Qualitative and Quantitative Analysis of a Bio-PEPA Model of the Gp130/JAK/STAT Signalling Pathway

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Abstract. Computational modelling of complex biochemical systems has grown in importance over recent years as a tool for supporting biological studies. Consequently, several formal languages have been recently proposed as modelling languages for biology. Among these, process algebras have been proved capable of providing researchers with new hypotheses on the behaviour of biochemical systems.

Bio-PEPA is a process algebra recently defined for the modelling and analysis of biochemical systems, which provides modellers with a wide range of analysis techniques: models can be analysed by stochastic simulation, model-checking, and mathematical methods based on ordinary differential equations.

In this work, we use Bio-PEPA for modelling the gp130/JAK/STAT signalling pathway, and we use both stochastic simulation and model-checking to analyse several qualitative and quantitative aspects of the system.

1 Introduction

Several modelling approaches have been used over recent years to analyse complex biological systems such as signaling pathways, ranging from traditional mathematical methods based on differential equations to computational methods based on stochastic simulation and model-checking. Each of these techniques can be more suitable than others in some context or to study some particular features of biological systems.

Process algebras are formal languages traditionally used to model distributed systems of concurrent computing devices. Starting from the biochemical π-calculus [1], several other process algebras have been recently adapted in order to model biochemical systems [2,3,4,5], following the "molecules as processes" paradigm introduced in the landmark paper [6]: molecules are modelled as concurrent processes, and biochemical reactions are represented by actions performed by synchronising processes.

Bio-PEPA [7,8] is a process algebra specifically defined to model and analyse biochemical networks. Compared to other process algebras, Bio-PEPA uses a more abstract view of biochemical systems, the so-called "species as processes" abstraction: processes represent molecular species instead of single molecules, and multi-way synchronisations of processes represent changes in the amounts of molecular species resulting from biochemical reactions. Such an abstract view enables modellers to deal with analysis techniques which are computationally infeasible when considering the "molecules as processes" abstraction.

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The main feature of Bio-PEPA is that it integrates several kinds of analysis techniques. Both discrete stochastic and continuous deterministic models can be automatically generated from Bio-PEPA models, thus allowing modellers to perform time-series analysis via stochastic simulation, Markovian analysis and ordinary differential equations (ODEs); in addition, system properties can be verified through model-checking and mathematical techniques such as bifurcation, stability and continuation analysis. Moreover, as for the other process algebras, Bio-PEPA is equipped with an operational semantics which supports various kinds of formal analysis (e.g. causality, equivalence, and reachability analysis).

In this work, we define a Bio-PEPA model of the gp130/JAK/STAT signalling pathway, a well-studied system which plays a major role in several biological processes both in human and other organisms. A lot of experimental data is available about the molecules in the pathway, and some mathematical and computational models have been already developed. For these reasons, the gp130/JAK/STAT pathway represents a good case study for exploiting some of the possible Bio-PEPA analysis methods in order to study different aspects (both qualitative and quantitative) of the system, and compare them with existing models.

The rest of the paper is structured as follows. First, the Bio-PEPA language is introduced in Sec. 2, while the pathway and the Bio-PEPA model are described in Sec. 3 and Sec. 4, respectively. The following three sections are devoted to the analysis of the model: in Sec. 5 several qualitative properties are analysed via model-checking, in Sec. 6 we present some stochastic simulation results, and in Sec. 7 model-checking is employed for quantitative analysis. Finally, Sec. 8 is an overview of the related work and Sec. 9 contains some concluding remarks.

2 Bio-PEPA

Bio-PEPA [7,8] is a process algebra which has been recently defined for the modelling and analysis of biochemical networks. It is a biologically-inspired language based on PEPA [9] and, differently from PEPA and other process algebras, it is able to explicitly represent details such as stoichiometric coefficients and the roles of species in reactions, and it supports the definition of general kinetic laws. Bio-PEPA models can be analysed by different techniques (stochastic simulation, analysis based on ODEs, numerical solution of the continuous-time Markov chain (CTMC), and probabilistic model-checking), since the mappings of Bio-PEPA models into specifications for those approaches have been defined [10].

The Bio-PEPA language is based on discrete levels of parameterised species: each component represents a species and its parameter may be interpreted as the number of molecules or discrete levels of concentration depending on the type of analysis to be applied. Parametric levels are considered for the definition of the transition system and for the derivation of a CTMC whose states represent the concentration levels of the species.

The syntax of Bio-PEPA is defined as:

$$S ::= (\alpha, \kappa)\ \mathsf{op}\ S \mid S + S \mid C \qquad P ::= P \underset{I}{\bowtie} P \mid S(x)$$

where $\mathsf{op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot$.