

Formal Analysis of the Wnt/ β -catenin Pathway through Statistical Model Checking

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Abstract. The Wnt/ β -catenin signalling pathway plays an important role in the proliferation of neural cells, and hence it is the main focus of several research aimed at understanding neurodegenerative pathologies. In this paper we consider a compact model of the basic mechanisms of the Wnt/ β -catenin pathway and we analyse its dynamics by application of an expressive temporal logic formalism, namely the Hybrid Automata Stochastic Logic. This allows us to formally characterise, and effectively assess, sophisticated aspects of the Wnt/ β -catenin pathway dynamics.

Keywords: HASL Model Checking, Stochastic modelling, biological pathways, Wnt/ β -catenin.

1 Introduction

Systems Biology [11] is concerned with the development of formalisms for building “realistic” models of biological systems, i.e. models capable of reproducing wet-lab observations. A biological model consists of a set biochemical agents (i.e. species) whose interactions are expressed by a set of *reaction equations*. This leads to either a continuous-deterministic interpretation (i.e. in terms of a system of differential equations), or to a discrete-stochastic interpretation (i.e. in terms of a discrete-state stochastic process).

Stochastic modelling and systems biology. Within the discrete-stochastic semantics realm, which is what we consider in this work, molecular interactions are assumed to be of stochastic nature hence biochemical reactions occur according to probability distributions. In this case what modellers normally do is to generate one (or several) trajectory(ies) through stochastic simulation and observe the evolution of the species (under different model’s configurations) in order to figure out how a given aspect of the model’s dynamics is affected by the various elements of the model (i.e. what species/reactions is responsible for a given observed behaviour). Such an approach has two main advantages: its simplicity and its low computational cost (the runtime for generating a single trajectory or a normally small number of trajectories is very low even for large models). On

the other hand the main disadvantage is that it is little formal, meaning that the modeller must draw conclusions based only on the observation of a single (stochastic) trajectory (or of a trajectory obtained by averaging a normally small number of trajectories).

Stochastic model checking and systems biology. Stochastic model checking [12] (SMC) is a formal technique that allows the modeller to formally express relevant properties in terms of a (stochastic) temporal logic and to assess them against a given stochastic model. This is achieved through an automatic procedure which can either provide an *exact answer* through exhaustive exploration of the model's state space (i.e. *numerical model checking* [2]) or an *estimated answer* resulting from a finite sampling of the model's trajectory (i.e. *statistical model checking* [13]). SMC has at least two main advantages with respect to informal approaches: first it provides the modeller with a language for capturing relevant properties formally; second the answer it calculates (e.g. probability that a property is satisfied by the model) are either exact (i.e. they reflect the complete set of possible behaviours of the model) or are accurate estimates (i.e. calculated over a sufficiently large sample of trajectories). The effectiveness of SMC in systems biology applications is demonstrated by an ever increasing number of publications, e.g. [8,10,5].

β -catenin and the WNT Pathway. In cellular biology signalling pathways are basic mechanisms responsible for controlling a cell's life-cycle. Simply speaking a signalling pathway represents a cascade of biochemical reactions which is triggered by a specific signal (i.e. type of molecules) whose presence, normally at the cell membrane, activates the cascade leading to the "transmission" of the signal inside the cell (i.e. cytosol and/or nucleus). In this paper we study a model of the Wnt/ β -catenin pathway, a signalling pathway known to be involved in the pathological degeneration of neuronal cells [14].

Our Contribution. In this work we present preliminary results of application of formal analysis, based on the so-called Hybrid Automata Stochastic Logic (HASL) statistical model checking, to a model of the Wnt/ β -catenin pathway presented in [15]. In particular we show how one can define specific HASL formulae for assessing sophisticated characteristics of the Wnt/ β -catenin pathway dynamics. This includes, for example, measuring the temporal location and the amplitude of transient peaks of nuclear β -catenin, exhibited by certain initial conditions, or assessing its oscillatory character resulting from other conditions. If in [15] the analysis of the Wnt/ β -catenin model is simply done through plotting of simulated trajectories, here we move analysis to a higher and more formal level by demonstrating how, through model checking, one gains access to the analysis of sophisticated dynamical aspects of the Wnt/ β -catenin pathway.

Paper Organisation. We introduce the Wnt/ β -catenin mechanism in Section 2 and describe the model presented in [15] which we have used for our analysis. In