The SBML ODE Solver Library: a native API for symbolic and fast numerical analysis of reaction networks

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ABSTRACT

The SBML ODE Solver Library (SOSlib) is a programming library for symbolic and numerical analysis of chemical reaction network models encoded in the Systems Biology Markup Language (SBML). It is written in ISO C and distributed under the open source LGPL license. The package employs libSBML structures for formula representation and associated functions to construct a system of ordinary differential equations, their Jacobian matrix and other derivatives. SUNDIALS’ CVODES is incorporated for numerical integration and sensitivity analysis. Preliminary benchmarking results give a rough overview on the behavior of different tools and are discussed in the Supplementary Material. The native application program interface provides fine-grained interfaces to all internal data structures, symbolic operations and numerical routines, enabling the construction of very efficient analytic applications and hybrid or multi-scale solvers with interfaces to SBML and non SBML data sources. Optional modules based on XMGrace and Graphviz allow quick inspection of structure and dynamics.

Availability: www.tbi.univie.ac.at/~raim/odeSolver/
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Supplementary information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION

Mathematical modeling of (bio)chemical reaction networks involves a variety of techniques and theories and has long been applied for many purposes in research and technology. The need for exchange of models between different computational tools motivated collaborative efforts to develop standard formats for describing the common chemical reaction networks underlying the differing derived mathematical descriptions. Of the two XML based standards SBML (Hucka et al., 2003) and CellML (Lloyd et al., 2004), the former is supported by a growing number of applications and an official programming library, libSBML (http://sbml.org/software/libsbml/). While the available tools (see http://www.sbml.org) cover a variety of methods to edit and analyze reaction networks and their dynamics and/or structure, they are mostly designed as platform-specific standalone tools, accessible mostly via complex graphical user interfaces. In contrast, SOSlib combines libSBML with the SUNDIALS package (http://www.llnl.gov/CASC/sundials/)

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The constructed ODE system and its derivative $J$ are then used to initiate
numerical integration by CVODE's implementation of the backward differen-
tiation formula (BDF) or the Adams-Moulton (AM) method with Newton or
Functional iteration to calculate $J(t)$ for a requested series of time points. BDF
and AM methods are used for stiff and non-stiff systems, respectively. Changing
variables $x(t)$ at any time point by either event assignments (see below) or by
calling applications simply requires reinitialization of the integral structures
with new initial values. SOSlib incorporates CVODES' methods for forward
sensitivity analysis using the parametric derivatives in $P$ to calculate $\delta x(t)J(t)$. The performance of the methods for iteration as well as for forward sensitivity
analysis (staggered direct, simultaneous or staggered corrector) depend on the
numerical properties of the specific system. When construction of $J$ or $P$ fails
because of undifferentiable structures in ODE, internal approximation routines of
CVODES are employed. Both, numerical integration and sensitivity analysis are
compatible with online variable manipulation. SBML event triggers are evaluated
at every time step and executed if fired. The flaws of this approach are that the
accuracy of event detection depends on the chosen time step and that the
order of events fired at the same time step is not further resolved.

Two optional modules support visualization of a model's structure and
dynamics. Time courses of concentrations, rates, reaction fluxes and Jacobian matrix
values can be directly visualized in XMGrace (http://plasma-gate.weizmann.ac.il/
Grace/). The Graphviz library is employed for graph drawing (http://www.graphviz.
org). Besides the usual bipartite reaction network, a species interaction and a
parameter dependency graph based on $J$ and $P$ respectively, proved useful for
visual exploration of dominating feedback cycles and parameter dependencies.

### 3 ACCURACY, SCOPE AND APPLICATIONS

#### 3.1 Numerical analysis

SOSlib's integration routines have been tested with the official
SBML Semantic Test Suite. All of the tests without algebraic
rules, events or delays were successfully solved. We have
bench-marked the performance of SOSlib and four other SBML ODE solv-
ers, namely Jarnac, Copasi, Dizzy and the SBML Toolbox for Matlab,
using four models from the BioModels DB (Le Novere et al., 2006)
and a variant of the repressilator model in a stiff parameter regime (S.
Müller, J. Hofbauer, L. Endler, C. Flamm, S. Wider and P. Schuster,
manuscript submitted). Models 22 and the repressilator are oscill-
atory models, the others approach a steady state. SOSlib performed
especially well with the high-dimensional model (DB Id 14) and with the
oscillatory models. The benchmark results provide first hints on the
performance implications of the implementation approaches used
by the selected tools. The results also show that SOSlib performs
better than the majority of those tools (Table 1). References for tools
and models, and a short discussion of benchmarking difficulties and
results are available as Supplementary Material.

#### Limitations

SOSlib (1.6.0) does not support user defined units
or unit conversions. Models with delays or algebraic rules
cannot currently be handled. The event detection and execution is
not generally valid and has to be used with care (see Methods).

#### 3.2 Symbolic analysis and hybrid systems

All formulae in SBML, ODE, $J$ and $P$ can be retrieved as libSBML
AST structures, evaluated with current data or further differentiated
with respect to arbitrary variables. This functionality for symbolic
operations opens SBML models for further analytic treatment.

The fine-grained interface to numerical routines directly enables
efficient multi-scale modeling or integration into hybrid (continuous +
discrete) solvers. Independent solver instances can ‘communicate’
between time steps via straight-forward functions to set all parameters
and variables, including the next time step of integration. Furthermore,

<table>
<thead>
<tr>
<th>Biomodel DB Id</th>
<th>NEQ/Time</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>22/150</td>
</tr>
<tr>
<td>14</td>
<td>86/300</td>
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<tr>
<td>33</td>
<td>28/60</td>
</tr>
<tr>
<td>22</td>
<td>10/2000</td>
</tr>
<tr>
<td>Repress.</td>
<td>oscil./stiff</td>
</tr>
</tbody>
</table>

CPU times of single runs in milliseconds for ODE construction and numerical integration
on a Pentium 4 CUP with 3.4 GHz and 1 GB RAM. See Supplementary Material for
details. The column numbers are the models’ IDs at the BioModels DB (Le Novere et al.,
2006), except for ‘repress.’ (‘repressilator’) which was taken from Müller et al. (2005).
NEO, number of ODEs. Timo, end time of integration in the model’s built in default unit.
Type, refers to the model’s dynamic behavior.

### 4 DISCUSSION

While systems biology has gained much attention only recently, its current methods are in large parts old and well-founded on math-
ematical and biochemical theories. We follow the spirit of SBML and
libSBML to provide application developers with detailed interfaces to
already existing standard methods under a very liberal licensing policy.
In other words we are not trying to ‘reinvent the wheel’, but offer its best
possible implementation to enable rapid scientific progress and un-
restricted further development in this field. SOSlib uniquely provides a
detailed native API, independent of any GUI or scripting environment,
that allows access to all the components of a deterministic reaction
network simulator enabling scientists to construct efficient applications
that are tailored to their research needs. We are not aware of any other
open source SBML analysis package that offers the time course sensi-
tivity analysis provided by SOSlib through CVODES. The next
releases (during 2006) will include exact event handling and extend
the CVODES interface to provide adjoint sensitivities and sophisticated
parameter identification routines that employ inverse methods. SUNDIALS’
IDA solver for differential algebraic equation systems will be
interfaced to provide integration for models with arbitrary algebraic
rules. Bifurcation and feedback analysis would be obvious next steps.

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### Conflict of Interest:

none declared.

### REFERENCES


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published, quantitative kinetic models of biochemical and cellular systems. Nucleic
Acids Res., 34, D689–D691.

85, 433–450.