

Systems Biology

libRoadRunner 2.0: A High Performance SBML Simulation and Analysis Library

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Abstract

Motivation: This paper presents libRoadRunner 2.0, an extensible, high-performance, cross-platform, open-source software library for the simulation and analysis of models expressed using the Systems Biology Markup Language (SBML). **Results:** libRoadRunner is a self-contained library, able to run either as a component inside other tools via its C++, C and Python APIs, or interactively through its Python or Julia interface. libRoadRunner uses a custom Just-In-Time (JIT) compiler built on the widely-used LLVM JIT compiler framework. It compiles SBML-specified models directly into native machine code for a large variety of processors, making it fast enough to simulate extremely large models or repeated runs in reasonable timeframes. libRoadRunner is flexible, supporting the bulk of the SBML specification (except for delay and nonlinear algebraic equations) as well as several SBML extensions such as hierarchical composition and probability distributions. It offers multiple deterministic and stochastic integrators, as well as tools for steady-state, sensitivity, stability and structural analyses. **Availability:** libRoadRunner binary distributions for Windows, Mac OS, and Linux, Julia and Python bindings, source code, and documentation are all available at <https://github.com/sys-bio/roadrunner>, and Python bindings are also available via pip. The source code can be compiled for the supported systems as well as in principle any system supported by LLVM-13, such as ARM-based computers like the Raspberry Pi. The library is licensed under the Apache License Version 2.0. **Contact:**hsauro@uw.edu

1 Introduction

Dynamic network models (Sauro, 2014) of metabolic, gene regulatory, protein signaling and electrophysiological models require the specification of components, interactions, compartments and kinetic parameters. The Systems Biology Markup Language (SBML) (Hucka et al., 2003; Keating et al., 2020) has become the *de facto* standard for declarative specification of these types of models (see SBML.org).

Popular tools for the development, simulation and analysis of models specified in SBML include COPASI (Hoops et al., 2006), the Systems Biology Workbench (SBW) (Bergmann and Sauro, 2006), the Systems

Biology Simulation Core Library (SBSC) (Panchiwala et al., 2021), libSBMLSim (Takizawa et al., 2013), iBioSim (Myers et al., 2009), PySB (Lopez et al., 2013), PySCeS (Olivier et al., 2005), and VirtualCell (Moraru et al., 2008), as well as many legacy tools that have been superseded by more modern software. Some of these applications are stand-alone packages designed for interactive use. Very few are reusable libraries. Currently, none are fast enough to support emerging applications that require large-scale simulation of network dynamics (Maggioli et al., 2020). For example, multicell virtual-tissue simulations (Hester et al., 2011) often require simultaneous simulation of tens of thousands of replicas of models residing in their cell objects and interacting between cells. In addition, optimization methods require the generation of time-series for tens of thousands of replicas to explore the high-dimensional parameter spaces typical of biochemical networks (Bouteiller et al., 2015).

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Previously we published libRoadRunner version 1, a cross-platform, multi-language library for fast execution of SBML model simulations. We designed libRoadRunner to provide: 1) Efficient time-series generation and analysis of large or multiple SBML-based models; 2) A comprehensive and logical API; 3) Interactive simulations in the style of IPython and MATLAB; and 4) Extensibility. The library achieves its performance capabilities by compiling SBML directly into machine code ‘on-the-fly’ using LLVM as a ‘just-in-time’ (JIT) compiler (Lattner and Adve, 2004). The SBML model description is lexed and parsed into an abstract syntax tree (AST) using libSBML. Then libRoadRunner creates the necessary low-level LLVM intermediate representation (IR) code for compiling the SBML. Once compiled, the SBML representation of the model has been converted into an in-memory dynamic library from which symbols representing model functions can be exported and loaded into other languages. libRoadRunner wraps this low-level interface in user-friendly C and C++ APIs, which, in turn, provide the foundation for critical systems modelling tasks, such as model integration, steady-state analysis and metabolic control analysis (Somogyi et al., 2015).

