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USING OPTIMAL CONTROL FOR TUMOR REMEDY AND PREVENTION OF ITS GROWTH

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ABSTRACT

Tumor needs angiogenesis for its growth naturally. One of the best ways for controlling tumor growth is prevention of tumor angiogenesis. In optimum position, we can formulate this act as an optimal control problem. In this paper, in the course of description of model, we find optimum remedy by using Embedding method for the first time. Numerical results show the effect of this method for tumor remedy.

Keywords: tumor angiogenesis, optimal control, radon measure, anti-angiogenesis inhibitors, linear programming.

INTRODUCTION

Different from normal cells, cancer cells are genetically highly unstable and thus quite diversified in their structure. Some cancer cells are simply not affected by current drug (intrinsic drug resistance); other cancer cells easily generate resistant mutations (acquired drug resistance). As a results, even if chemotherapy shows success initially, only all too often cancer comes back in a resistant form. Hence there is strong interest in substituting treatments that would not make drug resistance. Anti-angiogenesis, a treatment approach is a mechanism that offers such a hope for the treatment of tumor cancers. A tumor, after it grows to just a few millimeters in diameter needs to develop its own system of capillaries. In facing this tumor reaction, angiogenesis inhibitors target those cells that prevent the tumor from developing its own blood vessel system and thus blocking its growth. Tumors deprived of necessary nutrition and as a result, descend its volume. Since the treatment target normal cells, no occurrence of drug resistance has been established [9-11].

In this paper, the researcher introduced the mathematical model of tumor growth that is no-linear model. After that, it transformed to linear model by using the measure theory. This method has many advantages that describe in the next sections. Numerical result shows the efficiency of this work.

MATHEMATICAL MODEL FOR DYNAMIC SYSTEM OF ANTI-ANGIOGENIC MONOTHERAPY

Studding show that tumor angiogenesis and its inhibitors have described by partial deferential equations. One of the earliest mathematical models was formulated by Hahnfeldt *et al*. in [1]. In this model, the volume of primary tumor cells and the volume of the vascular endothelial cells are distinguished and their interactive growth is modeled in the dynamics. An analysis of dynamic properties of this model and some extents has been given by d'Onofrio and Gondolfi in [2]. The model in [2] also was modified and mathematically simplified by Ergun *et al*. They could express tumor angiogenesis and its treatment as an optimal control problem. After them, Ledzewicz and Schattler studied on Ergun *et al*.'s model and a complete solution of the problem was given by them in [3-5]. In this paper, in the course of examination and description control model of Ergun *et al*., we took action to solve it by using a new and simple method that has different advantages in compare with other methods [6].

Let p and e denoted the volume of primary tumor cells and the volume of the vascular endothelial cells, respectively. We assumed that tumor growth is Gompertzian and hence, the following equation is the rate of the changes in the volume of primary tumor cells:

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

where ξ denoting as the tumor growth parameter. Moreover the rate of the changes in the volume of vascular endothelial cells is taken in the form of:

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

where b (birth) and d (death) are endothelial stimulation and inhibition parameters, respectively; Also the variable u represents the control function of the system and corresponds to the angiogenic dose rate; the constant G represents the anti-angiogenic killing parameter. In this manner Ergun *et al.* considered the following optimal control problem:

$$Min \quad p(T)$$

$$S.to \quad \dot{p} = -\xi p \ln\left(\frac{p}{e}\right), \qquad (1)$$

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

over the set of all Lebesgue measureable functions $u:[0,T] \to [0,a]$ which more than the constraints (1), are satisfied in a constraint of the form: $\int_0^T u(t)dt \leq A$. We

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set $s = x^3$, $y = \int_0^T u(t)dt$ for simpler mathematical analysis. Hence we consider the following equivalent optimal control problem:

$$Mini \quad p(T)$$

$$S.to: \quad \dot{p} = -\xi p \ln\left(\frac{p}{x^3}\right), \qquad (2)$$

$$\dot{s} = b - dx^2 - Gux,$$

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

Linear form of model

Embedding method is an efficient method that had used for solving optimal control problem in two recent decades and based on measure theory. Some advantages of this method are guarantee of exist solution, convert complicated and no-linear relations into simple and linear form and determine optimal control as piece wise constant function. At first, we need to introduce some functions and sets for present solution of control tumor angiogenesis and its treatment.

