ALTERNATIVE APPROACHES TO CANCER TREATMENT: TOWARDS STOCHASTIC TUMOUR CONTROL

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In this study, we address the challenge of controlling tumor growth by leveraging a low-dimensional model based on the Chemical Reaction Network (CRN) formalism. Designed to function in both deterministic and stochastic frameworks, our findings demonstrate that the deterministic approach adequately characterizes the system behavior in presence of high number of tumor cells, particularly for the purpose of control planning. In this context, we propose different control strategies involving constant or variable treatment plans, exploiting complete or partial knowledge of the system state, and providing asymptotical guarantees of tumour eradication. However, after the tumour mass has been consistently reduced (namely when the number of tumor cells becomes relatively low), random fluctuations are not negligible any more, implying that a stochastic formalization can be more accurate. We preliminarily show by numerical simulations that, due to the properties of the underlying Continuous-Time Markov Process, finite-time tumour eradication can be obtained in the stochastic framework with statistical guarantees.

Keywords: *tumour growth and treatment, control theory, qualitative behavior analysis, numerical simulation, stochastic control*

1. Introduction

Model-based control has gained increasing interest in recent decades due to its ability to design sophisticated feedback regulations that consider the inherent dynamics of the system under investigation. In biomedical applications, minimal models are often utilized as they capture the basic relationships among variables without explicitly detailing all the physical or molecular mechanisms. These models can be easily identified through standard perturbation experiments and enable the synthesis of affordable and readily implementable control laws. Starting from the seminal work by Hahnfeldt et al. [1], proposing a low-dimensional minimally parametrized Ordinary Differential Equation (ODE) model for vascular tumor growth, several theoretical and experimental advancements have been made, including model extensions [2, 3] and investigations into closed-loop and open-loop anti-angiogenic drugging combined with chemotherapy treatments [4, 5, 6, 7, 8, 9, 10], both in the deterministic and in the stochastic setting [11, 12].

More recently, tumor growth models based on the Chemical Reaction Network (CRN) formalism have been proposed [13, 14, 15]. As described in [16], the chemical players considered by this formulation are the growing

cancer cells X_1, the necrotic cancer cells X_2, and the drug molecules X_3, subject to the following set of reactions:

$$\begin{aligned} &R_1 - \text{proliferation}: && X_1 \to 2X_1, \\ &R_2 - \text{necrosis}: && X_1 \to X_2, \\ &R_3 - \text{dead cell washout}: && X_2 \to \emptyset, \\ &R_4 - \text{drug clearance}: && X_3 \to \emptyset, \\ &R_5 - \text{drug action}: && X_1 + X_3 \to X_2, \\ &R_6 - \text{drug administration}: && \emptyset \to X_3. \end{aligned} \tag{1}$$

The advantage of this approach lies in its ability to model CRNs in a stochastic framework exploiting Continuous-Time Markov Chains (CTMCs) or, alternatively, in a mean-field ODE model approximating its average dynamics [17], which is more manageable from a computational viewpoint and can be effectively utilized when the copy number of chemical players is high. The contribution [18] builds upon the qualitative analysis presented in [16] for the ODE model associated with the CRN and further investigates deterministic feedback control laws, with possibly partial information, highlighting their advantages compared to constant administration therapies.

With respect to [18], which is devoted to deterministic control, in this study we perform a preliminary simulative investigation of the potential of feedback in a stochastic sense, i.e. by using stochastic models. To this end, we build a stochastic differential equation (SDE) version of model [13], exploiting the formalism of the Chemical Langevin Equation [19]. This approach has the computational advantage of accounting for the stochastic nature of the phenomenon at hand (in an approximate sense) while preserving the low dimensionality of the ODE model. Since all the states of the CRN reaction graph (Figure 1, left panel) with $X_1 = 0$ are absorbing states, we are able to obtain a statistics of the eradication time over $1,000$ random paths (Figure 1, right panel), showing the potential of this approach for future investigations.

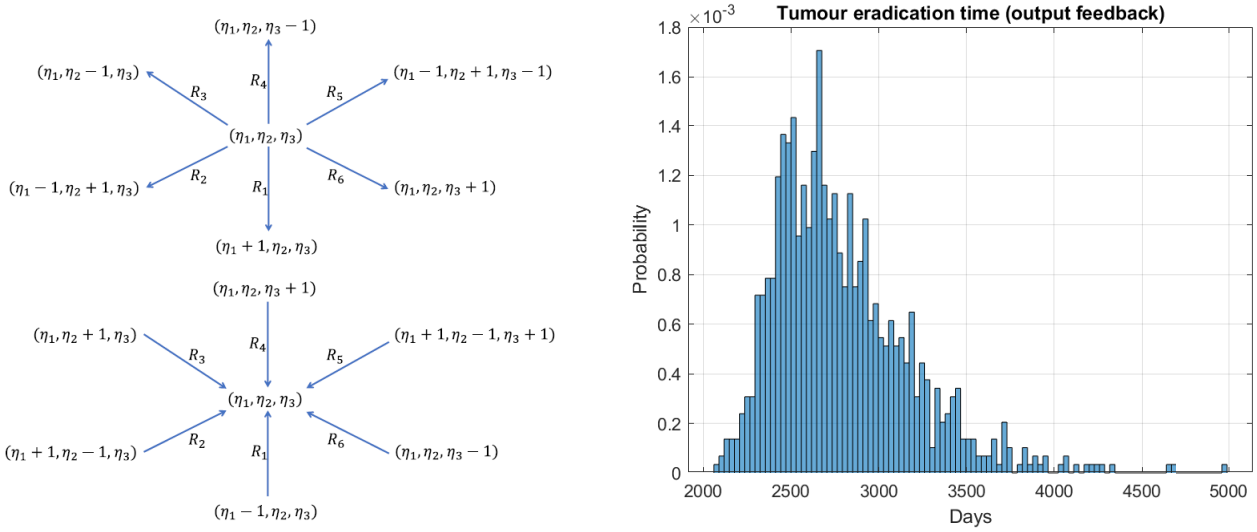

Figure 1: Left panel: State transition diagram for the CRN tumour model. Right panel: example of finite-time eradication in stochastic tumour control.

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