Research Article

Mathematical model based assessment of the cancer control by chemo-immunotherapy

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Abstract

This work is an approach to check the controllability and observability for a mathematical model of immunotherapy and chemotherapy for cancer treatment. The measured output of tumor cells and the input is interleukin-2 (IL-2) in the first model. The measured output of effectors cell and the input is interleukin-2 (IL-2) in the second model, interferon- α ($IFN-\alpha$) and their combinations. These models are used to treat for the control purpose of cancer treatment. A control system can only be used in the form of closed-loop control to stabilize the system. The concept of controllability and observability for the linearized control is used to have a feedback control. Our contribution in chemo/immuno and concurrent chemo immunotherapy shows that the chemo/immuno sequence is more effective while concurrent chemo immunotherapy. Cancer control aims to reduce the incidence, morbidity and mortality of cancer and to improve the quality of life of cancer patients in a defined population, through the systematic implementation of evidence-based interventions for prevention, early detection, diagnosis, treatment, and palliative care.

Keywords: Controllability; Chemotherapy; Immunotherapy; Interleukin-2; Interferon- α ($IFN-\alpha$); Observability; Tumor cell

Introduction

Mathematics is a branch of science because of its role in developing other branches of science. Its involvement enriches the field. Biomathematics is one of its major examples. It is obvious that it cannot be developed without the help of a mathematician. Hence the involvement of mathematics in Biosciences is mandatory for its progress and development [1]. Controllability is concerned to the opportunity of forcing the system into a particular state by using suitable control of

signal. If a state is not convenient, then no signal will be capable to control the state. Observability is associated to the possibility of examining through output capacity, the state of the system. If a state is not visible the controller will never be able to establish the behavior of an unobservable state and cannot use it to claim the system. The final step in the control system proposed problem is to understand the mathematical model of a controller by a general physical device. A control system

can only be used in the form of closed loop controlled to stabilize the system [2, 3].

Out of control cell growth is known as cancer. The mechanism of the destruction and establishment of cancer is yet a puzzle. Advanced treatments like surgery, radiotherapy and chemotherapy, but still relapses occur. Hence, the more advanced treatment is very obvious. The major aim is to attempts for developing schemes with other therapy methods and immunotherapy or its combination, that are useful for reducing the heightening tumor immunogenicity, tumor mass and removing the imuno suppression during the process of tumor growth. By immunotherapy recent progress in this line has been achieved, which refers to the use of cytokines usually together with adoptive cellular immunotherapy (ACI) [4, 5].

Chemotherapy is used for treatment of cancer through drugs. Chemotherapy drugs directly destroy cancer cells by acting either on cancer sites or through bloodstream [6]. Immunotherapy increases antitumor resistance and give better immune system condition. Three major categories of immunotherapy are already used in cancer immunotherapy [7-10].

The aim is to choose the correct schedule with the combination of immune modifiers as $IL-2$ and interferon $-\alpha$ ($IFN-\alpha$) therapy by using chemotherapy. When immunotherapy is administered right after

the cardiovascular disease, it was observed that the concurrent chemo immunotherapy is almost as effective a chemo/immune sequence. At the same time, the concurrent chemo immunotherapy is found to be less toxic than these quintal regimens [7]. Consider the mathematical model of immunotherapy. The model description is effector cell, tumor cell, $IL-2$ and second model is chemo-immunotherapy. The four ordinary differential equations model gets affected by treatments chemotherapy, interleukin-2 and adoptive immunotherapy of immune response to tumor growth. The numerical solution of this model describes the complex situation of different treatment. Our main work is to check the controllability and observability of this mathematical model of immunotherapy and chemotherapy [4, 5].

Materials and methods

Model of immunotherapy

The kirschner model was used to simulate the interaction between three parameters, effector cells, x , tumor cells, y , interleukin $IL-2$, z . The model predicts real situations in cancer patients [4].

$$\frac{dx}{dt} = cy - u_2x + \frac{p_1xz}{g_1+z} + s_1 \quad (1)$$

$$\frac{dy}{dt} = r_2y(1 - by) - \frac{axy}{g_2+y} \quad (2)$$

$$\frac{dz}{dt} = \frac{p_2xy}{g_3+y} - u_3z + s_2 \quad (3)$$

Following is the (Table 1) of parameters values.