libRoadRunner users usually fall into one of two categories: modellers or tool developers. Modellers use the libRoadRunner tool directly in their research for modelling dynamic systems (Karagöz et al., 2021; Köller et al., 2021; Köller et al., 2021) or for developing new computational approaches such as detecting bistable switches (Reyes et al., 2022) or performing dynamic flux balance analysis (Watanabe et al., 2018). Tool developers, on the other hand, use libRoadRunner as a core SBML handling component in their modular software design, such as in Tellurium (Choi et al., 2018), runBiosimulations (Shaikh et al., 2021), MASSPy (Haiman et al., 2021), SBMLsim (König, 2021), CompuCell3D (Swat et al., 2012), PhysiCell (Ghaffarizadeh et al., 2018), pyBioNetFit (Neumann et al., 2022), pyViPR (Ortega and Lopez, 2020) and DIVIPAC (Nguyen et al., 2015).

In this work, we present libRoadRunner version 2. We have improved performance both for single-model and multi-model simulations. We have expanded the range of available features to include additional steady-state solvers, as well as time-dependent sensitivity analysis (see example in Figure 1).

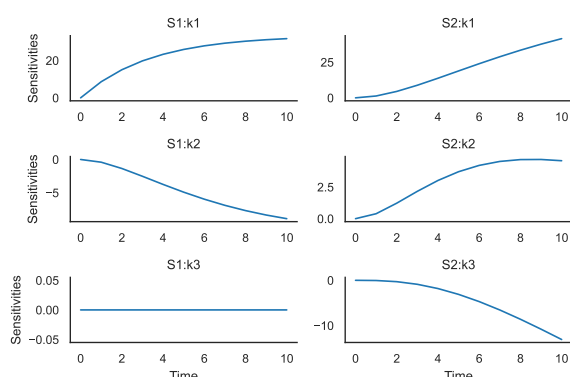


Fig. 1. Time-dependent sensitivities for a simple linear chain model: $X_0 \rightarrow S_1$; $k_1 \cdot S_1$; $S_1 \rightarrow S_2$; $k_2 \cdot S_2$; $S_2 \rightarrow$; $k_3 \cdot S_2$; $k_1=0.1$; $k_2=0.3$; $k_3=0.14$; $X_0=10$. Here all possible combinations of the species (S_1 , S_2) and parameters (k_1 , k_2 , k_3) are shown. However, the API allows us to be more selective if needed. The plots were generated by helper functions in libRoadrunner.

2 Major Changes to 2.0

2.1 Performance Improvements

In previous versions of libRoadRunner, loading many RoadRunner instances was slow because each model must JIT compile SBML to binary code. We have addressed this problem in several ways: 1) by increasing the speed of compilation of a single model; 2) by making it easy to compile multiple models simultaneously and 3) by providing a ‘direct’ API for access to the model topology outside of modifying the SBML directly (reducing the amount of re-compilations).

2.1.1 LLJit: A New JIT Compiler

To increase the speed of compiling SBML to machine code we have built a new JIT compiler called LLJit to replace the previous MCJit. LLJit uses LLVM version 13’s ‘ORC JIT v2’ API which provides an out-of-the-box but modular and customizable tool for JIT compiling LLVM IR code to machine code. It was not necessary to modify the LLVM Intermediate Representation (IR) generation stage of the compilation process, but a new strategy was designed to perform the compilation step. Our implementation of LLJit uses the standard object linking layer but a customized compile layer that automatically caches model object files in memory for fast reloading. The process of switching to the LLJit compiler is shown in Listing 1.

```
from roadrunner import RoadRunner, Config
Config.setValue(
    Config.LLVm_BACKEND, Config.LLJIT)
rr = RoadRunner(sbmlFile)
```

Listing 1: Python example of how to turn on the LLJit compiler. Variables: `sbmlFile(str)` is absolute path to sbml file on the disk.

