

Optimal Control Brain Tumor System with Drog and Its Stability

S.A. Alavi¹, J. Norabadi², M. Arjmand³

^{1,2,3}Dept. of Maths, College of Mathematics and Computer Science, Hakim Sabzevari University, sabzevar, Iran.

²Javad.nurabadi@gmail.com

Received: February 2012, Revised: May 2012

Online Publication: July 2012

Abstract

It is quite known that there are various methods for treatment of cancer. Although virus therapy has been proved to effective in the improvement of cancer, this method is still at its primary stage. Therefore, treatment methods such as chemotherapy and radiotherapy are still versatile. In these methods, drugs are prescribed. The most important question in the treatment of brain tumors is the rate of drug prescription for the patient so that it can help the patient recover and minimize damages to the healthy cells. A.El-Gohary demonstrated that a mathematical model of brain tumor system can be seen in an optimal nonlinear control problem. In this paper, attempt is made to transform the nonlinear optimal control problem into an optimal control problem in the measure theory and to approximate a new problem with a linear programming problem and subsequently, to specify the drug dose for the patients with cancer. In addition, we deal with the examination of stability of system balance points. Using drug dose control stabilizes the unstable balance points of the tumor system. In the end, a comparison is made between the results obtained from the above mentioned method and the approximate solution proposed by Al-Gohary.

Keywords: Nonlinear optimal control, Measure theory, Tumor, linear programming.

1. Introduction

Cancer means growth, multiplication and sometimes abnormal proliferation of cells in the human body which is the second major cause of death around the world and an estimated number of 8,500,000 people die every year. Surgical operation, chemotherapy, hormone therapy and radiotherapy are considered the effective ways of cancer treatment. Any of the specific methods mentioned above are used based on the kind, stage and location of cancer. Human body is formed by millions of cells which, altogether, build tissues such as muscles, bones and skin. In response to the stimuli, most natural human cells penetrate from the

inside and outside of the body and grow and duplicate and finally die. If this process happens in balance and under its proper condition, body remains healthy and keeps on performing in a natural order. But problems occur when some genes of a natural cell suffer mutation and the cell transforms into a cancer cell. In cancer, the cells lose their ability to divide and grow normally and this issue results in the capture, destruction and decay of the healthy tissues. These cancer cells are accumulated and then destroy the healthy cells of the tissues and create a mass called tumor.

If the tumor is restricted by a limited layer and doesn't permeate the other tissues and organs the tumor is called "benign" (non-cancerous) and if the tumor is extended or potentially spreads and encompasses other tissues and organs is called "malignant" or cancerous.

Different mathematical models have been presented for tumor, the model proposed in this paper have been proposed in 2006 by Rassel and Dinjelli[3], then it has been revised and modified by Al-Gohary [1].it will be demonstrated that a mathematical model for the treatment of cancer through drug prescription is an optimal control problem with nonlinear systems which using measure theory it has been transformed into a linear optimization problem and solved.

2. Tumor model

This section concerns with the construction of the mathematical model of tumor system with drug. Also the linear stability analysis of this model is introduced. The tumor system with drug will be constructed based on the following processes. The growth of immune cells can be stimulated by the presence of tumor cells, and these immune cells destroy the tumor cells through a kinetic process. It should be noted that the presence of a detectable tumor does not necessarily imply that the tumor has completely escaped from active immunosurveillance. It is completely possible that although a tumor is immunogenetic, the immune response is not sufficient on its own to entirely combat the rapid growth of the tumor population and the final development into a tumor. Actually, there is even some speculation that all tumors are immunogenetic[7]. The normal cells and tumor cells compete for available resources, while immune cells and tumors cells compete in a prey-predator behavior. Finally, the optimal drug therapies are calculated from the conditions that minimize both the final tumor population cells, the average tumor over time, while keeping the normal cells above a requested level. For more details about the kinetics processes of this model can be found in Refs. [8-10]. we start with the building of the tumor with drug mathematical model.

Assume that $I(t)$ denote the number of immune cells at time t , while $T(t)$ is the number of tumor cells at same time t and $H(t)$ is the number of the host cells or normal cells at the same time t . We consider that the resource of the immune cells is to be outside the system so it is reasonable to assume that the immune cells have a constant influx rate s . In the absence of any tumor, the cells will die off at a per capita rate d_1 , resulting in long-term population size of s/d_1 cells. Therefore, immune cell proliferation will suffer from immunity upon immune crowding. The immune response stimulates by positive nonlinear growth in the presence of tumor cells That is

$$\frac{r_3 I(t) T(t)}{\alpha + T(t)} \tag{1}$$

Where r_3 and a are positive real constants. Moreover, the reaction of immune cells and tumor cells represents in either death of tumor cells or the inactivation of the immune cells which can be represented by the following two competition terms:

$$\frac{dI}{dt} = -c_1 T(t)I(t) \quad , \quad \frac{dT}{dt} = -c_2 T(t)I(t) \tag{2}$$

where c_1 and c_2 are also positive real constants.

