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From Solvable to Executable Models of Biological Systems

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Abstract

Modeling in biology is mainly grounded in mathematics, and specifically on ordinary differential equations (ODE). The programming language approach is a complementary and emergent tool to analyze the dynamics of biological networks. Here we focus on BlenX showing how it is possible to easily re-use ODE models within this framework. A budding yeast cell cycle example demonstrates the advantages of using a stochastic approach. Finally, some hints are provided on how the automatically translated model can take advantage of the full power of BlenX to analyze the control mechanisms of the cell cycle machinery.

Abstract models of biological systems are becoming an indispensable conceptual and computational tool for biologists. In order to be useful, a model has to be computable, to allow automatic analysis, and extensible, to permit the addition of further details without changing too much the already modeled knowledge.

Chemical kinetics has traditionally been analyzed using a mathematical formalism in which continuous (real) variables evolve deterministically, even if molecular populations in a biological/chemical systems are integer variables that evolve stochastically [1]. There is not yet a precise and agreed upon characterization of what is the best "usable form" in modeling biology, because some aspects are better handled with the deterministic approach, while for others the stochastic one is more suitable. For example, in the literature, beside deterministic ordinary differential equations (ODE for short), we find stochastic cell cycle models built with stochastic ODE Langevine type [2], with the Gillespie method [3] and with stochasticity on transitions [4].

After the work of Regev et al. [5], a promising trend is to use programming languages to generate executable models of biological

systems. This strategy diverge from classical mathematical modeling, because it is executable and not just simply solvable [6]. Execution means that we can describe the flow of control between species and reactions, e.g. not only the time, but also the causality relation among the events that constitute the history of the dynamics of the model. This interpretation is very similar to programming the behaviour of a system rather than describing only its outcome with respect to time. As a consequence, a number of process calculi have been adapted or newly developed for building biological models and performing stochastic simulations (i.e. stochastic π-calculus [7, 8], BioAmbients [9], Brane Calculi [10], CCS-R [11], k-calculus [12], Bio-PEPA [13]).

The main contribution of this work will be a semi-automatic method to translate existing deterministic models written with ODEs into programs written in the stochastic modeling language BlenX [14, 15]. The simple translation from general terms of the differential equations into the transitions of the stochastic BlenX model is possible because of the expressive power of the language that allows the definition of general rate functions for the transitions. The level of abstraction of a biological model, indeed, has important implications on the selection of the modeling formalism used to define its stochastic counterpart.

The translation procedure of existing ODE models into BlenX cannot be completely automatized, because it has to face the *inverse problem* of reaction kinetics [16]: more than one structurally different network of chemicals can produce the same set of ODEs. To disambiguate between those networks we need to have the knowledge of the interactions between all the species, but usually this knowledge is hidden in wiring diagrams that are not following strict or general conventions.

Our translation creates a model that can be stochastically simulated in order to answer questions that cannot be directly tackled by deterministic models. The simple mapping is possible because of the expressive power of BlenX that allows the definition of general rate functions for reactions. However the usage of the SSA algorithm with simple and complex kinetic laws leaves to the user the responsibility to validate simulation results. The example that we want to consider uses those different levels of abstraction and it will be be validated against experimental results.

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