An introduction to modeling and simulation with COPASI

Pedro Mendes

http://www.comp-sys-bio.org
Reactions and kinetic functions

The rate of each reaction is a function of:

- concentration of the substrates
- concentration of the products
- concentration of the modifiers
- a set of constants

The rate of each reaction is given by:

\[ v = f(A, B, I; V, K_{ms}, K_{mp}, K_i) \]

\[ v = \frac{A}{K_{ms}} \cdot V \]

\[ v = \frac{A}{K_{ms}} \cdot \frac{B}{K_{mp}} + \frac{I}{K_i} \]

where:

- \( A \) and \( B \) are the concentrations of the substrates
- \( I \) is the concentration of the modifiers
- \( K_{ms} \) and \( K_{mp} \) are Michaelis constants
- \( K_i \) is the inhibition constant

\[ v = \frac{A}{K_{ms}} \cdot \frac{B}{K_{mp}} + \frac{I}{K_i} \]
Species concentrations are represented by ODEs

\[
\frac{dA}{dt} = v_1 - v_2 \quad \quad \frac{dB}{dt} = v_2 - v_3 - v_4
\]

The rate of change of a species concentration is the algebraic sum of the rates producing it and the ones consuming it.
An example

\[
\begin{align*}
\delta &= \frac{V_1 f}{S - V_1} \frac{A}{K_{1A}} - \left( \frac{V_2 f}{A} \left( 1 - \frac{B}{S \cdot K_{2eq}} + \frac{A}{K_{2B}} \right) \right) \left( \frac{A}{K_{2A}} + \frac{B}{K_{2B}} \right)^{h-1} \\
&= \left( \frac{A}{K_{2A}} + \frac{B}{K_{2B}} \right)^h + \frac{1 + \left( \frac{C}{K_{2C}} \right)^h}{1 + \alpha \left( \frac{C}{K_{2C}} \right)^h} \\
&= \left( \frac{A}{K_{2A}} + \frac{B}{K_{2B}} \right)^h + \frac{1 + \left( \frac{C}{K_{2C}} \right)^h}{1 + \alpha \left( \frac{C}{K_{2C}} \right)^h} \\
&= \left( \frac{A}{K_{2A}} + \frac{B}{K_{2B}} \right)^h + \frac{1 + \left( \frac{C}{K_{2C}} \right)^h}{1 + \alpha \left( \frac{C}{K_{2C}} \right)^h}
\end{align*}
\]
An example

\[
\begin{bmatrix}
1 & -1 & 0 & 0 \\
0 & 1 & -1 & 0 \\
0 & 0 & 1 & -1
\end{bmatrix}
\]

\[
\frac{V_1^f}{K_{1S}} \frac{S}{K_{1A}} - \frac{V_1^r}{K_{1A}} \\
1 + \frac{S}{K_{1S}} + \frac{A}{K_{1A}} \\
\left( \frac{V_2^f}{K_{2A}} \right) \left( 1 - \frac{B}{S \cdot K_{2eq}} \right) \left( \frac{A}{K_{2A}} + \frac{B}{K_{2B}} \right)^{h-1} \\
\frac{A}{K_{2A}} + \frac{B}{K_{2B}} \\
1 + \left( \frac{C}{K_{2C}} \right)^h \\
1 + \alpha \left( \frac{C}{K_{2C}} \right)^h \\
\frac{V_3^f}{K_{3B}} \frac{B}{K_{3C}} - \frac{V_3^r}{K_{3C}} \\
1 + \frac{B}{K_{3B}} + \frac{C}{K_{3C}} \\
\frac{V_4^f}{K_{4C}} \frac{C}{K_{4P}} - \frac{V_4^r}{K_{4P}} \\
1 + \frac{C}{K_{4C}} + \frac{P}{K_{4P}}
\]

\[
\mathbf{x} = \mathbf{N} \cdot \mathbf{v}(\mathbf{x}, \mathbf{k})
\]
COPASI simulation methods

COPASI allows simulations based on:

- ODEs
  - Built directly from reaction kinetics
  - Arbitrary ODEs
  - Compartment volumes can be variables (ODE)
- Stochastic kinetics based on Gillespie's SSA
- Models can have:
  - Algebraic assignments
  - Discrete events
Parameters and variables

