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Observer-based techniques for the identification and analysis of avascular tumor growth

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ABSTRACT

Cancer represents one of the most challenging issues for the biomedical research, due its large impact on the public health state. For this reason, many mathematical methods have been proposed to forecast the time evolution of cancer size and invasion. In this paper, we study how to apply the Gompertz's model to describe the growth of an avascular tumor in a realistic setting. To this aim, we introduce mathematical techniques to discretize the model, an important requirement when discrete-time measurements are available. Additionally, we describe observed-based techniques, borrowed from the field of automation theory, as a tool to estimate the model unknown parameters. This identification approach is a promising alternative to traditional statistical methods, and it can be easily extended to other models of cancer growth as well as to the evaluation of not measurable variables, on the basis of the available measurements. We show an application of this method to the analysis of solid tumor growth and parameters estimation in presence of a chemotherapy agent.

1. Introduction

Cancer represents one of the leading causes of death in the developed countries. In US, in 2009, almost 1.5 million new cancer cases have been diagnosed and, in the same year, more than half a million deaths due to cancer have been registered [1]. This has huge effects and implications in the health state, that calls for innovative treatment solutions: within this framework, the availability of algorithms to improve treatment infusion processes design might concretely contribute to reduce morbidity and economic burden, making the novel care-strategy more efficient and with smaller side-effects.

In the last decades, many mathematical models have been proposed, to describe the untreated [2–23] and treated tumors growth [24–30] at different level of complexity, specifically from the macroscopic to the microscopic molecular scale of analysis. These models have been aimed at improving the knowledge of the tumor growth mechanism and/or at acquiring useful hints of chemotherapy and radiotherapy outcomes. On the other hand, they have been only marginally used to implement a therapy strategy and, more in general, in clinical applications [24–27,19,29,30], mainly due to the intrinsic complexity of phenomena related with tumor growth and to the difficulties in identifying the model parameters from a limited set of available measurements. This problem is dramatically true for *in vivo* applications, since in this case the available information is provided just by means of biomedical image techniques (TAC, RNM, US) [31].

Generally speaking, detailed mathematical models for tumor growth must take into account several factors and, specifically, the nutrient concentration profiles into the tumor mass. To accomplish this task, even in the unrealistic assumption of perfectly spherical symmetry, partial differential equations must be solved, to include the space and time dependence for all variables of interest.

In the early stage of the invasion, called the avascular phase, a solid tumor exhibits a spheroidal form: in this phase, nutrients enter in the tumor mass only by means of diffusion. As the tumor grows, its inner cells are progressively less supplied with these nutrients, eventually switching to a quiescent state, further followed by death, if the nutrients falls below a critical concentration value C_C. The formation of this necrotic core, including dead and quiescent cells, is a critical stage in tumor invasion, since quiescent cells produce signaling molecules, called Tumor Angiogenic Factors (TAF's), responsible for the tumor angiogenesis [10,18,23]. Thus, the forecast of the necrotic core onset is a remarkable tool to predict the tumor invasion evolution.

Interesting results can be achieved by adopting models based on ordinary differential equations (ODEs), aimed at describing the evolution over time of the number of proliferant, quiescent and dead cells; even neglecting the nutrient concentration variation in the tumor mass, they are able to reproduce with reasonable accuracy the typical tumor growth. These models generally rely on

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an empirical definition of the dynamics of the tumor cell growth, based on parameters that characterize its kinetic features. Among them a relevant place is occupied by the Gompertz model, a model of the growth of a population in the case of limited resources, that has been seen chosen as a benchmark for the description of the tumor growth [32–35].

In this work, we use the Gompertz model to describe the time evolution of the number $N(t)$ of tumor cells. We have extended the model to take into account the action of a chemotherapy drug, so the corresponding dynamical system describes the time evolution of the number of neoplastic cells $N(t)$ and the plasma drug concentration $A(t)$.

The practical applicability of this model is limited by two factors, namely:

1. *Parameter identification:* there is no straightforward method to infer the value of the parameters contained in the model from biological evidence.
2. *Discretization*: as many other models based on non-linear ODEs, the Gompertz model cannot be immediately applied when only discrete-time measurements are available.

As for the second point, it must be noticed that the time interval between available measurements is usually much larger than the threshold allowed for simple linearization techniques, thus more sophisticated methodologies are required in order to analyze experimental data.

