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Dependency graphs and mass conservation in reaction systems

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ABSTRACT

Reaction systems is a new mathematical formalism inspired by the biological cell, which focuses on an abstract set-based representation of chemical reactions via facilitation and inhibition. In this article we focus on the property of mass conservation for reaction systems. We show that conservation of sets gives rise to a relation between the species, which we capture in the concept of the conservation dependency graph. We then describe an application of this relation to the problem of listing all conserved sets. We further give a sufficient negative polynomial criterion which can be used for proving that a set is not conserved. Finally, we present a simulator of reaction systems, which also includes an implementation of the algorithm for listing the conserved sets of a given reaction system.

1. Introduction

Reaction systems is a framework inspired by the functioning of the living cells, which was originally introduced in [1]. This formalism focuses on reactions exclusively and only considers two basic ways in which they can interact: promotion and inhibition. Reaction systems are based upon two fundamental principles. The first one, referred to as the "threshold principle", states that, whenever a resource is available, it is available in unlimited amount. This implies in particular that no competition for resources takes place. The second principle, referred to as the "no-permanency principle", states that unless a resource is explicitly sustained by a process, it will vanish and thus it will not be present in the next state of the system.

One of the central features of reaction systems is that they are explicitly conceived as open-ended systems: the influence of the environment is represented as an inflow of resources (the context).

The research topics investigated in the domain of reaction systems are various [2], but they can generally be classified along two lines. The first line comprises the research focusing on the mathematical properties of reaction systems: the set functions they can implement, their state sequences, connections to Boolean functions, etc. (e.g., [3–7]). The second main line of research regards reaction systems as an instrument for biological modeling (e.g., [8–10]). Quite naturally, investigations along this second line led to the study of model checking for reaction systems. For example, in [11], the authors introduce a temporal logic to define and subsequently verify certain properties of reaction systems. They prove that the general model checking problem is PSPACE-complete. On the other hand, [8] starts with defining a series of biologically

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inspired properties for reaction systems and shows that checking some of them, while still intractable, is a problem of lower computational complexity.

In this paper we conduct a detailed study of the biologically inspired property of mass conservation in reaction systems, originally introduced and shown to be coNP-complete in [8]. We get a new insight into the connection between the internal structure of the reaction system and mass conservation by revealing a relation that the latter induces between the species, and we capture this relation by defining the conservation dependency graph. We then present an application of this graph to the inherently difficult problem of listing the conserved sets and show that, in certain cases, the algorithm we devise to solve this problem is capable of performing better than the naive exponential approach. We continue by regarding mass conservation from a yet another perspective and formulate a sufficient polynomial criterion which allows one to quickly decide that a given set of species is not conserved. Finally, we present the reaction system simulator we have developed with the goal of automating the process of running reaction systems, and which is also capable of building the conservation dependency graph of a reaction system and of using it to list the conserved sets.

This paper is structured as follows. In Section 2 we remind the basic notions of reaction systems, as well as the notion of mass conservation. In Section 3 we discuss the relationship between mass conservation and the inner structure of the reaction system, and introduce the conservation dependency graph. In Section 4 we describe the algorithm for listing the conserved sets, which is based on the conservation dependency graph. In Section 5 we provide a negative polynomial heuristics for mass conservation, as well as for a generalized conservation problem. Finally, in Section 6 we give a short presentation of our reaction systems simulator. We conclude the paper in Section 7 with a discussion of our work.

2. Preliminaries

In this section we remind the notion of a reaction system as well as some related concepts capturing the static structure and the dynamic aspects of the model. For the original introduction the reader is referred to [1] and [3].

Definition 2.1. (See [1].) Let S be a finite set, whose elements will be referred to as *species* (very often in the reaction systems literature they are also called *entities*). A *reaction* a in S is a triplet of finite sets $a = (R_a, I_a, P_a)$, where $R_a, I_a, P_a \subseteq S$ and $R_a \cap I_a = \varnothing$. We say that R_a, I_a, and P_a are the sets of *reactants*, *inhibitors*, and *products* of a, respectively. The set of all reactions in S is denoted by $\mathrm{rac}(S)$.

A *reaction system (RS)* is an ordered pair $\mathcal{A} = (S, A)$, where S is a finite set of species and $A \subseteq \mathrm{rac}(S)$. The set S is called the *background* (set) of $\mathcal{A}$.

We use the following notations of [8]:

$$\mathcal{R} = \bigcup_{a \in A} R_a, \mathcal{P} = \bigcup_{a \in A} P_a, \text{ and } \mathrm{supp}(\mathcal{A}) = \mathcal{R} \cup \mathcal{P}.$$

The set $\mathrm{supp}(\mathcal{A})$ will be called the *support set* of $\mathcal{A}$.

The following definition introduces the result of a reaction and of a reaction system.

Definition 2.2. (See [1].) Let $\mathcal{A} = (S, A)$ be a reaction system, $W \subseteq S$ a set of species, and $a \in A$ a reaction. We say that a is *enabled* by W, denoted by $\mathrm{en}_a(W)$, if $R_a \subseteq W$ and $I_a \cap W = \varnothing$.

(1) The *result of a on W* is defined as follows:

$$\mathrm{res}_a(W) = \begin{cases} P_a, & \text{if } \mathrm{en}_a(W), \\ \varnothing, & \text{otherwise.} \end{cases}$$

(2) The *result of $\mathcal{A}$ on W* is defined as follows:

$$\mathrm{res}_{\mathcal{A}}(W) = \bigcup_{a \in A} \mathrm{res}_a(W).$$

Next, we introduce a running example for this section, as well as Sections 3 and 4.

Example 2.1. One of the best preserved defense mechanisms in the living cell is the *heat shock response*. Whenever the cell is exposed to environmental stress, its proteins start to misfold, which may eventually lead to cell death. The heat shock response mechanism causes an increase in the production of molecular chaperons called the heat shock response proteins (hsp). These chaperons bind to misfolded proteins and facilitate their refolding. A different group of proteins, the heat shock factors (hsf), control hsp expression by binding to the promoter site of the hsp-encoding gene (the heat-shock element hse) and thus activate the transcription of hsp. A molecular model of such a mechanism is proposed in [12] and its corresponding reaction system based model is presented in [9]. In this paper we will consider the following simplified version of the model from [9]: