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An Optimal Control of Bone Marrow in Cancer Chemotherapy by Artificial Neural Networks

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Abstract

Although neural network models for cancer chemotherapy have been analyzed since the early seventies, less research has been done in actually formulating them as optimal control problems. In this paper an artificial neural networks-based method for optimal control of bone marrow in cell-cycle-specific chemotherapy is proposed. In this method, we use artificial neural networks for approximating the optimal control problem which maximizes both bone marrow mass and drug's dose at the same time. The corresponding model be transfer to Hamiltonian function and using Pontryagin principle we create the boundary conditions. After defining boundary conditions, we use the approximating property of artificial networks and put the boundary conditions in error functions to satisfy the limitations..

Keywords: *Optimal control, Bone marrow, Cancer chemotherapy, Artificial neural networks.*

1. Introduction

Chemotherapy is a category of cancer treatment that uses chemical substances, especially one or more anti-cancer drugs (chemotherapeutic agents) that are given as part of a standardized chemotherapy regimen. Since two decades ago we have seen a lot of researches in terms of cancer chemotherapy [1-5]. Almost in most of them, administering drugs was their first priority. All of us know cancer is one of the biggest challenges which human has faced with it. This disease hurts a lot of part in the body, but maybe the most important one is bone marrow damaging. While biomedical research concentrates on new drugs and treatments, mathematicians analyze the models for the purpose of testing various treatment strategies and searching for the optimal ones. After early, simple structures were considered [6], classes of models which are cell-cycle-specific were developed. These so-called compartmental models, introduced in the nineties [7] and analyzed further recently [8, 9], divide the cell-cycle into clusters, called compartments, which allow to model drug applications at the stages where they are the most effective.

The bone marrow produces blood cells which is containing both white and red globules. So defensing and oxygen transporting duties could be damaged by this matter. There are some treatments for facing this issue. One of these treatments is chemotherapy, which our focus is on the cell-cycle-specific kind of it, in which chemotherapies' drugs will act only in …. Phase of cell's life time. For reaching this purpose we use a known model. Pantta [10] and, Fister and Panetta [11] had introduced a model and then analyzed it. They used dynamical control system which includes both active and resting phases of cell-cycle to analyze the effect of cell-cycle-specific chemotherapy. This system is as:

$$\begin{cases} \dot{X}(t) = (\gamma - \delta - \alpha - su(t))X(t) + \beta Q(t), \\ \dot{Q}(t) = \alpha p(t) - (\lambda + \beta)Q(t) \end{cases} \quad (1)$$

Where $p(.)$ and $Q(.)$ are the proliferating and quiescent cells mass in the bone marrow respectively, and bounded measurable function $u(.)$ shows the drugs treatment which takes values in interval [0,1] and acts only on the proliferating cells. Moreover, the parameters are all considered constant, positive, and are defined as follows. γ , cycling cells' growth rate; α , transition rate from proliferating to resting; δ , natural cell death; β , transition rate from resting to proliferating; λ , cell differentiation-mature bone marrow cell leaving the bone marrow and entering the blood stream as various types of blood cells; and s, the strength or effectiveness of the treatment. Note that $u(.)$ is control function and $u(t) = 0$ means no drug is injected at time t while $u(t) = 1$ means maximum rate is used.

Noori Skandari et al [12] use Alamir and Cheyron constraint suggestion [11, 13] and exploit the following optimal control problem:

$$\begin{aligned} &Maximize \quad I(X,Q,u)=\int_0^T (3X(t)+3Q(t)-(1-u(t))^2)dt \\ &Subject \quad to \quad \dot{X}(t)=(\gamma-\delta-\alpha-su(t))X(t)+\beta Q(t), \\ &\dot{Q}(t)=\alpha X(t)-(\lambda+\beta)Q(t), \quad 0\le u(t)\le 1 \\ &X(0)=X_0, \quad Q(0)=Q_0, \quad t\in[0,T] \end{aligned} \tag{2}$$

Where X_0 and Q_0 are initial values of the proliferating and quiescent cells mass in the bone marrow respectively.

Moreover, the proliferating and quiescent cells mass in final time T is $p(T)$ and $Q(T)$, respectively. Note that T is the therapy interval and it is equal to 3. The rest of the numerical values are taken from [11]:

$$\gamma=1.47\ ,\ \alpha=5.64\ ,\quad \lambda=0.16\ ,\quad \delta=0$$
$$\beta=0.48\quad ,\quad X_0=1\quad ,\quad Q_0=1\ ,\ s=1$$

In the last decade, artificial neural networks and other elements of soft computing and artificial intelligence played an important role in solving hard to solve problems arising in science and engineering phenomenons. Applying the mentioned methods in many contests was successful, and the results were comparable with the other results obtained by mathematical algorithms. In [14] an approximated solution of optimal control problems, based on the neural network approach is presented. Researchers use measure theory to solve the corresponding model. But we use an approximating method base on artificial neural networks to solve and analyze it. But the thing is that the cell-cycle-specific chemotherapy's model has two state variables. So this paper introduces a new method for facing the problem.