Now, the tumor cells as well as hosting cells can be modelled by a logistic growth law with parameters r_1 and b_1 , representing the per capita growth rate and reciprocal carrying capacity of the tumor cells, r_2 and b_2 represent the same rates for the host cells. In addition, there are two terms which represent the competition between tumor and host cells. Based on the above description of the model, all the terms together give the following system of nonlinear ordinary differential equations:

$$\begin{aligned} \frac{dT}{dt} &= T(t)[r_1(1 - b_1 T(t)) - c_2 I(t) - c_3 H(t)] \\ \frac{dH}{dt} &= H(t)[r_2(1 - b_2 H(t)) - c_4 T(t)] \\ \frac{dI}{dt} &= s + I(t)\left[\frac{r_3 T(t)}{\alpha + T(t)} - c_1 T(t) - d_1 \right] \end{aligned} \tag{3}$$

This model describes the tumor model without drug interaction [11]. Next, we will extend the mathematical model (3) to describe the dynamical behavior of the tumor system with drug interaction. Now we add the effect of the drug on the tumor system. We denote the amount of drug at the tumor site at time t by $D(t)$. Also we assume that the drug kills all types of cells, but that the kill rate differs for every type of cell, with the response curve in all the cases given by an exponential

$$\varphi(D) = (1 - e^{-kD}) \tag{4}$$

where $\varphi(D)$ is the fractional cell kill for a given amount of drug D , at the tumor site and k is positive real constant.

We denote the response system coefficients by a_1 ; a_2 and a_3 . Now let us add these terms to the system (3) as well as an equation for $D(t)$, the amount of drug at the tumor site. This can be determined by the dose given $v(t)$, and a per capita decay rate of the drug once it is injected. This decay rate incorporates all the pathways of elimination of the drug. Therefore, tumor system with drug interaction can describe the following system of nonlinear differential equations

$$\begin{aligned} \dot{T}(t) &= T(t)[r_1(1 - b_1 T(t)) - c_2 I(t) - c_3 H(t) - \alpha_1(1 - e^{-D(t)})] \\ \dot{H}(t) &= H(t)[r_2(1 - b_2 H(t)) - c_4 T(t) - \alpha_2(1 - e^{-D(t)})] \\ \dot{I}(t) &= s + I(t)\left[\frac{r_3 T(t)}{\alpha + T(t)} - c_1 T(t) - d_1 - \alpha_3(1 - e^{-D(t)})\right] \\ \dot{D}(t) &= v(t) - d_2 D(t). \end{aligned} \tag{5}$$

Where d_2 is per capita death rate of the drug amount. Next we look at the linear stability analysis of both tumor and tumor with drug systems. Also, we study the optimal control of the

tumor system with drug using the dose $v(t)$ as control variable and tumor, host, immune cells and drug as state variables.

3. Reduction of the system parameters

In this subsection, we will reduce the system parameters by defining new variables and new system parameters. Now, the following new variables are used to reduce the number of the system parameters from 16 to 12 only:

$$x_1 = b_1T(t), \quad x_2 = b_2H(t), \quad x_3 = \frac{d_2}{s}I(t), \quad v(t) = d_2u(t), \quad x_4 = D(t), \quad \tau = d_2t \quad (6)$$

where the new system parameters are related to old system parameters by the following relations:

$$\begin{aligned} \dot{x}_1 &= x_1[k_1(1 - x_1) - n_2x_3 - n_3x_2 - m_1(1 - e^{-x_4})] \\ \dot{x}_2 &= x_2[k_2(1 - x_2) - n_4x_1 - m_2(1 - e^{-x_4})] \\ \dot{x}_3 &= 1 + x_3 \left[\frac{k_3x_1}{v_1+x_1} - n_1x_1 - v_2 - m_3(1 - e^{-x_4}) \right] \\ \dot{x}_4 &= u - x_4. \end{aligned} \quad (7)$$

where the new system parameters are related to old system parameters by the following relations:

$$\begin{cases} k_i = \frac{r_i}{d_2}, & m_i = \frac{\alpha_i}{d_2}, & (i = 1,2,3) & n_1 = \frac{c_1}{d_2b_1} & v_2 = \frac{d_1}{d_2} \\ n_2 = \frac{c_2s}{d_2^2}, & n_3 = \frac{c_3}{b_2d_2}, & n_4 = \frac{c_4}{b_1d_2}, & v_1 = \alpha b_1 \end{cases} \quad (8)$$

The system (7) is more simple than (5) for the mathematical study since the number of system parameters has been reduced from 16 to 12 only.

