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The Infobiotics Workbench: an integrated *in silico* modelling platform for Systems and Synthetic Biology

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ABSTRACT

Summary: The Infobiotics Workbench is an integrated software suite incorporating model specification, simulation, parameter optimization and model checking for Systems and Synthetic Biology. A modular model specification allows for straightforward creation of large-scale models containing many compartments and reactions. Models are simulated either using stochastic simulation or numerical integration, and visualized in time and space. Model parameters and structure can be optimized with evolutionary algorithms, and model properties calculated using probabilistic model checking.

Availability: Source code and binaries for Linux, Mac and Windows are available at http://www.infobiotics.org/infobiotics-workbench/; released under the GNU General Public License (GPL) version 3.

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1 INTRODUCTION

A comprehensive and generic framework for modelling biological systems from the molecular to organismal scales remains a distant prospect. As a step towards this, we have developed a modelling framework and supporting simulation and analysis software that is general enough to model a diverse range of systems, and tailored towards large, multi-compartment cellular systems. We have used our software to successfully model and address a number of problems in Systems and Synthetic Biology, including abscisic acid-related signal transduction networks (Dupeux *et al.*, 2011), multicellular molecular transport in *Arabidopsis thaliana* (Twycross *et al.*, 2010), and also in synthetic biology design (Cao *et al.*, 2010).

2 MODELLING FRAMEWORK

To facilitate the incremental modelling and rapid prototyping of multi-compartment systems, we have developed two complementary model representation languages: mcss-SBML, an extension of the Systems Biology Markup Language (SBML) (Hucka *et al.*, 2003); and a domain specific language (DSL), implementing lattice population P systems (Romero-Campero *et al.*, 2009). Both languages allow the specification of sets of, perhaps different, reactions in multiple compartments and transport of molecules between compartments (internal and adjacent in 2D space). These, in turn, can be organized in modules (parameterizable sets of reactions), which promote (sub)model reuse and hence facilitate debugging of model entities capturing biological functions. mcss-SBML models can be easily designed using existing visual editing tools such as CellDesigner (Funahashi *et al.*, 2003), and allow straightforward interchange of models with other software tools that support SBML. Our DSL is designed to provide a higher degree of control over the models being specified, and enables reuse of top-level compartments and modules between models.

3 CAPABILITIES

Infobiotics Workbench provides an assistive graphical interface to guide users in their parameter choices when performing simulation, model checking and parameter optimization experiments, and in analysing the results of these experiments. For computationally expensive models, experiments can be performed on high-performance computing clusters using the command line interface, and results analysed with the desktop GUI.

3.1 Simulation

The simulator offers a choice of either deterministic numerical approximation with standard solvers or execution with a stochastic simulation algorithm (SSA) (Gillespie, 2007). For performing deterministic simulations, we use the ODE solvers provided by the GNU Scientific Library (GSL) (Galassi *et al.*, 2009). These include explicit Runge-Kutta and implicit ODE solvers. As well as providing a baseline implementation of the canonical Gillespie Direct Method for stochastic simulations, we have developed a number of optimised multi-compartment SSAs (Romero-Campero *et al.*, 2009) which greatly improve performance and decrease simulation time for large models. With these algorithms, one can simulate models with tens of thousands of compartments and hundreds of reactions and species per compartment. The simulation results interface (Fig. 1A and B) enables the extraction and plotting of selected data. Time series are plotted combined in one plot or stacked/tiled with individual amounts or concentration axes for better comparison of fluctuations

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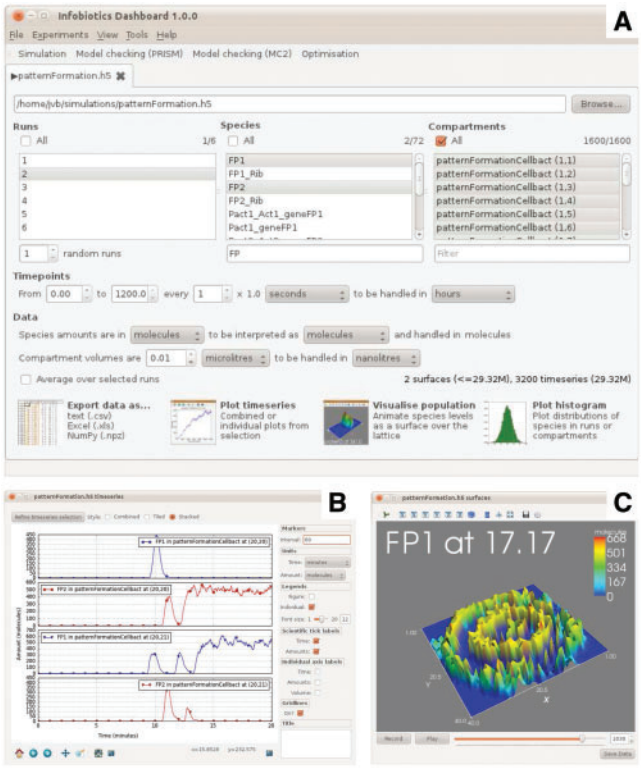

Fig. 1. The Infobiotics Workbench user interface enables the user to, e.g. (**A**) select data points, (**B**) edit time series plots and (**C**) visualize species amounts over the spatial lattice as a 3D surface.

with different orders of magnitude, and exported in text and Excel formats for further processing. For larger 2D models, a more intuitive overview of system behaviour is provided, which visualizes the spatially distributed amounts of selected species as 3D surfaces, animated over time (Fig. 1C). Frequency of species quantities at a given time can also be plotted as a histogram across compartments or runs.

3.2 Model checking

The Infobiotics Workbench interfaces with two model checkers: PRISM (Kwiatkowska *et al.*, 2010) and MC2 (Donaldson and Gilbert, 2008), allowing model properties, such as the probability of a species exceeding a certain threshold, to be determined. The results for each formula can be plotted in two ways: a 2D plot of the probability that the property is satisfied against one variable, or a 3D plot of probability against two variables. Both plot types can be used for queries with higher numbers of variables, enabling N-dimensional results sets to be interrogated.

3.3 Parameter and structure optimization

The Infobiotics Workbench can adjust the simulated behaviour of a model such that it fits time series data, e.g. molecular concentrations. This is done by optimizing the values of stochastic rate constants or the collection of modules that define a model's structure. Several parameter optimization algorithms are provided, e.g. differential evolution (Storn and Price, 1997) and covariance matrix adaptation (Hansen and Ostermeier, 2001). Structure optimization is performed using a genetic algorithm approach that we have developed (Cao *et al.*, 2010). The output of an optimization experiment is overlaid on the target, enabling a visual interpretation of fit.

4 CONCLUSIONS AND FUTURE WORK

The Infobiotics Workbench is an integrated *in silico* platform for model specification, simulation, formal verification and optimization of large-scale systems and synthetic biology models. We are currently implementing advanced simulation algorithms to further improve its computational efficiency, and intend to leverage GPGPU technology in the near future. Moreover, we would investigate how to link the Infobiotics Workbench with community-wide model repositories (Cooling *et al.*, 2010). Further information, tutorials and examples are available at http://www.infobiotics.org/infobiotics-workbench/. The community can report bugs or request features at http://bit.ly/qn9pUA.

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