SBML: Where It’s Been and Where It’s Going

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Background
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- Conviction that computational modeling is crucial
- Enables *quantitative* hypothesis testing
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  - Theoretical & technological advances made since then
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  - Enables **quantitative** hypothesis testing
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  - Theoretical & technological advances made since then
- Support is better than ever
  - General mathematical environments
  - Special-purpose software tools
Specialized software tools for computational modeling in biology

- > 100 available
- Range of capabilities
  - Editing/creating models
  - Simulating/analyzing
  - Visualizing
  - Databasing
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COPASI
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<table>
<thead>
<tr>
<th>Reaction</th>
<th>Name</th>
<th>Type</th>
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<tbody>
<tr>
<td>Ma-&gt;Mi</td>
<td>MPF Inactivation</td>
<td>Mass Action</td>
</tr>
<tr>
<td>Mi-&gt;Ma</td>
<td>MPF activation</td>
<td>k_cat</td>
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<tr>
<td>Ca-&gt;Cl</td>
<td>Cdc25 inactivation</td>
<td>Michaelis-Menten</td>
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<tr>
<td>Cl-&gt;Ca</td>
<td>Cdc25 activation</td>
<td>Michaelis-Menten</td>
</tr>
<tr>
<td>Wa-&gt;Wp</td>
<td>Wee1 inactivation</td>
<td>Michaelis-Menten</td>
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<tr>
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<td>Wee1 activation</td>
<td>Michaelis-Menten</td>
</tr>
<tr>
<td>L-&gt;L2</td>
<td>Labelled inactive MPF affected by Cdc25</td>
<td>Local</td>
</tr>
</tbody>
</table>

JigCell
Specialized software tools for computational modeling in biology

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SBML Model Integration Server

A web interface to the SBML_odeSolver program

This server will integrate a valid SBML model.
At this stage the web service is experimental!!!

Instructions

- Please upload a valid SBML Model
- Please provide a valid email address (you will be notified by email)
- Your model will be validated prior to integration using the function
- If validation errors occur, please correct them and resubmit your model

Choose File: no file selected

Your Email Address

Simulation Time (use scientific notation e.g. 1e7 for 10000000)

Print Step

Absolute Error

Relative Error

SBML ODE Solver
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Virtual Cell
Ability to exchange models is critical
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- Simply publishing equations is not enough
- Don’t want to transcribe equations from papers
- You want a common file format
Ability to exchange models is critical

- Simply publishing equations is not enough
  - Don’t want to transcribe equations from papers
  - You want a common file format
- **Not** a new idea—seems obvious
  - Still, a format hadn’t existed before year 2000
    - Each tool had its own unique proprietary format
    - (Fewer tools too)
JST ERATO
Kitano Project

One initial component: get 8–10 software systems interacting
SBML =
Systems Biology Markup Language
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- Machine-readable format for computational models
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- Suitable for reaction networks
- Arbitrary rate functions

2 A + B ⇌ C
C ⇌ D + F
...

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- Models can also include
  - Compartments
  - Mathematical “extras”

\[
2 \text{A} + \text{B} \rightarrow \text{C} \\
\text{C} \leftrightarrow \text{D} + \text{F} \\
\text{...}
\]
SBML = Systems Biology Markup Language

- Machine-readable format for computational models
- Suitable for reaction networks
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- Models can also include
  - Compartments
  - Mathematical “extras”
- Declarative, not procedural
SBML is an XML format

- SBML defined using UML and XML Schema
- Targeted at XML, but mostly independent of it
- A lingua franca for software, not humans
- Think HTML
Where is SBML today?
Now the de facto standard

Systems Biology Markup Language

Supported by >100 systems

Accepted by journals

Nature

PLoS

BMC

Used in textbooks & courses
A community of modelers and software developers

- **sbml-discuss** (275+ people), **sbml-announce**
- **Annual SBML Forum meeting** (at ICSB)
- **Annual SBML Hackathon**
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SBML development process so far

- **Informal discussions** lead to proposals for change
  - Fix errors, lacunae, and niggling issues
  - Self-organized community efforts for significant extensions
    - Whitepapers, discussions, software implementations
- **SBML editors**: Hucka, Andrew Finney, Nicolas Le Novère
  - **Reconcile** proposals for changes
  - **Write** final specifications
Support by SBML Team

