Journal of Theoretical Biology 384 (2015) 59–69

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

On probabilistic certification of combined cancer therapies using strongly uncertain models

Mazen Alamir*

CNRS, GIPSA-LAB, Control Systems Department, University of Grenoble, 11 Rue des Mathématiques, 38400 Saint Martin d'Hères, France

HIGHLIGHTS

- A general framework for the use of the concept of probabilistic certification is proposed for combined therapy of cancer.
- It is shown that this concept is more suited when a high number of uncertain parameters are involved in the definition of the dynamic model of the cancer.
- While the proposed framework is general, and may apply to a wide class of model and control design, it is illustrated through the particular case of combined therapy of cancer involving immunotherapy and chemotherapy.
- Two design frameworks with probabilistic certification frameworks are proposed for two different criteria to be optimized, namely, the quantity of drugs being used or the total duration of the hospitalization.

ARTICLE INFO

Article history:
Received 22 February 2015
Received in revised form
9 July 2015
Accepted 11 August 2015
Available online 20 August 2015

Keywords:
Cancer therapy
Feedback design
Certification of therapy success
Randomized method
Uncertain models

ABSTRACT

This paper proposes a general framework for probabilistic certification of cancer therapies. The certification is defined in terms of two key issues which are the tumor contraction and the lower admissible bound on the circulating lymphocytes which is viewed as indicator of the patient health. The certification is viewed as the ability to guarantee with a predefined high probability the success of the therapy over a finite horizon despite of the unavoidable high uncertainties affecting the dynamic model that is used to compute the optimal scheduling of drugs injection. The certification paradigm can be viewed as a tool for tuning the treatment parameters and protocols as well as for getting a rational use of limited or expensive drugs. The proposed framework is illustrated using the specific problem of combined immunotherapy/chemotherapy of cancer.

1. Introduction

The use of dynamic models in the optimization of drug scheduling is nowadays a common practice in academic works. This long tradition involves different paradigms such as optimal control (Swan, 1988; DePillis and Radunskaya, 2001; Ledzewicz et al., 2008; Ledzewicz and Schättler, 2007, 2008; Alamir and Chareyron, 2007), predictive control (Chareyron and Alamir, 2009), robust control (Alamir, 2014) or nonlinear analytic control design (Kassara and Moustafid, 2011; Matveev and Andrey, 2002).

The dynamic models involved in such studies are typically population models that are built by concatenating functional terms (death rate, transition rates, drug effect terms to cite but few examples). Such models qualitatively capture the main phenomena and represent their strength and their interaction/coupling through dedicated parameters.

While the qualitative representativity of these models is rather easy to assess, the quantitative matching with reality strongly depends on the model parameters. The latter are unfortunately unknown for a given patient, are highly dispersed between patients and vary with time and during the therapy for a given patient.

Some recent works (Kiran and Lakshminarayanan, 2010; Jonsson et al., 2013; Alamir, 2014) started attempts to address this issue by using robust design in which the therapy is computed so that some statement can be obtained for a set of parameters rather than for the single nominal parameter vector. A robustness-like statement typically takes the following form:

The scheduled feedback therapy leads to a predefined tumor contraction for ANY *realization of the vector of parameters involved in the model within a predefined bounded set*

Therefore, robust design is based on the worst-case analysis and can lead to very conservative/pessimistic design. This is

* Tel.: +33 476826326; fax: +33 476826388.
E-mail address: mazen.alamir@grenoble-inp.fr

http://dx.doi.org/10.1016/j.jtbi.2015.08.008
0022-5193/

because the worst case is considered no matter how small its probability of occurrence is.

In order to avoid focusing on few unlikely although very bad scenarios, the probabilistic approach seeks statement of the form:

The scheduled feedback therapy leads to a predefined tumor contraction with a probability no less than $(1-\eta)\%$ *over all realizations of the parameter vector assuming that the latter obeys a given probability distribution.*

This obviously marginalizes very bad realizations if their probability of occurrence is really small.

This paper formalizes this paradigm for the specific case of cancer therapy and gives a complete and understandable instance of it in the specific case of combined therapy of cancer that involves immunotherapy and chemotherapy.

It is obvious that given the wide range of problems that can be defined in this context and various kinds of relevant models (Bozic et al., 2011; Katouli and Komarova, 2011) of combined therapies, this paper should be viewed as an introduction to a rich paradigm and a starting point to a large set of variations around the necessary specific formulation adopted in the present paper.

To be more specific, the methodology proposed in the present paper can be reproduced as soon as the following items are available:

(1) A dynamic open-loop model of the tumor evolution.
(2) A proposed feedback that is defined up to some parameters choice.
(3) A probabilistic description of the model's parameter discrepancy.
(4) A set of constraints to be respected.
(5) A criterion to be optimized.
(6) A targeted certification level.

