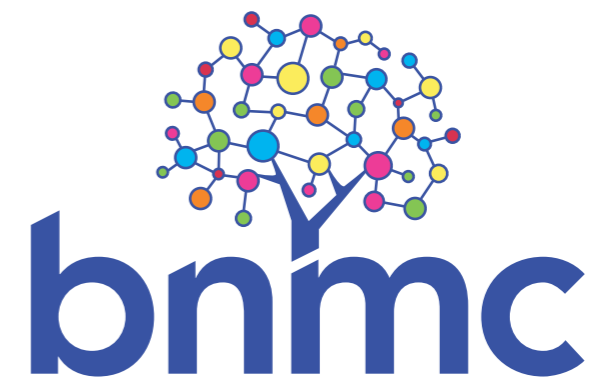


SBML, BioModels.net, and SBGN

Michael Hucka

*Co-director—Biological Network Modeling Center (BNMC), Beckman Institute
Senior Research Fellow—Control and Dynamical Systems*

*California Institute of Technology
Pasadena, California, USA*



SBML background

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- ▶ Conviction that computational modeling becoming crucial
 - ▶ Mechanistic modeling and dynamical simulation enables **quantitative hypothesis testing**

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 - ▶ Mechanistic modeling and dynamical simulation enables **quantitative hypothesis testing**
- ▶ Not a new idea—dates to 1940's if not earlier

SBML background

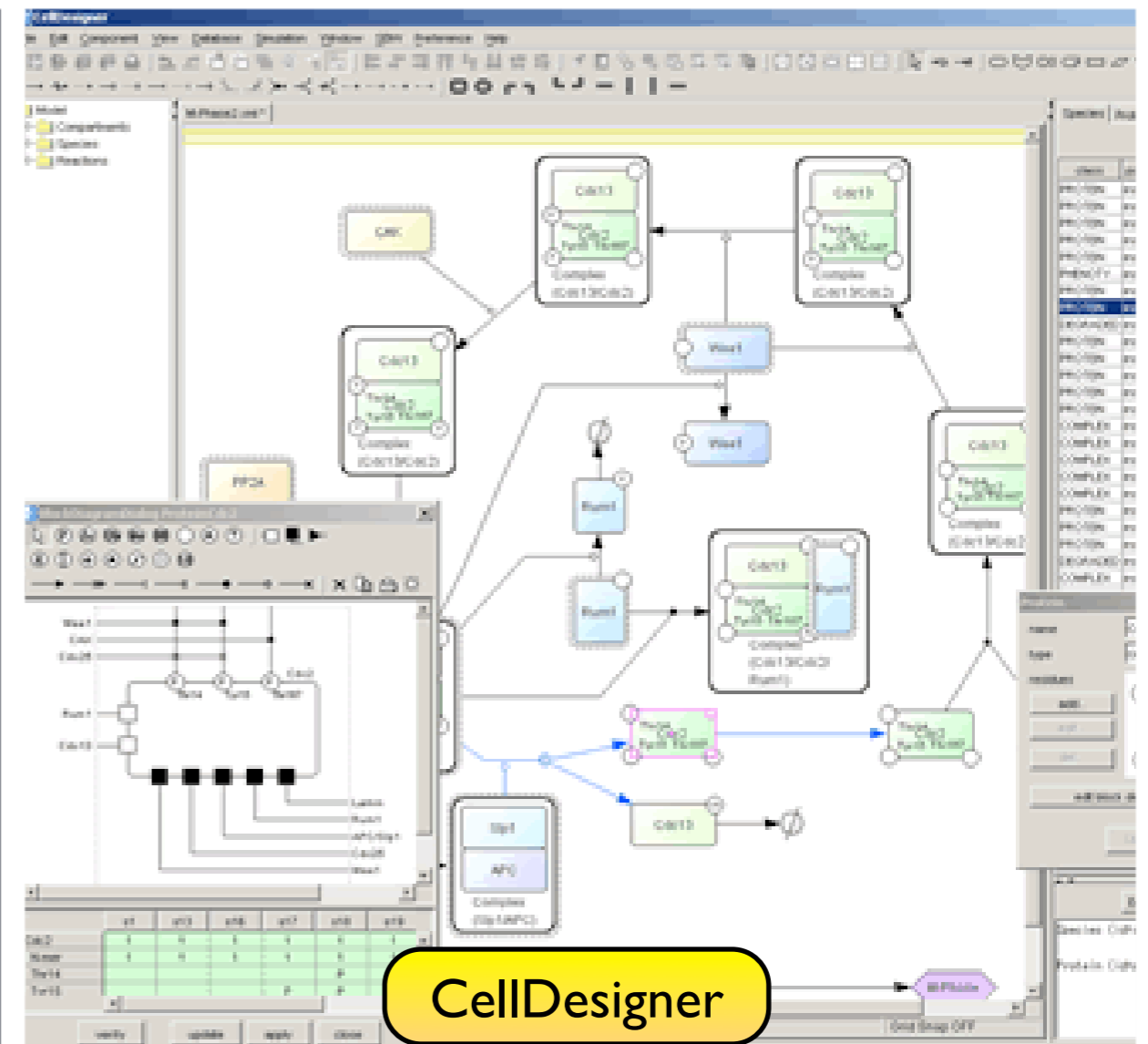
- ▶ Conviction that computational modeling becoming crucial
 - ▶ Mechanistic modeling and dynamical simulation enables **quantitative hypothesis testing**
- ▶ Not a new idea—dates to 1940's if not earlier
- ▶ Today software tool support is better than ever

Specialized software tools for computational modeling in biology

- ▶ > 100 available
- ▶ Range of capabilities
 - ▶ Editing/creating models
 - ▶ Simulating/analyzing
 - ▶ Visualizing
 - ▶ Databasing

