EasyModel 1.1: User-friendly Stochastic and Deterministic Simulations for Systems Biology Models

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Abstract: EasyModel is a user-friendly web application that uses Wolfram webMathematica for performing simulations and analysis of systems biology models. EasyModel lets users create new models, load models from the BioModels database, and import preexisting models from SBML files. EasyModel mainly targets the student of bioinformatics or systems biology without the need of having Mathematica programming knowledge. In addition, expert programmers may find it useful as a tool for quickly implementing new models in Mathematica, which can then be downloaded as Mathematica notebooks to be tailored locally for more advanced simulation and analysis. The version described in this manuscript introduces the stochastic simulation feature. EasyModel is freely available at https://easymodel.udl.cat

1 INTRODUCTION

Molecular systems biology is a quantitative and integrative discipline. This implies that using software for mathematical modeling is a required skill for the systems biologist. Learning to create mathematical models for molecular systems biology is usually a task with a slow learning curve, as it requires a significant amount of technical skill.

Currently, there is a considerable array of tools for modeling and simulating of biological systems (SBML.org, 2019)(Alves et al., 2006). Most of these tools are standalone and can be used in a normal PC. There is a small number of general platforms for mathematical computation (PMC) such as Mathematica or Maple that can be adapted for systems biology modeling. These platforms offer a wide range of mathematical solutions, with flexible graphical user interfaces (GUI). Mathematica and Maple stand aside from other PMC because they support symbolic analysis. A drawback of using these and other PMCs is that the user must become an expert in coding for the platform. This drawback can be partially overcome by implementing a user-friendly application that uses a PMC as the motor for calculations, as other modeling tools have already demonstrated (Peters et al., 2017)(Helikar et al., 2012)(Benque et al., 2012).

For this reason we designed EasyModel, a web application for mathematical modeling in systems biology. It stands out for its user-friendly GUI that is usable by both beginner and expert users (Bartolome et al., 2019).

EasyModel 1.0 focused on the simulation of systems of ordinary differential equations using deterministic algorithms (Ascher and Petzold, 1997). Nevertheless, when the systems being modeled are composed of a small number of molecules, stochastic algorithms are more accurate (Maarleveld et al., 2013), and linear noise analysis is a more appropriate tool than sensitivity analysis to understand the limitations and regulation of the system (Paulsson, 2004). While stochastic simulation and linear noise analysis are available in several simulation applications (SBML.org, 2019)(Maarleveld et al., 2013)(Ballet et al., 2016), they lack the usability characteristics EasyModel provides to new systems biologists. Because of the importance of stochasticity in molecular systems biology, it is important that EasyModel also provides this functionality to its users. Hence, this manuscript describes the prototype for the next production version of EasyModel. This prototype, which we call EasyModel 1.1, enables a user-friendly sim-

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ulation and analysis of stochastic models in systems biology.

2 EasyModel

2.1 Origin and Objectives

Wolfram Mathematica provides many ready-to-use mathematical functions that are perfectly suited for simulating and analyzing mathematical models of biological systems. Nevertheless, its use requires that one knows how to create models for systems biology and how to program in the Mathematica language. This makes Mathematica less than ideal for use by beginners and students of systems biology. EasyModel is a web application that was created for facilitating the use of Wolfram Mathematica for modeling by beginner computational systems biologists, waiving the need to know how to program in Mathematica or develop mathematical models from scratch. Overall, our application provides a user-friendly interface that allows users to input the information for creating models in a simple way. Afterwards, it formats, wraps, and processes the information to create a Mathematical notebook and configure the simulation and analysis. This notebook is then sent to a webMathematica engine that performs the calculations. webMathematica returns the output in graphical and text form and our GUI picks up that information and provides it to the user.

2.2 EasyModel Working Context

EasyModel uses a conceptual representation of molecular biology networks and transforms that representation into systems of autonomous ordinary differential equations (ODE) that can be used to simulate the dynamic behavior of the network. The networks are represented in terms of individual processes or reactions that consume substrates, generate products, and whose reaction rate can be modulated by modifiers (activators or inhibitors). The rate of each reactions is described by a kinetic function that depends on some of the species in the networks and on reaction specific parameters. The integration of all these elements conforms a mathematical model of the biological network of interest (Figure1).

