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SBMLWebApp: Web-based Simulation, Steady-State Analysis, and Parameter Estimation of Systems Biology Models

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Abstract: In systems biology, biological phenomena are often modeled by Ordinary Differential Equations (ODEs) and distributed in the *de facto* standard file format SBML. The primary analyses performed with such models are dynamic simulation, steady-state analysis, and parameter estimation. These methodologies are mathematically formalized, and libraries for such analyses have been published. Several tools exist to create, simulate, or visualize models encoded in SBML. However, setting up and establishing analysis environments is a crucial hurdle for non-modelers. Therefore, easy access to perform fundamental analyses of ODE models is a significant challenge. We developed SBMLWebApp, a web-based service to execute SBML-based simulations, steady-state analysis, and parameter estimation directly in the browser without the need for any setup or prior knowledge to address this issue. SBMLWebApp visualizes the result and numerical table of each analysis and provides a download of the results. SBMLWebApp allows users to select and analyze SBML models directly from the BioModels Database. Taken together, SBMLWebApp provides barrier-free access to an SBML analysis environment for simulation, steady-state analysis, and parameter estimation for SBML models. SBMLWebApp is implemented in Java™ based on an Apache Tomcat® web server using COPASI, the Systems Biology Simulation Core Library (SBSCL), and LibSBMLSim as simulation engines. SBMLWebApp is licensed under MIT with source code available from https://github.com/TakahiroYamada/SBMLWebApp. The program runs online at http://simulate-biology.org.

Keywords: SBML; kinetic models; time-course simulation; steady-state simulation; parameter estimation; model calibration; software; web application

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1. Introduction

Kinetic models allow capturing the complex relationships of biological systems, e.g., between enzyme expression, metabolite levels, reaction fluxes, and regulatory processes [1]. Kinetic models are of particular interest when exploring dynamic effects [2]. The mathematical description of kinetic models can be formalized using a system of coupled nonlinear ODEs [3], which defines the state variables of the model and their possible evolution. These ODEs quantitatively describe the dynamics of kinetic systems and facilitate predicting the response of the model state to various perturbations, i.e., different inputs, altered kinetic parameters, or changing initial conditions [4]. The theory of creating kinetic models is generally established, and simplifying assumptions for the choice of particular equations were have been proposed [5]. Their predictive power has

turned kinetic models into a valuable resource for understanding biological systems. This, in turn, helped to excel advances in, e.g., biotechnological fields such as improving microbial strain design [6].

Three primary analyses are typically performed with kinetic models: (a) time–course simulation, (b) steady-state analysis, and (c) parameter estimation. The objective behind the *time-course simulation* is to mathematically describe the evolution of the investigated ODE system from given initial conditions. Thereby, the dynamics of the biological system can be investigated, e.g., the model's behavior in response to varying inputs or other perturbations. Biological systems often reach a steady state after a long enough time, i.e., a state in which the metabolic concentrations remain constant. For some systems, multiple steady states may exist, and transitions between them may take place. *Steady-state analysis* numerically calculates possible steady states and evaluates likely transitions into a particular system's state under the given conditions. *Parameter estimation* is a method to determine plausible values model's parameters based on experimental data, e.g., reaction rate constants. For this reason, this procedure is sometimes called *model calibration* because data from laboratory experiments are compared to the output of model simulations aiming to fit the model to the data. Consequently, parameter estimation is often a prerequisite step for subsequent analyses, and it uses repeated time-course simulations.

SBML is the *de facto* standard file format for computational models of biological systems [7,8]. For the analysis of kinetic models in SBML, several tools are available, e.g., the COmplex PAthway SImulator (COPASI) [9], the Systems Biology Toolbox for Matlab™ [10], libRoadRunner [11], or SBMLsimulator [12]. Many of these tools may cause difficulties to inexperienced users during installation or use of their algorithms and conventions. Some tools focus on a limited set of highly specialized functions, while others overwhelm their users with a large variety of features. Often, the users are indirectly assumed to understand the internal structures of systems biology model formats. In addition, many scientific software tools require a profound computational background or even coding skills to interact with the software. Installing these applications may not always be allowable if it requires administrator rights requires admin rights which are not always granted to every user in a research environment. These points might represent a considerable challenge for novice modelers or collaborators with an experimental background. A practical solution to these problems is to provide user-friendly and barrier-free access to a web application that can execute all the abovementioned analyses without requiring coding skills or admin setup rights.