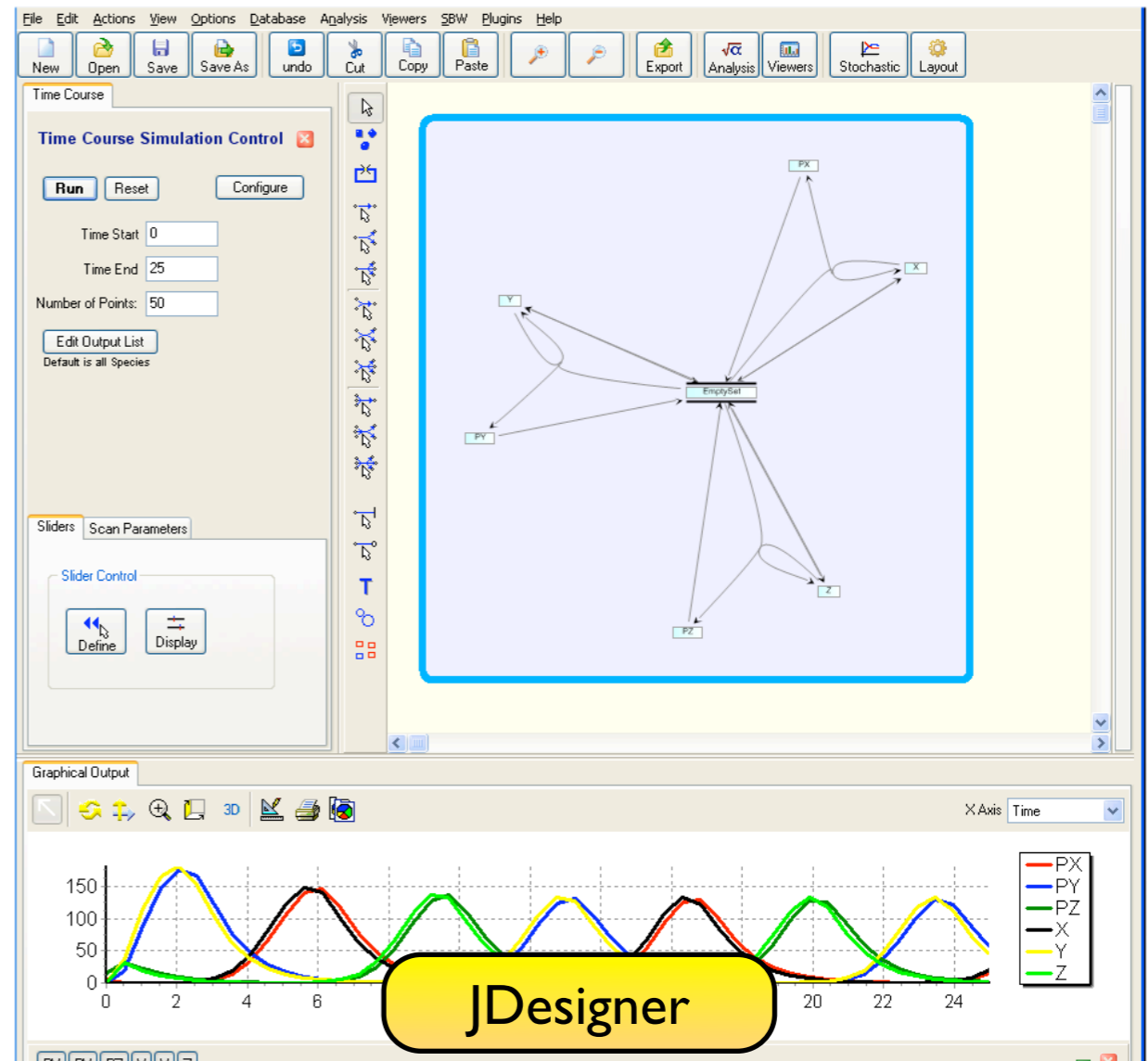
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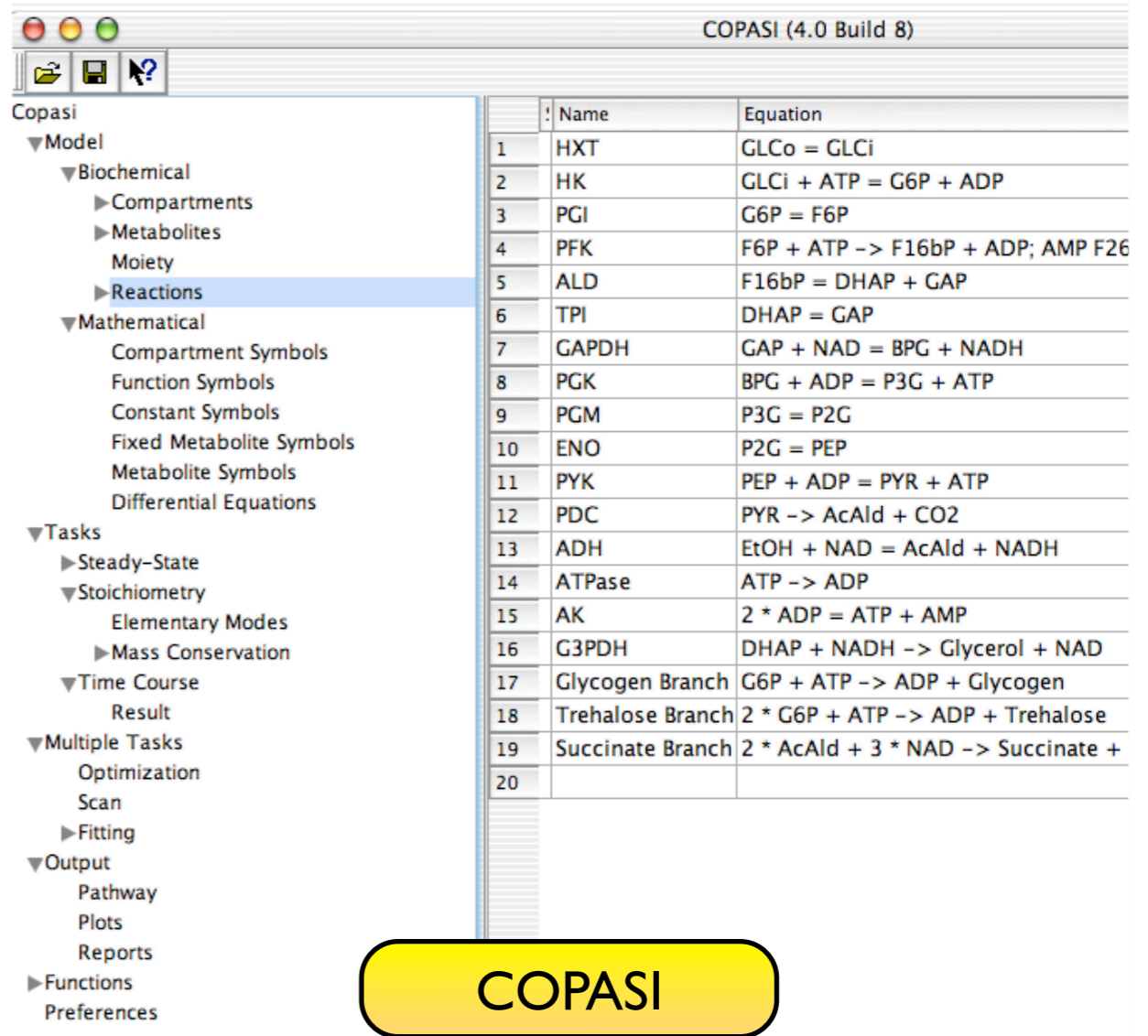
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COPASI (4.0 Build 8)

