Approximate model reduction for the differential semantics of rule-based models

Internship proposal, Master 2 MPRI, year 2014-2015

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Note: Other internships are possible on the topic of static analysis, abstract interpretation, and applications to Systems Biology. Please contact the internship supervisor for more information.

Motivation

Mechanistic models of systems of interaction between proteins are difficult to design and to analyse because of the large combinatorial complexity. Indeed, proteins can gather together or activate one another, and thus they can form many bio-molecular complexes (see [4, 6]).

Kappa [5] is formal language to describe these models by the means of graph rewrite rules. In particular, these rules are context free, they describe transformations between patterns, and there is no need to describe explicitly the whole structure of bio-molecular complexes. Kappa comes with several semantics. In particular, the differential semantics describe the evolution of the concentration of each bio-molecular complexes as the solution of a system of ordinary polynomial equations. Thus even if context free rules solve the problem describing the system, combinatorial issues raise again when one want to write (or solve) the differential semantics of these systems.

In [7, 3, 2], we have proposed a framework for the model reduction of the differential semantics of Kappa. This framework is based on a static analysis that inspect the rewrite rules and detect a change of variables. As a result, in compute a smaller differential system, the solution of which is an exact projection of the initial system (which does not need to be written explicitly). In this internship, we propose an complementary approach, given a set of patterns of interest, we would like to derive a system of ordinary differential equation so as to compute timely-dependent bounds for the concentration of these patterns. This framework will allow to tune the trade-off between accuracy and complexity, while having a sound estimation of the numerical approximations. For instance, it will allow to truncate the set of variables if there are too many of them (even after exact model reduction), and to apply different relational abstractions over the concentrations of the patterns of interest.

Expected works

The intern shall design a framework for deriving sound equations for the lower and the upper bounds of the concentration of some bio-mollecular patterns in a rule-based model. In particular, this derivation will use two basic operations, one partitioning primitive, so as to split the state of the system into two parts and to apply different kind of abstractions to each of them, and a reduced product so as to combine different kinds of properties and to refine what is known about a part of the state, and thus to describe more precise equations. This framework will be implanted and integrated in the development plate-form of Kappa [1].

References

[1] Pierre Boutillier, Jérôme Feret, Jean Krivine, and Lý Kim Quyên. http://www.kappalanguage.org.

[2] Ferdinanda Camporesi and Jérôme Feret. Formal reduction of rule-based models. In *Postproceedings of the Twenty-seventh Conference on the Mathematical Foundations of Programming Semantics, MFPS XXVII*, volume 276C of *Electonic Notes in Theoretical Computer Science*, pages 31–61, Pittsburg, USA, 25–28 May 2011. Elsevier Science Publishers.

[3] Vincent Danos, Jérôme Feret, Walter Fontana, Russell Harmer, and Jean Krivine. Abstracting the differential semantics of rule-based models: exact and automated model reduction. In Jean-Pierre Jouannaud, editor, *Proceedings of the Twenty-Fifth Annual IEEE Symposium on Logic in Computer Science, LICS '2010*, volume 0, pages 362–381, Edinburgh, UK, 11–14 July 2010. IEEE Computer Society.

[4] Vincent Danos, Jérôme Feret, Walter Fontana, and Jean Krivine. Abstract interpretation of cellular signalling networks. In *Proceedings of the 9th International Conference on Verification, Model Checking and Abstract Interpretation (VMCAI'08)*, volume 4905, pages 42–58, 2008.

[5] Vincent Danos and Cosimo Laneve. Core formal molecular biology. *Theoretical Computer Science*, 325:69–110, 2003.

[6] Jérôme Feret. Reachability analysis of biological signalling pathways by abstract interpretation. In T.E. Simos, editor, *Proceedings of the International Conference of Computational Methods in Sciences and Engineering, ICCMSE '2007, Corfu, Greece*, number 963.(2) in American Institute of Physics Conference Proceedings, pages 619–622, Corfu, Greece, 25–30 September 2007. American Institute of Physics.

[7] Jérôme Feret, Vincent Danos, Jean Krivine, Russ Harmer, and Walter Fontana. Internal coarse-graining of molecular systems. *Proceedings of the National Academy of Sciences*, 106(16):6453–6458, April 2009.