2.1.2 RoadRunnerMap: A parallel RoadRunner container

Because RoadRunner models are computationally expensive to compile, we have made it easy for users to make use of their multi-core system for compiling multiple models in parallel. libRoadRunner uses a lightweight abstraction around the standard C++17 threading library called `thread_pool` (Shoshany, 2021) for queuing build jobs and then storing references to compiled RoadRunner models in a thread-safe hash map structure called `RoadRunnerMap`. To construct a `RoadRunnerMap`, a collection of SBML files or strings are passed to the `RoadRunnerMap` constructor, along with an integer specifying the number of threads to use (Listing 2).

```
from roadrunner import RoadRunnerMap
rrm = RoadRunnerMap(listOfSBML, 3)
```

Listing 2: Python example of loading a list of SBML models in parallel using three threads. Variables: `listOfSBML(List[str])` is a list of full paths to SBML files on the disk or strings in memory (or a mix thereof).

To demonstrate the capabilities of libRoadRunner v2, we have measured the time it takes for the MCJit and LLJit compilers to load and simulate over 1100 models from the curated section of the BioModels database (Malik-Sheriff et al., 2020) using either the native-Python `concurrent` package, or using the `RoadRunnerMap` construct, both with different numbers of threads. As can be seen in Figure 2, the new LLJit compiler is

more than three times faster than the previous MCJit compiler in both contexts, making it the fastest compiler we have built to date. Increasing the number of threads decreases runtime but with diminishing returns. The RoadRunnerMap construct was seen to be faster than the native Python ‘concurrent’ multithreading approach at lower numbers of threads, but slower than the native at higher numbers of threads. We hypothesize this is due to the RoadRunnerMap controlling thread taking up a significant portion of the clock time: because the parallelization occurs entirely in C++, the Python thread itself remains unoptimized. When using the native-Python concurrent package, that control is better managed by Python itself.

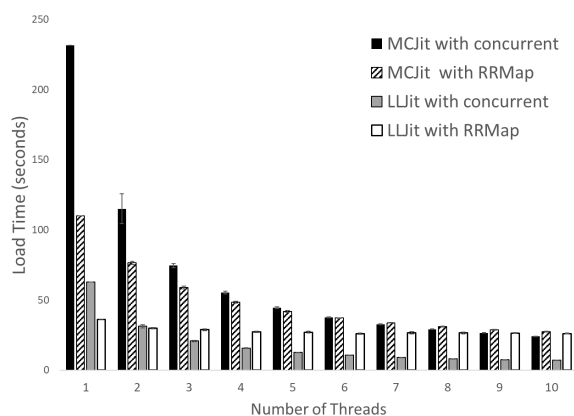


Fig. 2. Time to load over 1100 models from the BioModels database with libRoadRunner. Data is included for the two different JIT backends (MCJit and LLJit), using the RoadRunnerMap construct or not, and using the given number of threads. Shown is the average of 10 replicates with their standard deviations. Not shown: when increasing the number of threads to 23, the total times were only reduced by a maximum of an additional 2%.

2.1.3 Pickled (Serialized) RoadRunner

Once loaded, users can save a model’s state either to a binary string for in-memory storage or to a disk for persistent storage. The result is a platform-specific binary snapshot of a RoadRunner object which can be reloaded with significant performance improvements compared to recompiling the model. Listing 3 demonstrates this functionality.

```
from roadrunner import RoadRunner
rr = RoadRunner(sbmlFile)
# save state to string
rr.saveState(fileName)
# load state
rrReloaded = RoadRunner()
rrReloaded.loadState(fileName)
```

Listing 3: Example of saving a RoadRunner object’s state to a file and then loading it again. Variables: `sbmlFile (str)` is a full path to a valid SBML file on the disk; `fileName (str)` is a full path to where to save the model state on the disk.

In Python, a prerequisite for using RoadRunner with various parallel or multithreading toolboxes is the ability to serialize an instance of a RoadRunner object using Python’s standardized ‘pickle’ protocol. We have built an adaptor between our in-house RoadRunner serialization

strategy and Python’s pickle protocol so that our users can now build their own parallel applications on top of libRoadRunner. We anticipate that this will be valuable to the systems biology community, particularly for problems involving repeated time-series simulations such as optimization or stochastic simulations. An example of the latter is shown in Listing 4.

```
from multiprocessing import Pool
from roadrunner import RoadRunner
def simulate_worker(rr: RoadRunner):
    rr.resetAll()
    return rr.simulate(0, 10, 11)
rr = RoadRunner(sbmlFile)
rr.setIntegrator('gillespie')
if __name__ == '__main__':
    p = Pool(processes=8)
    results = p.map(
        simulate_worker,
        [rr for i in range(100000)])
```

Listing 4: Example of using RoadRunner object with Python’s multiprocessing library to stochastically simulate a model hundred thousand times.