Copasi

- ▼ Model
 - ▼ Biochemical
 - ▶ Compartments
 - ▶ Metabolites
 - Moiety
 - ▶ Reactions
 - ▼ Mathematical
 - Compartment Symbols
 - Function Symbols
 - Constant Symbols
 - Fixed Metabolite Symbols
 - Metabolite Symbols
 - Differential Equations
 - ▼ Tasks
 - ▶ Steady-State
 - ▼ Stoichiometry
 - Elementary Modes
 - ▶ Mass Conservation
 - ▼ Time Course
 - Result
 - ▼ Multiple Tasks
 - Optimization
 - Scan
 - ▶ Fitting
 - ▼ Output
 - Pathway
 - Plots
 - Reports
 - ▶ Functions
 - Preferences

	Name	Equation
1	HXT	GLCo = GLCi
2	HK	GLCi + ATP = G6P + ADP
3	PGI	G6P = F6P
4	PFK	F6P + ATP -> F16bP + ADP; AMP F26
5	ALD	F16bP = DHAP + GAP
6	TPI	DHAP = GAP
7	GAPDH	GAP + NAD = BPG + NADH
8	PGK	BPG + ADP = P3G + ATP
9	PGM	P3G = P2G
10	ENO	P2G = PEP
11	PYK	PEP + ADP = PYR + ATP
12	PDC	PYR -> AcAld + CO2
13	ADH	EtOH + NAD = AcAld + NADH
14	ATPase	ATP -> ADP
15	AK	2 * ADP = ATP + AMP
16	G3PDH	DHAP + NADH -> Glycerol + NAD
17	Glycogen Branch	G6P + ATP -> ADP + Glycogen
18	Trehalose Branch	2 * G6P + ATP -> ADP + Trehalose
19	Succinate Branch	2 * AcAld + 3 * NAD -> Succinate +
20		

COPASI

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Reaction	Name	Type	
Ma->Mi	MPF inactivation	Mass Action	kw*Ma
Mi->Ma	MPF activation	Mass Action	kc*Mi
Ca->Ci	Cdc25 inactivation	Michaelis-Menten	(vcp _{ppp} _
Ci->Ca	Cdc25 activation	Michaelis-Menten	(vc_*Ci*
Wa->Wi	Wee1 inactivation	Michaelis-Menten	(vw_*W*
Wi->Wa	Wee1 activation	Michaelis-Menten	(vw_*w*
L->	Labelled inactive MPF affected by Cdc25	Mass Action	kc*L
->L2	Labelled inactive MPF affected by Wee1	Local	kw*(1-L
kc		Species	vcp*Ci+
kw		Species	wwp*Wi+
vcp_		Species	vcp*Cdc
vcpp_		Species	vcpp*Cd
vcppp_		Species	vcppp/C
wwp_		Species	wwp*We
wpp_		Species	wpp*W
wppp_		Species	wppp/W
kmc_		Species	kmc/Cdc
kmcr_		Species	kmcr/Cd
kmw_		Species	kmw/We
kmwr_		Species	kmwr/W
vc_		Species	vc*Cdc2
vw_		Species	vw*Cdc2
Cdc25Total_		Species	Cdc25T

JigCell

Specialized software tools for computational modeling in biology

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SBML Model Integration Server

A web interface to the SBML_odeSolver pro

This server will integrate a valide 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 `libSBML::validateModel()`
- If **validation errors** occur, please correct them and resubmit your model

