AN OPTIMAL CONTROL POLICY APPLIED TO DISCRETE TIME MODEL

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ABSTRACT: *In this paper an optimal control problem for a discrete time model is applied to minimize the tumor density and drug side effects . A generalization of Gompertz growth model is introduced and used for the proposed model. The necessary conditions and the characterization of the optimal solution are given through the use of Pontryagin's Maximum Principle . Numerical results are provided to illustrate the theoritical results.*

KEYWORDS. Discrete optimal control , Mathematical model ,Tumor growth, Gompertz model.

1 -INTRODUCTION

Many strategies to modelling chemotherapeutic induced killing of tumor cells have been widely investigated in the literature [2,3,7,8,9]. The paper of Schable, Skipper and Wilcox[14] is one of the early approaches in cell-Kill, their assumption is that a chemotherapeutic drug was proportional to the tumor size, while Norton and Siman[10,11] considered the cell-kill is proportinoal to the growth rate of the tumor. However the hypothesis that describes the cell-kill in terms of a saturable function of Michaelies-Menton form was developed by Holford and Sheiner[5]. In an optimal control problem one needs to achieve a goal by adjusting controls, so that some mathematical works have been done to understand, how tumor develops as well as the tumor growths [13,16]. Some of these works are to treat and optimize or to predict the activitey of new treatments or to give more common sense into the improvement and implementation of tumor treatment . In this work we will consider a kind of generalization to Gompertz model which it describes the tumor growth . We will also apply an optimal control stratigy to minimize the the tumor density and drug side effects over a given time interval. To achieve this goal the standrad terminology of optimal control of a single discrete time difference equation with a single control variable will be applied. For that we consider the following first order difference equation:

$x_{k+1} = f(k, x_k, u_k)$, $k=0,1,\ldots T$ (1)

With a given initial condition x_0. Equation (1) is called the state equation, where $f(k,x_k,u_k)$ is a given continuously differentiable function of three real variables k, x, u, The vectors $x= (x_0, x_1, \ldots, x_T)$ and $u=(u_0, u_1, \ldots, u_{T-1})$ are called the state and the control variable respectively. The control has one component less than the state and the first state component or the initial condition is given by x_0. The terminal time T is well known as the time horizon, here we assume that T is finite. The general case of infinite horizon is rather challanging and complicated. The objective function is defined by :

$J(u_k) = \Phi(x_T)+ \sum_{k=0}^{T-1} g(k, x_k, u_k)$ (2)

The problem is to optimal maximize or minimize J(u) over vectors u in R^{T-1}. The term function $\Phi(x_T)$ is the payoff term or salvage term , the population may be wanted to be large at the final time [6]. Such maximization or minimization vector u^* and the corresponding state x^* must satisfy the necessary conditions of the pontryagins maximum principle , For more details about derivation of the necessary conditions can be found in the book of Lenhart and workman [6]. The Maximum Principle is most conveniently formulated in terms by the Hamiltonian expression which is given at each time step k =0,1,..T-1, by:

$H_k= g(k,x_k,u_k) + \lambda_{k+1}f(k,x_k,u_k)$ (3)

Here $\lambda = (\lambda_0, \lambda_1, \ldots, \lambda_T)$ is an additional unknwon function which is called the adjoint function or shadow price [1]. Note that the indexing on the adjoint in (3) is one step ahead of the indexing for the others.

For more details about interpolation the Hamiltonian and the adjoint function for biological models we refer to [1,6]. According to Pontryagins Maximum principle the optimal control vector u* with corresponding state variable x^* must optimize the value of Hamiltonian expression at each time step k over all admissible vectors $u \in R^{T-1}$. Then the necessary conditions for the optimality are:

$$\lambda_k = \frac{\partial H_k}{\partial x_k}$$

$\lambda_T = \dot{\emptyset}(x_T^*)$ and $\frac{\partial H_k}{\partial u_k} = 0$ at u^*

Note that the state function x* must satisfy the initial conditions while the adjoint function must satisfy the final times conditions . It is also well known that if the objective functional is linear for control variable then the optimal solution is called a bang-bang solution. There are many applications to the above formulation in control biological system as well as in control of speard deaseases and epidemics. We refer to the excellent book of Lenhart. [6] and one can also see the survey of R. F. Hartl, S. P. Sethi [4] and book of S.P. Sethi and G.L. Thomson [15] about the discrete optimal control theory.