The approach that we propose in this paper to overcome these issues is a combination of a novel discretization schema together and a non-linear discrete-time state observer. In control theory, a state observer is a mathematical tool that allows to track the behavior of the unknown state variables of a system starting from the value of a measurable subset. A state observer is based on the knowledge of the dynamics of the system and its evolution from an initial estimate of the state variables converges asymptotically to the true value. Even though linear systems observers, such as the Luenberger observer, are standard tools in control applications, observers for non-linear cases [36] are more difficult to design.

The discrete-time version of the Gompertz's model of the tumor growth, together with the state observer, represents a valuable tool in practical applications, for example:

1. It is possible to estimate the unknown parameters of the model for specific tumor cells, starting from *in vivo* or *in vitro* measurements taken at large time intervals;
2. It is possible to quantify the impact of a chemotherapy agent from experimental measurements through the estimation of the parameters of the combined tumor–drug dynamical system;
3. The knowledge of the model parameters can be used to devise more efficient strategies of chemotherapy infusion;
4. An efficient chemotherapy infusion can be devised even when the initial knowledge of the tumor and drug dynamics are uncertain.

We have validated this approach *in silico* on the first two practical applications sketched above, and, specifically, we have tested the ability of the discrete-time model to approximate the dynamics of the continuous-time original model, as well as to identify the unknown parameters of the model starting from measurements of the tumor size and chemotherapic concentration after the application of different drug infusion sessions. These results comply satisfactorily with *in vivo* literature data, collected in similar conditions.

The paper is organized as follows. In Section 2 the mathematical model of the tumor growth case is discussed, with reference to its energetic interpretation. The discretization scheme and discrete-time non-linear observer are illustrated in Section 3; as a direct application of this methodology, this section also present the parameters estimation schema. Simulation results and related discussion are sketched in Section 4, whereas Section 5 presents the conclusions.

2. Mathematical model

Gompertz model has been proposed in the early XIX century, for epidemiological purposes [37]; since then, it has been applied in many different fields, to explain the controlled growth of entities under limiting supply conditions.

In the biological area, this model was applied efficiently to represent the cell population growth in the case of limited nutrients and also for the tumor cell growth in the avascular phase [10–12,20,21,23], recently, the Gompertz model has been revised in terms of an energetic interpretation of its kinetic parameters [32].

The Gompertz model is defined as solution of the equation:

$$\dot{N}(t) = \gamma \cdot N(t) \cdot \log\left(\frac{N_\infty}{N(t)}\right), \tag{1}$$

where $N(t)$ is the size of the cell population at the time t, γ is the kinetic constant of the growth rate, N_∞ is the theoretical saturation value that depends on the kind of cells and the environmental properties.

In the case of solid tumors, $N(t)$ can also be expressed in terms of the cell growth kinetics r_N that is supposed to be a linear function of the number of proliferant cells $P(t)$ (the ones that are able to replicate) [32]:

$$\dot{N}(t) = r_N(t) = const \cdot P(t), \tag{2}$$

where the *const* does not depend on N. Comparing (1) and (2) we derive $const = \gamma$, and

$$P(t) = N(t) \cdot \log\left(\frac{N_\infty}{N(t)}\right). \tag{3}$$

The fraction of proliferant cells is therefore

$$f_P = \frac{P(t)}{N(t)} = \log\left(\frac{N_\infty}{N(t)}\right). \tag{4}$$

Since it must be $0 \leqslant f_P \leqslant 1$, we have the two following conditions on $N(t)$:

$$f_P \geqslant 0 \rightarrow N \leqslant N_\infty,$$
$$f_P \leqslant 1 \rightarrow N \geqslant N_{min} = \frac{N_\infty}{e}.$$

The first condition is trivial: the overall cell number must not exceed the asymptotic saturation value. The second one is a lower bound to the cell population number, since for $N < N_{min}$ the cells are very few and they behave independently. In this case, nutrients supply is far larger than the amount strictly required to cell maintenance and replication, so all the N cells are vital and the kinetic expression can be approximated by an exponential growth.

Thus, the unconstrained growth law, *i.e.* without any chemotherapy action, is described in terms of the function

$$\begin{cases} \dot{N}(t) = \gamma \cdot N(t) & N(t) < N_{min}, \\ \dot{N}(t) = \gamma \cdot N(t) \cdot \log\left(\frac{N_\infty}{N(t)}\right) & N(t) \geqslant N_{min}. \end{cases} \tag{5}$$

In this paper only the case with $N(t) \geqslant N_{min}$ will be considered, due to its significance in health issues (only larger cell spheroids are detectable by the common diagnostic techniques).

We introduce the chemotherapy effect of just one drug, that acts on the proliferant cells P: