

Standards in Computational Systems Biology

Supplementary Material:

Statements About Specific Computational Tools

Edda Klipp¹, Wolfram Liebermeister¹, Anselm Helbig¹, Axel Kowald^{1,2}, Jörg Schaber¹

¹Max Planck Institute for Molecular Genetics, Berlin, Germany

²Ruhr University Bochum, Bochum, Germany

The following table contains the complete list of the 105 software tools that were considered in the questionnaire plus 24 additional software tools that were mentioned by the respondents. These additional tools are marked with an asterisk behind the name. The table also contains all the comments that were given for the different tools. We did not edit the comments in any way (except for spelling), as to provide the reader with an unbiased overview of the results of the questionnaire.

Tool	URL	Comments
13C Flux*	www.simtec.mb.uni-siegen.de/software_13cflux.0.html	
BALSA	dead link	
BASIS	www.basis.ncl.ac.uk	Carry out simulations remotely, store models and results, easy to get data for export, easy to make changes to models.
Berkeley Madonna*	www.berkeleymadonna.com	Berkeley Madonna is arguably the fastest, most convenient, general purpose differential equation solver available today.
BIOCHAM	contraintes.inria.fr/BIOCHAM	
BioCharon	www.cis.upenn.edu/biocomp/new.html	
biocyc2SBML	genome.dfci.harvard.edu/~zucker/BPHYS/biocyc-open	
BioGrid	biocomp.ece.utk.edu/tools.html	
BioModels	www.biomodels.net	Curated database.
ByoDyn*	arva.imim.es/ByoDyn	
BioNetGen	cellsignaling.lanl.gov/bionetgen	
BioPathway Explorer	limsfinder.com/BlogDetail.aspx?id=982_0_3_0_C38	
Bio Sketch Pad	www.cis.upenn.edu/biocomp/new.html/biosketch.php3	
BioSens	www.chemengr.ucsb.edu/~ceweb/faculty/doyle/biosens/BioSens.htm	
BioSPICE Dashboard	biospice.org	
BioSpreadsheet	biocomp.ece.utk.edu/tools.html	
BioTapestry	labs.systemsbiochemistry.net/bolouri/software/BioTapestry/	

BioUML	www.biouml.org	
BSTLab	bioinformatics.musc.edu/bstlab	
C/C++		<p>C and C++ are popular programming languages, which you can use on any platform and obviate the use of customized modeling software. The executable code generated runs quickly.</p> <p>Easily available, free download (gcc), speed of computation, good flexibility, good portability with appropriate programming techniques and libraries (Qt), good and flexible representation of results with appropriate libraries.</p> <p>Building applications based on SBML ODE Solver and libSBML.</p> <p>Geometric calculations.</p> <p>Only for certain computation time intensive programs.</p> <p>Flexible, ideal for purpose.</p>
CADLIVE	kurata21.bse.kyutech.ac.jp/cadlive	
CellDesigner	celldesigner.org	<p>Graphical representation of the network.</p> <p>Communication / model exchange with other tools.</p> <p>CellDesigner is great for diagramming reaction networks enabling us to document our models and develop model proposals and 'sell' our model. We have had some problems simulating complex models with CellDesigner.</p> <p>CellDesigner is great for graphical modeling. However, for mathematical modeling it is almost unusable. To many clicks to complex editing of a models mathematics.</p> <p>I like the GUI for cell designer.</p> <p>Easy to use.</p> <p>Diagramming biochemical reaction networks.</p> <p>My favorite one for graphical representation.</p> <p>Availability, good Graphical representation, SBML.</p> <p>Used mostly for graphical presentation, however it doesn't label the reaction on the graph.</p>
Cellerator	www-aig.jpl.nasa.gov/public/mls/cellerator	
CellML2SBML	sbml.org/software/cellml2sbml	
Cellware	www.bii.a-star.edu.sg/achievements/applications/cellware	
CL-SBML	common-lisp.net/project/cl-sbml	

CLEML*	sg.ustc.edu.cn/MFA/cleml	
COPASI	www.copasi.org/tiki-index.php	Copasi is the favorite tool in our group since the developers maintain a very close contact to a wide range of users and thereby we hope that the further development of Copasi will be substantial and actually happen. Easy to use, latest version had some problems with simulation time in formulas.
Cytoscape	www.cytoscape.org	Interaction network visualization, GO annotation.
Dbsolve	biosim.genebee.msu.su/en	The most powerful and useful tool for biological kinetic modeling and developing of ODE models. Very good combination of model design, calculating and representation modules.
Dizzy	magnet.systemsbiology.net/software/Dizzy	I've used Dizzy in a classroom setting. It is good for teaching, but it has some limitations making it difficult to use in general. It is not very efficient and only supports SBML level 1. It does have a nice mix of analyzers though.
E-CELL	www.e-cell.org/software/e-cell-system	
ecellJ	www.jweimar.de/ecellJ	
ESS	biocomp.ece.utk.edu	ESS is a pretty efficient stochastic simulator. It is, however, limited in the types of kinetic laws that it can support.
Excel	www.microsoft.com	Microsoft Excel is widely used and very easy to use for simple data management. Used only for simple calculations. Useful in spreadsheet calculation and graphics. Only for user-friendly software development.
FluxAnalyzer	www.mpi-magdeburg.mpg.de/projects/flux-analyzer	
Fluxor	arep.med.harvard.edu/moma/FluxorPipeline.tar.gz	
Genetic Network Analyser (GNA)*	www-helix.inrialpes.fr/article122.html	
Gepasi	www.gepasi.org	
Gillespie2*	www.basis.ncl.ac.uk/software.html	
GRIND*	theory.bio.uu.nl/rdb/grind.html	
INA*	www2.informatik.hu-berlin.de/~starke/ina.html	INA is a tool package supporting the analysis of Place/Transition Nets (Petri Nets) and Colored Petri nets.
INSILICO discovery	www.insilico-biotechnology.com	
JACOBIAN	numericatech.com/jacobian.htm	
Jarnac	www.sys-bio.org	Jarnac is free and is a good model development environment but it is significantly slower than both Matlab and SBML ODE Solver.
JAVA	www.java.com	Is freely distributed, provides a lot of well established functionality. All purpose.
JavaEvA*	www-ra.informatik.uni-	

	tuebingen.de/software/JavaEvA	
JCell*	www-ra.informatik.uni-tuebingen.de/software/JCell	
JDesigner	www.sys-bio.org	
JigCell	jigcell.biol.vt.edu	
JSim*	nsr.bioeng.washington.edu/PLN/Members/butterw/JSIMDOC1.6/JSim_Home.stx	
JWS Online	jjj.biochem.sun.ac.za	
Karyote	biodynamics.indiana.edu/CellModeling	
KEGG2SBML	www.sbml.org/kegg2sbml.html	
Kinsolver	lsdis.cs.uga.edu/~aleman/kinsolver	
libSBML	www.sbml.org/software/libsbml	Building applications using C++.
Mathcad*	www.mathcad.com	
Mathematica	www.wolframresearch.com	<p>Mathematica is a general programming language and thus has in principle no limitations. It combines analytical, numerical and graphical task in a very elegant way.</p> <p>I prefer Mathematica as I can work both in symbolic and numerical analysis. This is important if you want to analyze design principles in metabolism and focus on classes of systems. The disadvantage is that the learning curve with Mathematica is not easy. It takes time and effort.</p> <p>Ease of inputting graph or equations, good representation of results, relatively good speed of computation.</p> <p>Hypothesis testing.</p> <p>Used for model building and testing.</p>
MatLab	www.mathworks.com	<p>Since it takes so much time to get up to speed with any software, the by far most important criterion is the flexibility to be able to do most things I/we need and simplicity. For the former reason mainly, MatLab is our tool of choice.</p> <p>Matlab provides the possibility to write own programs/tools (-> method development!). It is easy to link other tools (Excel, solvers...) and to access data. Visualization of networks is not satisfying as is the visual presentation of the results. I also prefer to use an external solver for optimizations problems.</p> <p>You can use it for any kind of modeling. Except graphical interpretations/gui are not so user friendly and time-consuming.</p> <p>Presence and quality of analysis tools.</p> <p>Matlab is flexible and has a good optimization package.</p> <p>MATLAB is in my opinion the best tool when it comes to flexibility. A wide range of inbuilt functionality together with a powerful scripting environment make it perfectly suited for</p>

		<p>research in systems biology. (static, deterministic, lumped models). The SBToolbox is a very useful MATLAB based platform that provides absolutely needed functionality in terms of model handling, models analysis, etc., that is not available in the standard MATLAB distribution. The user still has all flexibility to perform the desired tasks. Performance issues with MATLAB and SBtoolbox exist. MATLABs simulators are SLOW. However, using the SBaddon package, that interfaces nicely with the SBtoolbox, this issue can be resolved, leading to high performance simulations. (www.sbtoolbox.org/SBaddon).</p> <p>It is nice for graphical representation, but most researchers in the developing world cannot afford the full version.</p> <p>MATLAB has the toolboxes; this is essential.</p> <p>Matlab allows for fast prototyping and is very flexible.</p> <p>Matlab has good graphical representation and can handle large data sets.</p> <p>MATLAB is a all-purpose (computing language, interactive environment for algorithm development, data visualization, data analysis, and numeric computation). - very good help and great error-locator - convenient and powerful 2-D and 3-D graphics functions for visualizing data. - easy access on already implemented mathematical functions for linear algebra, statistics, Fourier analysis, filtering, optimization, and numerical integration - Functions for integrating MATLAB based algorithms with external applications and languages (e.g. C, C++, Fortran, Java, COM, and Excel) disadvantages: very expensive, very memory intensive.</p> <p>Provides a huge functionality to solve ordinary differential equations numerical and also a easy programming language as well as technical support.</p> <p>Gives many flexibility for analysis, fast, numbers of available toolbox, results/graphs can be exported in various formats.</p> <p>Parameter optimization, modeling.</p> <p>Only rarely for simulation, mainly for data/simulation output analysis.</p> <p>Hypothesis testing.</p> <p>My students use and love it.</p> <p>Standard for the Industry, high performance and flexibility, availability at universities.</p> <p>Enables fast development and good visualization.</p>
MathSBML	sbml.org/software/mathsbml	