Users provide the program with the individual processes using the following notation:

$$K_1 * S_1 + ... -> C_1 * P_1 + ...; M_1; ... \quad (1)$$

In Equation 1 K_x,C_x represent the species coefficients, S_x represents the substrates (left-hand side of the arrow), P_x represents the products (right-hand side of the arrow), and M_x represents modifier species that influence the rate but are not substrates.

After the structure of the model is defined through its processes, a kinetic rate law needs to be associated to each of the reactions. These rate laws are standard mathematical functions that depend on a subset of the network species and on parameters whose values are specific for each reaction. EasyModel allows users to select rate laws with a predefined formalism (Power Law, Mass Action, Saturating and cooperative (Sorribas et al., 2007) or create custom made formulas.

2.3 Usage and Features

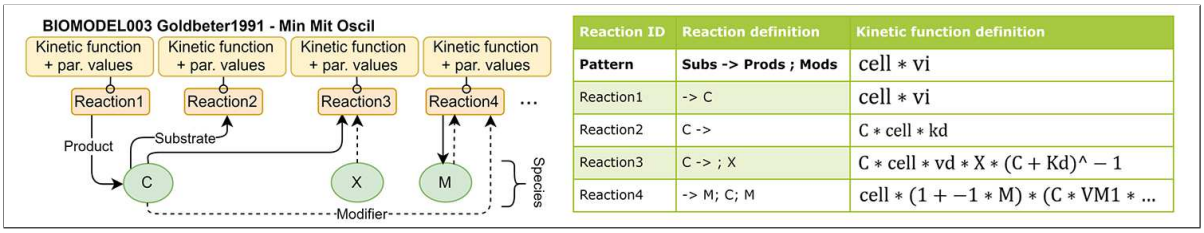
In the initial page of the web application, the visitor can log in as a registered user or try the application as a guest user. Guest users are provided with a brief tutorial on how to use EasyModel before accessing the application itself. The tutorial can be skipped and it is always available to consult in the *Tools* option. In addition to the the tutorial, the application has *Information* buttons all across the GUI so that users can consult what to do next at each step.

The application is designed in 4 basic steps:

1. Select the model (or create a new one)
2. Modify or build the model
3. Configure the simulation/s
4. Get the simulation results

In step one, users must select a model repository: public or private (see Figure 2). The public repository includes built-in models. Many of these are either from the BioModels Database (Le Novère et al., 2006) or developed and published by the other users of the platform. The private repository permits users to create new models or continue editing unfinished models. Guest users can create new models to use but they cannot be saved in the system. They can however download them in SBML form and re-upload again at a later time by importing the SBML file. In fact EasyModel complies with SBML (Hucka et al., 2003) Level 3 Version 2 specification and it can upload models described with that specification. SBML facilitates the interchange of biologic system models between many available modeling tools.

Model building in step two requires defining the individual reactions of the model (see Figure 3), as well as the rate laws (see Figure 4). Users can either select a predefined rate law or define a new one as a standard mathematical function. Each reaction of the system must have an assigned rate law, with its set of parameter values. The parameters may have a



Reaction ID	Reaction definition	Kinetic function definition
Pattern	**Subs -> Prods ; Mods**	cell ∗ vi
Reaction1	-> C	cell ∗ vi
Reaction2	C ->	C ∗ cell ∗ kd
Reaction3	C -> ; X	C ∗ cell ∗ vd ∗ X ∗ (C + Kd)^ − 1
Reaction4	-> M; C; M	cell ∗ (1 + −1 ∗ M) ∗ (C ∗ VM1 ∗ ...

Figure 1: Biological system model BIOMODEL003 (Goldbeter, 1991).

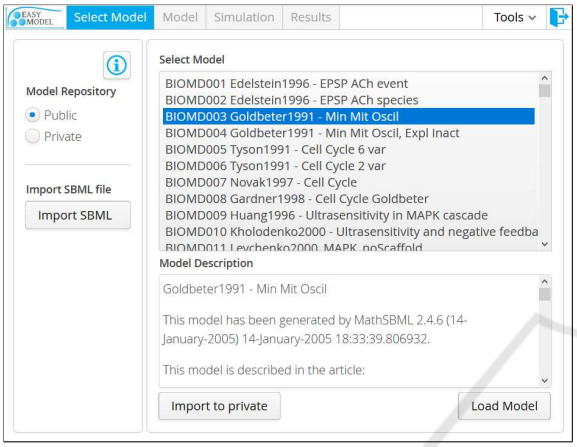


Figure 2: Selecting model.