2.2 Direct API

In libRoadRunner version 1, any changes to the model structure required the modification, re-parsing and re-compiling of the SBML. Since these operations are computationally expensive and potentially convoluted, we have implemented an API for interacting directly with the internal object model. This ‘direct’ API allows users to add and remove SBML components such as compartments, species, reactions and events programmatically, without the need to re-parse the model after each change. Since these changes require model recompilation before use, we provide an argument called `forceRegenerate` to all direct API functions which give users the ability to control when the model is recompiled - i.e. only after all model changes are complete. Listing 5 provides an example using this API.

```
from roadrunner import RoadRunner
rr = RoadRunner(sbmlFile)
rr.addSpecies("A", "cell",
    initConcentration=5.0,
    forceRegenerate=False
)
rr.addReaction("ADeg", ["A"], [], 0.5*A, True)
```

Listing 5: Example of adding a simple first order mass action degradation reaction to a loaded SBML model. The code assumes the a compartment called `"cell"` was loaded in the initial `sbmlFile`. Variables: `sbmlFile (str)` is a full path to a valid SBML file on the disk.

2.3 Julia Language bindings

The Julia programming language has gained traction with the systems biology community in recent years. We have therefore implemented language bindings to connect Julia users to libRoadRunner. While our Python bindings are implemented using SWIG (Beazley et al., 1996), there

is no Julia interface for SWIG, so our Julia bindings use `ccall` internally to expose symbols from the libRoadRunner shared library to a Julia API. Listing 6 demonstrates the use of this API in Julia.

```
# get julia bindings
import Pkg
Pkg.add("RoadRunner")
# simulate a model
using RoadRunner
rr = RoadRunner.createRRInstance()
RoadRunner.loadSBML(rr, sbmlString)
S = RoadRunner.getFloatingSpeciesIds(rr)
data = RoadRunner.simulateEx(rr, 0, 40, 500)
```

Listing 6: An example showing how to load an SBML model and perform a simulation in Julia. The first two lines install the libRoadRunner language bindings and the rest of the code compiles an SBML model `sbmlString` and runs a simulation using the `simulateEx` method.

2.4 Plugin System

We have developed a flexible and robust plugin system that tightly integrates extensions to the libRoadRunner with various functionalities. Anyone can incorporate a computational routine based on an instance of libRoadRunner which can greatly increase the performance, with the only requirement being the plugin code to be written in C++ and available at the compile time. Several examples such as parameter estimation algorithms that use libRoadRunner solvers and an interface to AUTO (Doedel, 1981) for bifurcation analysis are available in the documentation. Listing 7 illustrates a simple example of using the AUTO plugin for bifurcation analysis.

```
from rrplugins import *
auto = Plugin("tel_auto2000")

# Set parameters
auto.setProperty("SBML", sbmlString)
auto.setProperty("NMX", 5000)
auto.setProperty("ScanDirection", "Positive")

# Execute the plugin
auto.execute()

# Plot bifurcation diagram
pts = auto.BifurcationPoints
lbls = auto.BifurcationLabels
biData = auto.BifurcationData
biData.plotBifurcationDiagram(pts, lbls)
```

Listing 7: An example showing how to load a model into AUTO plugin, set parameters, run bifurcation analysis, and plot the bifurcation diagram.

2.5 Miscellaneous New Functionality

In 2019, a new SBML specification was released (level 3 version 2 (Hucka et al., 2019)). We now support the features of the new specification, including additional MathML functions, cases with ‘missing’ elements that

are now valid in SBML, and the presence of Boolean values where numeric values are expected, and visa versa. In addition, we now fully support the ‘Distributions’ SBML package (Smith et al., 2020), which defines new functions that stochastically draw values from known distributions, even in otherwise deterministic conditions (such as initial species levels).