MesoRD	mesord.sourceforge.net	Meso RD is freely available, very fast, and it is easy to do stochastic and deterministic reaction diffusion simulations of new systems using SBML input. Efficiency, ease of testing new systems, availability.
MetaboLogica	www.MetaboLogica.com	
MetaFluxNet	mbel.kaist.ac.kr/mfn	
MMT2	www.simtec.mb.uni-siegen.de/software_mmt2.0.html	
Modesto	bioinformatics.oxfordjournals.org/cgi/content/abstract/20/3/316?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=kiehl&searchid=1130434154165_1865&stored_search=&FIRSTINDEX=0&journalcode=bioinfo	
Moleculizer	www.molsci.org/~lok/moleculizer	
Monod	monod.molsci.org	
Narrator	narrator-tool.org	
NetBuilder	strc.herts.ac.uk/bio/maria/NetBuilder	
Octave*	www.octave.org	Matlab clone
Oscill8	oscill8.sourceforge.net	
Pajek*	vlado.fmf.uni-lj.si/pub/networks/pajek	Program for Large Network Analysis.
PANTHER Pathway	www.pantherdb.org/pathway	
PathArt	jubilantbiosys.com/pd.htm	
PathScout	eminch.gmxhome.de/pathscout11	
PathwayLab	innetics.com	Not for free (-) but free trial * Excellent graphical representation * User definable graphics (multi-diagram formalism support, model close to textbook pictures if sufficiently well described in terms of actual functional dependencies) * Easy to enter equations, external (measured) signals, etc * Large on-line help and a set of example models * Fast ODE solver (CVODE) and just in time byte-code generation for high speed without the overhead of using a real C-compiler (although some loss of performance of course). * Quick preview plot functionality after simulation (mouse select object to see response) * Phase plane preview plot * Other analysis output in terms of text in report window of the application * Analysis tools: transient simulation, state computation, metabolic control analysis, parametric scanning * Export to SBML, Mathematica (+ application package with many utilities), and Matlab (both stand alone and suitable for SBtoolbox) SBtoolbox * Free download * No graphical representation (but well connected to graphical environment via PathwayLab) * Easy to enter equations defining the model via text based tailored GUI (special sections for state equations, auxiliary variables, parameters, etc) * Alternative reaction equation input form: $A+B \rightarrow C$, $v_f = k \cdot A \cdot B$ * Good online Matlab help, ppt-tutorial material, brief web

		<p>descriptions * Matlab-speed which can be improved by using SBaddon (which compiles the code and links to CVODE for very fast simulations) * Representation of results in terms of plots and data in Matlab. Tailored plot window for quick selection of simulation results in terms of variable names. * Analysis tools: transient simulation, steady state computation, sensitivity analysis, "source of complex behavior" tools, parameter estimation (to some extent more to come) * Export/import to SBML</p> <p>For graphical representation mostly.</p>
Pathway Tools	bioinformatics.ai.sri.com/ptools	
PathwayBuilder	biospice.lbl.gov/PathwayBuilder	We use PathwayBuilder for schematic entry of reaction-based models. It is fairly easy to use and we know the designer, so we have gotten bug fixes and feature enhancements quickly.
PATIKAweb	www.patika.org	
PaVESy	pavesy.mpimp-golm.mpg.de/PaVESy.htm	
PNK	page.mi.fu-berlin.de/~trieglaf/PNK2e/index.html	
Reactome		
Perl		Perl is a extremely useful tool for specific tasks because it is versatile and readily applicable to many tasks.
PET*	mpf.biol.vt.edu/software/homegr/own/pet	
Powerpoint	www.microsoft.com	<p>The advantage of Powerpoint is that the generated diagrams can be used for presentations and for publication purposes.</p> <p>Presentations + well integrated with PathwayLab (Visio).</p> <p>Now use Apple's Keynote.</p> <p>Perfect for purpose.</p> <p>Only for presentations.</p>
ProcessDB	www.integrativebioinformatics.com/processdb.html	
PROTON	dead link	
pysbml	www.basis.ncl.ac.uk/software.html	
PySCeS	pysces.sourceforge.net	<p>PySCeS is freely available, works in both Windows and Linux. Very stable program. Very elegant program: model definition is very easy. Program also gives some indication of syntax errors. Analysis tools are also very powerful and very easy to implement, and data may be saved easily. Program can be used for undergrad teaching as well as post-grad research.</p> <p>PySCeS is my primary modeling tool and has been developed as an extendible, free, open source modeling tool. To a large degree the advantages of using PySCeS are inherited from Python whereby one has full access to an object oriented, dynamically interpreted language as well as to optimized low</p>