A few freely available web applications for working with models in SBML format exist. APMonitor [13] supports simulation and parameter estimation but does not support steady-state analysis. One of the available standalone tools for simulation and parameter estimation is SBMLsimulator [12], which can be used via command-line or its Java™-based Graphical User Interface (GUI), but does not run online. Cycsim [14] supports visualization and time-course simulation of metabolic networks but no parameter estimation. The Systems Biology Workbench (SBW) [15] supports time course simulation and steady-state analysis but not parameter estimation. JWS Online [16] supports simulation and steady-state analysis but does not support parameter estimation. The tool suite RunBioSimulations [17] offers time course simulation and steady-state analysis but lacks support for parameter estimation. Additionally, RunBioSimulations offers many third-party analysis tools with many options and is hence most suitable for experienced users.

This article presents the user-friendly web application *SBMLWebApp* which allows the integrated analysis of kinetic models using time-course simulation, steady-state analysis, and parameter estimation. To the authors' best knowledge, currently, no other web application exists besides the SBMLWebApp, with which novice users can effortlessly conduct all three analysis steps described above within a single framework. The SBMLWebApp, therefore, drastically expedites a profound and detailed analysis of

kinetic models since all three steps are deeply intertwined, and the knowledge gained from a previous analysis step is often essential for following analyses. For example, time-course simulations with varying inputs are often executed after an initial system steady-state has been reached, i.e., first, a steady-state analysis is performed following by time-course simulations with varying inputs. For example, parameters determined via its parameter estimation features are subsequently used in time course and steady-state simulations to analyze the system behavior.

Providing a directly accessible web application with an intuitive user interface that combines services for time-course simulation, steady-state analysis, and parameter estimation makes a large portion of typical analyses within systems biology research accessible to less experienced users. In this way, the SBMLWebApp supports interdisciplinary collaboration as it allows experimentalists to effortlessly try out *in-silico* models from their dry-lab collaborators, which may help to accelerate the iterative cycles of alternating model development and wet-lab experimentation towards scientific progress.

2. Implementation

SBMLWebApp is implemented in Apache Tomcat® (https://tomcat.apache.org), and all servlets were written in Java™. The app uses the Bootstrap framework and is deployed on a Java application server using JQuery. SBMLWebApp uses AJAX software within the communication configuration between frontend and backend (GWT, http://www.gwtproject.org). The time course simulation servlet is executed using COPASI [9], SBSCL [18,19] with JSBML [20] as its internal data structure, and LibSBMLSim [21] that is based on libSBML [22]. The steady-state analysis servlet and parameter estimation servlet use COPASI [9]. The SBMLWebApp is accessible at http://simulate-biology.org. Our app uses the standard file format for computational models, SBML [7,8], and is compatible with SBML Level 3 Version 1 [23].

3. Using the SBMLWebApp

Either a local SBML model or models from the BioModels Database [24] can be selected on the front page. BioModels is a highly curated database for computational biological models, currently containing 1,017 manually curated SBML models (August 2021).

After selecting the SBML model, the relationships between species and reactions (stoichiometric network) are visualized (figure 1) based on cytoscape.js [25].

To run a time course simulation with the model, the user can specify the end time, the number of time points, the absolute tolerance, and the simulation library to use as solver backend. After setting these parameters and pressing the execute button, the simulation result is visualized as a graph (figure 2), and the numerical results are provided in a table. Via the window on the right side, the initial amount of each species, the size of compartments, and values of kinetic parameters in the model can be edited. The respective simulation is executed on the fly.

To run a steady-state analysis with the model, the available parameters that the user can specify the resolution, derivation factor, and iteration limit to search steady states. After steady-state analysis, a single steady-state point of given initial expression for each species and the corresponding Jacobian matrix of this point is visualized as a numerical table (figure 3).

To run a parameter estimation with the model, the algorithm, iteration limit to search fitted parameters, and fitting tolerance can be set. Available algorithms include the Levenberg-Marquardt algorithm [26,27], the Nelder Mead-algorithm [28], the particle swarm optimization method [29], and the differential evolution method [30]. The two latter optimization methods had been found to be particularly promising for the task of dynamic model calibration in systems biology applications [31]. The execution of a parameter estimation leads to a visualization of the simulation result with calibrated parameter and experimental results in figure 4 and fitted parameter as a numerical

table. The range of search parameters can be set in the window on the right side, and an analysis based on it can be executed after pressing return.

All result data can be downloaded via the "Download" tab. The graph and table are downloaded as PNG and CSV, respectively. In parameter estimation, the model with calibrated parameters can be downloaded in SBML format.

4. Conclusion

SBMLWebApp is a web-based and freely available application to execute time course simulation, steady-state analysis, and parameter estimation for models in SBML. As open-source software, SBMLWebApp can be used as an example implementation of such a service and allows contributions and feature requests from the scientific community. It was developed to provide novice modelers and other non-specialist intuitive access to the core analyses for kinetic SBML models.

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Data Availability Statement: The SBMLWebAPP is accessible from http://simulate-biology.org.