no file selected

Your Email Address

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

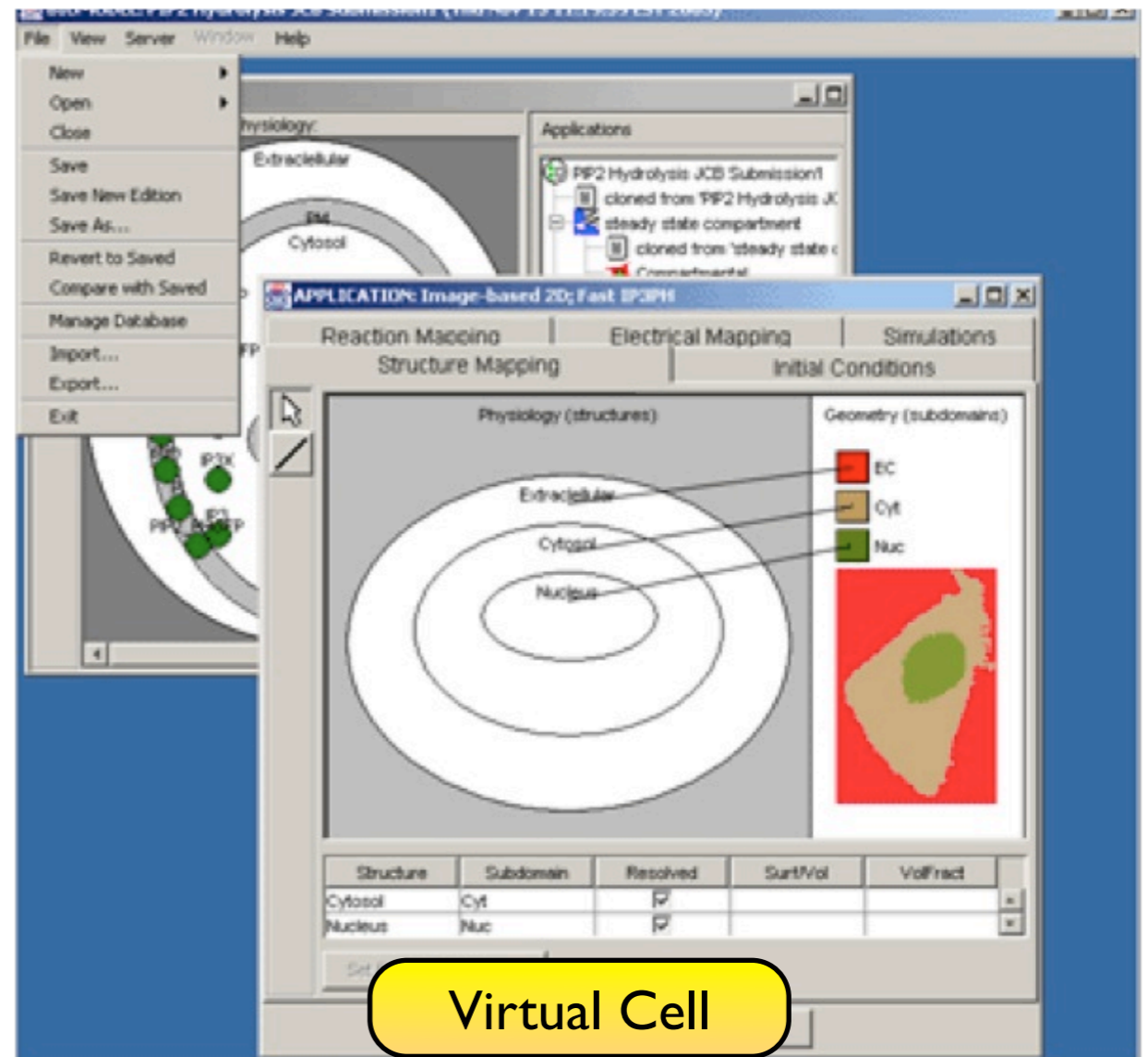
Print Step

Absolute Error

Relative Error

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Many common types of model representation frameworks

- ▶ (Continuous) nonlinear differential equations
- ▶ (Discrete) stochastic systems
- ▶ Boolean networks
- ▶ Bayesian networks
- ▶ Petri Nets
- ▶ others...

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

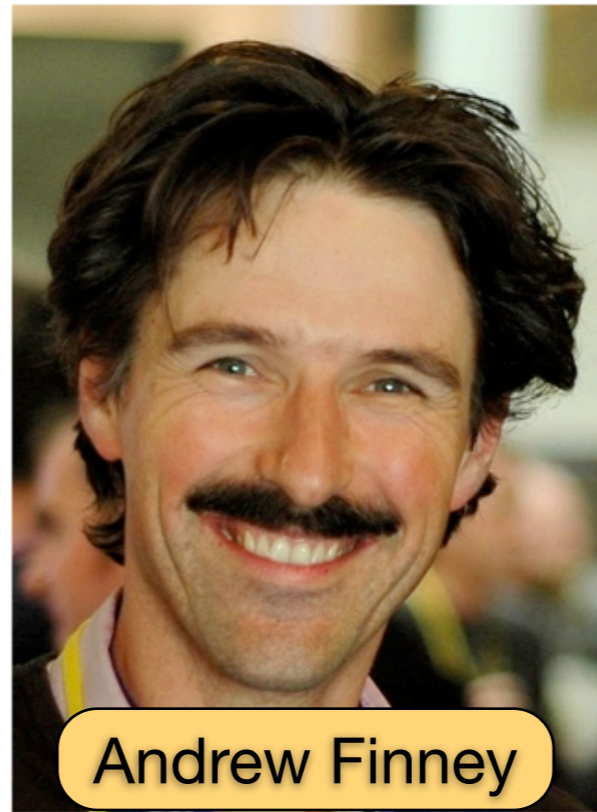
- ▶ Simply publishing equations is not enough
 - ▶ Don't want to transcribe equations from papers
 - ▶ You want a common file format
- ▶ **Not** a new idea—seems obvious
 - ▶ Still, a format hadn't existed before year 2000
 - ▶ Each tool had its own unique proprietary format
 - ▶ (Fewer tools too)



Hiroaki Kitano



John Doyle



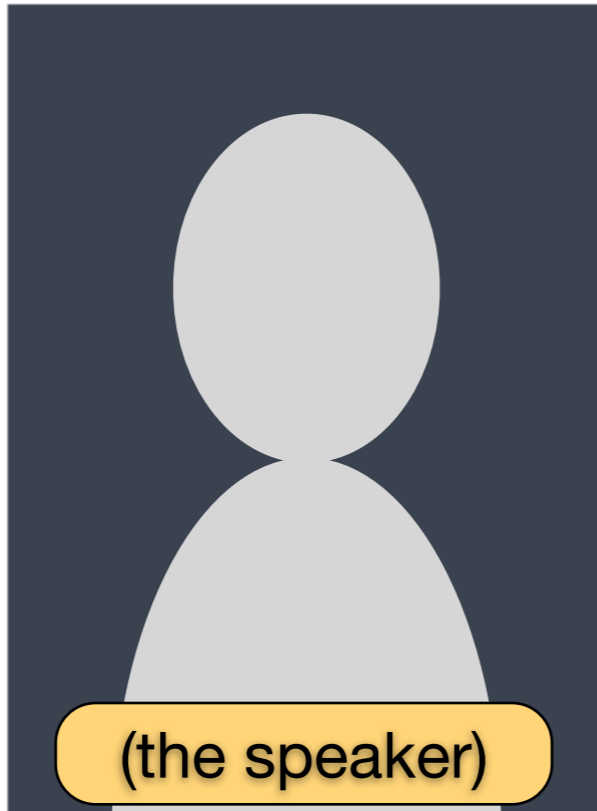
Andrew Finney



Herbert Sauro



Hamid Bolouri



(the speaker)