2-Mathematical model and control problem:

In this section a generalization of the Gompertzian growth model is introduced and used to describe the growth of tumor.The model under investigation is described by the following difference equation.

$$N_{k+1} = rN_k \ln\left(\frac{1}{N_k^n}\right) - \delta u_k N_k \quad (4)$$

n is a constant greater than 1, N_k is the tumor volume, r is the growth rate of the tumor, and u_k is the control variable, which describes the pharmacohinetics of the drug, that means the drug effect will only be presented when $0 \leq u_k \leq M$. Otherwise there is no drug effect. Where M is the maximum amount of drug and δ is the magnitude of the amount of dose.In this control optimal control the goal is to minimize tumor density and drug side effects. The objective functional that represents our aim is then given by

$J(u_k) = \min_{uk} \sum_{k=0}^{T-1} aN_k^2 + u_k^2$ (5)

Where a is a positive weight parameter. The optimal control problem is to find the function u^* and the corresponding state such that minimize the objective functional i.e

$J(u^*) = \min J(u)$ for all u belong to U where

$U =\{u_k : 0 \leq u_k \leq M$, k-0,2,…,T-1 }, is the set of controls . To perform this the extension version of Pontryagin's maximum principle will be applied [12]. The exitence of such optimal is guarantee due to the finite dimension. The characterization of the optimal solution is given by the next theorem.

Theorem1:

Given an optimal solution u^* with corresponding state solution N^* that minimizes the objective functional $J(u_k)$ then there exists adjoint function λ_k which satisfies:

$$\lambda_k = 2aN_k + \lambda_{k+1}\left(r\ \ln\left(\frac{1}{N_k^n}\right) - nr - \delta u_k\right) \text{ with } \lambda_T = 0$$

Furthermore the characterization of the optimal control is

$$u^*_k = \begin{cases} 0 & if \quad \delta N_k \lambda_{k+1} \le 0 \\ \delta N_k \lambda_{k+1} & if \quad 0 < \delta N_k \lambda_{k+1} \le M \\ M & if \quad M < \delta N_k \lambda_{k+1} \end{cases}$$

Proof: The Hamiltonian for k=0,1,……T-1, is

$$H_k = aN_k^2 + u_k^2 + \lambda_{k+1}\left(rN_k \ln\left(\frac{1}{N_k^n}\right) - \delta u_k N_k\right) \quad (6)$$

By using the extension of Pontry's Maximum principle [6,12,15]. Then the necessary conditions are for k=1,2,…T

$$\lambda_k = \frac{\partial H_k}{\partial N_k} = 2aN_k + \lambda_{k+1}\left(r\ \ln\left(\frac{1}{N_k^n}\right) - nr - \delta u_k\right) \quad (7)$$

And the optimality condition is

$$\frac{\partial H_k}{\partial u_k} = 2u_k + \lambda_{k+1}(-\delta N_k) = 0$$

Therefore the characterization of the optimal control becomes

$$u^*_k = \begin{cases} 0 & if \quad \delta N_k \lambda_{k+1} \le 0 \\ \delta N_k \lambda_{k+1} & if \quad 0 < \delta N_k \lambda_{k+1} \le M \\ M & if \quad M < \delta N_k \lambda_{k+1} \end{cases} \quad (8)$$

3-Numerical resutls:-

The numerical solutions for the optimal control variable and the corresponding variable are obtained for n=2. An iterative method is used to solve the optimality which is found in the book of lenhart in [6], for details of this method. The initial condition for the state variables is given at k = 0 , while the initial condition for the covariable is stated at k = T. This numerical procedure begins to guess an initial solution for the control variable so that with the initial condition of state variable, one can solve the state equation forward and the adjoint equation backward. The control variable is updated by using a convex combination between the previous control values and values which are given by the current iterations. This procedure continues until successive iterates are close enough and the optimal solutions are obtained.

We choose r=0.5, a=3, δ=0.45 and the initial value N_0=0.368. In Figure 1, the tumor density without treatment is plotted in dotted line that means the u_k=0 for all k, while the solid line shows the tumor density with optimal treatment. The plot also shows that the optimal treatment begins with a high drug which followed by reduction then no drug at all on day 30. In Figure 2 ,the numerical optimal control is plotted as a function of time.

