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Verification of Spatial and Temporal Modalities in Biochemical Systems

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Abstract

Biochemical systems such as metabolic and signaling pathways tend to be arranged in a physical space: the product of one reaction must be in the right place to become the reactant for the subsequent reaction in the pathway. Moreover, in some cases, the behavior of the systems can depend on both, the location of the reactants as well as on the time needed for the reaction to occur. We address the problem of specifying and verifying properties of biochemical systems that exhibit both temporal and spatial modalities at the same time. For that, we use as specification language a fragment of intuitionistic linear logic with subexponentials (SELL). The subexponential signature allows us to capture the spatial relations among the different components of the system and the timed constraints for reactions to occur. We show that our framework is general enough to give a declarative semantics to P-Systems and we show that such logical characterization has a strong level of adequacy. Hence, derivations in SELL follow exactly the behavior of the modeled system.

Keywords: Biochemical systems, linear logic, spatial and temporal modalities.

1 Introduction

One of the main difficulties of building computational models for biological systems arise from the characteristics of the available information. Indeed, even for the best-studied systems, the known data cannot describe exhaustively the properties of each molecular species; even less known are the details of spatial information and the

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timing of events. Thus, desirable features of a computational modeling framework should regard the capability of dealing with information often both incomplete and of non-uniform quality.

Another desirable feature for computational models is the ability to describe a biological system at different levels of abstraction. This may be useful to capture the variability of subnetworks in the topology of a biochemical reactions network, for instance, at the level of metabolic or signaling pathways.

Several computational frameworks for modeling in different ways various aspects of biological systems have been defined in the last decade (see e.g., [28,21,20,25,38,52,39,12,7,29]). However, so far we have not seen one single formalism for modeling reaction systems with both time and space, and, at the same time, with the ability to express a logic for proving properties which can depend both on time and space locations. Normally, there is one formalism and a language for the modeling and the specification of a biological system and at least another different formalism for expressing the properties of interest (e.g., a temporal logic) and for proving them (e.g., by using a model checker).

Our approach for specifying and studying biological systems grounds on Concurrent Constraint Programming (CCP) [50] and on linear logic (LL) [30]. The former is a model for concurrency where agents interact by telling and asking constraints (i.e., logical formulas) into a store of partial information; the latter, is a substructural logic where formulas are seen as *resources*. Interestingly, the language of CCP processes is flexible enough to faithfully capture different modalities of concurrent systems (e.g., temporal, spatial and epistemic modalities) while keeping a declarative semantics based on (intuitionistic) LL as shown in [27,42]. This means that CCP models can be seen as *runnable specifications*: the model can be executed to observe the traces of the systems and, more importantly, the underlying theory of CCP and all the meta theory developed for LL can be used to verify systems' properties.

Another salient characteristic of CCP is its ability to deal with partial information: constraints add information on the system variables (e.g., $x > 42$) rather than determining the value of the variables. Hence, the more information is obtained the more constraints are accumulated and more information can be deduced from the system. Constraints also provide a compact representation of the *state of the system* (as predicates on system variables). Moreover, being able to deal with partial information is certainly useful in situations where either some components of the system are not fully specified or we do not have enough quantitative information about them.

In a previous work [16] we used the `ntcc` calculus [41], a non-deterministic temporal extension of CCP, for representing reaction rules in biological systems. This language allowed us to model discrete-time, and hence biological systems where reactions have a duration over time. Later, in [36], we described a modeling strategy based on `ntcc` where starting from an abstract model, we built refinements adding further details coming from experimentation or abstract assumptions. In a following work [14], we modeled spatial distributions in biochemical reactions. This thus