4. Stability of the equilibrium states

The present section is devoted to study the linear stability of the tumor system whit drug.

(1) The first equilibrium state is given by $E_1 = \left(0,0,\frac{1}{v_2},0\right)$. The eigenvalues of the Jacobian matrix about this position are

$$\begin{aligned} \gamma_1 &= k_1 - \frac{n_2}{v_2} \\ \gamma_2 &= k_2 \\ \gamma_3 &= -v_2 \\ \gamma_4 &= -1 \end{aligned}$$

It is to verify whether two of these eigenvalues are positive if $k_1 > \frac{n_2}{v_2}$ so this equilibrium point is absolutely unstable.

(2)The second equilibrium state is given by $E_2 = (0, 1, \frac{1}{v_2}, 0)$. The eigenvalues of the Jacobian about this position are

$$\gamma_1 = k_1 - \frac{n_2}{v_2}$$

$$\gamma_2 = -k_2$$

$$\gamma_3 = -v_2$$

$$\gamma_4 = -1$$

It is easy to verify that the system is absolutely unstable if $k_1 > \frac{n_2}{v_2}$.

(3) The third equilibrium state is given by $E_3 = (a, 1, \frac{k_1(1-a)}{n_2}, 0)$, where the values of a are the real roots of the cubic equation:

$$n_1 n_2^2 x_1^3 + (v_2 + 2n_1 + n_1 v_1 - k_3) n_2 k_1 x_1^2 + (n_1 k_1 - n_2 - k_1 k_3 + v_1 v_2 k_1 + n_1 v_1 k_1 + v_2 k_1) k_1 x_1 - k_1^2 (1 + v_1) = 0$$

which has exact three roots giving three equilibrium states; among them at least one real root yields at a real equilibrium state and the eigenvalues of the Jacobian about this state are

$$\gamma_1 = k_2 - n_4 a$$

$$\gamma_2 = \frac{n_2(\delta - 1) - k_1^2 a(1 - a)}{2k_1(1 - a)}$$

$$\gamma_3 = \frac{n_2(-\delta - 1) - k_1^2 a(1 - a)}{2k_1(1 - a)}$$

$$\gamma_4 = -1$$

Where

$$\delta = \{(n_2^2 + k_1^4 a^2 (1 - a)^2 + 2k_1^2 n_2 a(1 - a) + 4k_1^3 a(1 - a)^3 [n_1(v_1 + a)^2 - k_3 v_1]) / n_2^2 (v_1 + a)\}^{\frac{1}{2}}$$

Since, the first eigenvalue of the Jacobian can be positive or negative depending upon the value of the parameters k_2, n_4 , so this equilibrium state is absolutely unstable if $k_2 > n_4 a$ and further the stability analysis of this equilibrium state depends on the two other eigenvalues.

(4) The fourth equilibrium state of the tumor system with drug is given by

$$E_4 = (0, 0, \frac{1}{v_2 + m_3(1 - e^{-d})}, d) \text{ where } x_4 = d = u \neq 0 \text{ which is absolutely unstable if}$$

$$k_1 + k_2 > (m_1 + m_2)(1 - e^{-d}) - n_2 [v_2 + m_3(1 - e^{-d})]^{-1}$$

(5)The fifth equilibrium state of the tumor system with drug is given by

$$E_5 = (0, \frac{k_2 - m_2(1 - e^{-d})}{k_2}, \frac{1}{v_2 + m_3(1 - e^{-d})}, d) \text{ where } x_4 = d = u \neq 0, \text{ which is absolutely unstable if}$$

$$k_1 + k_2 > (m_1 + m_2)(1 - e^{-d}) - n_2 [v_2 + m_3(1 - e^{-d})]^{-1} + n_3 m_2 (1 - e^{-d}) / k_2$$

4. Optimal drug for the tumor

In this section, we will study the problem of optimal control of the tumor system with drug. We consider the effect of chemotherapy to our tumor system. For the purpose of optimal control, we will use Pontryagin minimum principle and measure theory. Since the state of the tumor system with drug is given by x_i with equilibrium states $x_i = \bar{x}_i$; ($i=1,2,3,4$). If $u = u(t)$ is the control variable, state equations that typifies potentially unstable behavior are

$$\begin{aligned} \dot{x}_1 &= x_1 [k_1(1 - x_1) - n_2x_3 - n_3x_2 - m_1(1 - e^{-x_4})] \\ \dot{x}_2 &= x_2 [k_2(1 - x_2) - n_4x_1 - m_2(1 - e^{-x_4})] \quad (9) \\ \dot{x}_3 &= 1 + x_3 \left[\frac{k_3x_1}{v_1 + x_1} - n_1x_1 - v_2 - m_3(1 - e^{-x_4}) \right] \\ \dot{x}_4 &= u - x_4 \end{aligned}$$

without any amount of drug, the tumor system with drug is absolutely unstable. The target of this section to be reached in a given time T is the equilibrium state with an optimal drug. Hence, the initial and final conditions are $x_i(0) = x_{i0}$, $x_i(T) = \bar{x}_i, i=1,2,3,4$

Next, we select the cost function as the one that penalizes the usage with large magnitude and define the cost by

$$J = \frac{1}{2} \int_0^T [\beta(u - \bar{u})^2 + \sum_{i=1}^4 \beta_i(x_i - \bar{x}_i)^2] dt, \quad (10)$$

Where $\beta, \beta_i, (i = 1,2,3,4)$, are positive constants.