a) A real closed interval $J = [0, T]$, with $0 < T$. The interior of this interval will be denote by J^0. # $J^0 = (0, T)$. This is the time interval in which the controlled system will evolve.
b) An absolutely continuous function of trajectory $X: J \to A$, where $X(t) = (p(t), x(t), y(t))$ and A is a bounded closed and path wise-connected set in $\mathbf{R}^4$, $A = [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$, such that the trajectory of the controlled system is constrained to stay in set A for $t \in J$. Initial and final states of trajectory are $X_0 \in A$, $X_T \in A$, respectively.
c) Control function $u: J \to U$, is a lebesgue measurable function where $U = [0, a]$.
d) Behavior of tumor angiogenesis and its growth expressed as differential equations $\dot{X}(t) = g(t, p(t), x(t), y(t), u(t))$, where g is a function on $\Omega = J \times A \times U$ such that:

$$g(t, p(t), x(t), y(t), u(t)) = \left(-\xi p \ln\left(\frac{p}{x^3}\right), \frac{1}{3}(b - dx^2 - Gux), u\right) \qquad (5)$$

e) Target function of our problem is $f_0 = p(T) = \frac{1}{T}\int_0^T p(T)dt$.

Definition: We shall say that a trajectory-control pair $P = (X(\cdot), u(\cdot))$ is admissible if the following conditions hold:

- The trajectory function $X(\cdot)$ satisfies $(t) \in A, t \in J$, and is absolutely condition on J.
- The control function $u(\cdot)$ takes its values in the set U, and is Lebesgue measureable on J.
- The boundary conditions are satisfied.
- The pair P satisfies the differential equation $\dot{X}(t) = g(t, p(t), x(t), y(t), u(t))$ on J^0.

The set of all admissible pairs is shown by W. We try to overcome the difficulties that we confront them in this problem and similar problems. For example:

a) The set W may be empty.
b) Even if the set W is nonempty, The infimum of I(p) over W may not be achieved at element of W; that is there may not be a minimizing pair for I(p) in W.
c) Even if the set W is nonempty, and a minimizing pair for I (p) does exist in W, it may be difficult to characterize it; Necessary conditions are not always helpful because the information they give may be impossible to interpret.
d) The minimizing (or optimal) pair may be very difficult or impossible to estimate numerically; there are no comprehensive computational methods for this purpose.

By regarding to above notices and type of the problem, transforming the problem into another appropriate space can guideline us to conquest these problems. It is the next aim.

Let $\mathbf{B} \subseteq \mathbf{R}^4$ be an open ball containing $J \times A$; we denote by $\acute{C}(\mathbf{B})$ the space of real-valued continuously functions on $\mathbf{B}$ such that they and their derivatives are bounded on $\mathbf{B}$. Let $\phi \in \acute{C}(\mathbf{B})$, and define:

$$\phi^g(t, p, x, y, u) = \phi_x(t, p, x, y)g(t, p, x, y, u) + \phi_t(t, p, x, y) \qquad (6)$$

For all $(t, p, x, y, u) \in \Omega$; note that both $\phi_x(t, p, x, y)$ and $g(t, p, x, y, u)$ are n-vector, and that the first term in the right-hand side of (6) in their inner product. It is simple to show that

$$\int_J \phi^g(t, p, x, y, u)dt = \phi(T) - \phi(0) = \Delta\phi \qquad (7)$$

Also, Let $\mathfrak{D}(J^0)$ be the space of infinitely differentiable real-value functions with compact support in J^0. Let $\psi \in \mathfrak{D}(J^0)$, and define:

$$\varphi(t, p, x, y, u) = X_j\dot{\psi}(t) + g_j(t, p, x, y, u)\psi(t), \qquad (t, p, x, y, u) \in \Omega \qquad (8)$$

Denote X_j, g_j, as the component of the vector X and function g, respectively. We have:

$$\int_J \varphi_j(t, p, x, y, u)dt = 0 \qquad (9)$$

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Since the trajectory and control functions in an admissible pair satisfy (3) a. e. on J°, and since the function ψ has compact support in J°, $\psi(t_a) = \psi(t_b) = 0$.

