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# Adaptive robust control of cancer chemotherapy in the presence of parametric uncertainties: A comparison between three hypotheses

Hamed Moradi *, Mojtaba Sharifi, Gholamreza Vossoughi

*Centre of Excellence in Design, Robotics and Automation, School of Mechanical Engineering, Sharif University of Technology, Tehran, Iran*

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ABSTRACT

In this paper, an adaptive robust control strategy is developed for the manipulation of drug usage and consequently the tumor volume in cancer chemotherapy. Three nonlinear mathematical cell-kill models including log-kill hypothesis, Norton–Simon hypothesis and $E_{max}$ hypothesis are considered in the presence of uncertainties. The Lyapunov stability theorem is used to investigate the global stability and tracking convergence of the process response. For the first time, performance of the uncertain process is investigated and compared for three nonlinear models. In addition, the effects of treatment period, initial value of tumor volume (carrying capacity) and the uncertainty amount on dynamic system behaviour are studied. Through a comprehensive evaluation, results are presented and compared for three cell-kill models. According to the results, for a wide range of model uncertainties, the adaptive controller guarantees the robust performance. However, for a given treatment period, more variation in drug usage is required as the amount of model uncertainty increases. Moreover, for both the nominal and uncertain models, less drug usage is required as the treatment period increases.



## 1. Introduction

During the drug delivery process in chemotherapy, normal healthy cells may be killed in addition to the cancer cells [1,2]. Some control strategies have been proposed for the effective killing of cancer cells and minimizing the negative aspects of drugs on healthy cells. For this purpose, drugs delivery must be regularly scheduled to maintain a specific level of the drug dosage in the body. Therefore, understanding the effects of chemotherapeutic drugs on tumors behaviour is important in development of efficient treatment strategies.

Several models have been presented for the killing of cancer tumor cells in chemotherapy process. In log-kill hypothesis as an early model, it was shown that cell killing (using the chemotherapeutic drug) is proportional to the tumor population [3]. Thus, it is shown in this hypothesis that the volume of larger tumors is reduced more rapidly than smaller tumors for a fixed dose of drug [3]. After that, in some clinical observations, the predictions of log-kill hypothesis fail in some cases such as Hodgkin's disease and acute lymphoblast leukemia (in these cases, larger tumors reduce slower than the similar smaller tumors) [4–6]. Consequently, Norton Simon hypothesis was proposed [4,5], in which the cell-kill was considered to be proportional to the tumor growth rate. Finally, in $E_{max}$ hypothesis, the cell-kill rate was assumed to be proportional to a saturable function of tumor mass [7]. This hypothesis is obtained from the fact that chemotherapy drugs must be metabolized by an enzyme before their activation. However, this metabolism is saturable because the amount of enzyme is fixed in the body.

For the above-mentioned hypotheses, open loop unconstrained and constrained control methods have been proposed [6,8–11]. As a constrained drug delivery control, bang-bang control strategy has been used for the nonlinear models. The application of feedback control with a quadratic performance criterion for the mathematical models of cancer chemotherapy has been studied in the early works [8,9]. In other researches [10,11], considering normal and tumor cells under the hypotheses of Gompertzian and logistic growth, the rate of drugs administration was controlled.

Another open-loop control strategy utilized for chemotherapy process is the control parameterization technique. In this method, optimal control problem is transformed into a numerical problem and the control variables are approximated with the constant values in specified time intervals [12,13]. Using this optimal control strategy, the dosage of specific drugs (e.g., paclitaxel) has been determined for the reduction of breast and ovarian cancers [14]. Moreover, it is concluded that treating with repeated shorter periods allows more drug to be given without excess damage to the bone marrow [14,15].

Mathematical details of optimal control techniques and their therapeutic performances in different cell-kill hypothesis including

* Corresponding author. Tel.: +98 21 66165545; fax: +98 21 66000021.
*E-mail addresses:* hamedmoradi@sharif.edu, hamedmoradi@asme.org (H. Moradi).

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treatment schedules have been studied in other researches, e.g., [6]. Moreover, some other approaches have also been investigated, such as: optimal singular control in chemotherapy [16,17], the influence of fixed and free final time of treatment on optimal chemotherapeutic protocols [18], optimal control for a stochastic model of cancer chemotherapy [19], optimal control for the tumor model with immune resistance and drug therapy [20], a comparison between linear and quadratic controls [21] and a comparison between optimal control for different models [22]. In some other researches, model simulation and experimental validation of intratumoral chemotherapy using multiple polymer implants [23], sensor-based cell and tissue screening for personalized cancer chemotherapy [24] have been accomplished. A multi-objective optimal chemotherapy control model for cancer treatment [25] has also been proposed.

It should be noted that chemotherapy processes similar to other dynamic systems are potentially accompanied with various sources of uncertainty. The dynamic model inaccuracies are in the form of structured and unstructured uncertainties; described through parametric or model (non-parametric) uncertainties, respectively. These uncertainties are due to either sensor fusion systems (direct measurement) or observers algorithms (indirect measurement). As a result, previous control strategies may not guarantee a robust performance in the presence of uncertainties and for a wide range of operating conditions, e.g., [8–14,16–22].

