Observer based feedback control of a biodynamical model of tumor growth with sampled measurements

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Abstract—This paper deals with the cancer treatment scheduling via observer-based feedback control of a tumor growth biodynamical model. An experimental nonlinear model is utilized to design a control algorithm. This model was validated by a pharmacological study on xenograft models obtained by transplantation of colon carcinoma cell lines in athymic mice. Input-output feedback linearization approach is used to linearize the nonlinear model of the system and design a control law. It is assumed that tumor weight can be measured in definite intervals. So a continuous-discrete observer is designed to estimate states of the system based on discrete sampled data which are tumor weight in this case. To investigate the effect of the drug on the normal cells, a body weight toxicity model is considered to be checked during the simulation. Finally, a discrete chemotherapy dose schedule is proposed. Simulation results show the effectiveness of the proposed observer-controller algorithms.

I. INTRODUCTION

Cancer is known as one of the major causes of death among people all around the world and according to WHO, it is anticipated to increase to 13.1 million deaths worldwide until 2030. Hence, developing mathematical models that provides a profound insight into the behavior of this disease and predicts the response of the patient to chemotherapy schedules would result in much more effective treatment plans. Over the last five decades enormous effort has been devoted to propose drug dosage schedules for cancer treatment. A broad variety of control synthesis methods have been employed to design effective control laws which determines the measure and frequency of drug administration during the treatment period. Due to existence of many constraints available in the problem, there are many references in the area of optimal control which consider the problem as an optimization one. The objective of these optimization problems, mostly, is minimization of the tumor population ([1]–[7]); however minimizing the total amount of drug ([8]–[14]); drug toxicity indices ([15], [16]) or maximizing the population of normal or immune cells ([17]–[19]) are also considered in the cost function in some cases. In [4] Martin proposed a low intensity therapy which is followed by a high intensity therapy by solving the optimal control problem numerically to minimize the population of cancerous cells. In [11] Itik et al. applied State Dependent Riccati Equation (SDRE) based optimal control technique to a nonlinear model which included normal tissue, tumor and immune cells. SDRE method was utilized to minimize the amount of drug used and drive the population of cancer cell toward the healthy equilibrium point of the system. Also Chen et al. employed model predictive control (MPC) and moving horizon estimation approach (MHS) for optimal scheduling of cancer chemotherapy and estimation of the states. The aim for this optimization problem was reducing the number of tumor volume as rapidly as possible, and finally, a continuous profile of the drug was proposed in [20]. Although sophisticated, but these open loop controllers, designed by optimal control algorithms, do not have the capability to be modified during the treatment. Hence, a closed loop controller calculating drug dosage based on the feedback from the system is more appreciated. This paper deals with input-output feedback linearization method to find an appropriate closed loop profile for dosage of anticancer agent during chemotherapy treatment. Moreover, in order to engage discrete measurements of tumor weight in the calculation, a continuous-discrete observer has been utilized to make more precise estimations for the states of the system and consequently control signal. Most of the available studies in this area propose a continuous profile for drug concentration as in ([4], [12], [20]). Although these control schemes are sophisticated, but they are based on an assumption which is not consistent with the real clinical constraints and hardly feasible. However, there are some studies which consider this issue in their study. Khaloozadeh et al. in 2008 proposed a dosage regimen for patients suffering from breast cancer using optimal fuzzy programming. In this study a profile with four discrete levels for drug dosage was suggested for different stages of treatment [21]. Also, in another study published by them in 2008, they employed optimal control to find a single level of dosage for each cycle of chemotherapy. Harrold et al. in 2009 published a study in which they used mixed integer programming method to find discrete dosage directly. They used a theoretical system and a preclinical mouse model to demonstrate the effectiveness and clinical relevance of their proposed methodology [23]. In 2011, Minelli et al. discussed controlled drug delivery in cancer immunotherapy. They treated a fifth order model containing tumor immune interaction with both continuous and discrete optimal control approach. In 2015, Gholami et al. suggested an interval type-2 fuzzy controller and a semi-continuous profile for drug delivery that is able to diminish the effects of incomplete and uncertain information in the system [24]. This study aims discrete dosage which
is more practical in clinical context. This paper includes a validated pharmacokinetic (PK) and pharmacodynamic (PD) model for growth of colon carcinoma cells in athymic mice; furthermore, due to the fact that the normal cells are also adversely affected by administration of anticancer agent, a toxicity model for overall body weight is considered in the simulations. Section 2 presents mathematical modeling of the system. Control scheme synthesis, observer design and discretization methodology for drug dosage are discussed in section 3. Also, simulation results are presented in section 4. Finally, some concluding remarks and future directions are given in section 4.