In the next section the analytical solution, using the Pontryagin minimum principle and in the end, we use measure theory to solve it.

4.1. Solution of the problem using Pontryagin minimum principle

We now go through the procedure of applying Pontryagin minimum principle. First, we replace the cost integral (10) by an additional state variable $x(t)$, which satisfies the state equation

$$\dot{x} = \frac{1}{2} [\beta(u - \bar{u})^2 + \sum_{i=1}^4 \beta_i(x_i - \bar{x}_i)^2] \quad (11)$$

Next, we introduce the five co-state variable $\rho_i, (i = 0,1,2,3,4)$ and so the Hamiltonian function is given by

$$H = \rho_0 \dot{x} + \sum_{i=1}^4 \rho_i \dot{x}_i, \quad (12)$$

Substituting (9) and (11) in (12) we get

$$H = \rho_0 [\beta(u - \bar{u})^2 + \sum_{i=1}^4 \beta_i(x_i - \bar{x}_i)^2] / 2 + \rho_1 x_1 [k_1(1 - x_1) - n_2x_3 - n_3x_2] + \rho_2 x_2 [k_2(1 - x_2) - n_4x_1] + \rho_3 x_3 \left[\frac{k_3x_1}{v_1 + x_1} - n_1x_1 - v_2 \right] + \rho_4 (u - x_4) - (1 - e^{-x_4}) \sum_{i=1}^3 \rho_i m_i x_i + \rho_3, \quad (13)$$

The Hamilton equations are

$$\dot{\rho}_0 = -\frac{\partial H}{\partial x} = 0, \quad \dot{\rho}_i = \frac{\partial H}{\partial x_i}, \quad \frac{\partial H}{\partial u} = 0 \quad i = 1,2,3,4 \quad (14)$$

The other pair of Hamilton equations are just the state Eq. (9) and (11). Without the loss of generality, we can choose $\rho_0 = -1$. Substituting (13) in (14), the co-state equations can be derived in the following form:

$$+m_1\rho_1(1 - e^{-x_4}) ,$$

$$\dot{\rho}_2 = \gamma_2(x_2 - \bar{x}_2) + n_3x_1\rho_1 - \rho_2[k_2(1 - 2x_2) - n_4x_1] + m_2\rho_2(1 - e^{-x_4}), (15)$$

$$\dot{\rho}_3 = \gamma_3(x_3 - \bar{x}_3) + n_2x_1\rho_1 - \rho_3[k_3x_1/(v_1 + x_1) - n_1x_1 - v_2] + m_3\rho_3(1 - e^{-x_4}),$$

$$\dot{\rho}_4 = \gamma_4(x_4 - \bar{x}_4) + \rho_4 + (m_2x_2\rho_2 + m_1x_1\rho_1 + m_3x_3\rho_3)e^{-x_4},$$

The control function that has to be used is determined from the condition $\frac{\partial H}{\partial u} = 0$. Hence, we get

$$u = \bar{u} + \frac{\rho_4}{\gamma} \quad (16)$$

Substituting (16) in (9), we get the nonlinear controlled state system

$$\begin{aligned} \dot{x}_1 &= x_1[k_1(1 - x_1) - n_2x_3 - n_3x_2 - m_1(1 - e^{-x_4})] \\ \dot{x}_2 &= x_2[k_2(1 - x_2) - n_4x_1 - m_2(1 - e^{-x_4})] \\ \dot{x}_3 &= 1 + x_3 \left[\frac{k_3x_1}{v_1 + x_1} - n_1x_1 - v_2 - m_3(1 - e^{-x_4}) \right] \\ \dot{x}_4 &= -x_4 + \bar{u} + \rho_4/\gamma, \end{aligned} \quad (17)$$

This system of nonlinear differential equations form a complete system to solve the optimal control of the tumor system with drug. This system has the following boundary conditions:

$$x_i(0) = x_{i0} , \quad x_i(T) = \bar{x}_i , \quad \rho_i(T) = 0 \quad i = 1,2,3,4. \quad (18)$$

Next, we look at the numerical integration of the nonlinear systems (17) with the boundary conditions (18) using Runge-Kutta numerical method with step size 0.01.