		level Fortran and C numerical libraries (eg SciPy). This provides an acceptable (in my opinion) balance between flexibility and performance. However, admittedly, as a console based application PySCeS can be "confusing" for the novice modeler.
Python	www.python.org	Nice language but not that fast.
R	www.r-project.org	Good for plotting and analyzing results. Ad-hoc statistical analysis. Statistics. My students used it. BioConductor Packages, many tools and programs available for omics-Data analysis; availability without cost, also for students. Free software and expert level routines. Many implemented algorithms. For plotting.
Reactome*	www.reactome.org	
runSBML	ariadnegenomics.com/technology/simulation.html	
SAAM II*	depts.washington.edu/saam2	The SAAM II software system is a general purpose modeling and simulation tool with a user-friendly interface based on compartmental models.
SABIO-RK	sabio.villa-bosch.de/SABIORK	
SBML ODE Solver	www.tbi.univie.ac.at/~raim/odeSolver	SBML ODE Solver is very fast, free, open source (we can fix bugs) and can be reused for custom applications without compromising performance. Building applications requiring fast simulation.
SBMLEditor	www.ebi.ac.uk/compneur-srv/SBMLEditor.html	My latest version has not been stable enough.
SBMLmerge	sysbio.molgen.mpg.de/sbmlmerge	VERY nice tool, missing some important databases.
SBML-PET*	sysbio.molgen.mpg.de/SBML-PET	
SBMLR	epbi-radivot.cwru.edu	
SBMLSim	www.dim.uchile.cl/~dremenik/SBMLSim	
SBMLToolbox	sbml.org/software/sbmltoolbox	For mathematical modeling and analysis.
SBliD	www-timc.imag.fr/timb/SBliD	
SBToolbox	www.sbtoolbox.org	Provides various analysis tools and SBML import to MATLAB.
SBW	sbw.kgi.edu	
SCIpath	www.ucl.ac.uk/oncology/MicroCore/microcore.htm	
Sigmoid	sigmoid.sourceforge.net	
SigPath	www.sigpath.org	Useless.

SigTran	dead link	
SIMBA	www.ifak-system.com/swt/simulation/index.php?level=swtSIMBA4	
SimBiology	www.mathworks.com/products/simbiology	
Simpathica	bioinformatics.nyu.edu/Projects/Simpathica	
SimWiz	projects.villa-bosch.de/bcb/software/software/Ulla/SimWiz	
SloppyCell*	sloppycell.sourceforge.net	
SmartCell	smartcell.embl.de	
Snoopy*	www-dssz.informatik.tu-cottbus.de/index.html?/software/snoopy.html	Snoopy is a software tool to design and animate hierarchical graphs, among others Petri nets.
SRS Pathway Editor	www.biowisdom.com/solutions/srs	
STELLA*	www.iseesystems.com/software/Education/StellaSoftware.aspx	STELLA is a flexible computer modeling package with an easy, intuitive interface that allows users to construct dynamic models that realistically simulate biological systems.
StochSim	www.pdn.cam.ac.uk/groups/com-p-cell/StochSim.html	
StochKit*	www.engineering.ucsb.edu/~cse/StochKit	
STOCKS	www.sysbio.pl/stocks	
TERANODE Suite	teranode.com/products	Ease of use, inputting graphs and equations.
Trelis	sourceforge.net/projects/trelis	
Virtual Cell	www.vcell.org	
Visio	www.microsoft.com	
WebCell*	webcell.kaist.ac.kr	
WinSCAMP	sbw.kgi.edu	
XPPAUT	www.math.pitt.edu/~bard/xpp/xpp.html	Free and easy to use, bifurcation analysis interface. Bifurcation analysis. Used via SBtoolbox interface.
yEd*	www.yworks.com/en/products_yed_about.htm	yEd is a very powerful graph editor that is written entirely in the Java programming language. It can be used to quickly and effectively generate drawings and to apply automatic layouts to a range of different diagrams and networks.