step 3.
Step 2: Take $T_l^{a_{k+1}} = \xi_k$ and $T_l^{b_{k+1}} = \xi_k$. Furthermore, let $\xi_{k+1} = \eta_k$, and let

$$\eta_{k+1} = T_l^{a_{k+1}} + \frac{F_{v-k-1}}{F_{v-k}}(T_l^{b_{k+1}} - T_l^{a_{k+1}}).$$

If $k = \vartheta - 2$, go to step 5; otherwise compute $T^*(\eta_{k+1})$ and then go to step 4.
Step 3: Take $T_l^{a_{k+1}} = T_l^{a_k}$ and $T_l^{b_{k+1}} = \eta_k$. Furthermore, take $\eta_{k+1} = \xi_k$, and let

$$\xi_{k+1} = T_l^{a_{k+1}} + \frac{F_{v-k-2}}{F_{v-k}}(T_l^{b_{k+1}} - T_l^{a_{k+1}}).$$

If $k = \vartheta - 2$, go to step 5; otherwise compute $T^*(\xi_{k+1})$ and then go to step 4.
Step 4: Replace k by $k + 1$ and go to step 1.
Step 5: Take $\xi_v = \xi_{v-1}$ and $\eta_\vartheta = \xi_{\vartheta-1} + 1$. If $T^*(\xi_v) > T^*(\eta_\vartheta)$, take $T_l^{a_v} = \eta_v$ and $T_l^{b_v} = T_l^{b_{v+1}}$.Otherwise if $T^*(\xi_v) \le T^*(\eta_\vartheta)$, take $T_l^{a_v} = T_l^{a_{v-1}}$ and $T_l^{a_v} = \xi_v$. Stop; the near optimal time will be $T^*(T_L)$ where $T_l = \frac{T_l^{a_v} + T_l^{b_v}}{2}$.

7. NUMERICAL SIMULATION

By regarding (1), the researchers consider the following parameters from Hahnfeldt et al. [7] and Ledzwicz and Schattler [8] for their numerical test:

$$a = 15,\ \xi = 0.084,\ b = 5.85,\ d = 0.00873,\ G = 0.15$$

$$a_1 = 0,\ b_1 = 18000,\ a_2 = 0,\ b_2 = 18000,\ a_3 = 0,\ b_3 = 45$$

$$A = 45,\ p_0 = 12000,\ y_0 = 0,\ T_u = 7,\ \gamma = 0.05,\ x_0 = \sqrt[3]{15000}$$

The researchers establish the linear programming problem (13) as described in section 3. By using the Fibonacci Search Technique, the researchers attained $T_L = 6.111$ and $T^*(T_L) = 6.439$. The researchers solve the aforementioned problem by using Simplex Method and applying Maple 12 software.
From the obtained results, the nearly piecewise-constant optimal treatment (optimal control) was calculated and plotted in Fig. 1. The final tumor volume was $2197.59\,mm^3$ and the tumor volume reduction under this treatment was plotted in Fig. 2.

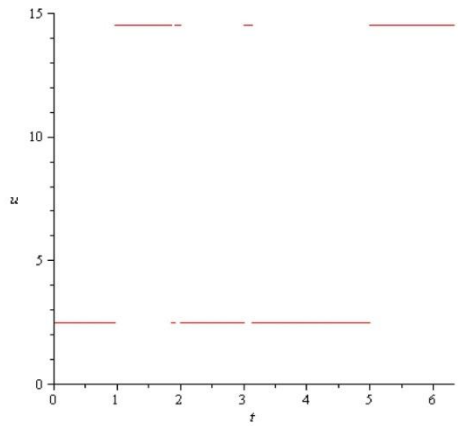

Fig. 1: Optimal control function.

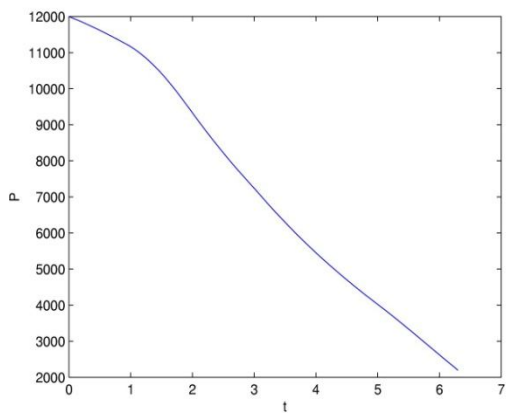

Fig. 1: Reduction of tumor volume.

