

An Analysis for Proving Temporal Properties of Biological Systems

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Abstract. This paper concerns the application of formal methods to biological systems, modeled specifically in BioAmbients [34], a variant of the Mobile Ambients [4] calculus. Following the semantic-based approach of abstract interpretation, we define a new static analysis that computes an abstract transition system. Our analysis has two main advantages with respect to the analyses appearing in literature: (i) it is able to address *temporal* properties which are more general than *invariant* properties; (ii) it supports, by means of a particular *labeling discipline*, the validation of systems where several copies of an ambient may appear.

1 Introduction

Nowadays one of the great challenges for computer science is to understand whether models, originally developed for describing systems of interacting components, can be applied for modeling and analyzing biological systems. This very promising and recent application to systems biology could offer biologists very useful simulation and verification tools that could replace expensive experiments in vitro or guide the experiments by making predictions on their possible results.

Among the many formalisms that have been successfully applied to biology there are traditional specification languages for concurrent and reactive systems [25,20,19], and process calculi, designed for modeling distributed and mobile systems. Process calculi turned out to be very appropriate for describing both the molecular and biochemical aspect, as pioneered by the application of stochastic π -calculus [35,33]. New process calculi have also been proposed in order to faithfully model biological structures such as compartments, membranes and hierarchy, which play a key role in the organization of biomolecular systems. Recent proposals are BioAmbients [34], Beta-Binders [32], and Brane calculi [2].

BioAmbients (BA) is a variant of a very popular calculus for mobile processes, the Mobile Ambients calculus (MA)[4], based on the key concept of *ambient*. An ambient represents a bounded location where computation happens; ambients are organized into a hierarchy, that can be dynamically modified as a consequence of an ambient movement or dissolution. For better modeling basic biological concepts, minor modifications are introduced in BA with respect to standard MA. Ambients are nameless; the primitive for opening is replaced by a primitive of merge, which realizes the fusion of two ambients; capabilities have corresponding co-capabilities; new primitives for communication and choice are introduced.

A great advantage of the BA calculus is that the variety of formal verification techniques, proposed for MA in the last few years, can be naturally adapted. In particular, due to the intrinsic complexity of biological systems, *static analysis* techniques appear very promising, and can be applied to infer information on the possible behavior of biological systems that cannot be handled by simulation tools [35,33] or by automatic verification techniques [23,24].

Static analyses define safe and computable approximations of the (run-time) behavior of a system, and they have been typically applied in the MA setting (see [27,18,14,21,15,26,11]) for verifying security properties, specifically for proving *invariant* properties. To this aim, they collect information about the reachable states by reporting approximate descriptions of the possible nesting of ambients and processes. This information can be exploited to show that certain events *will not happen* in *each* state of the system; for example, that an ambient *will never* end up inside another one; and similarly, that an interaction between two ambients *will never* take place.

As expected, some of these techniques [27,14,11,21,15] were successfully translated to the BA calculus (see [29,28,30,31,15]). Nonetheless, we believe that *temporal* properties, much more general than invariant properties, should be addressed in order to reason on real biological systems. Examples of interesting temporal properties could be: for each path of computation “after A interacts with B than it does not interact with C anymore”; for each path of computation “event A may happen only after event B”. Such properties could help biologists to better understand both the *spatial* and *temporal* evolution of complex biological systems, such as pathways and networks of proteins, as already pointed out in [5,23,24,1].

As an example, we consider a typical specification of an enzymatic reaction, following the approach proposed in [34] based on ambient movements,

$$\begin{aligned}
 & [M]^{mol} \mid \dots \mid [M]^{mol} \mid [E]^e \dots \mid [E]^e \\
 M & ::= \text{in } m. \text{out } n. P \quad E ::= \text{rec } Y. \overline{\text{in } m}. \overline{\text{out } n}. Y
 \end{aligned} \tag{1}$$

The system (1) describes an (irreversible) enzymatic reaction; the enzyme and its substrate are modeled by ambients, labeled¹ *e* and *mol*, resp.. Processes *M* and *E* realize the reaction in this way: the binding is modeled as entry of the substrate ambient inside the enzyme ambient; symmetrically, the release of product *P* is modeled as ambient exit.

In the reaction described in (1), for *any* ambient *mol*, the binding with an ambient *e* is a *necessary* for the release of product *P*. Even this very simple property, however, cannot be captured by standard reachability analyses for BA / MA [27,18,11,14,21,29,28,30,31]. In fact, these proposals predict the possible contents of ambients, at any evolution step, and can just conclude that any ambient *mol* may reside both at top-level and inside an ambient *e*. In order to infer that the former event is a so called *necessary check-point* for the latter, information about the possible moves of the system is needed.

It is clear that the validation of such properties requires *more powerful analyses* able to observe the possible evolution of a system, i.e., to compute an

¹ In BA labels are attached to ambients as comments, in that ambients are nameless.