In a recent study [26], for achieving the robust performance against uncertainties, three control approaches including optimal linear regulation, nonlinear optimal control based on variation of extremals and $H_\infty$-robust control were developed. It was shown that $H_\infty$ controller has the most efficient performance for the uncertain plants; however its conceptual design is rather complex. For some previous linear controllers, e.g., [8–14,16–22] and two other linear controllers recently proposed in [26] ($H_\infty$-robust and optimal linear regulation), the nonlinear model should be linearized around its operating points. Therefore, choosing these operating points affects the performance of the controller, and the controller has desired performance only in the areas close to these operating points.

In this research, a nonlinear adaptive control strategy is developed for the chemotherapy process described through log-kill hypothesis, $E_{\max}$ hypothesis and Norton–Simon hypothesis. The nonlinear adaptive controllers are designed based on Lyapunov stability theorem which guarantees the global stability and tracking convergence of the problem. Unlike the linear controllers in [8–14,16–22,26] that require the linearization around the operating points, the proposed nonlinear controller does not require linearization and its performance is not related to some operating points or areas. As a result, the nonlinear controller could achieve to its goal with the desired performance independent from the points (or states) during the process.

Moreover, unlike the previous works, parametric uncertainties associated with the dynamic models are also included. It should be mentioned that the linear controllers [8–14,16–22,26] are affected from the parameters of the original nonlinear model and their uncertainties especially in linearization procedure. However, for the proposed nonlinear adaptive controller, the nonlinear model parameters are considered to be completely uncertain and their magnitudes do not affect the controller design. The amount of tumor volume is manipulated by adaptive variation of drug usage. For the first time, performance of the uncertain process is investigated and compared for three nonlinear models (with an adaptive controller). In addition, the effects of treatment period, initial value of tumor volume (carrying capacity) and the uncertainty amount on dynamic system behaviour are studied. Results are presented and compared for three cell-kill models.

## 2. Cell-kill models in cancer chemotherapy process

As it is mentioned, several approaches have been developed for modeling the process of tumor cells killing; which is also called chemotherapeutic induced cell-kill. In an early work by Schabel, Skipper and Wilcox, it was hypothesized that cell-kill due to a chemotherapeutic drug was proportional to the tumor population [3]. This hypothesis was obtained based on in-vitro studies in the murine leukemia cell-line L1210. According to this hypothesis, a specified dose of drug kills a constant fraction of the cells independently from the tumor size. Moreover, there is a relationship between the drug dosage and the percentage of the killed leukemia cells. Consequently, large tumors are diminished more rapidly than smaller tumors with a specific dosage of drug. This proposed hypothesis is called as the log-kill mechanism in the literature. This model is valid for experimental leukemia because the growth dynamics of the cancer is constant during the course of observation. However, it failed when applied to the experimental solid tumors of human in which tumor size approached a plateau level (in which tumor dynamics is approximated by Gompertzian growth curves) [27,28].

After that, Norton and Simon [4,5] found that the log-kill model contradicts some clinical observations, such as acute lymphoblastic leukemia and Hodgkin's disease. In these cases, reduction in small tumors was histologically faster than in similar larger tumors. Consequently, Norton and Simon hypothesized that the cell-kill is proportional to the growth rate of the tumor (e.g., as an exponential, logistic, or Gompertzian functions). In a recent work, a simple realistic biophysical model of tumor growth in the presence of a constant continuous chemotherapy is studied, and it was shown that if an extended Norton–Simon hypothesis holds, the system may have multiple equilibria [29]. Therefore, the tumor carrying capacity and/or the drug pharmacodynamics (and/or the drug pharmacokinetics) are affected by the bounded stochastic fluctuations which cause the transition from a small equilibrium to a far larger one, not compatible with the life of the host. Finally, in another hypothesis, it was mentioned that some chemotherapeutic drugs must be metabolized by an enzyme before being activated. Due to the fixed amount of enzyme, this reaction is saturable. Accordingly, Holford and Sheiner [7] proposed $E_{\max}$ hypothesis in which the cell-kill is described in terms of a saturable function of Michaelis–Menton form. The concentration effects of drugs is essentially considered and discussed in $E_{\max}$ model. This model introduces theoretical support from the physicochemical principles (by inclusion the law of mass action); governing the binding of drug to the receptor [30].

In this section, Skipper's log-kill hypothesis (called Model 1), $E_{\max}$ hypothesis (called Model 2) and Norton–Simon hypothesis (called Model 3) are considered. General dynamics of these systems is presented through differential equations as [3–6]:

$$\frac{dx}{dt} = rxF(x) - G(x,t) \tag{1}$$

where $x$ is the tumor volume, $r$ is the tumor growth rate, $F(x)$ is the generalized growth function and $G(x,t)$ describes the pharmacokinetic and pharmacodynamic effects of the drug. While the tumor burden and toxicity level are defined as the time-integral of the drug concentration, the Growth function (Gompertzian) is expressed as:

$$F(x) = \ln\left(\frac{\Theta}{x}\right) \tag{2}$$

where $\Theta$ is the constant of scaling. For the mentioned hypotheses, $G(x,t)$ is described as:

$$\text{For log} \ -\text{kill hypothesis (Model 1)} : G(x,t) = \delta\left(\frac{x}{\Theta}\right) u(t) \qquad (3-1)$$