Version 2 of libRoadRunner also includes a number of other miscellaneous changes. These include additions to numerical routines used to solve differential equations for the time course and for computing the steady-state. In particular, we have implemented a basic Euler integration method which has been used for certain time-critical applications and the RK45 solver which can be used to double-check the accuracy of the time course solution generated by the default CVODE implementation. We have also included support for variable stoichiometries in reactions. The Antimony language (Smith et al., 2009) has been updated to reflect this change.

Like our CVODE implementation, our time series sensitivity implementation uses the popular Sundials package (Hindmarsh et al., 2005). Specifically, we have two strategies for solving the sensitivity equations. They can either be solved simultaneously with the system equations (Maly and Petzold, 1996) or solved using a staggered approach (Caracotsios and Stewart, 1995).

libRoadRunner version 2 also makes use of the Sundials ‘kinsol’ library for new steady-state solvers. Specifically, we support the Inexact Newton approach (Brown, 1987). As a result, version 2 now gives the user access to two nonlinear solvers.

For Windows users, we also provided an updated installer that will install an independent but complete working environment for biochemical modeling. The installer distributes the latest Spyder IDE (<https://www.spyder-ide.org/>) as well as the Jupyter notebook interface (Kluyver et al., 2016). Note that libRoadRunner and associated tools can be easily installed on open platforms such as Colaboratory (Carneiro et al., 2018) using pip.

User control over roadrunner functionality has also been improved. Time-series simulations, steady-state calculations, and approximation routines, among others, now have more options for the user and can be used on a wider variety of models. Other changes in libRoadRunner version 2 include improved compliance with the SBML Test Suite (Smith, 2022), and a new automatic build and test system using updated dependencies, which allows us to release more frequently, with fewer bugs. Overall, we have resolved over 250 issues since 2018, filed by 23 different people.

3 Discussion

libRoadRunner is a fast and convenient tool for both individuals who are investigating the dynamics of a biological system and tool developers who are building new methods for solving and analysing such systems. In version 2, we have built a variety of new tools for the construction, compilation, analysis and solving of dynamical systems described in SBML.

libRoadRunner version 1 was highly optimized for the simulation of dynamical systems thanks to our JIT compilation strategy. As a result, libRoadRunner was the fastest available SBML dedicated simulator (Somogyi et al., 2015; Maggioli et al., 2020; Panchiwala et al., 2022). However, one of the disadvantages of our strategy is that when the need arises for the simulation of many SBML models together, the run time is dominated by the compile time. Examples of such a need include ensemble modelling, where many instances of SBML with varying parameters or typologies need to be simulated simultaneously. With the

new changes we describe in this paper, our performance metrics have increased even further.

To alleviate this bottleneck, we have prioritized new features that enhance the speed with which a model can be compiled. One such feature is an entirely new compiler called `LLJit` which sits side-by-side with the older `MCJit`. We have demonstrated that `LLJit` is significantly faster than earlier libRoadRunner implementations (Figure 2) at compiling the same code. Similarly, once loaded, a model may be modified (even to the extent of adding or removing model elements) more rapidly than loading a new model from scratch, and new functions have been added to allow this, as well.

While decreasing the compile time is a worthy goal, there is a natural limit to the speed with which a single model can be compiled. An alternative mechanism for enhancing performance in multi-model problems is to make better use of the available resources that exist in most modern computer systems using parallelism. We have introduced parallelism in two ways. First, we have built a RoadRunner container called `RoadRunnerMap` which is capable of orchestrating parallel compiles. Secondly, we have implemented support for Python's pickle protocol. While the former enables us to abstract parallelism away from the user completely, the latter allows our more experienced users to devise their own parallel computation.

4 Conclusion

With the advent of the changes introduced into libRoadRunner version 2, the library is now more efficient in running, loading and changing models at runtime. These features were added to support a number of specific use cases. These include two main applications: parameter optimization on large compute clusters, and using libRoadRunner to create large model ensembles that include variation in parameters as well as rate laws and network topology.