Table 1. Value of Parameters of the models

Parameter	Value	Description
C	0.00005	Antigenicity of tumor
s_1	0	Adoptive immunotherapy term, a constant influx
s_2	96000000	$IL-2$ therapy term, a constant influx
u_2	0.03	Fixed constant
u_3	10	Fixed constant
r_2	0.18	Fixed constant
g_1	20000000	Fixed constant
g_2	100000	Fixed constant
g_3	1000	Fixed constant
A	1	Fixed constant
B	0.000000001	Fixed constant
p_1	0.1245	Fixed constant
p_2	5	Fixed constant

Model after parameter substitution takes the form as

$$\frac{dx}{dt} = 0.00005y - 0.03x + \frac{0.1245xz}{2 \times 10^7 + z} \quad (4)$$

$$\frac{dy}{dt} = 0.18y(1 - 1 \times 10^{-9}y) - \frac{1xy}{100000+y} \quad (5)$$

$$\frac{dz}{dt} = \frac{5xy}{1000+y} - 10z + 96000000 \quad (6)$$

From equation (4)-(6) substitutes left hand side equal to zero, we get the equilibrium point $(x, y, z) = (0, 0, 9.6 \times 10^6)$. Hence equilibrium point lie in feasible region, so system is stable.

The linearized model is about stability point as

$$\begin{aligned} \frac{dx}{dt} &= 0.0100378378x + 0.00005y + 2.84194667 \times 10^{-9}z \\ \frac{dy}{dt} &= 0.18y \\ \frac{dz}{dt} &= -10z \end{aligned}$$

Linear control system

A linear system whose inputs are forced to change in a desired manner as time progresses. A mathematically linear control system is given by the following two equations

$$\begin{aligned} \dot{x}(t) &= Px + Qv, & t \in I \\ y(t) &= Sx, & t \in I \\ x(t) &\in \mathbb{R}^n, v(t) \in \mathbb{R}^p \text{ and } y(t) \in \mathbb{R}^k \end{aligned}$$

for $t \in I$. The matrices $P(t)$, $Q(t)$ and $S(t)$ are defined on I and have correct dimensions (i.e., $P(t)$ is $n \times n$, $Q(t)$ is $n \times p$ and $S(t)$ is $k \times n$ matrices). I is closed interval $I = [t_0, t_e]$, $t_0 < t_e < \infty$ respectively $I = [t_0, \infty)$. Suppose the elements of the matrices $P(\cdot)$, $Q(\cdot)$ and $S(\cdot)$ are in $L^2(I; \mathbb{R})$. The $n \times np$ controllability matrix is given by $R = [P, PQ, P^2Q, P^3Q, \dots, P^{n-1}Q]$. The rank (i.e. $(R) = n$), so the system is said to be controllable. The $nk \times n$ the observability

matrix is given by $O = [S, SP, SP^2, SP^3, \dots, SP^{n-1}]^T$. The rank (i.e. $\text{rank}(O) = n$), so the system is said to be observable [2, 3, 11]. Then $w = [x, y, z]^T$ and $P =$

$$\begin{bmatrix} 0.0100378378 & 0.00005 & 2.84194667 \times 10^{-9} \\ 0 & 0.18 & 0 \\ 0 & 0 & -10 \end{bmatrix}$$

Here by taking the only measured output of tumor cells and the only input is interleukin-2 then $Q = [0, 0, 1]^T$ and $S = [1, 0, 0]$. The matrix for controllability is $R = [Q; PQ; P^2Q]$ and its rank is 2. The matrix for observability is $O = [S \ SP \ SP^2]^T$ and its rank is 3. Hence concluded that the system is not controllable but observable.