In paper we create artificial neural networks structures and define a suitable error function to optimal control of bone marrow in cancer chemotherapy. The structure of paper is as follows: In Section 2, we transform optimal control problem. In Section 3, basic structure of proposed method is defined. In Section 4, final step of proposed method is defined. Section 5 is including experimental result and finally section 6 contains concluding.

2. Binderies

By replacing numerical values in (2) we have:

$$\begin{aligned} &Minimize \quad I(p,Q,u)=\int_0^T (-3X(t)-3Q(t)+(1-u(t))^2\,dt \\ &Subject \quad to \quad \dot{X}(t)=-4.17X(t)-u(t)X(t)+0.48Q(t), \\ &\dot{Q}(t)=5.64X(t)-0.64Q(t), \quad 0\le u(t)\le 1 \\ &X(0)=1, \quad Q(0)=1, \quad t\in[0,T] \end{aligned} \tag{3}$$

As you see the signs of the primary model are changed. We did that because model (2) is a maximizing model so by changing the signs, we made it to a minimizing model.

Now we have the model and it is time to solve it. We use pontryagin's boundary conditions to reaching this purpose. First of all we create the Hamiltonian equation of the corresponding model. You can see it as:

$$\begin{aligned} &H(X,Q,u,p_1,p_2,t)=(-3X(t)-3Q(t)+(1-u(t)^2))+ \\ &p_1(-4.17X(t)-u(t)X(t)+0.48Q(t))+ \\ &p_2(5.64X(t)-0.64Q(t)) \end{aligned} \tag{4}$$

Where p_1 and p_2 are two necessary control-state variable and we will find their value.

PMP says any answer which addresses the following condition, is the true answer of an optimal control problem. For equation (3) PMP conditions can be exploited as:

$$\begin{cases} \dfrac{\partial H}{\partial X}=-3-4.17p_1-u(t)p_1-u(t)p_1+5.64p_2=-\dot{p}_1(t) \\ \dfrac{\partial H}{\partial Q}=-3+0.48p_1+0.64p_2=-\dot{p}_2(t) \\ \dfrac{\partial H}{\partial p_1}=-4.17X(t)-u(t)X(t)+0.48Q(t)=\dot{X}(t) \\ \dfrac{\partial H}{\partial p_2}=5.64X(t)-0.64Q(t)=\dot{Q}(t) \\ \dfrac{\partial H}{\partial u}=2u(t)-2-X(t)p_1=0 \end{cases} \tag{5}$$

Before any other step we need to define artificial neural networks. These neural networks must have a suitable structure. For this purpose we use multi-layer perceptron. You can see a basic perceptron below:

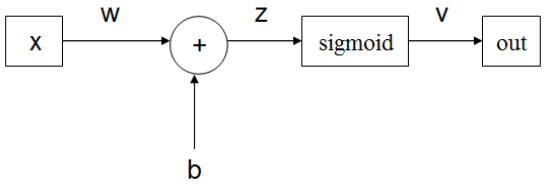

Fig 1. A basic perceptron.

Here W is the weight vector of input layer, b is a vector containing bias weights, and V is the output layer weights. It can be observed that we can calculate the output from the following formulation:

$$\begin{cases} out=\sum_{i=1}^{k} v_i\sigma(z_i) \\ z_i=\sum_{i=1}^{k} w_i x+b_i \end{cases} \tag{6}$$

Where k is the number of sigmoid units. The activation function here is the sigmoid function in the following formula:

$$\sigma(x)=\frac{1}{1+e^{-x}} \tag{7}$$

Based on Kolmogorov theorem, it is proved that we can implement any continuous function with a multi-layer perceptron (for more details, see [15]). According to this theorem, we use the ability of neural networks in function approximation, to approximate the state, co-state and control function for optimal control problem (3).