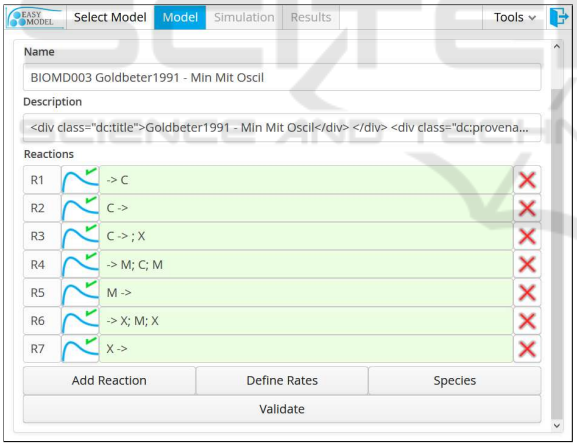


Figure 3: Modeling the reactions.

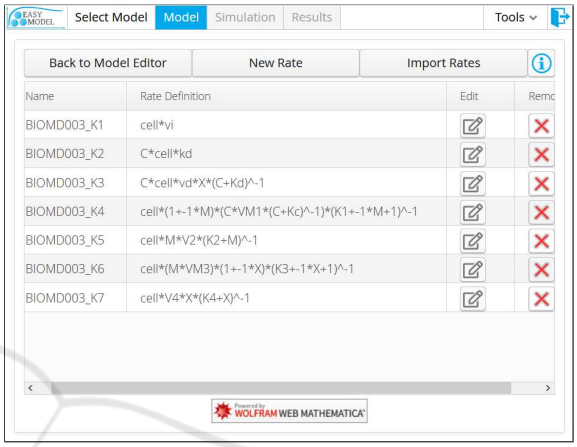


Figure 4: Defining the rate laws.

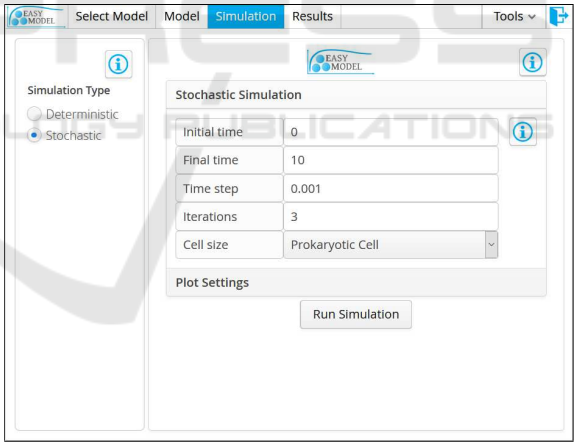


Figure 5: Stochastic simulation configuration.

numerical value or be linked to a substrate or modifier species of the network.

Initial concentrations of the system species must be specified as well. If not, EasyModel automatically sets them to 1.

To proceed to step three, EasyModel must validate the model, warning the user if additional information or modifications are required.

In step three, and after model validation, users define what simulations and analyses are to be performed in webMathematica (see Figure 5).

During the simulation configuration step, users can choose whether they will perform a deterministic simulation (if the system has a large number of molecules) or a stochastic simulation. This later type of simulation is a new feature of the version being described here.

For deterministic simulations, the user may perform time course and steady state simulations, as well as sensitivity analysis with respect to model parameters and independent variables. Sensitivity analysis can be requested for steady state and time-course simulations. A linear stability analysis of steady states can also be performed.