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Abbreviations

The following abbreviations are used in this manuscript:

CSV	Comma-Separated Values
COPASI	COmplex PAthway SImulator
GUI	Graphical User Interface
GWT	Google Web Toolkit
ODE	Ordinary Differential Equation
PNG	Portable Network Graphics
SBML	Systems Biology Markup Language
SBSCL	Systems Biology Simulation Core Library
SBW	Systems Biology Workbench

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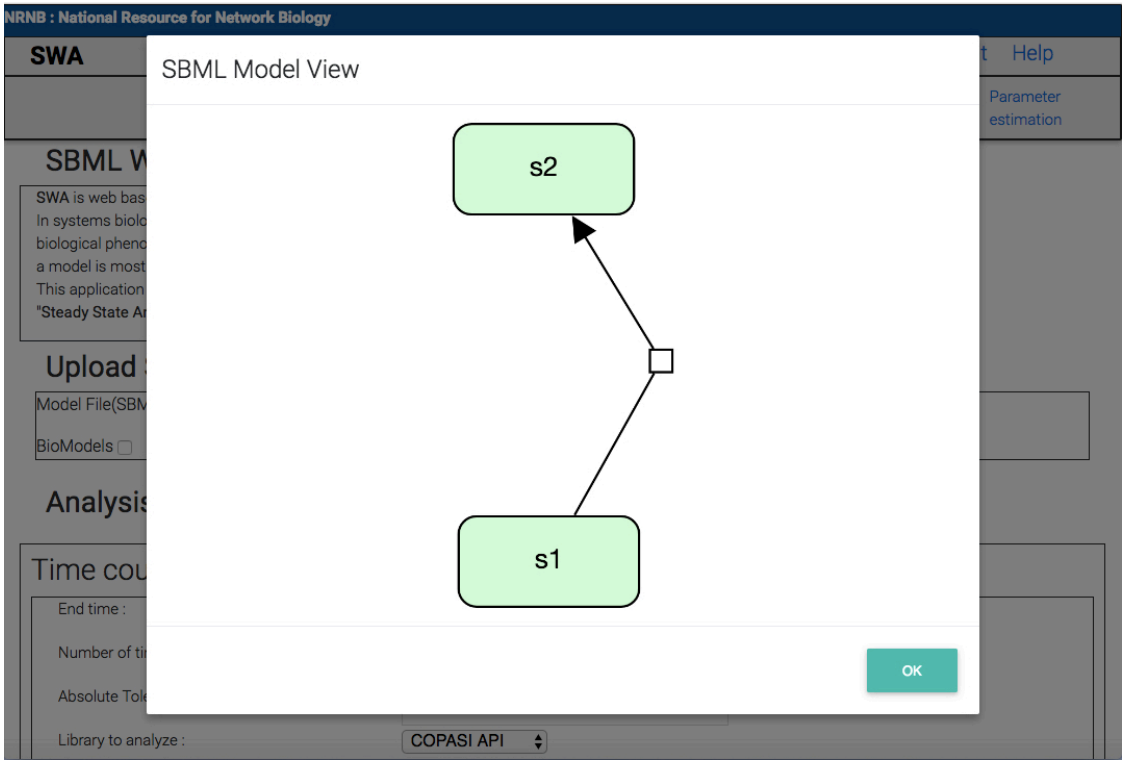

Figure 1. SBML graph visualization of a simple example model consisting of the species s1 and s2. The graph shows the relationships between species and reactions in the SBML model. Species with a reactant role have no arrow (s1), whereas species with a product role have an arrow (s2).