II. DESCRIPTION OF THE MODEL

An experimental nonlinear model validated in a pharmacological research on xenograft models by Simeoni et al. [25] is used in this study. In their research, the model was obtained by transplantation of colon carcinoma cell lines in athymic mice. Also, Effect of CPT-11 drug was investigated on this model and an appropriate pharmacokinetic model for describing the dynamics of the injected drug in body was acquired. Details of mathematical explanations of these models are discussed in the two following subsections. Since injected drug damages both cancer cells and normal cells, a toxicity model based on overall body weight of mice is considered to be checked during the simulation. Mathematical description of this model is discussed in the last subsection of this part.

A. Tumor growth modeling

Cycling cells growth model is made as an exponential growth followed by a linear function. For the case under our consideration, the switching point occurs at 3 gr for tumor weight but due to the fact that during the simulation, tumor weight never exceeds this value, so the exponential term is sufficient for description of the tumor growth. Administration of anticancer agents makes some of the cancer cells nonproliferating and brings them into death through many consequent stages. Fig. 1 demonstrates the scheme of the model. In this model $x_1(t)$ introduces the portion of cancer cells in the cycling stage. Drug affects the tumor by a term proportional to $c_2(t)x_1(t)$ which is added to decrease tumor growth rate i.e. $c_2$ represents drug concentration of anticancer agent. Similar to other signal transduction processes, a transit compartment model is used for describing the delayed death of tumor perturbed by drug treatment. After being affected by drug, cancer cells are getting damaged progressively through $n$ stages (considered 3 for our case) until they die completely. Portion of the cells in each of these stages are presented by $x_2$ to $x_{n+1}$ shown in Fig. 1. $\lambda_0, k_1$ and $k_2$ characterize the exponential growth of tumor weight, first order rate of transit and measure of drug potency, respectively. $\lambda_0 = 0.146 \text{ day}^{-1}, k_1 = 0.469 \text{ day}^{-1}$ and $k_2 = 8.42 \times 10^{-3} \text{ ml ng}^{-1} \text{ day}^{-1}$ were computed in [25] by studying the xenograft models obtained by inoculation of colon carcinoma cell lines into athymic mice. Total tumor weight is indicated by $N$.

$$\begin{align*}
\dot{x}_1(t) &= \lambda_0 x_1(t) - k_2 c_2(t) x_1(t) \\
\dot{x}_2(t) &= k_2 c_2(t) x_1(t) - k_1 x_2(t) \\
\dot{x}_3(t) &= k_1 (x_2(t) - x_3(t)) \\
\dot{x}_4(t) &= k_1 (x_2(t) - x_4(t)) \quad (1) \\
N(t) &= x_1(t) + x_2(t) + x_3(t) + x_4(t) \\
x_1(0) &= N_0, x_1(0) = x_2(0) = x_3(0) = x_4(0) = 0
\end{align*}$$

B. Pharmacokinetic modeling

A pharmacokinetic model with two compartments shown in 2 was studied in [25] for i.v. bolus injection of anticancer agent, CPT-11, to describe dynamics of the drug in body. Pharmacokinetic parameters are $V_1 = 4.85 \text{ liter kg}^{-1}, V_2 = 8 \text{ liter kg}^{-1}, k_{10} = 0.533h^{-1}, k_{12} = 0.0115h^{-1}$ and $k_{21} = 0.0616h^{-1}$. Drug dosage is characterized by $D$ in the equations. In two compartmental pharmacokinetic models, body is assumed to be divided into central and peripheral compartments. Drug is administered into the central part and then distributed into peripheral parts and finally achieves an equilibrium between two compartments [26]. Plasma concentration of drug in the peripheral part perturbs tumor growth which is presented by $c_2$.

$$\begin{align*}
\dot{c}_1(t) &= k_{21} c_2(t) \frac{V_2}{V_1} - k_{12} c_1(t) - k_{10} c_1(t) + \frac{D(t)}{V_1} \quad (2) \\
\dot{c}_2(t) &= k_{12} c_1(t) \frac{V_1}{V_2} - k_{21} c_2(t)
\end{align*}$$

C. Toxicity modeling

Drug administration not only affects tumor cells but also makes loss in bodyweight so a minimum allowable value for body weight must be considered in simulations. According to experimental protocols a reduction of 20% of initial weight is acceptable during treatment. We considered an initial weight of 16 gr and minimum allowable weight of 12.8 gr for bodyweight according to Hadjiandreou et al. study [13]. In 3, $w_{\text{net}}$ indicates body weight excluding tumor weight and $k_g = 0.0163 \text{ day}^{-1}, k_j = 5.98 \times 10^{-4} \text{ ml day}^{-1}$ and $k_{12} = 1.83 \times 10^{-4} \text{ day}^{-1}$ are proportional constants.

$$w_{\text{net}}(t) = k_g w_{\text{net}}(t) k_{11} c_2(t) - k_{12} N(t) \quad (3)$$

III. CONTROL SYNTHESIS AND OBSERVER DESIGN

Chemotherapy treatment plan is designed by input output feedback linearization method. In order to be able to design a discrete dosage regimen, plasma concentration of drug, $c_2$, is considered as control signal in the initial steps of design. After designing control law, area under curve of plasma concentration of drug and analytical solution of pharmacokinetic equations are employed to find discrete values of drug dosage for the beginning of each day. Additionally, a
A. Input-output feedback linearization formulation

To design a control law via input output feedback linearization method, equations of the system should be reformulated and internal stability of the system has to be examined in the case that the relative degree of the system is not equal to the rank of the system. The process of designing the control law and examining the internal dynamics of the system are presented in the two following subsections, respectively.

1) Input-output feedback linearization formulation: Output of the biodynamical model of the system is the weight of the tumor which has to become minimized during the chemotherapy process. To that end, according to standard input output linearization techniques, output of the system are presented in the two following subsections, respectively.

By solving the above equations and definition of \( z_1 = y \) and \( z_2 = \dot{y} \), deforming \( T(x) \) can be found as presented by 8.

\[
T^{-1}(z_1, z_2, \eta_1, \eta_2) = [x_1, x_2, x_3, x_4]^T \quad \text{is given in (9)}.
\]

By differentiation of equations presented in 8 and replacing the state variables of the system from 9, the transformed model of the system is:

\[
\dot{z}_1 = z_2 - 2k_1 \eta_1
\]
\[
z_2 = (\lambda_0 - k_2)u (k_1 z_1 + z_2 - k_1 \eta_1) - k_1^2 (\eta_1 - \eta_2)
\]
\[
\eta_1 = z_2 - k_1 (\eta_1 + \eta_2)
\]
\[
\eta_2 = (2k_1 + k_1^2) z_1 + (1 + \frac{k_1}{\lambda_0}) z_2 - (k_1 + \frac{k_1^2}{\lambda_0}) \eta_1 - 2k_1 \eta_2
\]

Internal stability of the system is analyzed by setting \( z_1 = z_2 = 0 \) in the last two equations in 10. By substituting the values of the parameters, eigenvalues would be calculated as \( \alpha_{1,2} = -0.7035 \pm 1.1067i \). Since both of the eigenvalues have negative real parts, the internal dynamic of the system is stable.

3) Continuous-discrete observer design: None of the states of the system can be measured continuously during the treatment. As a consequence, their values are required to be estimated by an observer. However, discrete measurement of the tumor weight is possible and can be used in the observer algorithm, to modify the estimation. To that end, a continuous-discrete observer proposed in this section is
used to estimate all states of the system based on sampled measurements of tumor weight. The block diagram of the control system in combination with observer is represented in Fig. 2.