4.2. approximate solution of the problem using Measure Theory

Assume:

$$x(t)=(x_1(t), x_2(t), x_3(t), x_4(t)),$$

$$f(t, x, u) = \left[\beta(u - \bar{u})^2 + \sum_{i=1}^4 \beta_i(x_i - \bar{x}_i)^2 \right] / 2$$

$$g_1(t, x, u) = x_1[k_1(1 - x_1) - n_2x_3 - n_3x_2 - m_1(1 - e^{-x_4})] (19)$$

$$g_2(t, x, u) = x_2[k_2(1 - x_2) - n_4x_1 - m_2(1 - e^{-x_4})]$$

$$g_3(t, x, u) = 1 + x_3 \left[\frac{k_3 x_1}{v_1 + x_1} - n_1 x_1 - v_2 - m_3(1 - e^{-x_4}) \right]$$

$$g_4(t, x, u) = u - x_4$$

$$g(t, x, u) = (g_1(t, x, u), g_2(t, x, u), g_3(t, x, u), g_4(t, x, u)),$$

$$x(0) = x_0 = (x_{10}, x_{20}, x_{30}, x_{40}), \quad U = [a, b], \quad x(T) = \bar{x} = (\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4), \quad J = [0, T],$$

Also A as a cell in R^4 , take:

$$\forall t \in J \quad x(t) \in A.$$

In this optimal control problem (19), it can totally be written as:

$$\text{Min } \int_0^T f(t, x, u) dt$$

$$\text{s.t: } x' = g(t, x, u) \quad t \in J = [0, T] \quad (20)$$

$$x(0) = x_0, \quad x(T) = \bar{x}_i \quad u \in U,$$

Where f and g are continuous functions over $Q = J \times A \times U$.

Assume that the control function $u(t): J \rightarrow U$ is measurable, $x(\cdot)$ is called a $u(\cdot)$ circuit. Whereas it is absolutely continuous and is applicable to the control system (20). Hence, control-circuit couples $S(\cdot) = (x(\cdot), u(\cdot))$ is called an admissible couple. If the u is the control function and x is a circuit for u that $x(0) = x_0$ and $x(T) = \bar{x}$, the total admissible couples are demonstrated by W . function $I: W \rightarrow R$ is defined as follows:

$$I(s) = \int_J f(t, x, u) dt$$

Therefore, classic optimal control problem (20) is transformed into optimal control problem:

$$\text{Min } I(s)$$

$$\text{s.t: } s \in W \quad (21)$$

Now the optimal control problem above is transformed into an optimal control problem in the measure theory. Assume B is an open set in R^5 including $A \times J$ and $C^1(B)$ are the collection of all the continuous function derivatives over B which in itself and their partial derivatives of the first rank on B are bounded, for each $\varphi \in C^1(B)$ the function of φ^g over the Q is defined as follows:

$$\varphi^g(t, x, u) = \varphi_x(t, x)g(t, x, u) + \varphi_t(t, x) \quad (22)$$

Therefore, we have:

$$\int_J \varphi^g(t, x, u) dt = \varphi(t_b, x_b) - \varphi(t_a, x_a) = \Delta\varphi, \quad (23)$$

In this particular state if $h(t, x, u)$ is a real continuous function over the Q so that it is just time-dependent:

$$\int_J h(t, x, u) dt = a_h, \tag{24}$$

The constant number a_h is the Lebesgue integral value of the function h over J .

Now, we assume that J^0 is the internal points of J and $D(J^0)$ is the space of all the real functions of infinite derivative compact base in J the functions ψ_j $j=1, 2, 3,$ and 4 , ψ_j over Q is defined as follows:

$$\psi_j(t, x, u) = x_j \Phi'(t) + g_j(t, x, u) \Phi(t) \quad \forall \Phi \in D(J^0)$$

Where g_j and x_j for $j=1,2,3,4$ are the components of the function g and x in the equation (19). In this case using integration by parts we have:

$$\int_J \psi_j(t, x, u) dt = 0, \quad j=1,2,3,4 \tag{25}$$

Equations 23-25 show the properties of the admissible couples. Such as the admissible couple s , we have:

$$\Lambda_s : F \rightarrow \int_J F(t, x, u) dt$$

A linear positive functional is over space $C(Q)$, the $C(Q)$ is the space of continuous real functions on Q . hence, for each acceptable couple s , there is a positive linear functional Λ_s which is applicable to the following properties:

$$\begin{aligned} \Lambda_s(\varphi^g) &= \Delta\varphi & \varphi \in C^1(B) \\ \Lambda_s(h) &= a_h & h \in C_1(Q) \\ \Lambda_s(\psi_j) &= 0 & \psi_j \in D(J^0), \quad j = 1,2,3,4 \end{aligned} \tag{26}$$

Where $C_1(Q)$ is a sub space of $C(Q)$ which these sets of functions are time dependent.