- **Parameters** are items that are independent of the system, *i.e.* are set by outside agents (*causes*).
- **Variables** are items of the system whose values are determined exclusively by the parameters (*effects*).
- **State** of the system is the set of all variables.
- One set of parameters determines unambiguously the variables.
- One set of variables can be caused by many parameter sets.
The central modelling question

- Given a model of a system: **how do the parameters affect the state of the system?**

- Answers explain:
  - which parameters have highest effect on desired outcomes (eg drug design)
  - what properties of the model are more fragile or robust
  - which parameters need accurate estimates (experimental design)
Modelling cycle

Model & parameters
Forward modelling
Inverse modelling
knowledge
Text mining
behaviour: simulation data
behaviour: experimental data

Knowledge formation
Knowledge retrieval
Publication of experiments
COPASI—a COmplex PAthway SImulator

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ABSTRACT

Motivation: Simulation and modeling is becoming a standard approach to understand complex biochemical processes. Therefore, there is a big need for software tools that allow access to diverse simulation and modeling methods as well as support for the usage of these methods.

Results: Here, we present COPASI, a platform-independent and user-friendly biochemical simulator that offers several unique features. We discuss numerical issues with these features; in particular, the criteria to switch between stochastic and deterministic simulation methods, hybrid deterministic–stochastic methods, and the importance of random number generation. 

Hoops et al. (2006) Bioinformatics 22, 3067-3074
Frequent releases...

**COPASI 4.8 (Build 35) Released**  
*By: Stefan Hoops  on: Tue 20 of Dec., 2011 17:21 GMT (3836 Reads)*

The COPASI team announces the immediate availability of the stable release COPASI 4.8 (Build 35).

**New Language Bindings for COPASI 4.7 (Build 34)**  
*By: gauges  on: Sat 13 of Aug., 2011 12:24 GMT (2128 Reads)*

New versions of the COPASI language bindings based on the latest COPASI 4.7 (Build 34) have been released.

**COPASI 4.7 (Build 34) Released**  
*By: Stefan Hoops  on: Thu 14 of July, 2011 01:57 GMT (3203 Reads)*

The COPASI team announces the immediate availability of the stable release COPASI 4.7 (Build 34).
Documentation and support

Several sources available at www.copasi.org:

• User manual
• FAQ
• User forum
• Issue tracker
• Technical documentation:
  • File format specification (including schema)
  • Documentation of API
User Support Forum

We have limited posting to this forum to registered users to prevent spamming. However, the registration is open to everyone. If you need any help regarding COPASI we kindly ask you to register.

Forums > User Support Forum  
New Topic Forum List Edit Forum Manage Reported Messages (1)
Chapter 2

Computational Modeling of Biochemical Networks Using COPASI

Pedro Mendes, Stefan Hoops, Sven Sahle, Ralph Gauges, Joseph Dada, and Ursula Kummer

Summary

Computational modeling and simulation of biochemical networks is at the core of systems biology and this includes many types of analyses that can aid understanding of how these systems work. COPASI is a generic software package for modeling and simulation of biochemical networks which provides many of these analyses in convenient ways that do not require the user to program or to have deep knowledge of the numerical algorithms. Here we provide a description of how these modeling techniques can be applied to biochemical models using COPASI. The focus is both on practical aspects of software usage as well as on the utility of these analyses in aiding biological understanding. Practical examples are described for steady-state and time-course simulations, stoichiometric analyses, parameter scanning, sensitivity analysis (including metabolic control analysis), global optimization, parameter estimation, and stochastic simulation. The examples used are all published models that are available in the BioModels database in SBML format.
Systems Biology Markup Language