3. Basic structures

We define an artificial neural network for each variable. It means for X , Q , p_1 , p_2 , u we have n_X , n_Q , n_{p_1} , n_{p_2} , n_u which every single of them has its own adjustable parameter. The structures of corresponding neural networks are written below:

$$\begin{cases} n_X=\sum_{i=1}^{i} v_X^i\sigma(z_X^i), \quad z_X^i=w_X^i t+b_X^i t \\ n_Q=\sum_{i=1}^{i} v_Q^i\sigma(z_Q^i), \quad z_Q^i=w_Q^i t+b_Q^i t \\ n_{p_1}=\sum_{i=1}^{i} v_{p_1}^i\sigma(z_{p_1}^i), \quad z_{p_1}^i=w_{p_1}^i t+b_{p_1}^i t \\ n_{p_2}=\sum_{i=1}^{i} v_{p_2}^i\sigma(z_{p_2}^i), \quad z_{p_2}^i=w_{p_2}^i t+b_{p_2}^i t \\ n_u=\sum_{i=1}^{i} v_u^i\sigma(z_u^i), \quad z_u^i=w_u^i t+b_u^i t \end{cases} \tag{8}$$

For $i=1,2,...,I$ where I is the number of neurons that can be different for each neural network.

It is supposed that defined artificial neural networks must produce their corresponding vectors. But there is still an important thing which is not included in the basic structure of solution. Optimal control model (3) has some limitation. One of these limitations is the first value of variables. In this case it must be $X(0)=1$ and $Q(0)=1$ so we should change the basic structures in which they can address these limitations. For reaching this purpose we define trial solutions which can make changes to final output. For this problem trial solution can be define in as what you see below:

$$\begin{cases} X_T=X_0+(t-t_0)n_X \\ Q_T=Q_0+(t-t_0)n_Q \\ p_{1_T}=(t-t_f)n_{p_1} \\ p_{2_T}=(t-t_f)n_{p_2} \\ u_T=n_u \end{cases} \tag{9}$$

We know vector p shows the constraint and also we can see that Eq.(3) is free at the ending points. It means it is not necessary to reach any specific value at the ending points. In the other word, we have $p_T^{t_f}=0$ so for p_{1_T} and p_{2_T} we omitted t_f from the interval which in artificial neural networks produce the answers.

Next step is considering PMP conditions Eq. (5). They will be considered in the error functions and also in the minimizing step. We will discuss about them in the next season.

4. Final step

In this section we discuss about the other limitations and also the rest of the process.

We have defined the Hamiltonian function before. Now by replacing trial solutions into the Hamiltonian function (4), we can define a trial Hamiltonian H_T which is conventional Hamiltonian function H where we replaced the functions X , Q , p_1 , p_2 and u by their corresponding trial format. This Hamiltonian function is:

$$\begin{aligned} &H_T(X_T,Q_T,u_T,p_{1_T},p_{2_T},t)=(-3X_T(t)-3Q_T(t)+(1-u_T(t))^2)+ \\ &p_{1_T}(-4.17X_T(t)-u_T(t)X_T(t)+0.48Q_T(t))+ \\ &p_{2_T}(5.64X_T(t)-0.64Q_T(t)) \end{aligned} \tag{10}$$

Function (10) contains the weights of neural network. Since the trial solutions Eq. (9) must satisfy conditions

$$\begin{cases} \frac{\partial H}{\partial X_T}+\dot{p}_{1_T}=0 \\ \frac{\partial H}{\partial X_T}+\dot{p}_{2_T}=0 \\ \frac{\partial H}{\partial p_{1_T}}-\dot{X}_T=0 \\ \frac{\partial H}{\partial p_{2_T}}-\dot{Q}_T=0 \\ \frac{\partial H}{\partial u_T}=0 \end{cases} \tag{11}$$

To solve the system (11), we define five error functions corresponding to each equation:

$$\begin{cases} E_1(\phi,t) = \left[\dfrac{\partial H_T}{\partial X_T} + \dot{p}_{1_T}\right]^2 \\ E_2(\phi,t) = \left[\dfrac{\partial H_T}{\partial Q_T} + \dot{p}_{2_T}\right]^2 \\ E_3(\phi,t) = \left[\dfrac{\partial H_T}{\partial p_{1_T}} - \dot{X}_T\right]^2 \\ E_4(\phi,t) = \left[\dfrac{\partial H_T}{\partial p_{2_T}} - \dot{Q}_T\right]^2 \\ E_5(\phi,t) = \left[\dfrac{\partial H_T}{\partial u_T}\right]^2 \end{cases} \quad (12)$$

And eventually a total error function

$$E(\phi,t) = E_1(\phi,t) + E_2(\phi,t) + E_3(\phi,t) + E_4(\phi,t) + E_5(\phi,t) \quad (13)$$

Where ϕ is a vector containing all weights of five neural networks (8). Moreover, ϕ contains all weights w_X , w_Q , w_{P_1} , w_{p_2} , w_u , b_X , b_Q , b_u , b_{p_1} , b_{p_2} , b_u , v_X , v_Q, v_{p_1}, v_{p_2} and v_u . Now instead of solving Eq. (11), we discretize the interval $[t_0, t_f]$ (by m points) and solve the following unconstrained optimization problem:

$$\min_{\phi} \quad \sum_{k=1}^{m} E(t_k, \phi) \quad (14)$$

To solve (14), which is an unconstrained optimization problem, we can use any optimization algorithms such as steepest descent, Newton, or Quasi-Newton methods as well as the heuristic algorithms such as GA (genetic algorithm) or particle swarm optimization, etc.