Assume that W_1 is the set of all the linear positive functions over $C(Q)$ which is applicable to the properties mentioned above. According to the Reiss theorem, there is corresponding positive measure for each function over Q which is applicable to the following conditions:

$$\begin{aligned} \mu(\varphi^g) &= \Delta\varphi & \varphi \in C^1(B) \\ \mu(h) &= a_h & h \in C_1(Q) \\ \mu(\psi_j) &= 0 & \psi_j \in D(J^0), \quad j = 1,2,3,4 \end{aligned}$$

The total measures which are applicable to the conditions above are shown by W_1 . Thus, choosing the linear function $\varphi: W_1 \rightarrow R$ and inserting in the following relation:

$$\varphi(\mu) = \int_Q f d\mu = \mu(f)$$

Classic optimal control problem is transformed into a new optimization problem in the measure theory, i.e. minimum of function φ over W_1 , so we have:

Theorem:

optimal problem in the measure theory, i.e.:

$$\begin{aligned} & \text{Min } \varphi(\mu) \\ & \text{s. t: } \mu \in W_1 \end{aligned}$$

has an answer such as $\mu^0 \in W_1$ (proof in [6]).

Obviously, the solution of the classic optimal problem, i.e. $\mu^0(f)$, is the same solution as the main optimal problem. For the calculation of its approximate value, we do as follows:

Primarily, we divide the length of each interval related with components t, x_1, x_2, x_3, x_4, u to a number of equal sub intervals, in this case Q is partitioned to sub cell $Q_j, (j = 1, 2, \dots, n)$. We choose point $Z_j = (t_j, x_{1j}, x_{2j}, x_{3j}, x_{4j}, u_j)$ in the region Q_j and assume $\sigma = \{Z_j ; j = 1, 2, \dots, n\}$, in this case σ is a density subset in Q . it can be proved that through choosing constant natural numbers N, M_1, M_2 , and M_3 the approximate value $\mu^0(f)$ is the solution to the linear planning problem with finite dimension [6]:

$$\begin{aligned} \text{Min } & \sum_{j=1}^N \alpha_j f(z_j) \\ \text{s.t: } & \sum_{j=1}^N \alpha_j \varphi_i^g(z_j) = \Delta \varphi_i && i = 1, 2, \dots, M_1, \\ & \sum_{j=1}^N \alpha_j h_i(t_j) = a_i && i = 1, 2, \dots, M_2, \\ & \sum_{j=1}^N \alpha_j \psi_{ki}(z_j) = 0 && i = 1, 2, \dots, M_3, \quad k = 1, 2, 3, 4 \\ & \alpha_j \geq 0, && j = 1, 2, \dots, N \end{aligned}$$

In which $a_i = \int_j h_i(t) dt, i=1, 2, \dots, M_2$.

For more simplification in the calculations functions φ_i, h_i and ψ_{ki} can be chosen as follows:

$$\Phi(i) = \begin{cases} x_1^k & i = 4k - 3 \\ x_2^k & i = 4k - 2 \\ x_3^k & i = 4k - 1 \\ x_4^k & i = 4k \end{cases} \quad i = 1, 2, \dots, M_1,$$

$$h_i(t) = \begin{cases} 1 & t \in (\frac{i-1}{M_2}, \frac{i}{M_2}) \\ 0 & \text{o.w} \end{cases} \quad i = 1, 2, \dots, M_2,$$

Also, functions Φ_i which is used for definition of functions ψ_{ki} can be chosen as follows:

$$\Phi_i = \begin{cases} \sin(2k\pi t) & i = 4k - 3, 4k - 2 \\ 1 - \cos(2k\pi t) & i = 4k - 1, 4k \end{cases}$$

Assuming $M = M_1 + M_2 + 2M_3$, linear planning problem containing N the variable M is unknown and solving it and calculating the coefficients α_j the approximate control function can be proved using the method proposed by Rubio [6].

5. Numerical solution

In this part nonlinear optimal control problem can be solved using the methods already mentioned and the diagrams of optimal values of tumor cells, healthy cells, immune cells, optimal dosage of drug in the tumor system with drug, in terms of primary variables and the proposed parameters are obtained:

$$\begin{aligned} k_1 = 30, k_2 = 48, \quad k_3 = 29, \quad n_1 = 2, n_2 = 1.3, n_3 = 0.47, n_4 = 8, m_1 = 9, \quad m_2 = 15 \\ m_3 = 4, \quad v_1 = 0.25, v_2 = 10, \gamma_1 = 10, \gamma_2 = 20, \gamma_3 = 8, \gamma_4 = 5, \gamma = 15, \quad x_1(0) = 2.5 \\ x_2(0) = 0.25, x_3(0) = 1.55, x_4(0) = 1.35, \quad T = 0.125 \end{aligned}$$