The different values of the parameter a are used in Figure 3, and it shows also the effect of the varying this parameter , so one can able to push the tumor density to a much lower level when minimizing side-effects has less importance by using a much higher value of a. Another intersesting parameter is the magnitude δ. Figure 4 shows the effects of this parameter. It clear that the higher value of δ the more reduction in tumor density.

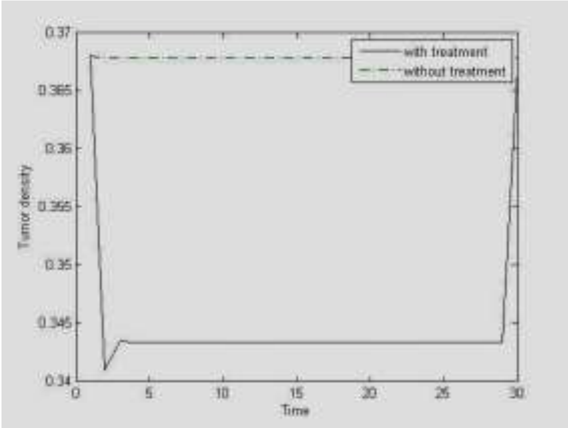

Figure 1:The plot shows the tumor density with optimal treatment soild line and without control in dashed line

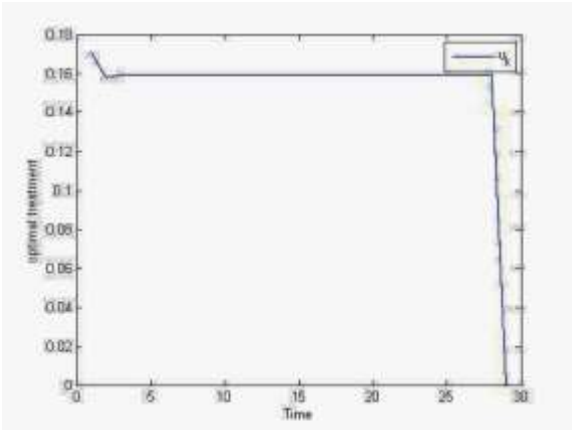

Figure 2:The optimal solition as a funtion of time

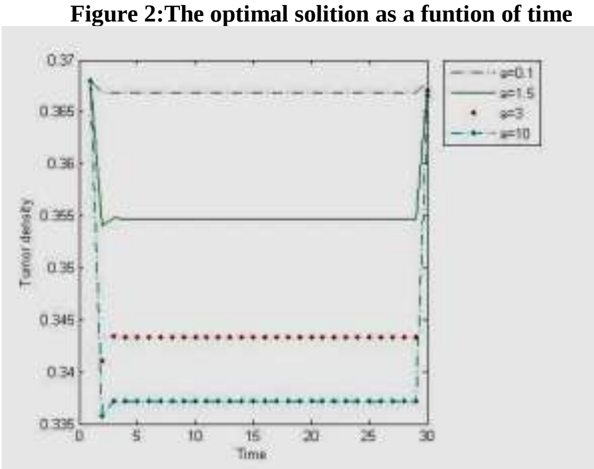

Figure 3 The plot illustrates the tumor density with different values of a.

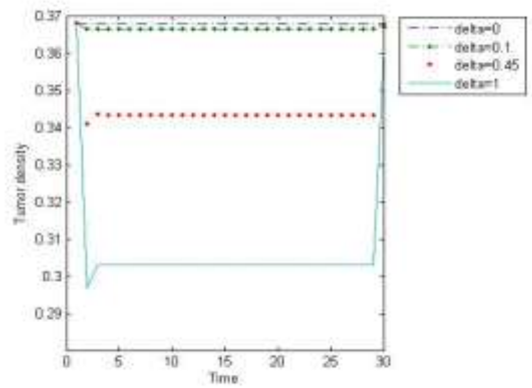

Figure 4: The plot shows the effect of the parameter δ on the tumor density.

4-CONCLUSIONS:-

This work presents generalization of Gompertz growth is used to obtain an optimal strategy for reducing the tumor mass over the treatment interval . The Ponryagins Maximum Principle have been used to derive the necessary conditions. We have been seen The effects of the important parameters a and δ so that for increasing value of a we are able to push the tumor density to a much level when minimizing side-effects has less importance. A varying values of the magnuited value δ is also investigated. So one can note that a higher magnuite drives the tumor density down. Numerical analysis illustrates and conforms the analytic results **.**

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