- Writing grants for core development
- Writing infrastructure software
  - libSBML
  - MathSBML, SBMLToolbox
- Maintaining web & mailing list resources
- Organizing workshops & other events
Software for working with SBML
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- libSBML: API library
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- Online SBML validator at http://sbml.org
SBML “Levels”

- Levels are meant to coexist
- **Level 1**: mostly basic compartmental modeling
- **Level 2**: significantly more features—e.g.:
  - User-defined functions
  - Events
  - “Types” for chemical species and compartments
  - Initial conditions, constraints, other “fiddly bits”
- **Level 3**: now (back) in development
Latest: SBML Level 2 Version 2

Final version released September 26

Systems Biology Markup Language (SBML) Level 2: Structures and Facilities for Model Definitions

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SBML Level 2, Version 2, Revision 1
26 September 2006

Corrections and other revisions of this SBML language specification may appear over time.
Notifications of revisions are broadcast on the email list sbml-announce@caltech.edu


This revision of the SBML Level 2 Version 2 specification is available at http://sbml.org/specifications/sbml-level-2/version-2/revision-1/
Examples of significant changes

- Much clarified explanation of interpreting reactions
- Simplification to units system
- Species types, compartment types
- “Constraints”
- Support for the Systems Biology Ontology (SBO)
- Recommended standard format for annotations
- “Revisions” process for handling errata
What lies ahead?
Full SBML Test Suite

- Allows developers to test implementation of SBML support
- Critical for improving software interoperability
- Currently have a partial “SBML semantic test suite”
- Needs further work to—
  - Complete coverage of SBML features
  - Improve ease of use
  - Update for Level 2 Version 2 and Level 3
  - Add web system for reporting results, comparisons, etc.
SBML Level 3
SBML Level 3

- Modular language extensions
- Core expected to be based “mostly” on Level 2 Version 2
SBML Level 3

- Modular language extensions
  - Core expected to be based “mostly” on Level 2 Version 2
- Layered on top of core: feature sets for—
  - Diagram storage
  - Multicomponent species
  - Models composed of submodels
  - Arrays and/or sets of components
  - Spatial geometry
  - Other capabilities
Modular extensions support in libSBML & SBML Test Suite

Goal: enable libSBML to be extended through plug-ins
- Proposals for SBML extensions can come with libSBML add-on
- Developers can pick & choose which ones are compiled in

Goal: enable Test Suite to be similarly extended
- Proposals for SBML extensions can come with Test Suite add-ons
Collateral standardization efforts

- **Systems Biology Ontology (SBO)**
  - For computational models
  - Add annotations about roles & meanings of the math
- **“Parameter sets”**
  - Single model, multiple sets of numerical values
Revised SBML governance & development process

- Borrow ideas from W3C & other organizations
- Implement a better-defined, regimented process
  - Calls for proposals, etc.
  - Voting, etc.
  - Issue tracking system
- Have an architectural board to steer development
- Have more SBML Editors
  - Elect SBML Editors for limited terms
Standards body recognition

- Currently not recognized by a standards-making body
  - At some point in the future, it probably should be
    - Of special interest to commercial efforts
- Questions remain
  - **When** to seek standardization
  - **Which agency?** ISO? OMG? W3C?
Closing
The funding

- JST ERATO Kitano Symbiotic Systems Project (Japan) (to 2003)
- National Institute of General Medical Sciences (USA)
- National Science Foundation (USA)
- International Joint Research Program of NEDO (Japan)
- JST ERATO-SORST Program (Japan)
- Japanese Ministry of Agriculture
- BBSRC e-Science Initiative (UK)
- DARPA IPTO Bio-SPICE Bio-Computation Program (USA)
- Air Force Office of Scientific Research (USA)
- STRI, University of Hertfordshire (UK)
- Beckman Institute, Caltech (USA)
- Molecular Sciences Institute (USA)
The SBML Team people

- Hamid Bolouri
- Herbert Sauro
- Andrew Finney
- Maria Schilstra
- Jo Matthews
- Akira Funahashi
- Ben Bornstein
- Ben Kovitz
- Bruce Shapiro
- Sarah Keating

A million thanks to the SBML Community too
Where to learn more

- [http://sbml.org](http://sbml.org)
- **Upcoming:**
  - SBML Hackathon 2007 in June at U. Newcastle, UK
  - SBML Forum 2007 in Long Beach, CA, USA, Oct. 5-6 (ICSB 2007)
- Thank you!