Chemo immunotherapy model

The model for cancer treatment consists of four ordinary differential equations of immune reaction to tumor growth this gets affected by treatments chemotherapy, interleukin-2 and adoptive immunotherapy. In the model $X(t)$, $Y(t)$, $Z(t)$, $\lambda(t)$, T represents the effector cell, tumor cell, immunotherapy, chemotherapy and time t respectively.

$$\frac{dx}{dt} = cy - \mu_1x + p_1 \frac{xz}{g_1+z} - C_x(1 - e^{-\lambda})x + S_1 \quad (7)$$

$$\frac{dy}{dt} = r_1y(1 - by) - \frac{axy}{g_2+y} - C_y(1 - e^{-\lambda})y \quad (8)$$

$$\frac{dz}{dt} = \frac{p_3xy}{g_3+y} - \mu_2z + S_2 \quad (9)$$

$$\frac{d\lambda}{dt} = V(t) - v\lambda \quad (10)$$

Where

$$C_y = C_y^{\text{chemo}}(1 - e^{-z/z_0}) \quad \text{and} \quad C_x = C_x^{\text{chemo}}(1 - e^{-z/z_0})$$

Following is the (Table 2) of parameters values.

Table 2. Parameter value of the model

Parameter	Value/units	Parameter	Value/units
C	0.035days^{-1}	C_x^{chemo}	0.6days^{-1}
g_1	$2 \times 10^7 \text{pg/l}$	C_y^{chemo}	0.9days^{-1}
p_1	0.124days^{-1}	p_3	$5\text{pg/cells} \times \text{days}$
r_1	0.18days^{-1}	g_3	$1 \times 10^3 \text{cells/ml}$
B	$1 \times 10^{-9} \text{cells/ml}$	μ_2	10days^{-1}
A	1day^{-1}	V	1day^{-1}
g_2	$1 \times 10^5 \text{cells/ml}$	V	6.4days^{-1}
μ_1	0.03days^{-1}	S_1	0
S_2	96000000		

After substitution parameter value in (7) - (10)

$$\frac{dx}{dt} = 0.035y - 0.03x + 0.1245 \frac{xz}{2 \times 10^7 + z} - 0.6(1 - e^{-z/0})(1 - e^{-\lambda})x + 0$$

$$\frac{dy}{dt} = 0.18y(1 - 1 \times 10^{-9}y) - \frac{xy}{1 \times 10^5 + y} - 0.9(1 - e^{-z/0})(1 - e^{-\lambda})y$$

$$\frac{dz}{dt} = \frac{5xy}{1 \times 10^3 + y} - 10z + 96000000$$

$$\frac{d\lambda}{dt} = 1 - 6.4\lambda$$

The equilibrium point of the model is $(x, y, z, \lambda) = (0, 0, 9.6 \times 10^6, 0.15625)$. Hence equilibrium point lie in feasible region, so system is stable. The linearized model according to equilibrium point is

$$\frac{dx}{dt} = -0.13758x + 0.035y + 2.841946 \times 10^{-9}z$$

$$\frac{dy}{dt} = -0.310189y$$

$$\frac{dz}{dt} = 0$$

$$\frac{d\lambda}{dt} = -6.4\lambda$$

Here $x = [X, Y, Z, \lambda]^T$

and $P =$

$$\begin{bmatrix} -0.013758 & 0.035 & 2.841946 \times 10^{-9} & 0 \\ 0 & -0.310189 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -6.4 \end{bmatrix}$$

Three different cases are calculated according to the treatment.

For case 1

The measured output of effector cell and the input interleukin $IL-2$ is used, then $Q = [0, 0, 1, 0]^T$ and $S = [1, 0, 0, 0]$. The rank of controllability and observability matrix is 2 and 3 respectively. Hence the system is neither controllable nor observable.

For case 2

The only measured output of effector cell and the input chemotherapeutic drug is used, then $Q = [0, 0, 0, 1]^T$ and $S = [1, 0, 0, 0]$. The rank of controllability and observability matrix is 1 and 3 respectively. Hence the system is neither controllable nor observable.

For case 3

The measured output of effector cell, the input interleukin $IL-2$ and chemotherapeutic drug are used, then $Q = [0, 0, 1, 1]^T$ and $S = [1, 0, 0, 0]$. The rank of controllability and observability matrix is 3 and 3 respectively. Hence the system is neither controllable nor observable.