• Exchange medium for systems biology models, based on XML (used by >100 programs)
• Specifies models based on the biology, not on the maths
• Software interpret the models and translate them into mathematical/computational representations
• Allows ODEs, assignment rules, and events

http://www.sbml.org
Model Definition

![Model Definition Diagram](image-url)
Model Definition
Stoichiometric analyses

<table>
<thead>
<tr>
<th>Moieties (7)</th>
<th>Stoichiometry</th>
<th>Link Matrix</th>
<th>Reduced Stoichiometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent Species</td>
<td>Total Amount</td>
<td>Expression</td>
<td></td>
</tr>
<tr>
<td>Protein2 bound NADPH</td>
<td>1.6862e+19</td>
<td>&quot;Protein2 bound NADPH&quot; + NADPH + NADP - Protein1 + &quot;Protein2 bound NADP&quot;</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td>1.20443e+21</td>
<td>ATP + MgATP + ADP + MgAMP + AMP + MgADP</td>
<td></td>
</tr>
<tr>
<td>MgGrI23F2</td>
<td>1.6862e+21</td>
<td>MgGrI23F2 + MgATP + Mg + MgAMP + MgADP</td>
<td></td>
</tr>
<tr>
<td>Protein2</td>
<td>-2.40886e+18</td>
<td>Protein2 - NADPH - NADP + Protein1</td>
<td></td>
</tr>
<tr>
<td>Protein1 bound NADPH</td>
<td>1.44531e+19</td>
<td>&quot;Protein1 bound NADPH&quot; + Protein1 + &quot;Protein1 bound NADP&quot;</td>
<td></td>
</tr>
<tr>
<td>NAD</td>
<td>3.9445e+19</td>
<td>NAD + NADH</td>
<td></td>
</tr>
<tr>
<td>Oxidized Glutathione</td>
<td>9.37758e+20</td>
<td>&quot;Oxidized Glutathione&quot; + 0.5 * &quot;Reduced Glutathione&quot;</td>
<td></td>
</tr>
</tbody>
</table>
Stoichiometric analyses
Deterministic time course simulations
Deterministic time course simulations
Hybrid ODE-discrete event

• System of ODEs is associated with events
• An event (conditional state transition) consist of:
  • a trigger (Boolean expression)
  • at least one assignment
  • a delay (optional)
• When trigger expression changes from FALSE to TRUE, the even triggers and causes the assignments. If there is a delay, the trigger will only be that time after the trigger
Stochastic time course simulations
Stochastic time course simulations
Histograms

Histogram of calcium concentration
Automatic conversion to irreversible reactions
Hybrid ODE-stochastic
Parameter scanning & sampling
Parameter scanning & sampling
Parameter scanning & sampling
Sensitivity analysis (MCA)
Sensitivity analysis (general)
Sensitivity analysis (general)
Global optimisation
Parameter estimation
Command line version

- **CopasiSE**

  All model relevant information is contained in .cps file (COPASIML, an XML schema)

  Usage: CopasiSE [options] [file]
  
  --configdir string  The configuration directory for copasi. The default is .copasi in the home directory.
  
  --configfile string  The configuration file for copasi. The default is copasi in the ConfigDir.
  
  --exportBerkeleyMadonna string  The Berkeley Madonna file to export.
  
  --exportC string  The C code file to export.
  
  --home string  Your home directory.
  
  --license  Display the license.
  
  --verbose  Enable output of messages during runtime to std::error.
  
  -c, --copasidir string  The COPASII installation directory.
  
  -e, --exportSBML string  The SBML file to export.
  
  -i, --importSBML string  A SBML file to import.
  
  -s, --save string  The file the model is saved to after work.
  
  -t, --tmp string  The temp directory used for autosave.
Condor-COPASI
high-throughput computing

Stochastic Simulation

Select the COPASI model to submit. Before submitting, ensure the model has been correctly configured:

- **Time Course task:**
  - The Time Course should be set up as if a single run were to take place on the local machine
  - An appropriate stochastic method must be selected

Condor-COPASI will automatically generate an appropriate report; no report needs to be set for the Time Course task.

Please note - it is very important that the COPASI file is saved using a supported version of COPASI. At present, only Build 33 (version 4.6.33) and Build 34 (version 4.6.34) are supported.

- **Model file:**
  - For your reference, enter a name for this job

- **Skip load balancing step:**
  - Select this to skip the automatic load balancing step, and make the run time of each parallel job as short as possible. Use with caution! This has the potential to overload the Condor system with huge numbers of parallel jobs. Not applicable for some job types - see documentation for further details.

- **Repeats:**
  - The number of repeats to perform

Compare Global Sensitivity Job Output