JST ERATO Kitano Project

One initial component: get 8-10 software systems interacting

SBML =

Systems Biology Markup Language

SBML =

Systems Biology Markup Language

- ▶ Machine-readable format for computational models

SBML = Systems Biology Markup Language

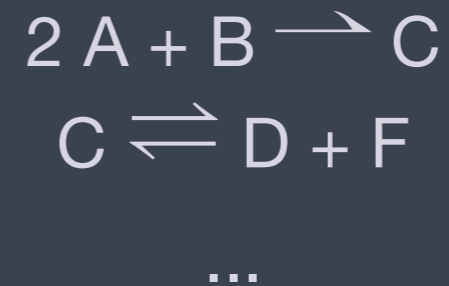
- ▶ Machine-readable format for computational models
- ▶ Suitable for reaction networks
 - ▶ Arbitrary rate functions



...

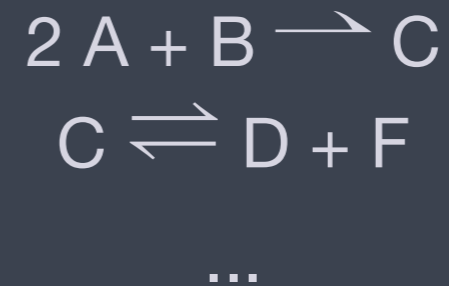
SBML = Systems Biology Markup Language

- ▶ Machine-readable format for computational models
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 - ▶ Arbitrary rate functions
- ▶ Models can also include
 - ▶ Compartments
 - ▶ Mathematical “extras”



SBML = Systems Biology Markup Language

- ▶ Machine-readable format for computational models
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 - ▶ Arbitrary rate functions
- ▶ 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

```
<?xml version="1.0" encoding="UTF-8" />
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1"
  xmlns:math="http://www.w3.org/1998/Math/MathML">
  <model>
    <listOfCompartments>
      <compartment id="cell"/>
    </listOfCompartments>
    <listOfSpecies>
      <species id="X0" compartment="cell" initialConcentration="1" />
      <species id="X1" compartment="cell" initialConcentration="1" />
      <species id="T" compartment="cell" initialConcentration="1" />
      <species id="S1" compartment="cell" initialConcentration="1" />
      <species id="S2" compartment="cell" initialConcentration="1" />
    </listOfSpecies>
    <listOfParameters>
      <parameter id="Keq" value="2.5"/>
    </listOfParameters>
    <listOfRules>
      <assignmentRule variable="S1">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <apply>
            <divide/>
            <ci> T </ci>
            <apply>
              <plus/>
              <cn> 1 </cn>
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          </apply>
        </math>
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    </listOfRules>
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</sbml>
```



Where is SBML today?

Now the *de facto* standard



The screenshot shows the SBML.org website in a browser window. The title bar reads "SBML.org - The home site for the Systems Biology M...". The address bar shows "http://sbml.org/index.psp". The main heading is "SBML Systems Biology Markup Language". Below the heading is a navigation menu with links: home, contacts, documents, downloads, FAQs, forums, Level 3, models. A paragraph describes SBML as a computer-readable format for representing models of biochemical reaction networks. Below this is a section titled "Internationally Supported and Widely Used" which lists various software systems that support SBML, including Balsa, Basis, Biocham, BioCharon, ByoDyn, BioCyc, BioGrid, BioModels, BioNetGen, BioPathway Explorer, Bio Sketch Pad, BioSnp, DBsolve, Dizzy, E-CELL, ecellJ, ESS, FluxAnalyzer, Fluxor, Gepasi, Gillespie2, HSMB, HybridSBML, INSII IGO discovery, MMT2, Modesto, Molecuizer, Monod, Narrator, NetBuilder, Oscill8, PANTHER Pathway, PathArt, PathScout, PathwayLab, Pathway Tools, SBMLmerge, SBMLR, SBMLSim, SBMLToolbox, SBliD, SBToolbox, SBW, SClpath, Sigmoid*, SigPath, SigTran, and 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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Support by SBML Team

- ▶ Writing grants for core development
- ▶ Writing infrastructure software
 - ▶ libSBML
 - ▶ MathSBML, SBMLToolbox
- ▶ Maintaining web & mailing list resources
- ▶ Organizing workshops & other events

Latest: SBML Level 2 Version 2

- ▶ Final version released
September 26

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

Andrew Finney
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Oxford Science Park
Oxford, OX4 4GA, UK

Michael Hucka
mhucka@sbml.org
Biological Network Modeling Center
Beckman Institute, Mail Code 139-74
California Institute of Technology
Pasadena, CA 91125, USA

Nicolas Le Novère
lenov@ebi.ac.uk
European Bioinformatics Institute
Wellcome Trust Genome Campus, Hinxton
Cambridge, CB10 1SD, UK

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 mailing list sbml-announce@caltech.edu

The latest revision of the SBML Level 2 Version 2 specification is available at
<http://sbml.org/specifications/sbml-level-2/version-2/>

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

- ▶ Many clarifications
- ▶ Simplification to the unit system
- ▶ Addition of species types, compartment types
- ▶ Addition of “constraints”
- ▶ Support for the Systems Biology Ontology (SBO)
- ▶ Recommended standard format for annotations
- ▶ “Revisions” process for handling errata



What lies ahead?

