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A LOGICAL PARADIGM FOR SYSTEMS BIOLOGY (INVITED TALK)

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Biologists use diagrams to represent complex systems of interaction between molecular species. These graphical notations encompass two types of information: interactions (e.g. protein complexation, modification, binding to a gene, etc.) and regulations (of an interaction or a transcription). Based on these structures, mathematical models can be developed by equipping such molecular interaction networks with kinetic expressions leading to quantitative models of mainly two kinds: ordinary differential equations (ODE) for a continuous interpretation of the kinetics, and continuous-time Markov chains (CTMC) for a stochastic interpretation of the kinetics.

The Systems Biology Markup Language (SBML) [8] uses a syntax of reaction rules with kinetic expressions to define such reaction models in a precise way. Nowadays, an increasing collection of models of various biological processes is available in this format in model repositories, such as for instance www.biomodels.net [9], and an increasing collection of ODE simulation or analysis software platforms are now compatible with SBML.

Since 2002, we investigate the transposition of programming concepts and tools to the analysis of living processes at the cellular level. Our approach relies on a logical paradigm for systems biology which consists in making the following identifications:

$$\begin{array}{c} \textit{biological model} = \textit{quantitative state transition system} \\ \textit{biological properties} = \textit{temporal logic formulae} \\ \textit{biological validation} = \textit{model-checking} \\ \textit{model inference} = \textit{constraint solving} \end{array}$$

Our modelling software platform Biocham [7] (implemented in Prolog) is founded on this paradigm [6]. An SBML model can be interpreted in Biocham at three abstraction levels:

- the Boolean semantics (asynchronuous Boolean state transitions on the presence/absence of molecules),
- the continuous semantics (ODE on molecular concentration),
- the stochastic semantics (CTMC on numbers of molecules).

The Boolean semantics is the most abstract one, it can be used to analyse large interaction networks without known kinetics. These formal semantics have been related in the framework of abstract interpretation in [5], showing for instance that the Boolean semantics is an abstraction of the stochastic semantics, i.e. that the possible stochastic behaviors can be

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checked in the Boolean semantics, and that if a Boolean behavior is not possible, it cannot be achieved in the quantitative semantics for any kinetics.

The use of model-checking techniques developed in the last three decades for the analysis of circuits and programs is the most original feature of Biocham. The temporal logics used to formalize the properties of the behavior of the system are respectively the Computation Tree Logic (CTL) for the Boolean semantics, and a quantifier-free Linear Time Logic with constraints over the reals (LTL($\mathbb{R}$)) for the quantitative semantics.

Biocham has been used for querying large Boolean models of the cell cycle by symbolic model-checking [1], formalizing phenotypes in temporal logic [3], searching parameter values from temporal specification [10], measuring the robustness of a system w.r.t. temporal properties [11], and developping in this way quantitative models of cell signalling and cell cycle for cancer therapies [2].

For some time, an important limitation of this approach was due to the logical nature of temporal logic specifications and their Boolean interpretation by true or false. By generalizing model-checking techniques to temporal logic constraint solving [3, 4], a continuous degree of satisfaction could be defined for temporal logic formulae, opening the field of model-checking to optimization in high dimension.

We believe that this mixing of discrete logical and continuous dynamics, pioneered by constraint logic programming and hybrid systems, and illustrated here in systems biology, is a deep trend for the future in programming and verification.

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