For some applications, consider a subspace of $C(\Omega)$, to be denote by $C_1(\Omega)$, of the functions in this space whish depend only on the variable t. let $f \in C_1(\Omega)$, we have:

$$\int_J f(t)dt = a_f, \qquad (10)$$

where a_f is the integrant of $f(t)$ on J. Now we can rewrite the problem (4) by using of above definition and relations as the following form:

$$Min \quad \frac{1}{T}\int_0^T p(T)dt$$

$$S.to \quad \int_J \phi^g(t,p,x,y,u)dt = \Delta\phi, \qquad \phi \in \hat{C}(B)$$

$$\int_J \psi_j(t,p,x,y,u)dt = 0, \qquad \psi_j \in \mathfrak{D}(J^0) \qquad (11)$$

$$\int_J f(t,p,x,y,u)dt = a_f, \qquad f \in C_1(\Omega)$$

Reformulation of model

The basis of embedding method is change of solution space problem into measure space. So for every admissible pair, $P = (p,x,y,u)$ consider a linear, bounded and positive function, Λ_P, such that:

$$\Lambda_P: \; F \in C(\Omega) \rightarrow \int_J F(t,p,x,y,u)dt \in \mathbb{R} \qquad (12)$$

Now, consider the transformation $P \rightarrow \Lambda_P$, of an admissible pair into a continuous, positive linear functional.

Proposition-1: The transformation P → Λ_P of the admissible pairs in W into the linear mappings Λ_P defined above is an injection.

Proof: [7]

By using the injective mapping P → Λ_P and (4), (5) and (6) we can represent the problem in the linear positive functional space in the below form:

$$Min \quad \Lambda(f_0)$$

$$S.to \quad \Lambda(\phi^g) = \Delta\phi, \qquad \phi \in \hat{C}(B) \qquad (14)$$

$$\Lambda(\psi_j) = 0, \qquad \psi_j \in \mathfrak{D}(J^0)$$

$$\Lambda(f) = a_f, \qquad f \in C_1(\Omega)$$

According to the Riesz Representation Theorem, for each linear positive functional like Λ_F, there is a positive Borel measure on Ω such that:

$$\Lambda_F(F) = \int_\Omega F(t,p,x,y,u)d\mu = \mu_F(F), \qquad F \in C(\Omega) \qquad (13)$$

Therefore the problem is transferable to the space of measures by one-to-one mapping. To overcome over probable difficulties that results from this mapping (like emptiness of the solution space, determining the optimum solution in set W and inexistent of a comprehensive computational method for estimating the optimum solution), we developed the solution space and consider the set of all positive radon measures like μ (not only the measures resulted from Riesz Representation Theorem) that satisfy conditions of following problem:

$$Min \quad \mu(f_0) \qquad \mu \in M^+(\Omega)$$

$$S.to \quad \mu(\phi^g) = \Delta\phi, \qquad \phi \in \hat{C}(B) \qquad (14)$$

$$\mu(\psi_j) = 0, \qquad \psi_j \in \mathfrak{D}(J^0)$$

$$\mu(f) = a_f, \qquad f \in C_1(\Omega)$$

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

Assume Q is the set of all positive radon measures in $M^+(\Omega)$ that satisfies equations of system (14).

By using of weak* topology according to following theorem existence of optimum measure μ^* for (9) is proved.

Proposition-2:

a) The set of measures Q is compact in the topology induced by the weak* topology on $M^+(\Omega)$.
b) The function $\rightarrow \mu(f)$, mapping Q into the real line, is continuous.

Proof: [7]

Proposition-3: If *S* is a compact subset of the Hausdorff space X and the function *Y: S → R*, is lower semi-continuous (lsc) in S, then:

$$i) \quad inf\{s \quad (Y(S) > \infty)\}$$

c) There is an element $s_0 \in S$ such that $Y(s_0) \le Y(s)$, for all $\in S$; that is the infimum of Y is attained on S.