After terminating the optimization step, we can replace the optimal values of the weights / (containing the weights of input and output layer and the bias vector) into the Eq. (8) and conclude the trial structures of state, co-state and control functions.

5. Experimental results

This is the first time that anybody uses this method to solve the dynamical optimal control problem of cell-cycle-specific chemotherapy. We have said about the other researches in term of optimal control of cell-cycle-specific chemotherapy before, but now we have not discussed about their result. In this season we show our results and compare those with the others works. What you see below is our simulation results:

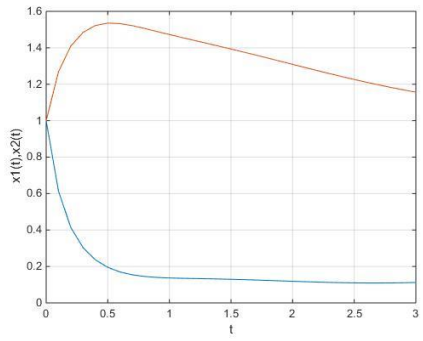

Fig 2. Optimal states X (top) and Q (bottom) for problem (3).

And the optimal states for [12] were:

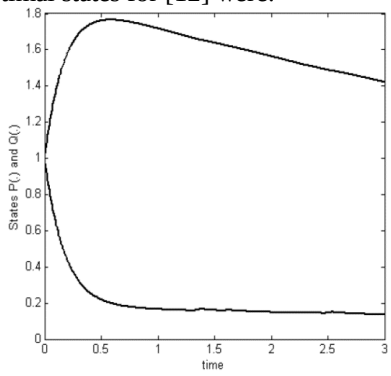

Fig 3. Optimal states

We know that cancer is caused by none-stop proliferating of cells, so the cells which are in the rest phase does not need to be stopped. As you can see, the mass of the cells in resting phase (Q) for both of them is almost the same, which shows our method dose not hurts healthy cells. Meanwhile for proliferating cells mass (X) we have decreasing about 0.23 which shows we saved healthy cells and at the same time didn't allow to proliferating cells to continue their process.

For problem (3) we have control function u as:

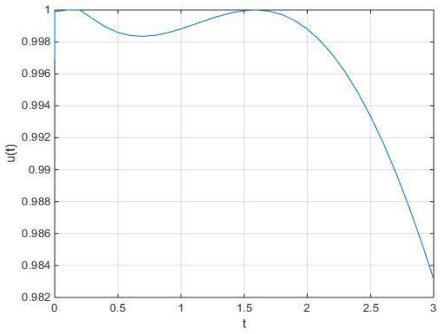

Figure 4. Control function u for problem (3)

And co-states are:

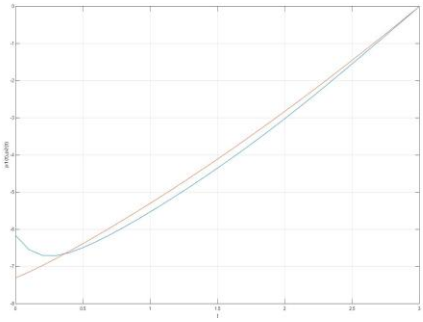

Figure 5. Co-states (p_1 and p_2) for problem (3)

Not that it was supposed to be $p_T^{t_f} = 0$ and as you can see it is. That's because of being free at the ending points.
And finally we have the error function as:

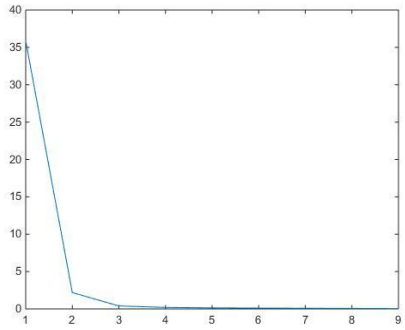

Figure 6. Final error function.

As you can see the final error is really near to zero.

6. Conclusions

In this paper we analyzed a model for cancer chemotherapy that aims at minimizing the damage done to bone marrow cells during the chemotherapy. We introduced a method based on artificial neural networks for controlling the bone marrow dynamics in cell-cycle-specific cancer chemotherapy. We defined 5 adjustable artificial neural networks. Then we used pontryagin's (PMP) conditions and introduce our boundary conditions then we put them into the error functions. Our work has some advantages including simplicity of implementation of the algorithm, reaching more accuracy by using more hidden layer and finally more accuracy comparing measure theory.

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