Parametric Model Checking of Multi-Agent Reaction Systems

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1 Scientific context

Reaction systems, introduced by Ehrenfeucht and Rozenberg in [25]), are a formal model for processes inspired by the functioning of living cells, which functioning is determined by the interactions of biochemical reactions. These interactions are based on the mechanisms of facilitation and inhibition: the (products of the) reactions may facilitate or inhibit each other. Reaction system related research topics [7, 8, 10, 12, 22] have been motivated by biological issues or by a need to understand computations/processes underlying the dynamic behaviour of reaction systems. Simplicity of reaction systems stems from their ability to express qualitative aspects of systems through finite sets of biochemical entities and reactions. Nevertheless, they allow for representing large numbers of complex processes. The behaviour of reaction systems from an initial state and within a context (given environment) can be represented as an automaton.

Analysis of reaction systems [6] allows for understanding their properties. Rather than considering all possible contexts, *context-restricted reaction systems* introduced by Męski [32] also specify the environment in which the system is functioning. Properties of such reaction systems heavily depend on their interactions with their environment. Thus, an adequate extension of the CTL branching-time temporal logic, rsCTL, was introduced. It not only captures usual temporal logic properties but also allows for expressing biologically-inspired properties such as conserved sets, invariant sets and steady states.

The reaction systems extended with the notion of participating agents are called distributed reaction systems (DRS). Adding agents in the reaction systems setting, allows for the natural modelling and representation of multi-agent and distributed systems [33]. In more detail, it is possible to model systems employing both synchronous and asynchronous execution semantics, and an extended notion of context automata allowing conditional generation of contexts. To enable specifying temporal-epistemic properties of DRS, a new logic for reaction systems was introduced: rsCTLK, which extends rsCTL with epistemic operators. Model checking for rsCTLK was proved to be PSPACE-complete.

Agent-based models in epidemiology have been popular, and have been widely used to study a variety of diseases including small-pox, west nile virus and influenza [28]. Agents proved to be useful for the applications that imply: repetitive and time-consuming activities; knowledge management, such as integration of different knowledge sources and modelling of complex, dynamic systems [13, 30, 31].

Agents can be suitably adopted for modelling at the appropriate level of abstractions such activities or better the biological components that are responsible for them. Agent abstraction makes it possible to model directly reactive and proactive behaviour of biological components, both considering internal and interactive activities.

The benefits of engineering new vaccines and drugs is undisputed, and is a clear demonstration of the applicability of synthetic biology. In such applications, development of methods for ensuring correctness of the results at the design stage is an important area of research. The paper published in Nature [35] presented an overview of the research results in synthetic biology. It highlighted the fact that the biological systems are being engineered to become more and more complex, and it is impossible to use intuition alone to analyse combinations of even small systems. Consequently, developing efficient methods that support such analyses is crucial. While reaction systems could not yet been mentioned in the paper, it has been demonstrated by various researchers (see [8, 9, 11, 21]) that they can be used for biological modelling. Furthermore, the paper points out the applicability of model checking in identifying various parameters of these systems. For example, model checking could support identifying the mutations to perform, and could help to predict the behaviour after these perturbations have been made.

2 PhD objectives

The PhD aims at leveraging several limitations of the current research, provide more flexibility, and show the applicability to practical case studies.

In order to verify properties of parametric reaction systems, [32] introduces bounded model checking (BMC) algorithms. In this context, parameters are elements of the reactions, *i.e.* for each reaction they refer to its reactants, inhibitors, and products. Although BMC may prove efficient, it suffers from inspecting only a part of the system's behaviour. It cannot be used to prove universal properties or to disprove existential ones. The PhD will propose an adaptation of LTL and CTL model checking algorithms (see *e.g.* [15]) that overcomes these limitations. Moreover, similar model checking methods will be used for rsLTL and rsCTL extended with the epistemic component. The PhD will also investigate an application of ATL [1, 29] for specifying and model checking strategic properties of DRS agents, under different definitions of strategies including perfect/imperfect information and recall, and counting strategies [4].

Another problem to be addressed by the PhD is the notion of time in reaction systems [16, 24]. Time could be a parameter since the duration of some biological reactions are unknown *a priori*. Synthesis of time parameters would provide a flexibility aspect, inspired by [2, 3, 5, 34].

Finally, the PhD may consider investigations on modularity and hierarchical modelling [18, 23, 26].

The applicability of the algorithms will be investigated on practical case studies issued from biology (*e.g.* metabolism of lactose in *E. coli* [21, 36], eukaryotic heat shock response [8], signalling pathways in pancreatic cancer [27] and carbohydrate oxidation [19], among others [14, 17, 20]). The PhD will investigate the expressive power and relevance of the property logics, and the ability of the algorithms to scale up.

3 International collaboration context

The IEA (International Emerging Action) project PARTIES between LIPN and IPI-PAS addresses verification of multi-agent systems and strategy synthesis in particular with incomplete knowledge. The PhD subject has strong ties with this project. Moreover, the polish partners have strong expertise in reaction systems while the french ones focus on model checking algorithms. Therefore, we aim at a co-supervision and the participation of the PhD candidate in the PARTIES project. We will also apply to funding programmes for supporting travel expenses of PhD students co-supervised by French and Polish partners.

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