Proof: [7]

The problem (14) is one of the linear programming; all the functions (objective function and

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constraints) are linear in the variable μ ; furthermore, the measure μ is required to be positive.

Although problem (9) is a problem of linear programming type (LP), It has infinite number of constrains, while the dimension of solution space of problem is infinite too.

For simplicity, it is desirable to obtain the solution of this problem by solving a finite linear programming problem (even in the approximated form). This process is applicable in two approximated steps as shown in the following:

We chose countable subsets of functions whose linear combinations are dense in the appropriate spaces, and then select a finite number of this. We consider the first set of equalities in (14). Let the set $\{\varphi_i, i = 1,2,\dots,M_1\}$ be such that the linear combinations of the functions $\varphi^i_{i\in c}(B)$ are uniformly dense (dense in the topology of uniform convergence) in the space $C'(B)$. For instance, this function can be taken to be monomials in the components of three variables, $p(t), x(t), y(t)$ and variable t. Also we chose M_2 functions from second set of equalities in (14) in the following forms:

$$\psi_j = \sin\left(\frac{2\pi j(t-t_0)}{\Delta t}\right), \qquad \psi_j = 1 - \cos\left(\frac{2\pi j(t-t_0)}{\Delta t}\right), \qquad j = 1,2,\dots M_2$$

For the third set of equalities, by dividing the time interval to L subintervals, we introduced the characteristic functions as the following form:

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

It must be noted that the problem from the viewpoint of number of variables, is still with infinite dimension.

Second step

By assuming $N = M_1 + M_2 + 1$, according to Rosenbloom Theorem [7], the optimum measure μ^* has the following form:

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

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 $\delta(z_k)(F) = F(z_k), F \in C(\Omega), z_k \in \Omega$.

By replacing μ^* in the problem (14), the problem changes into a nonlinear programming problem with unknown coefficients α_k and z_k. If we can minimize the problem with respect to coefficients α_k then the problem is changed into a linear programming problem. This process is possible if we employ a discretization space Ω and choose the nodes which belong to a dense subset of Ω . Finally by performing the above steps on problem (14), we attained the following linear programming problem:

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

$$S.to: \sum_{i=1}^{N} \alpha_i \phi_i^g(z_i) = \Delta\phi_i, \ \ \phi_i \in \hat{C}(B), \qquad i = 1,2,\dots,M_1 \qquad (15)$$

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

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

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

By using of the dense property of space, it can be proved when M_1 , M_2 , l → ∞ then solution of (10) will tend to solution of main problem.

In [7] proved that the solution certainly exists, but it is difficult to find it. We enforced admissible and suitable approximation to reach the solution.

In fact, optimal control function is optimal treatment for prevent tumor angiogenesis in [0, T].

NUMERICAL SIMULATION

By using the following data in [5, 8]:

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

$$\alpha = 15, T = 10, \qquad \xi = 0.084, b = 5.85, d = 0.00873, G = 0.15$$

$$A = 45, p_0 = 12000, x_0 = \sqrt{15000}, y_0 = 0$$

We established the linear programming problem, as described above, and solved it by Maple 12 software. Figure-1 shows optimum treatment (control). The final tumor volume that achieved in [8] is 8124.4 while our final tumor volume is 6238.72 in the same duration of remedy.

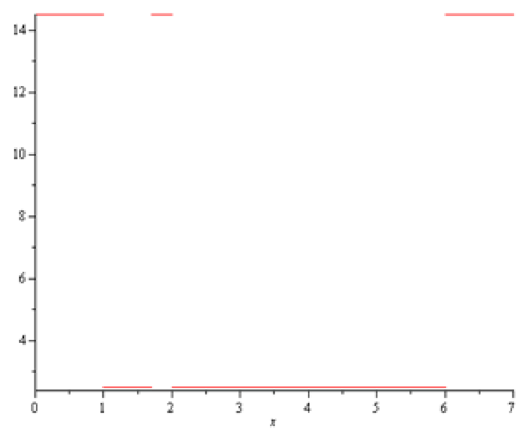

Figure 1

CONCLUSIONS

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 physician verdict confirmed the researchers' piecewise constant function of optimal control which is illustrated in Figure-1.

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