Revised SBML governance & development process

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

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*

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.



BioModels.net

Got models?

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  xmlns:math="http://www.w3.org/1998/Math/MathML">
  <model>
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    </listOfParameters>
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          <apply>
            <divide/>
            <ci> T </ci>
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<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/1.0" xmlns:math="http://www.w3.org/1998/Math/MathML">
  <model>
    <listOfCompartments>
      <compartment id="cell"/>
    </listOfCompartments>
    <listOfSpecies>
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unregulated

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```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" version="1"
      xmlns:math="http://www.w3.org/1998/Math/MathML">
  <model>
    <listOfCompartments>
      <compartment id="cell"/>
    </listOfCompartments>
    <listOfSpecies>
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unregulated

low info content

BioModels.net consortium

- ▶ International collaboration to develop:
 1. A public database of **curated, annotated** models: **BioModels Database**
 2. Guidelines for curation and annotation of models: **MIRIAM**
 3. Ontology suited to computational models: **SBO**
- ▶ Main collaborators
 - ▶ Nicolas Le Novère's Computational Neurobiology group at EBI (UK)
 - ▶ Hucka and SBML Team at Caltech (USA) and U. Hertfordshire (UK)
 - ▶ Herbert Sauro's group at Keck Graduate Institute
 - ▶ Hans Westerhoff & Jacky Snoep's JWS Online (ZA and UK)
 - ▶ Hiroaki Kitano's Systems Biology Institute

BioModels Database

<http://www.ebi.ac.uk/biomodels>

- ▶ Stores & serves **quantitative** models of bio. interest
 - ▶ **Free, public** resource
 - ▶ Models must be described in **peer-reviewed** publication(s)
- ▶ Imports models in **SBML** & **CellML** formats
 - ▶ Exports in **SBML**, **CellML**, **SciLab**, **XPP** and **BioPAX**

The screenshot shows the BioModels Database website interface. At the top, there is a navigation menu with links for 'Home', 'About EBI', 'Groups', 'Services', 'Toolbox', and 'Databases'. Below this is the EMBL-EBI logo and the text 'European Bioinformatics Institute'. The main content area displays a model entry for 'BIOMD0000000005 Tyson1991_CellCyc'. The entry includes a list of supported formats: 'SBML L2 V1', 'CellML', 'SciLab', 'XPP', and 'BioPAX'. There are also links for 'View Model Graph', 'View Model SVG', and 'View Simulation Result'. A 'Submit Model Comment/Bug' button is visible. Below the model entry, there is a section for 'Reference Publication' with a 'Publication ID: 1831270' and the citation: 'Proc Natl Acad Sci U S A. 2000; 97(12): 6102-6107. Modeling the cell division cycle. Tyson JJ. Department of Biology, University of California, San Diego, La Jolla, CA 92092, USA.'

Models are curated

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- ▶ Human curators check correspondence to publication

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 - ▶ General info about model, author, publication, etc.

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- ▶ Human curators add annotations
 - ▶ General info about model, author, publication, etc.
 - ▶ References to external data resources: UniProt, KEGG, NCBI, Gene Ontology, ChEBI, BIND, Reactome



Features of BioModels Database

- ▶ **True database:** can search model content & annotations
 - ▶ SBML XML stored in XINDICE; annotations in an SQL database
- ▶ Some statistics today (6th release in Oct. 2006):
 - ▶ **70+ curated, dynamical models**
 - ▶ E.g.: Tyson yeast cell cycle models, Elowitz E. coli repressilator, Teusink et al. yeast glycolysis, Rohwer et al. E. coli glucose transport
 - ▶ 26 non-curated models (e.g., models lacking kinetics, such as FBA)
- ▶ Model sources: us, Nature/EMBO ***Molecular Systems Biology***, repositories such as JWS Online and CellML, individual researchers

MIRIAM

- ▶ “Minimal info. requested in the annotation of biochemical models”
- ▶ Proposed guidelines for basic annotation of models
 - ▶ **Reference correspondence**, e.g.,
 - ▶ Be encoded in a public, standardized format (SBML, CellML, etc.)
 - ▶ Must be instantiated in a simulation & all quantitative attributes defined
 - ▶ **Attribution annotation** (info about model creators, source reference, etc.)
 - ▶ **External source annotations** (linking model element to data source)
- ▶ Goal: minimal common standards enabling sharing of curation effort

SBO = Systems Biology Ontology

- ▶ Occupies a space not filled by other ontologies
 - ▶ Primarily for describing rate laws and constituents
 - ▶ **Classification of rate laws**
 - ▶ Each term includes a mathematical function definition
 - ▶ Controlled vocabulary for the **roles of reaction participants**
 - ▶ E.g.: “substrate”, “catalyst”, “competitive inhibitor”, etc.
 - ▶ Controlled vocabulary for the **roles of parameters** in quantitative models

BioModels.net portal

The image shows a screenshot of the BioModels.net portal. The main header features the EMBL-EBI logo and the text "European Bioinformatics Institute". Below the logo is a navigation menu with links for "EBI Home", "About EBI", "Groups", "Services", and "Tools". The main content area is titled "SBO Ontology Browser" and displays a tree structure of the SBO ontology. The tree is expanded to show the "sbo" category, which includes "quantitative parameter", "participant role", and "reactant".