1- The optimal diagrams obtained Pontryagin minimum principle:

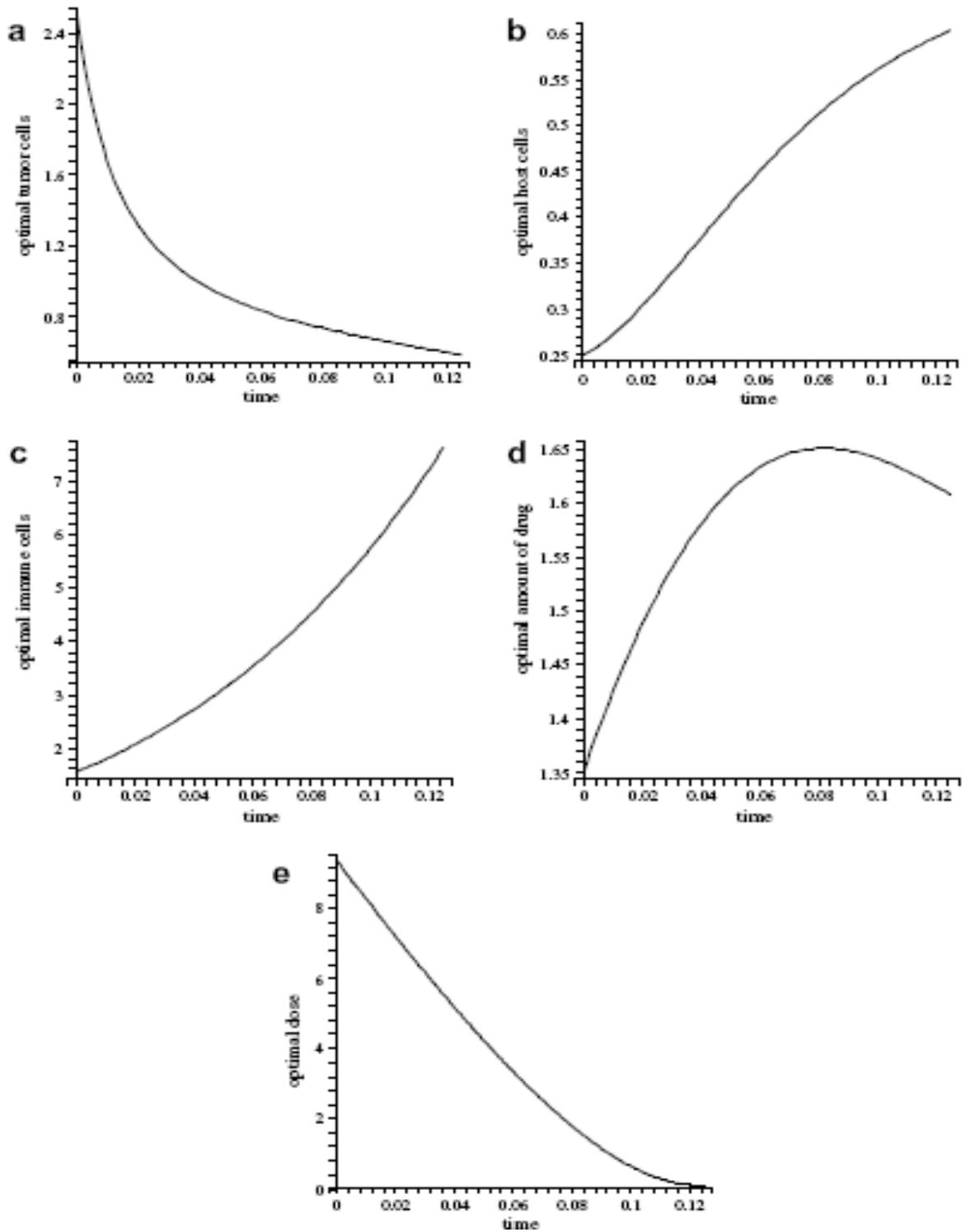


Fig. 1. (a) Optimal density of tumor cells. (b) Optimal density of host cells. (c) Optimal density of immune cells. (d) Optimal amount of drug. (e) Optimal dose of drug.

