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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- Not a new idea—dates to 1940’s if not earlier
- Theoretical & technological advances made since then
Background

- Conviction that computational modeling is crucial
  - Enables **quantitative** hypothesis testing
- Not a new idea—dates to 1940’s if not earlier
  - 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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CellDesigner
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![CellDesigner](image)

![JDesigner](image)

![COPASI](image)

![JigCell](image)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Name</th>
<th>Type</th>
</tr>
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<tbody>
<tr>
<td>M1-&gt;M1</td>
<td>MPF inactivation</td>
<td>Mass Action</td>
</tr>
<tr>
<td>Mi-&gt;M1</td>
<td>MPF activation</td>
<td>Mass Action</td>
</tr>
<tr>
<td>Cdc25 inactivation</td>
<td>Michaelis-Menten</td>
<td>vDCDC *CAC</td>
</tr>
<tr>
<td>Cdc25 activation</td>
<td>Michaelis-Menten</td>
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</tr>
<tr>
<td>Wee1 inactivation</td>
<td>Michaelis-Menten</td>
<td>vDCDC *CAC</td>
</tr>
<tr>
<td>Wee1 activation</td>
<td>Michaelis-Menten</td>
<td>vDCDC *CAC</td>
</tr>
<tr>
<td>L+</td>
<td>Labelled inactive MPF affected by Cdc25</td>
<td>Michaelis-Menten</td>
</tr>
<tr>
<td>L2</td>
<td>Labelled inactive MPF affected by Wee1</td>
<td>Michaelis-Menten</td>
</tr>
</tbody>
</table>

![JigCell](image)
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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; use the function
- If validation errors occur, please correct them and resubmit your model

Choose File: no file selected

Your Email Address

1000 Simulation Time (use scientific notation e.g., 1e7 for 10000000)

100 Print Step

1e-09 Absolute Error

0.0001 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

\[ 2A + B \rightarrow C \]
\[ C \leftrightarrow D + F \]

...
SBML = Systems Biology Markup Language

- Machine-readable format for computational models
- Suitable for reaction networks
  - Arbitrary rate functions
  - 2 A + B → C
  - C ↔ D + F
  - ...  
- Models can also include
  - Compartments
- Mathematical “extras”
SBML = Systems Biology Markup Language

- Machine-readable format for computational models
- Suitable for reaction networks
  - Arbitrary rate functions
- Models can also include compartments
- Mathematical “extras”
- Declarative, not procedural

\[ 2A + B \rightarrow C \]
\[ C \leftrightarrow D + F \]  
...
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**

The Systems Biology Markup Language (SBML) is a computer-readable format for representing models of biochemical reaction networks. SBML is applicable to metabolic networks, signaling pathways, regulatory networks, and many others.

**Internationally Supported and Widely Used**

SBML has been evolving since mid-2000 through the efforts of an international group of researchers and users. Today, SBML is supported by over 100 software systems, including the following (where "**" indicates SBML support in development):

- RALSA
- BASIS
- BIOCHAM
- BioCharon
- ByoDyn
- BioCyc
- BioGrid
- BioModels
- BioNetGen
- BioPathway Explorer
- BioSketchPad
- BioSpell
- DBsolve
- Dizzy
- E-CELL
- ecellJ
- ESS
- FluxAnalyzer
- FluxDr
- Gepasi
- Gillespie2
- HSMB
- HybridSBML
- HMSL-CC
- MMT2
- Modesto
- Moleculizer
- Monod
- Narrator
- NetBuilder
- Oscill
- PANTHER Pathway
- PathArt
- PathScout
- PathwayLab
- PathwayTools
- SBMLmerge
- SBMLR
- SBMLSim
- SBMLToolbox
- SBjID
- SBToolbox
- SBW
- SigPath
- SigTran
- SIMBA

- 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
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 mail list sbml-announce@caltech.edu

The latest revision of the SBML Level 2 Version 2 specification is available at

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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
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
- **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!**