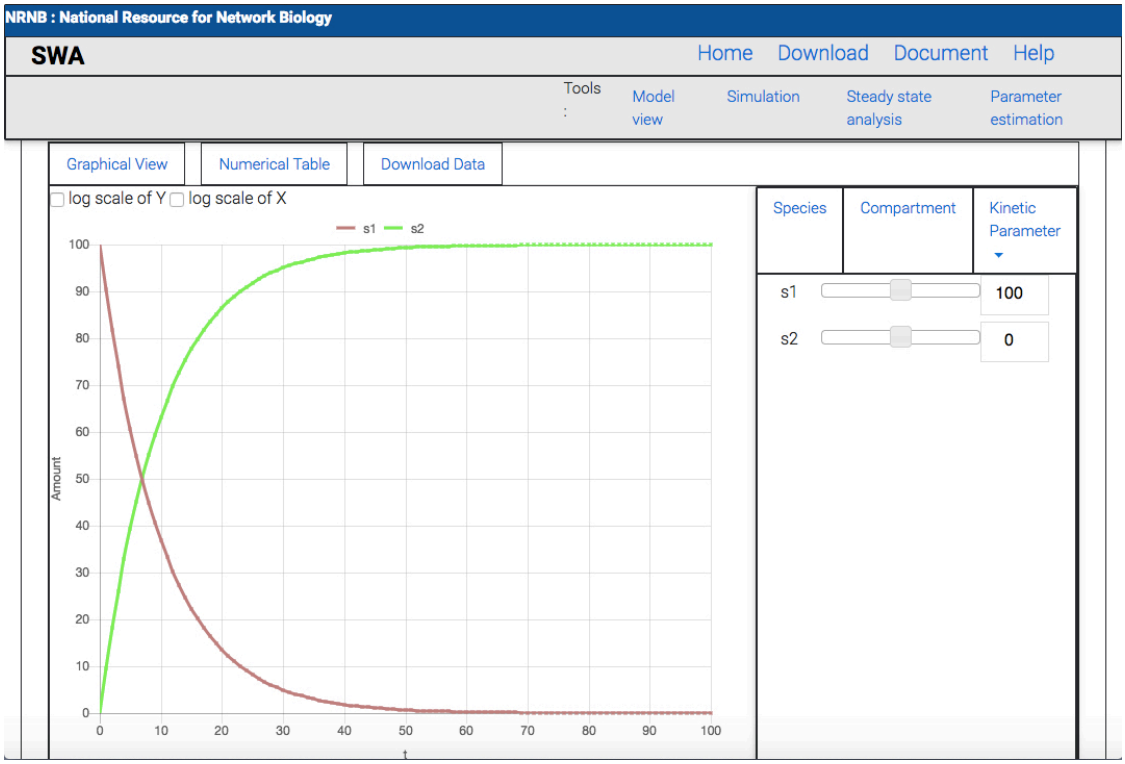

Figure 2. Results of time-course simulation analysis. The x-axis shows the time, and the y-axis indicates amounts or concentrations of species depending on which of either the SBML model defines for the respective species. Each line in the graph corresponds to the time course of a single species. The check box of "log scale of Y" and "log scale of X" allows switching between linear and logarithmic axis scales. The initial values of species, compartment sizes, and kinetic parameters can be changed via the window on the right side. When a value is changed, the simulation is executed on the fly.

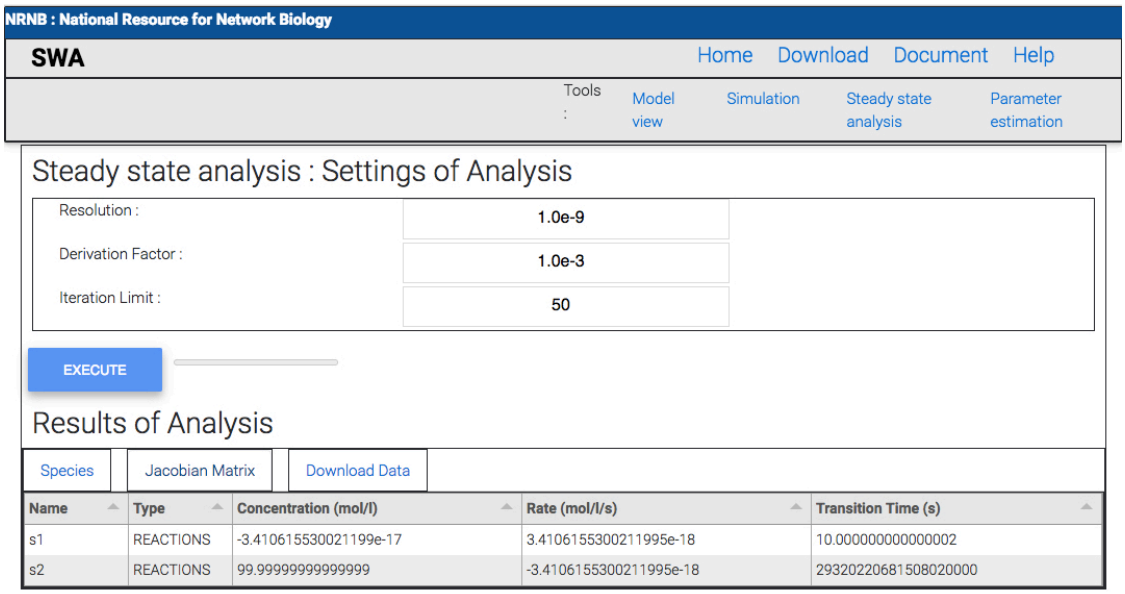

Figure 3. The result of a steady-state analysis. The result shows the type of species, concentration in the steady-state point, the rate at this point, and transition time to reach this point from the initial value of each species.

Figure 4. The result of parameter estimation. The x- and y-axis in the graph show time vs. amount or concentration in the SBML model. Each line shows the simulation result with a fitted parameter of each species. Each plot shows the experimental value of each species. The check box of "Before Fitting" can visualize the simulation result with the original parameter value. The range searching proper parameter can be set using the slider on the window's right side