5 Availability

libRoadRunner source code is available from our GitHub webpage at <https://github.com/sys-bio/roadrunner/> and precompiled binaries are available for Windows, Mac OS and Linux operating systems at <https://github.com/sys-bio/roadrunner/releases>. The Windows front end for Tellurium (which includes the latest version of roadrunner) is available at <https://github.com/sys-bio/tellurium#front-end-1-tellurium-spyder-ide>. Python bindings are available both as wheel files from the releases page and from pypi.org installable through pip:

```
pip install libroadrunner
```

The Julia source code is available at <https://github.com/sys-bio/RoadRunner.jl> and can be installed via Julia's package manager with `Pkg.add("RoadRunner")`.

The scripts used to generate the data for this paper are available at https://github.com/sys-bio/rr2.0_paper.

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References

- Beazley, D. M. et al. (1996). SWIG: An easy to use tool for integrating scripting languages with C and C++. In *Proceedings of the 4th USENIX Tcl/Tk workshop*, pages 129–139.
- Bergmann, F. T. and Sauro, H. M. (2006). SBW - A modular framework for systems biology. In *WSC '06 Proceedings of the 38th conference on Winter simulation*, pages 1637–1645. Winter Simulation Conference.
- Bouteiller, J.-M. C. et al. (2015). Maximizing predictability of a bottom-up complex multi-scale model through systematic validation and multi-objective multi-level optimization. In *2015 7th International IEEE/EMBS Conference on Neural Engineering (NER)*, pages 300–303. IEEE.
- Brown, P. N. (1987). A local convergence theory for combined inexact-newton/finite-difference projection methods. *SIAM Journal on Numerical Analysis*, **24**(2), 407–434.
- Caracotsios, M. and Stewart, W. (1995). Sensitivity analysis of initial-boundary-value problems with mixed pdes and algebraic equations: applications to chemical and biochemical systems. *Computers & chemical engineering*, **19**(9), 1019–1030.
- Carneiro, T. et al. (2018). Performance analysis of google colaboratory as a tool for accelerating deep learning applications. *IEEE Access*, **6**, 61677–61685.
- Choi, K. et al. (2018). Tellurium: an extensible python-based modeling environment for systems and synthetic biology. *Biosystems*, **171**, 74–79.
- Doedel, E. J. (1981). Auto: A program for the automatic bifurcation analysis of autonomous systems. *Congr. Numer.*, **30**(265-284), 25–93.
- Ghaffarizadeh, A. et al. (2018). Physicell: An open source physics-based cell simulator for 3-d multicellular systems. *PLoS computational biology*, **14**(2), e1005991.
- Haiman, Z. B. et al. (2021). Masspy: Building, simulating, and visualizing dynamic biological models in python using mass action kinetics. *PLoS computational biology*, **17**(1), e1008208.
- Hester, S. D. et al. (2011). A multi-cell, multi-scale model of vertebrate segmentation and somite formation. *PLoS Computational Biology*, **7**(10), e1002155.
- Hindmarsh, A. C. et al. (2005). SUNDIALS: Suite of nonlinear and differential/algebraic equation solvers. *ACM Transactions on Mathematical Software (TOMS)*, **31**(3), 363–396.
- Hoops, S. et al. (2006). COPASI—a complex pathway simulator. *Bioinformatics*, **22**(24), 3067–3074.
- Hucka, M. et al. (2003). The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, **19**(4), 524–531.