Results and discussion

Treated the linear system if it is controllable and observable, then a nonlinear system may or may not be controllable and observable. So, if a nonlinear system is neither controllable nor observable then a new model will be design. Controllability of combined treatment is considered to discuss the condition for local controllability of nonlinear model in given time interval. The method presented by Jerzy and Andrzej [12] is quite general and covers a wide class of semilinear dynamical control systems. Therefore, similar constrained controllability results may be derived for more general class of semilinear dynamical control systems in [12]. Most of literature in this direction has been mainly concerned with controllability problems for finite dimensional nonlinear dynamical systems with unconstrained controls and

without delays or for linear dynamical systems with constrained controls and delays. Similarly, Kaczorek [13] presents controllability, observability and duality results for continuous and discrete positive linear dynamical systems. The results are given in the (Table 3). First model the system is observable but not controllable. For second model, considering both Chemotherapy drug and Interleukin-2 as input and effector cell as an output. Observe that model is partially controllable and

observable in third case. The ranks of controllability matrix are improved. It should be noted that model is partially controllable and observable in each case. It means rank is improved by taking chemo-immunotherapy treatment. In this paper model is treated for fully controllability and observability in given time interval for effect of combined therapy in the cancer treatment. The results clearly show that the combined therapy is more beneficial for cancer treatment.

Table 3. Results of controllability and observability

Description of Model	Rank of Controllability matrix	Rank of Observability matrix
Model 1 (n=3): Input is interleukin-2 and tumor cells is only output	3	2
Model 2 (n=4): Case 1, Input is interleukin-2 and tumor cells is only output	2	3
Case II, Input is chemotherapy drug and tumor cells is only output	1	3
Case III : Input is Chemotherapy drug and Interleukin-2 and tumor cells is only output	3	3

Conclusions

Three different cases are discussed according to input value. For case1, Interleukin-2 as input and effector cell is used as output. In this case the system is neither controllable and nor observable. For case 2, Chemotherapy drug as input and effector cells used as output. In this case the system is neither controllable nor observable. For case 3, Chemotherapy drug and Interleukin-2 used as input and effector cell is an output. In this case the system is neither controllable nor observable. Model is partially controllable and observable in case 3. Its rank of controllability is improved. It means that by taking both important particular as an input it has more effect on immune system to control the cancer disease.

Authors' contributions

Conceived and designed the experiments: MU Saleem, Performed the experiments: MU Saleem & M Farman, Analyzed the data: MA Meraj, Contributed materials/ analysis/ tools: MA Meraj & A Ahmad, Wrote the paper: M Farman & A Ahmad.

Reference

1. Friis E & Jensen B (2007). Modeling and Simulation of Glucose-Insulin Metabolism, technical university of Denmark informatics and mathematical modeling.
2. Saleem MU (2011). Controllability and Observability in Glucose Insulin Systems in Human, PhD Thesis, Karl-Franzens University, Graz, Austria.
3. Saleem MU, Farman M & Meraj MA (2016). A linear control of Hovorka Model. *Sci Int (Lahore)* 28(1): 15-18.

4. Banerjee S (2008). Mathematical Model of Immunotherapy with Interleukin-2. *Int J Appl Math Comput Sci* 18(3): 389–398.
5. Rana US & Baloni J (2014). Mathematical Modeling of Strategic Treatments on Tumor Growth, Global Journal of Science frontier Research. *Mathematics and Decision Sci* 14(3): 90-99.
6. Namazi H, Kulish V & Wong A (2015). Mathematical Modelling and Prediction of the Effect of Chemotherapy on Cancer Cells, Scientific Reports 5, Article number: 13583.
7. Isaeva OG & Osipov VA (2007). Different strategies for cancer treatment: mathematical modeling a Bogoliubov Laboratory of Theoretical Physics, Joint Institute for Nuclear Research, 141980, Dubna, Moscow region, Russia.
8. Buzaid AC & Atkins M (2001). Practical guidelines for the management of biochemotherapy-related toxicity in melanoma. *Clin Cancer Res* 7: 2611-2619.
9. Buzaid AC (2000). Strategies for combining chemotherapy and biotherapy in melanoma. *Cancer Control* 7(2): 185-197.
10. Rosenberg SA & Lotze MT (1986). Cancer immunotherapy using interleukin-2 and interleukin-2-activated lymphocytes. *Annual Review of Immunology* 4: 681-709.
11. Coron JM (2007). Control and nonlinearity, American Mathematical society, volume 136.
12. Jerzy KI & Andrzej S (2013). Controllability of a model of combined anticancer therapy. *Control and Cybernetics* 42: 123-138.
13. Kaczorek T (2002). Positive 1D and 2D Systems. Springer-Verlag, London.