The proposed methodology enables to compute the control parameters (involved in item 2 above) so that the criterion is optimized while guaranteeing with the prescribed level (involved in item 6 above) the satisfaction of the constraints.

The paper is organized as follows: First a general formulation of a class of cancer therapy-related problems is given in Section 2. Section 3 recalls the framework and useful results of randomized optimization approach also called the scenario-based approach. The application of this framework to the cancer problem defined in Section 2 is proposed in Section 4 in the general case. Finally, Section 5 fully illustrates the previous sections in the particular case of combined immuno/chemotherapy of cancer. The paper ends with Section 6 that summarizes the paper contribution and gives some hints for future investigation.

2. Probabilistic certification of a therapy

In this section, the concept of a cancer therapy with probabilistic certification is clearly stated.

2.1. The dynamic model

Dynamic models describing the evolution of tumors and health indicator under various therapies are generally population models. In these models, the components of the state vector x represent the size of populations (number of cells) in the various compartments that are necessary to correctly describe the mechanisms being involved.

Cancer treatment is generally a double-edged sword in the sense that aggressive drugs are necessary to achieve a high contraction rate of the tumor but, for some drugs, this generally corresponds to a high level of negative side effects. To avoid this dilemma, targeted therapies aim at accumulating therapeutic agents precisely at the tumor side by using tumor specific antibodies (Schrama et al., 2006; Brannon-Peppas and Blanchette, 2012). On a different track, the combined therapy involving chemotherapy/radiotheraoy and anti-angiogenesis recently attracted attention of many researchers (Alamir et al., 2015; Ergun et al., 2003; Gevertz, 2012; Hahnfeldt et al., 1999). Consequently, there are as many models as there are combinations of therapeutic agents, drugs and tumor specific antibodies.

Let us consider a general form of a dynamic system representing the evolution of the tumor and the number of circulating lymphocytes among other necessary quantities under a combined action of several drugs injection rates $u \in \mathbb{R}^{n_u}$:

$$\dot{x} = F(x, u, p) \tag{1}$$

where $x \in \mathbb{R}^n$ is the state of the model while $p \in \mathbb{R}^{n_p}$ stands for the vector of parameters involved in the model. It is assumed in the remainder of the present paper that

- x_1 stands for the tumor size (to be reduced).
- x_2 stands for the amount of circulating lymphocytes that is commonly used as an indicator of the patient health/resistance and therefore, any strategy has to be defined such that $x_2(t) := C(t) \geq C_{min}$ for all $t \geq 0$.

Other state components may be necessary to describe the model (namely $n \geq 2$), in particular, the description of targeted therapies might need the dynamic of auxiliary agents/antibodies to be described by dedicating some components of the state vector x to represent corresponding sub-populations. Therefore, as far as the general structure (1) of the model is used, there is no a priori restriction to the class of models (combined/targeted) that is concerned with the framework proposed in the present paper.

It is a fact however that dynamic models for combined (but not targeted) therapies are more frequently available in the literature (d'Onofrio et al., 2009; de Pillis et al., 2006; Ergun et al., 2003; Gevertz, 2012; Hahnfeldt et al., 1999). That is the reason why such a combined therapy is used for the sake of illustration in Section 5. Note however that before that section, the proposed framework has a general scope including that of targeted therapies.

It is assumed that the dynamic model (1) describes the evolution of the system under the combined effect of n_u different drugs such as chemotherapy, immunotherapy, anti-angiogenesis and so on.

2.2. The feedback-based therapy protocol

Let us consider a feedback-based therapy of duration T consisting of N_T sub-periods (of duration $T_s = T/N_T$) each of which involving a treatment phase and a rest phase as shown in Fig. 1 where the injection curves have to be interpreted as a multivariable signals when several drugs are combined.

It is assumed that during a treatment period, a sampled feedback injection law is used with a sampling period τ (for instance 2, 4, 6 h or such) during which the injection is maintained constant (see Fig. 1):

$$u(k\tau + t) = K(x(k\tau), \theta_c), \quad t \in [0, \tau] \tag{2}$$

where $x(k\tau)$ denote the state of the model at instant $k\tau$ while $\theta_c \in \mathbb{R}^{n_c}$ is a vector of parameters that are used in the definition of the feedback law K.

In the remainder of the paper, the notation $x(k)$ is used instead of $x(k\tau)$ to simplify the expressions when no ambiguity is possible. It is also assumed that the sampling period is a divisor of γT_s such