2- The optimal diagrams obtained Measure Theory:

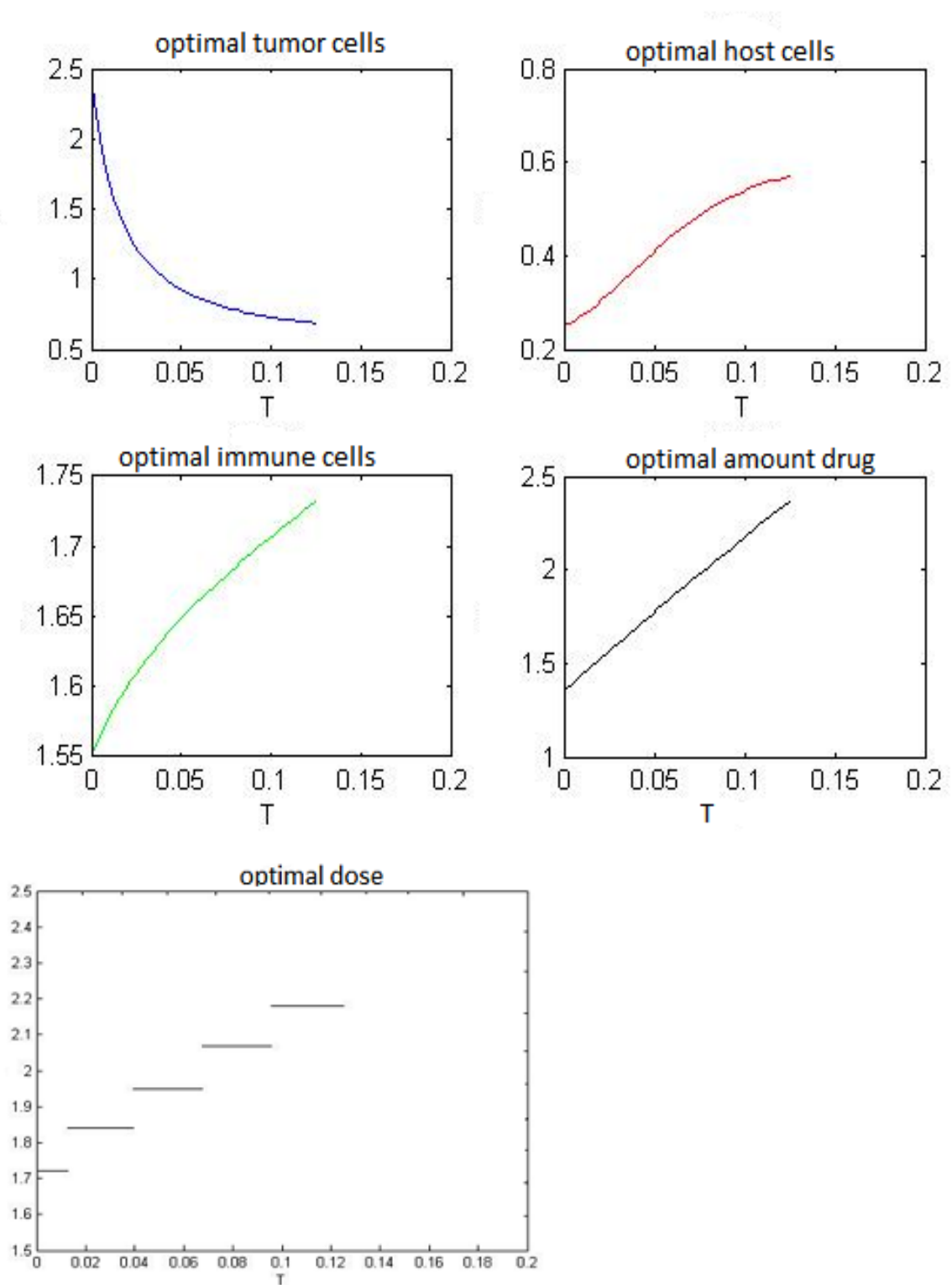


Fig. 2. (a) Optimal density of tumor cells. (b) Optimal density of host cells. (c) Optimal density of immune cells. (d) Optimal amount of drug. (e) Optimal dose of drug.

References

- [1]El-Gohary, A., Chaos and optimal control of equilibrium states of tumor system with drug, Chaos, Solitons& Fractals, 2009; 14: 425-435.
- [2]El-Gohary, A., chaos and optimal control of cancer self-remission and tumor system steady states, Chaos, solitons& Fractals, 2008;37(5):1305-16.
- [3]Dingli, D., Cascino, D., Josic, K., Russell, J., Bajzer, Z., Mathematical modling of cancer radiovirtherapy, Math Biosci, 2006:199:55-78.
- [4]Mehmat,L., Metin U., Salamci, Stephan P.Banks, Optimal control of drug therapy in cancer treatment, Nonlinear Analysis 71, 2009; e1473-e1486.
- [5]Kirschner, D., Panetta, J., modeling immunotherapy of tumor-immune interaction, J. Math.Biol., 1998;37(3):e235-52.
- [6]Rubio, J. E., Control and Optimization: The Linear Treatment of nonlinear problems, Manchester Univercity Press,1986.
- [7]Alavi, S.A., Kamyad, A.V., Farahi, M.H., Optimal control of an inhomogeneous heat problem by using measure theory, Iranian international journal science, 2000, 55-78.