



Applications of an expressive statistical model checking approach to the analysis of genetic circuits



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ABSTRACT

Stochastic temporal logics have demonstrated their efficiency in the analysis of discrete-state stochastic models. In this paper we consider the application of a recently introduced formalism, namely the Hybrid Automata Stochastic Language (HASL), to the analysis of biological models of genetic circuits. In particular we demonstrate the potential of HASL by focusing on two aspects: first the analysis of a genetic oscillator and then the analysis of gene expression. With respect to oscillations, we formalize a number of HASL based measures which we apply on a realistic model of a three-gene repressilator. With respect to gene expression, we consider a model with delayed stochastic dynamics, a class of systems whose dynamics includes both Markovian and non-Markovian events, and we identify a number of relevant and sophisticated measures. To assess the HASL defined measures we employ the COSMOS tool, a statistical model checker designed for HASL model checking.

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1. Introduction

Biological systems are regulated by complex information processing mechanisms which are at the basis of their survival and adaptation to environmental changes. Despite the continuous advancements in experimental methods, many of those mechanisms are still not well understood. The end goal of computational systems biology [39] is thus to develop formal methods for rigorously representing and effectively analyzing biological systems. Understanding what cells actually compute, how they perform computations, and eventually how such computations can be modified/engineered, are essential tasks which computational modeling aims at. In this context, the ability to “interrogate” a model by asking relevant “questions”, referred to as *model checking*, is critical. Model checking approaches have proved to be an effective means for analyzing biological systems, both in the framework of non-probabilistic models [28,16] and in that of stochastic models [43,35,14]. In the realm of stochastic modeling, such questions have a *quantitative* nature as they most often take into account timing as well as likelihood of events. In this paper we consider the application of a recently introduced stochastic formalism, namely HASL, to the verification of stochastic models of biological mechanisms. HASL uses Linear Hybrid Automata (LHA) as a means for characterizing relevant dynamics of a model, and, as such, it allows one to conceive and evaluate sophisticated measures.

Our contribution. We consider the application of HASL to the verification of biological systems. Our contribution is twofold. In the first part we illustrate the application of HASL to a relevant aspect of many biological mechanisms, namely the

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analysis of oscillatory trends in stochastic models of biological systems. In so doing we extend the very preliminary results presented in [13] (where we showed how HASL can be used to count the average number of oscillation periods on a simple example of a 3-species oscillator) by introducing an elaborate approach based on two different oscillation related behaviors (i.e. noisy periodicity and noisy alternance). We then illustrate the proposed approach on a stochastic oscillator case-study: the so called repressilator.

In the second part, we demonstrate the effectiveness of HASL verification by developing a comprehensive case study of gene expression, a relevant biological mechanism represented by means of non-Markovian models, that cannot be analyzed by means of classical (numerical) stochastic model checking.

Paper organization. In Section 2 we present the background material the paper is based upon, i.e. how systems can be modeled and analyzed using HASL formalism. Section 3 is devoted to the application of HASL to the analysis of oscillations while Section 4 illustrate the HASL-based analysis of a model of gene-expression. Finally a conclusion is given in Section 5.

2. Statistical model checking with HASL

Model checking [9] is a well established methodology introduced in the early 80s for the automatic verification of discrete-state models against temporal logic properties. The original approach was then extended to probabilistic models, and in particular to continuous-time Markov Chains (CTMCs) [54], resulting in the introduction of the Continuous Stochastic Logic (CSL)[6,8] and subsequent extensions. The basic idea of stochastic model checking is that, given a stochastic model and a property (expressed in terms of a stochastic logic formula), algorithms (either based on numerical methods or statistical ones) are applied to approximate the probability with which the property is fulfilled by the model.

The Hybrid Automata Stochastic Language (HASL) [11] is a recently introduced formalism widening the family of model checking approaches for stochastic models. Its main characteristics are as follows: first it addresses a broad class of stochastic processes which includes but, unlike most stochastic logics, is not limited to CTMCs. Second the HASL formalism turns out to be a powerful specification language through which temporal reasoning is naturally blended with elaborate reward-based analysis. In that respect HASL unifies the expressiveness of CSL [8] and its action-based [7], timed-automata [25,19] and reward-based [33] extensions, in a single powerful formalism. Third HASL model checking belongs to the family of statistical model checking approaches (i.e. those that employ stochastic simulation as a means to obtain estimates of relevant properties of the considered model). More specifically HASL statistical model checking employs confidence-interval methods to estimate the expected value of random variables which may represent either a measure of probability or a generic real-valued measure.

In the following we recall the basics of the HASL formalism. First we present Discrete Event Stochastic Process (DESP), the expressive class of stochastic models to which HASL formalism can be applied. Then we describe an extended version of generalized stochastic Petri nets (GSPN), called non-Markovian stochastic Petri nets (NMSPN), which is the modeling formalism used within HASL (note that the semantics of an NMSPN is a DESP). We then introduce the notion of HASL specifications, which consist of an automaton for selecting relevant executions of the DESP and obtaining information about them, and a target measure to be evaluated. We finally briefly describe the statistical model checking scheme, upon which the COSMOS tool [10] (i.e. the model checker supporting the HASL approach) is based. For a comprehensive and more formal treatment of HASL we refer the reader to [11].

2.1. Discrete event stochastic process

A DESP is a stochastic process consisting of a (possibly infinite) set S of states and whose dynamic is triggered by a (finite) set E of discrete events. As mentioned beforehand, no restrictions are considered on the nature of the delay distribution associated with events, thus any distribution with non-negative support may be considered. This model is very similar to Generalized Semi Markov Processes [31]. The only difference, set aside the way to present the functions, being the introduction of “indicators” needed when synchronizing the DESP with an LHA. The automaton will indeed not have access to the actual state of the DESP but will get partial information through the values of chosen indicators.

Definition 2.1. A DESP is a tuple $\mathcal{D} = \langle S, \pi_0, E, \text{Ind}, \text{enabled}, \text{target}, \text{delay}, \text{choice} \rangle$ where:

- S is a discrete set of states,
- $\pi_0 \in \text{dist}(S)$ is the initial distribution on states,
- E is a set of events,
- Ind is a set of functions from S to \mathbb{R} called state indicators (including the constant functions and the set *Prop* of state propositions, taking values in $\{0, 1\}$),
- **enabled:** $S \rightarrow 2^E$ are the enabled events in each state
- **target:** $S \times E \rightarrow S$ is a partial function describing the state reached from state s on occurrence of an enabled event $e \in \text{enabled}(s)$
- **delay:** $S \times E \rightarrow \text{dist}(\mathbb{R}_{\geq 0})$ is a partial function describing the distribution of the delay of an enabled event $e \in \text{enabled}(s)$

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