BioModels.net

EMBL-EBI
European Bioinformatics Institute

EBI Home | About EBI | Groups | Services | Tools

SBO Ontology Browser

SBO::Systems Biology Ontology

- [Refresh tree](#)
- sbo**
 - [quantitative parameter](#)
 - [participant role](#)
 - [reactant](#)

BioModels

A Database

BioModels Database search and retrieval interests. Models linked to relevant pathways, control

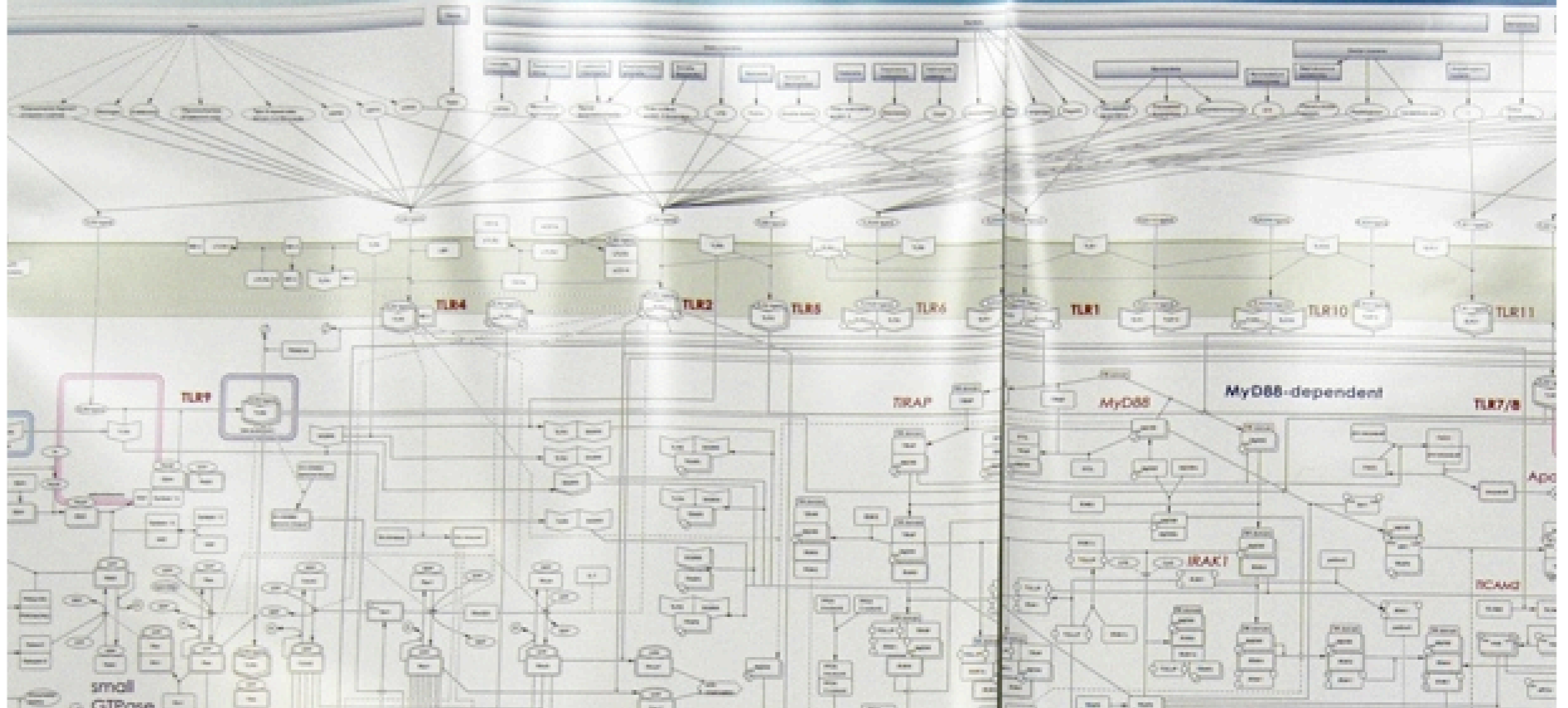
[Browse curated](#)

A comprehensive map of Toll-like receptor signaling

(TLR2/1001291.0)

Kanoe Oda (1, 2), Hiroaki Kitano (1, 2, 3)

1) The National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan; 2) Department of Fundamental Science and Technology, Tokyo Institute of Technology, Tokyo, Japan; 3) Department of Fundamental Science and Technology, Tokyo Institute of Technology, Tokyo, Japan



