The Systems Biology Simulation Core Library

Hemil Panchiwala1†, Shalin Shah2,3†, Hannes Planatscher4,5, Mykola Zakharchuk3, Matthias König5,6, and Andreas Dräger5,7,8,9,*

1Department of Computer Science and Engineering, Indian Institute of Technology, Roorkee, India - 247667
2Department of Electrical and Computer Engineering, Duke University, Durham, NC 27701, United States of America
3Bloomberg LP, New York, NY 10022, United States of America
4Signatope GmbH, 72770 Reutlingen, Germany
5Department of Computer Science, University of Tübingen, 72076 Tübingen, Germany
6Institute for Theoretical Biology, Humboldt University of Berlin, 10115 Berlin, Germany
7Computational Systems Biology of Infections and Antimicrobial-Resistant Pathogens, Institute for Bioinformatics and Medical Informatics (IBMI), University of Tübingen, 72076 Tübingen, Germany
8German Center for Infection Research (DZIF), partner site Tübingen, Germany
9Cluster of Excellence ‘Controlling Microbes to Fight Infections,’ University of Tübingen, Tübingen, Germany
*These authors contributed equally to the manuscript.
†Corresponding author: draeger@informatik.uni-tuebingen.de

ABSTRACT

Summary: Studying biological systems generally relies on computational modeling and simulation, e.g., for model-driven discovery and hypothesis testing. Progress in standardization efforts led to the development of interrelated file formats to exchange and reuse models in systems biology, such as SBML, the Simulation Experiment Description Markup Language (SED-ML), or the Open Modeling EXchange format (OMEX). Conducting simulation experiments based on these formats requires efficient and reusable implementations to make them accessible to the broader scientific community and to ensure the reproducibility of the results. The Systems Biology Simulation Core Library (SBSCL) provides interpreters and solvers for these standards as a versatile open-source API in Java™. The library simulates even complex bio-models and supports deterministic Ordinary Differential Equations (ODEs); Stochastic Differential Equations (SDEs); constraint-based analyses; recent SBML and SED-ML versions; exchange of results, and visualization of in silico experiments; open modeling exchange formats (COMBINE archives); hierarchically structured models; and compatibility with standard testing systems, including the Systems Biology Test Suite and published models from the BioModels and BiGG databases.

Availability and implementation: SBSCL is freely available at https://draeger-lab.github.io/SBSCL/.

Keywords: Systems Biology, Numerical Solver, Java™, API Library, SBML, SED-ML, OMEX, Constraint-Based Modeling, Stochastic Simulation, Ordinary Differential Equation Systems

1 Introduction

The Systems Biology Simulation Core Library (SBSCL) is an open-source, cross-platform pure Java™ programming library that numerically solves systems biology models in multiple mathematical frameworks. A popular file format for representing computational models in a standard way and facilitating the exchange of models between different tools is the Systems Biology Markup Language (SBML)7. SBML encodes biological models in a declarative form. The Simulation Experiment Description Markup Language (SED-ML) format defines a workflow of simulation experiments. Using SED-ML and SBML in combination enables the reproducibility of typical model workflows in in silico experiments, including the choice of interpretation framework and the postprocessing of the results15. SBSCL interprets the SBML models using the JSBML library4,13 and simulates them according to dedicated API calls. Alternatively, it extracts an in silico experimental configuration from SED-ML to simulate the SBML models. To this end, SBSCL implements and ships several solvers for a wide range of mathematical frameworks, including ODEs8, SDEs6, and constraint-based analysis. SBSCL is designed as a lightweight API and intended for use as a simulation backend within end-user software, such as SBMLsimulator2,3. This article introduces the SBSCL library, especially the new features introduced in version 2.0, along with a brief description of all other capabilities that are pictorially summarized in figure 1 on the following page.

