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Stochastic Hybrid Automata with delayed transitions to model biochemical systems with delays

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ABSTRACT

To study the effects of a delayed immune-response on the growth of an immunogenic neoplasm we introduce Stochastic Hybrid Automata with delayed transitions as a representation of hybrid biochemical systems with delays. These transitions abstractly model unknown dynamics for which a constant duration can be estimated, i.e. a delay. These automata are inspired by standard Stochastic Hybrid Automata, and their semantics is given in terms of Piecewise Deterministic Markov Processes. The approach is general and can be applied to systems where (*i*) components at low concentrations are modeled discretely (so to retain their intrinsic stochastic fluctuations), (*ii*) abundant component, e.g., chemical signals, are well approximated by mean-field equations (so to simulate them efficiently) and (*iii*) missing components are abstracted with delays. Via simulations we show in our application that interesting delay-induced phenomena arise, whose quantification is possible in this new quantitative framework.

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1. Introduction

Tumor-immune system interaction involves a number of distinct components, such as effector cells of the innate and adaptive immune systems (e.g., macrophages, natural killers, cytotoxic T lymphocytes) and chemical signals (e.g., cytokines). The immune response to a tumor is triggered by specific neo-antigens, eventually created by a large number of genetic and epigenetic events characterizing tumor cells [43]. Once triggered, the immune system may control and in some case eliminate tumors: this is the so-called *immune surveillance* hypothesis [28]. However, this extremely complex interaction has other possible outcomes, e.g., neoplasm evasion from control, neoplasm constriction in an oscillatory regime or in a microscopic undetectable "dormant" steady-state [23].

Many attempts at modeling this interplay have been pursued by using *Ordinary Differential Equations* (ODEs) or *Delay Differential Equations* (DDEs), e.g., see [37,38,12,45] and references therein. However, to study a neoplasm and its interaction with few immune-system effector cells, an individual-based stochastic representation of the cellular populations seems to be more appropriate. Unfortunately, the exchange of large quantities of chemicals with many kinds of cells (e.g., immune system effector cells, cells of the healthy tissues, endothelial cells), often present in an extremely higher number than cells, makes this interaction "multiscale". Thus, the usual discrete techniques to represent chemical systems, e.g., [30], do not allow an efficient model simulation. In this respect, a hybrid model combining a discrete representation of components at low/intermediate concentrations (e.g., cells) with mean-field equations for abundant entities (e.g., chemicals) seems to be

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the best setting to study this interaction [14,24]. In particular, it allows one to quantitatively estimate the effects of the *intrinsic stochastic fluctuations* of the discrete components which, in the tumor-immune system case, determine the outcome of the interaction. In [14], for instance, by resetting an ODE model of effector cells, tumor cells and cytokines in a hybrid framework, the probability of tumor eradication was evaluated. This biologically plausible outcome was not predictable by the original ODE model formulation [37]. In this sense, a hybrid setting is not only a better computational choice, but can also provide more *informative forecasts*.

A further step can be done to consider, in a hybrid setting, other techniques often used to model chemical systems. We focus here on *delays* used to approximate missing dynamical components, at any level of abstraction. Generally, they are used to abstract complex and often only partially known sequential dynamics in a single step, once an estimate of the duration of the dynamics is available, e.g., [12,45]. In the tumor-immune system case, delays can be used to describe the unavoidable and quite remarkably long lag period in the immune-response, as induced by chemical transportation of signals and the time needed for differentiation/division of effector cells [15]. Even though this abstraction is macroscopical and simplistic, it provides useful insights of this fundamental and complex interaction, especially when a full phenomenological model is missing. Delays are available, in various form, in deterministic models, or in individual-based models as *Continuous-Time Markov Chains* (CTMCs) with deterministic delays [5,4,8]. In terms of formal languages, they are supported in bio-specific process algebras, e.g., see [17] or more generally [13], but their characterization in hybrid systems is, to the best of our knowledge, missing.