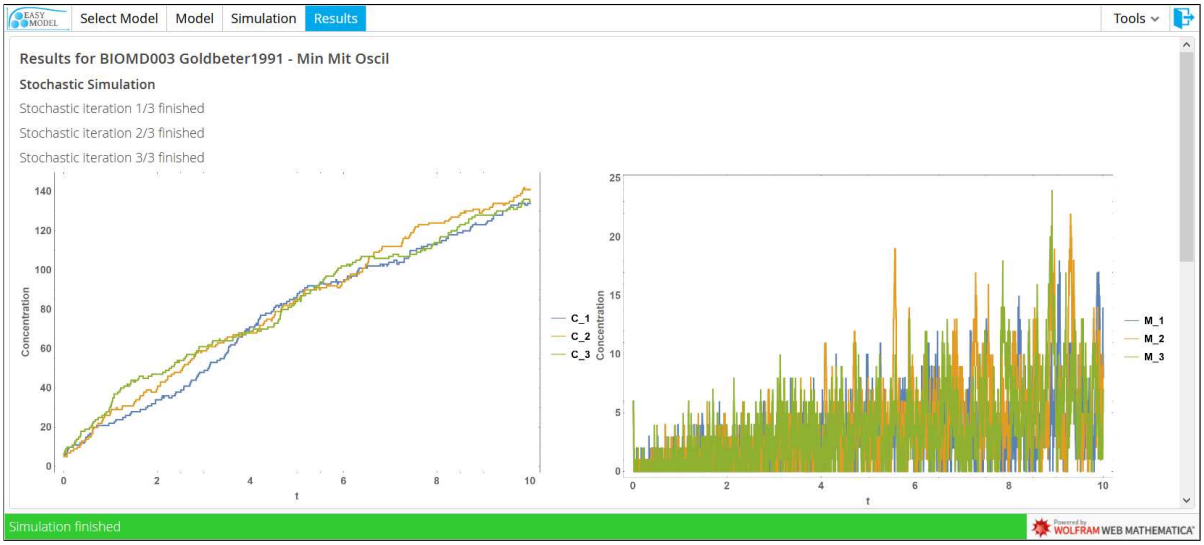


Figure 6: Stochastic simulation results.

For stochastic simulations, users define the physical size of the system, how many times they want to repeat the simulation and how long the system is to be simulated. EasyModel also provides the intrinsic noise of the system for each dependent variable by calculating the coefficient of variation and the quartile coefficient of dispersion for each species. Default cell size is considered by the program to be that of *Prokaryotic cell*. Default number of repeat simulation is set to 3. Default end time of the simulation is set to 10 time units.

Once all actions are configured, the user presses the simulation button and the program goes to step four. In this step all the data is sent to the webMathematica calculation engine (Mathematica kernel), which performs the simulation and returns the results to the user. Individual results are returned immediately after being computed, in real-time (see Figure 6). Results are represented in plots and tables that can be downloaded. The user can cancel the simulation at any time and the system will stop after the execution of the webMathematica command that was being evaluated before pressing the button. In addition to the graphical representation of the results, users may also download the generated Mathematica notebook and the model in SBML format.

EasyModel stores user account information as well as the the models and rate laws the users introduce into the system. Simulation results are not stored into the database.

2.4 Implementation

EasyModel is implemented by merging various technologies. The web application is written in Java EE, using the open-source Vaadin 8 Framework for developing the web user interface (UI). The calculation engine is the Wolfram webMathematica (Wolfram Research Inc., 2108), which communicates with the Java EE application. User data, such as user account, models and rate laws, is stored in a database using the open-source MySQL 8 Community Server database manager. Finally, the web application is deployed on the Apache Tomcat 9 web application server.

To implement the SBML file format compatibility, JSBML Java library (Dräger et al., 2011) is used.

The source code is available at https://github.com/jordibart/easymodel and licensed under the GNU GPL. All the dependencies of EasyModel are open-source except for webMathematica, which requires a commercial license.

3 CONCLUSIONS

EasyModel is a user-friendly tool for creating and analyzing simple mathematical models of biological networks in systems biology. While it is aimed at novel systems biologists and students, the tool can also be of profit for more advanced researchers, as they can quickly implement their models and download them for further local tailoring for more advanced analysis.

While the production version of EasyModel is limited to deterministic simulation and analysis, here

we present an evolution of the tool that enables stochastic simulations and biological noise analysis in the context of those simulations. Stochastic simulations are significantly more complex in computational terms and require longer CPU times to conclude than analogous deterministic simulations. Nevertheless, this type of simulations accurately describes the dynamic behavior of systems with a small number of molecules, something that deterministic simulations can not always do.

This new prototype of EasyModel 1.1 is now being tested before it is rolled out to replace the current 1.0 production version. Once this task is done we will implement additional functionality to enable user-friendly ways to merge individual models, to scan parameter values and independent variables, and to perform bifurcation analysis.

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