2 Description

Differential equation solver: The most fundamental feature of SBSCL is simulating ODEs. Version 2.0 adds interpreters and solvers for SDEs to support the latest SBML standards. SBSCL efficiently implements three deterministic numerical solvers, namely, Rosenbrock, Euler, and Runge-Kutta, as well as three stochastic solvers, namely, Gillespie, Gibson-Bruck, and Tau-Leaping.6

Constrained optimization solver: SBML Level 3 combined with the fbc package12 added support for constrained-based models and their analysis. Typically, Flux Balance Analysis (FBA) is used for such time-invariant steady-state
simulations. SBSCL performs FBA on SBML models using the SCP Solver (http://www.scpSolver.org), a linear programming API with support for various solver backends. This lightweight abstraction allows users to define model constraints and an objective function and solve the corresponding optimization problem.

Result tables and plots: Since viewing is an essential aspect of understanding the results of a simulation experiment, SBSCL provides experiment output in graphical and tabular form, which it can export in conventional formats such as CSV.

Archival format support: Working towards exchangeability and reproducibility, SBSCL version 2.0 supports the OMEX format as input. These archive files contain the information on running simulation experiments based on SBML and SED-ML\(^1\). SBSCL uses the COMBINE Archive Simulation Experiment Management for Systems Biology (SEMS) package to read and extract the required information from the OMEX files.

Hierarchical model simulations: The SBML extension package comp\(^{14}\) enables encoding complex and coupled biological systems that can be distributed or hierarchically structured. SBSCL version 2.0 efficiently supports simulation of this addition, including the automatic assembly of models from multiple and possibly remote input files.

Tests against benchmark suites: A crucial part of implementing new features is providing robust testing of the added functionality and use-cases. SBSCL tests all newly added features against the SBML Test Suite in a continuous integration approach. SBSCL provides full testing support against the genome-scale models from the BiGG Models database with COBRApy\(^5\) and kinetic models from the BioModels database.

3 Conclusion

The open-source library SBSCL simulates complex biological models in various frameworks specified in SBML format, optionally together with their in silico experiment definition.
SED-ML file or wrapped within OMEX archives. Benchmarks of SBSCL using the SBML Test Suite and a broad range of published models from relevant databases ensure its correctness and reliability. With the support for exciting new features such as constraint-based model optimization, hierarchical model decomposition, stochastic algorithms, archival input formats, this lightweight library is well suited as a simulation engine within any software with support for the Java Virtual Machine, e.g., Kotlin, Scala, or Groovy. The SBSCL project aims to provide a high-quality open-source simulation library to the scientific community to push frontiers and reproducibility in biology and related fields.

Acknowledgments

The authors acknowledge contributions by Nicolas Rodriguez, Alexander Dörr, Roland Keller, and the Harvey Mudd College for the ODEToolkit.

Funding: The National Resource for Network Biology (NRNB) and Google Inc. supported this work as part of their summer of code programs (GSoC). AD was funded by the German Center for Infection Research (DZIF), grant No. 8020708703, and supported by infrastructural funding from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), Cluster of Excellence EXC 2124 Controlling Microbes to Fight Infections. MK is supported by the Federal Ministry of Education and Research (BMBF, Germany) within the research network Systems Medicine of the LiSyM, grant No. 8020708703, and supported by the German Research Foundation (DFG, German Research Foundation), Cluster of Excellence EXC 2124 Controlling Microbes to Fight Infections. The authors acknowledge contributions by Nicolas Rodriguez, Alexander Dörr, Roland Keller, and the Harvey Mudd College for the ODEToolkit.

Conflict of interest: None

Abbreviations

API Application Programming Interface  
BiGG Biochemically, Genomically, Genetically structured  
BMBF Federal Ministry of Education and Research  
COMBINE Computational Modeling of Biological Networks  
comp SBML extension package for Hierarchical Model Composition  
CSV Comma-Separated Values  
DFG Deutsche Forschungsgemeinschaft, German Research Foundation  
DZIF German Center for Infection Research  
FBA Flux Balance Analysis  
fbc SBML extension package for Flux Balance Constraints  
GSoC Google Summer of Code  
NRNB National Resource for Network Biology  
ODE Ordinary Differential Equation  
OMEX Open Modeling EXchange format  
SBML Systems Biology Markup Language  
SBSCL Systems Biology Simulation Core Library  
SDE Stochastic Differential Equation  
SED-ML Simulation Experiment Description Markup Language  
SEMS Simulation Experiment Management for Systems Biology  

References