Given these premises, in this paper we extend the well-known framework of *Stochastic Hybrid Automata* (SHA [11]) to model *hybrid biochemical systems with delays*. Technically, these automata extend classic SHAs with *non-Markovian delayed transitions* joining both exponential and deterministic distributions, in the control part. In this paper: (*i*) Gillespie models of stochastic chemical reactions [30] are related to SHAs, to settle the background, and (*ii*) Gillespie models with delays [5] are related to SHAs extended with delayed transitions. The semantics of these automata is given in terms of *Piecewise Deterministic Markov Processes* (PDMPs [26]), so to have a well-defined characterization in terms of stochastic processes, as it is for SHAs [6], and an equivalence with delay CTMCs [8] is provided under some conditions.

The paper is structured as follows. In Section 2 background is introduced. In Section 3 our case study is introduced, so to make clear to the reader what we want to model. In Section 4 we define SHAs to model hybrid biochemical systems and show their mapping to PDMPs, in Section 5 we do the analogs for SHAs with delays. In Section 6 we apply such automata to the case study introduced in Section 3. Via numerical analyses (*i*) we study the effect of various delays on tumor mass growth, (*ii*) we quantitatively determine eradication times as probability distributions, (*iii*) perform sensitivity analysis on tumor mass and delay amplitude and (*iv*) we prove, in the oscillatory regime, the existence of a transitory state transition resulting in delay-induced tumor eradication, unpredictable in either the mean-field or the hybrid non-delayed representation of the model.

2. Background

Some notions from stochastic chemical systems are introduced [30]. We consider a system of N distinct species $\mathcal{S} = \{S_1, \ldots, S_N\}$, and denote its state $\mathbf{x}$; component $\mathbf{x}_j$ counts the copies of S_j. The stochastic process $\mathbf{X}_t = \{\mathbf{X}(t) \mid t \in \mathbb{R}\}$ takes values in $\mathbb{N}^N$, if it is generated by a *Continuous Time Markov Chain* (CTMC). When it is hybrid, some of its components take values in $(\mathbb{R}^{\geqslant 0})^N$.

A set of reactions $\mathcal{R} = \{R_1, \ldots, R_M\}$ is described by a *stoichiometry matrix* $M = [\, \nu_1 \quad \ldots \quad \nu_M \,]$ where $\nu_i \in \mathbb{Z}^N$ for $i = 1, \ldots, M$. Each ν_j is a *stoichiometry vector*: when R_i fires in $\mathbf{x}$ it yields the new state $\mathbf{x} + \nu_i$. Each reaction is further described by a *propensity function* $a_i(t)$ so that $a_i(t)\,dt$ is the probability of R_i to fire at time t, within the infinitesimal time $[t, t + dt)$. These are defined according to either well-known or custom kinetics, e.g., mass-action or Michaelis–Menten.[2] When $\mathbf{X}_t$ is time-homogenous we simply write $a_i(\mathbf{x})$ to make $\mathbf{x}$ explicit.

Definition 1. We denote a *chemical system* in this sense as $(\mathcal{R}, \mathcal{S}, M)$.

It is generally convenient to distinguish between the "cause" (the reactants, ν_i^r) and the "effect" (the products, ν_i^p) of a reaction, so we write $\nu_i = -\nu_i^r + \nu_i^p$. In this formulation R_j can fire in $\mathbf{x}$ if enough reactants are present, i.e. if $\nu_i^r \preccurlyeq \mathbf{x}$ where $\preccurlyeq$ is the standard component-wise ordering. So, in a logical sense reactants closely mimicking the biochemical reality are a necessary condition to fire a reaction. The evolution of a chemical system is often evaluated algorithmically realizing a trajectory of $\mathbf{X}_t$ given an initial condition $\mathbf{X}(t_0) = \mathbf{x}_0$, see [30].

Such a trajectory is defined over a state space, which we assume to be *countable*, and that is defined constructively by this operator.

[2] The law of mass-action states that the rate at which a reaction occurs is proportional to the product of the concentrations of its reactants (see [30] for a detailed derivation). Mass-action propensity functions have some desirable properties, e.g., they are *Lipschitz continuous*.

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