Fig. 2. Block diagram of the control system

The nonlinear biodynamical model of the system defined in previous section can be rewritten in the form of $\dot{x} = f(x) + g(x)u, y = h(x)$. To design an observer according to [27], a nonlinear transformation $w = \left[h(x)L_x(h(x)) \ldots L_x^{n-1}(h(x))\right]^T$ was applied on the states of the system. So equations of the system can be rewritten in the form of $\dot{w} = Aw + F(w, u), y = Cw$, where $A = \begin{bmatrix} 0 & L_x \\ 0 & 0 \end{bmatrix}$ and $L_x$ denotes the $(n-1) \times (n-1)$ identity matrix, $n$ is the number of the states which is 4 in our model, $F(w, u) = \psi(w, u)$ and $C = [1, 0, 0, 0]$. In these equations, $\psi(w, u) = \{0, 0, 0,0, ke_{y0}w_0 - w_2 + 3ke_{y0}w_2 - w_3 + 3k(e_{y0}w_3 - w_4) + \lambda\}$ and $\psi(w)$ is given in (11).

$$
\psi = \begin{cases}
0 & \left( k_3 \lambda_0 (-k_3^2 w_1 - 3k_3^2 w_2 - 3k_3 w_3 - w_4) \right)
\left( k_2 \lambda_0 (-k_2^2 w_1 - 3k_2^2 w_2 - 3k_2 w_3 - w_4) \right)
\left( k_1 \lambda_0 - k_1 \lambda_0 \right)^2 (k_1 + \lambda)^2
\end{cases}
$$

To estimate the states of the system, a continuous-discrete observer shown in 12 is designed to improve the feedback of the nonlinear controller. This observer includes two distinct steps. At prediction step estimation equations exactly duplicate the equations of the model and in correction step, the estimation values are improved by using values of the variables being available for measurement. This observer can estimate the states of the system exponentially [27].

$$\hat{\dot{w}} = \hat{A}w + F(\hat{w}(t), u(t)), t \in [t_k, t_{k+1})$$

$$\hat{w}(t_{k+1}) = \hat{w}(t_k) - \rho \delta S_{(\rho, \theta, \delta)}^{-1} C^T(C\hat{w}(t_k) - y(t_k))$$

In (12), $\hat{w}$ is the vector of estimated states, $\rho$ and $\theta$ are tuning parameters, $\delta$ is a positive real value which defines the time interval between discrete measurements. It is assumed that samples are measured at $t_{k+1} = t_k + \delta, k \in \{0, N\}$ and $t_{k+1}$ addresses the moment just before the measurement time. $S_{(\rho, \theta, \delta)}$ is the solution of the algebraic equation defined in 13. Due to space consideration, the detailed procedure for designing this observer is skipped here; however, it can be found in [27]. The values of $\rho$ and $\theta$ were found as $4 \times 10^6$ and 60 by trial and error to fulfill the requirements for designing an appropriate exponential observer.

$$S_{(\rho, \theta, \delta)} = e^{-\theta \delta} e^{-\theta \delta A^T} S_{(\rho, \theta, \delta)} e^{-\theta \delta A} + \rho \delta C^T C$$

**B. Dosage regimen computation**

Control law which was obtained by the previously explained method is continuous and it is not practically useful in clinical applications, so it should be discretized. Assuming one day interval for drug administration, analytical solution of the pharmacokinetic model of the drug and the area under the curve of drug concentration obtained from control law is used to determine the appropriate discrete drug dosage. For the intravenous injection of drug, the pharmacokinetic model of the system is rewritten in the form of (14) in which $c_1(t^-)$ demonstrates the moment just before the injection of the drug and $c_1(t^+)$ demonstrates the moment just after the injection of the drug dosage. $F$ equals one for CPT-11 drug and $c_1(0) = c_{01}$ and $c_2(0) = c_{02}$ are initial values for concentration of the drug in central and peripheral parts of the body, respectively.

$$
\begin{align*}
\dot{c}_1(t) &= \frac{c_{21} - c_{12} - k_{12} c_1(t) - k_{10} c_1(t)}{V_0} \\
\dot{c}_2(t) &= \frac{c_{12} - k_{21} c_2(t)}{V_1} \\
c_1(t^-) &= c_1(t^-) + F \frac{D(t)}{V_1}
\end{align*}
\tag{14}
$$

Analytical solution of the mentioned model is found as $c_1(t) = e^{-15t}(e^{1.45t} + 0.0028e^{13.6t} - 0.2e^{-15t}(e^{13.6t} - e^{1.45t}))c_{01}$ and $c_2(t) = 0.014e^{-15t}(e^{13.6t} - e^{1.45t})c_{01} + e^{-15t}(0.0028e^{1.45t} + e^{13.6t})c_{02}$. By integrating the analytical solution of $c_2$ during the first day of the treatment, we have:

$$
\int_0^1 c_2(t) dt = 0.0063c_{01} + 0.5273c_{02} \tag{15}
$$

The LHS can be found based on the control law ($c_2$) computed previously and it is a function of the states of the system. Due to the assumption that at the beginning of the treatment period, initial concentration of drug at the peripheral compartment ($c_{02}^+$) (at the moment just before and after the injection) remains zero, the only unknown value in RHS is $c_{01}^+$, which is the concentration of drug in the central compartment of the body at the moment just after the injection of the drug. Since for the first day of the treatment, $c_{01}$ at the moment just before the injection of the drug is equal to zero, the first dosage can be determined by using the formula presented in 16.

$$D(t) = F \frac{c_{01}^+ - c_{01}}{V_1} \tag{16}
$$

Values of $c_1$ and $c_2$ at the end of the first interval can be used to obtain the second amount of the drug dosage for the second interval and so on. The discrete dosage designed by this method is utilized instead of the continuous time control law obtained by feedback linearization method, and simulation results are shown in the next section.

**IV. SIMULATION RESULTS**

To reduce the tumor cell during the treatment and also retain the body weight in a suitable interval, the treatment
period was divided into three separated periods i.e. within each of them a distinct target is considered. For instance, for the first 180 days of the treatment tumor weight has to be reduced to about 0.03gr, and in the second and third periods, respectively, the target value is 0.008 and 0.001. This trend should continue until the tumor is not able to be detected. Simulation results show that this method guarantees the suitable values of body weight during treatment, because by this method the body weight after a decreasing phase shows an increasing phase which causes the subject of the treatment to stay in a normal condition. Fig. 3 demonstrates the simulation results for continuous administration of drug.

![Fig. 3. Continuous administration of drug](image)

In order to find a practical dosage for intravenous administration of the drug, the obtained results have to become discretized by the method explained before. Discrete set of drug dosage is injected to the model to check whether the tumor and body weight are still in the appropriate condition or not. Fig. 4 and Fig. 5 demonstrate the simulation results of the effect of intravenous administration of drug on the biodynamical model of the system. Fig. 5(a) and 5(b) show that discretizing the dosage by the mentioned method would not adversely affect treatment and the tumor weight and body weight status are both in the suitable conditions. For better vision of the plots, simulation results for drug concentration and body weight are shown for 60 days.

![Fig. 4. Discrete dosage and concentration presented by feedback linearization method](image)

Continuous-discrete observer is capable of estimating the states of the system for the case that they are not fully measured. Fig. 6 shows the time evolution of the estimation of tumor weight and the sampled measurements which are assumed to be available for two times per day. For the simulation tests, the tumor weight samples were corrupted by an additive noisy signal. To see the details of the curves more precisely, simulation result for estimation of tumor weight are reported for 30.

![Fig. 5. Intravenous administration of drug](image)

![Fig. 6. Evolution of estimated tumor weight and its measurements](image)

To evaluate the effect of the discrete dosage on the system with feedback from continuous-discrete observer, continuous profile of the drug concentration from previous simulation was employed to develop a discrete schedule of drug. The proposed drug profile presented in Fig. 7(b), was applied to the system and time evolution of the tumor weight and body weight and drug concentration are shown in Fig. 8 and Fig. 7(a).

![Fig. 7. Discrete dosage and concentration presented with observer feedback](image)

![Fig. 8. Continuous administration of drug with observer feedback](image)

V. CONCLUSION AND FUTURE WORKS

A mathematical approach for designing treatment plan for colon cancer chemotherapy based on a biodynamical model for tumor growth in athymic mice was addressed in
this paper. Validated pharmacokinetic and pharmacodynamic models were employed to design a control law to reduce population of the cancerous cells. Moreover, a toxicity model was examined to remain in the allowable range. Input-output feedback linearization method was employed to design the control law. To reduce the gap between the real clinical constraints and the proposed profile of treatment schedule, a discrete profile was proposed by using the area under the curve of concentration of the drug. Since the states of the systems are not fully measured, a nonlinear observer was applied to the system. To have an estimation of the states, a continuous-discrete observer was applied to use available discrete sample measurements of tumor weight for estimating the states between two successive measurements. In this paper, the model includes mathematical description for tumor growth, drug distribution and body weight; however, extended models including immune response, specifically for human, might be dealt with as future works.

REFERENCES