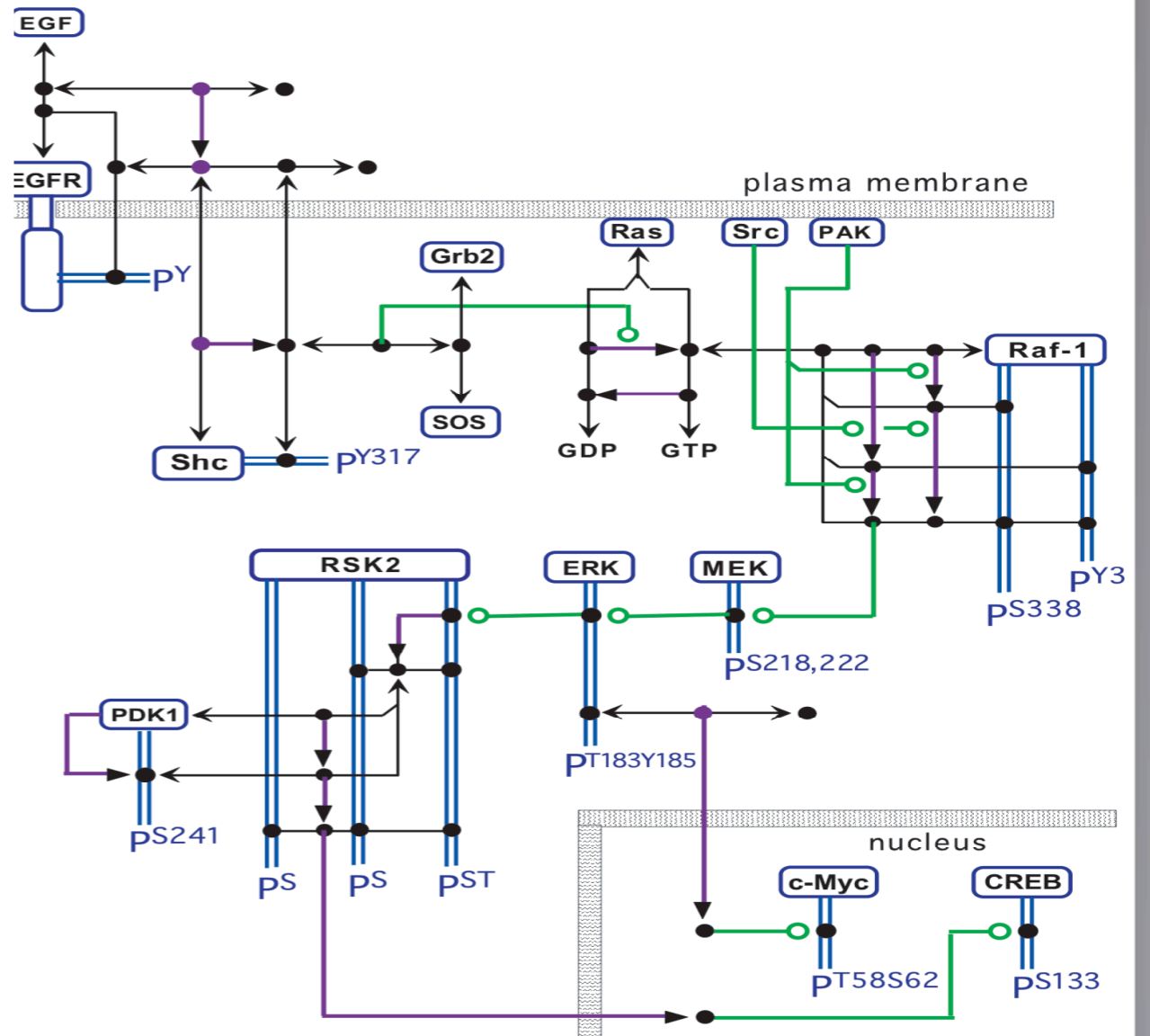
SBGN

Background

- ▶ No current standard for network diagrams in biology
- ▶ No consistency—
 - ▶ Between authors
 - ▶ Between papers
 - ▶ Between publications

Background

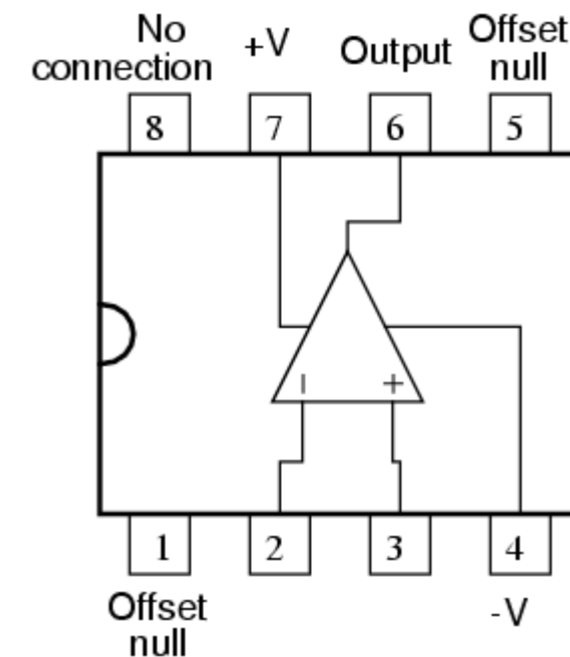
- ▶ No current standard for network diagrams in biology
- ▶ No consistency—
 - ▶ Between authors
 - ▶ Between papers
 - ▶ Between publications



Standardization would bring benefits

- ▶ Notations standardized in electrical/electronics, software engineering, etc.
- ▶ Taught in textbooks
- ▶ Supported by software
 - ▶ Automated verification
- ▶ Consistency makes it easier to read new diagrams

Typical 8-pin "DIP" op-amp integrated circuit



SBGN = Systems Biology Graphical Notation

- ▶ Goal: bring simulation/modeling community together and develop a proposal for a standard notation for **some** types of diagrams
 - ▶ Starting with metabolic & signaling networks
- ▶ Begun late '05 by Kitano/Le Novère/Hucka thanks to NEDO funding
- ▶ 2 SBGN workshops held so far (Feb and Oct 2006)
 - ▶ Many groups participating: Goryanin group (U. Edinburgh), BioPAX (MSKCC New York), SRI, CellML, EML (Germany), many others
 - ▶ Join if you're interested!
- ▶ Currently working towards a first proposal



Closing

The funding

- ▶ National Institute of General Medical Sciences (USA)
- ▶ JST ERATO Kitano Symbiotic Systems Project (Japan) (to 2003)
- ▶ National Science Foundation (USA)
- ▶ International Joint Research Program of NEDO (Japan)
- ▶ JST ERATO-SORST Program (Japan)
- ▶ Japanese Ministry of Agriculture
- ▶ Japanese Ministry of Educ., Culture, Sports, Science and Tech.
- ▶ 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)

SBML Team	BioModels DB Team	SBGN Team
Michael Hucka	Nicolas Le Novère	Hiroaki Kitano
Andrew Finney	Chen Li	Nicolas Le Novère
Ben Bornstein	Mélanie Courtot	Michael Hucka
Sarah Keating	Lu Li	Akira Funahashi
Bruce Shapiro	Camille Laibe	
Ben Kovitz	Nicolas Rodriguez	
Hamid Bolouri	Harish Dharuri	
Herbert Sauro	Marco Donizelli	
Maria Schilstra	Alexander Broicher	
Jo Matthews	Arnaud Henry	

A million thanks to the SBML Community too

Where to learn more

- ▶ <http://sbml.org>
- ▶ <http://biomodels.net>
- ▶ <http://sbgn.org>
- ▶ *Upcoming:*
 - ▶ BioModels.net Training Camp 2007 January 13-15, Manchester, UK
 - ▶ SBML Hackathon 2007 in June at U. Newcastle, UK
 - ▶ SBGN Workshop in 2007 (probably March 2007, Gosau, Austria)
 - ▶ SBML Forum 2007 in Long Beach, CA, USA, Oct. 5-6 (ICSB 2007)
- ▶ **Thank you!**