- Hucka, M. et al. (2019). The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core Release 2. *Journal of Integrative Bioinformatics*, **16**(2), /j/jib.2019.16.issue-2/jib-2019-0021/jib-2019-0021.xml.
- Karagöz, Z. et al. (2021). Win, lose, or tie: Mathematical modeling of ligand competition at the cell–extracellular matrix interface. *Frontiers in bioengineering and biotechnology*, **9**, 340.
- Keating, S. M. et al. (2020). SBML Level 3: An extensible format for the exchange and reuse of biological models. *Molecular systems biology*, **16**(8), e9110.
- Kluyver, T. et al. (2016). Jupyter Notebooks—a publishing format for reproducible computational workflows., volume 2016. IOS Press.
- Köller, A. et al. (2021). Physiologically Based Modeling of the Effect of Physiological and Anthropometric Variability on Indocyanine Green Based Liver Function Tests. *Frontiers in Physiology*, **12**, 757293.
- Köller, A. et al. (2021). Prediction of Survival After Partial Hepatectomy Using a Physiologically Based Pharmacokinetic Model of Indocyanine Green Liver Function Tests. *Frontiers in Physiology*, **12**, 730418.
- König, M. (2021). SbmSim: SBML simulation made easy. *zenodo*.
- Lattner, C. and Adve, V. (2004). LLVM: A compilation framework for lifelong program analysis & transformation. In *Code Generation and Optimization 2004*, pages 75–86. IEEE.
- Lopez, C. F. et al. (2013). Programming biological models in python using pysb. *Molecular systems biology*, **9**(1), 646.
- Maggioli, F. et al. (2020). Sbm2modelica: integrating biochemical models within open-standard simulation ecosystems. *Bioinformatics*, **36**(7), 2165–2172.
- Malik-Sheriff, R. S. et al. (2020). Biomodels@15 years of sharing computational models in life science. *Nucleic acids research*, **48**(D1), D407–D415.
- Maly, T. and Petzold, L. R. (1996). Numerical methods and software for sensitivity analysis of differential-algebraic systems. *Applied Numerical Mathematics*, **20**(1-2), 57–79.
- Moraru, I. I. et al. (2008). Virtual Cell modelling and simulation software environment. *IET Systems Biology*, **2**(5), 352–362.
- Myers, C. J. et al. (2009). iBioSim: a tool for the analysis and design of genetic circuits. *Bioinformatics*, **25**(21), 2848–2849.
- Neumann, J. et al. (2022). Implementation of a practical Markov chain Monte Carlo sampling algorithm in PyBioNetFit. *Bioinformatics*, **38**(6), 1770–1772.
- Nguyen, L. K. et al. (2015). Dyvipac: an integrated analysis and visualisation framework to probe multi-dimensional biological networks. *Scientific reports*, **5**(1), 1–17.
- Olivier, B. G. et al. (2005). Modelling cellular systems with PySCeS. *Bioinformatics*, **21**(4), 560–561.
- Ortega, O. O. and Lopez, C. F. (2020). Interactive multiresolution visualization of cellular network processes. *iScience*, **23**(1), 100748.
- Panchiwala, H. et al. (2021). The Systems Biology Simulation Core Library. *Bioinformatics (Oxford, England)*, page btab669.
- Panchiwala, H. et al. (2022). The systems biology simulation core library. *Bioinformatics*, **38**(3), 864–865.
- Reyes, B. C. et al. (2022). A numerical approach for detecting switch-like bistability in mass action chemical reaction networks with conservation laws. *BMC bioinformatics*, **23**(1), 1–26.
- Sauro, H. M. (2014). *Systems Biology: An Introduction to Pathway Modeling*. Ambrosius Publishing.
- Shaikh, B. et al. (2021). RunBioSimulations: an extensible web application that simulates a wide range of computational modeling frameworks, algorithms, and formats. *Nucleic Acids Research*, **49**(W1), W597–W602.
- Shoshany, B. (2021). A c++ 17 thread pool for high-performance scientific computing. *arXiv preprint arXiv:2105.00613*.
- Smith, L. (2022). Test results: libroadrunner 2.2.0.
- Smith, L. P. et al. (2009). Antimony: a modular model definition language. *Bioinformatics*, **25**(18), 2452–2454.
- Smith, L. P. et al. (2020). Systems Biology Markup Language (SBML) Level 3 Package: Distributions, Version 1, Release 1. *Journal of Integrative Bioinformatics*, **17**(2-3).
- Somogyi, E. T. et al. (2015). libroadrunner: a high performance sbml simulation and analysis library. *Bioinformatics*, **31**(20), 3315–3321.
- Swat, M. H. et al. (2012). Multi-scale modeling of tissues using compucell3d. *Methods in cell biology*, **110**, 325–366.
- Takizawa, H. et al. (2013). LibSBMLSim: a reference implementation of fully functional SBML simulator. *Bioinformatics*, **29**(11), 1474–1476.
- Watanabe, L. H. et al. (2018). Dynamic Flux Balance Analysis Models in SBML. *Bioinformatics*.