The final tumor volume in the researchers' model was $2197.59\ mm^3$ lower than the final tumor volume in Ledzewicz and Schattler model (almost 2900 mm^3) [10]. The researchers' treatment duration was also lower (6.432 days) than their model (11 days).

8. CONCLUSION

The main purpose of tumor angiogenesis treatment is reducing the tumor volume to zero in an unspecified time. Even if this problem modelled as an optimal control problem and studied in many lecture areas, no identified method has been presented for determining the optimal time of treatment. In this paper, the researchers studied the tumor treatment by angiogenesis inhibitors as a time optimal control problem and introduced an applicable solution method for determining the optimal treatment. The method has many advantages such as the guarantee of the existence solution, strong theoretical supports and applicability by computer.

The researchers evaluated the optimal control trajectory in the sight of physician with respect to real case. The physician verdict confirmed the researchers' piecewise constant function of optimal control which is illustrated in Fig. 1. Moreover, the simulation test showed that in comparison with the others, the time of treatment and also the amount of the tumor volume reduction were considerably better.

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9. REFERENCES

[1] A.Onofrio D. and Gandolfi A., 2004. Tumour Eradication by Anti-Angiogenic Therapy: Analysis and Extensions of the Model by Hahnfeldt et al. (1999). Math. Biosci., 191, pp. 159-184.

[2] Bryson, A. E. and Ho, Y. C., 1975. Applied Optimal Control, Hemisphere Publishing.

[3] Cotran, R. S., Robbins, S. L. and Kumar, V., 1997. Basic Pathology, Sixth Edition, W.B. Saunders Company.

[4] Ergun, A, K. Camphausen and L. M. Wein, 2003. Optimal Scheduling of Radiotherapy and Angiogenic Inhibitors, Bull. of Math. Biology, 65, pp. 407-424.

[5] Fakharzadeh J,A. and Rubio, J . E., 2009. Best Domain for an Elliptic Problem in Cartesian Coordinates by Means of Shape-Measure. Asian Journal Of Control, Vol 11, pp 536-547.

[6] Gachpazan, M., Hashemi B, A. and Vahidian K,A., 2006. A Measure –Theoretical Approach for Solving Discrete Optimal Control Problems. Applied Mathematics and Computation, Vol 173, pp 736-752.

[7] Hahnfeldt P., Panigrahy D., Folkman J. and Hlatky L., 1999. Tumor Development Under Angiogenic Signaling: A Dynamical Theory of Tumor Growth, Treatment Response and Post Vascular Dormancy, Cancer Research, 59, pp. 4770-4775.

[8] Ledzewicz, U., Schaettler H., Faraji M., 2013. Optimal Protocols for a Mathematical Model of Tumor-Immune Interactions under Chemotherapy with Immune Boost, Special Issue of Discrete and Continuous Dynamical Systems, Series B, 18 (4), pp. 1031-1051.

[9] Ledzewicz, U., A. d'Onofrio, H. Schaettler, 2012. Tumor Development under Combination Treatments with Anti-Angiogenic Therapies, in Mathematical Methods and Models in Biomedicine, Springer-Verlag, pp. 311-337

[10] Ledzewicz, U. and Schättler, H., 2006. Optimal Control for a System Modelling Tumor anti-Angiogenesis, ICGST - Int. J. on Automatic Control and Systems Engineering, 6, pp. 33-39.

[11] Ledzewicz, U. and Schättler, H., 2007. Anti-Angiogenic Therapy in Cancer Treatment as an Optimal Control Problem. J. on Control and Optimization, 46(3), pp 1052-1079.

[12] Rubio, J. E., 1985. Control and Optimization: The Linear Treatment of Nonlinear Problem, Hemisphere Publishing.

[13] Rubio, J. E., 1990. Modern Trends In The Calculus Of Variations and Optimal Control Theory. In R. Geise, editor, Vortagsauszuge, Mathematiker Kongress, Berlin, Mathematische Gesellschaft, pp 155-163.

[14] Rudin, W., 1983. Real and Complex Analysis, Tata McGraw-Hill Publishing Co. Ltd, New Delhi.