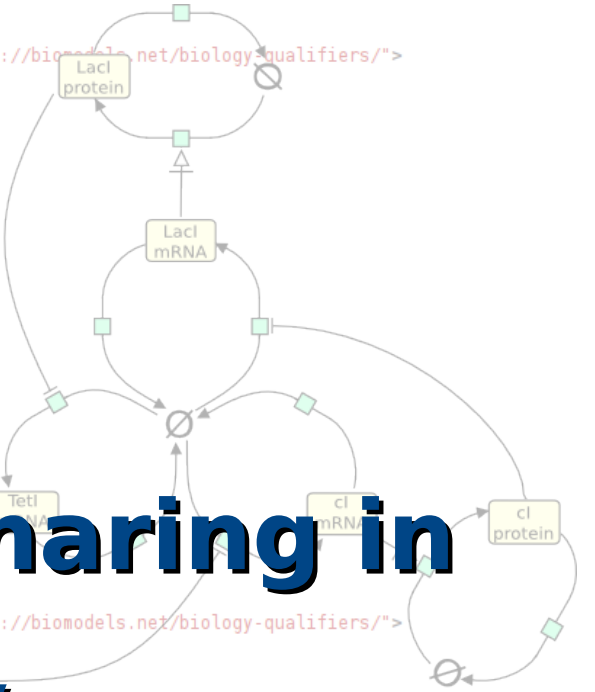
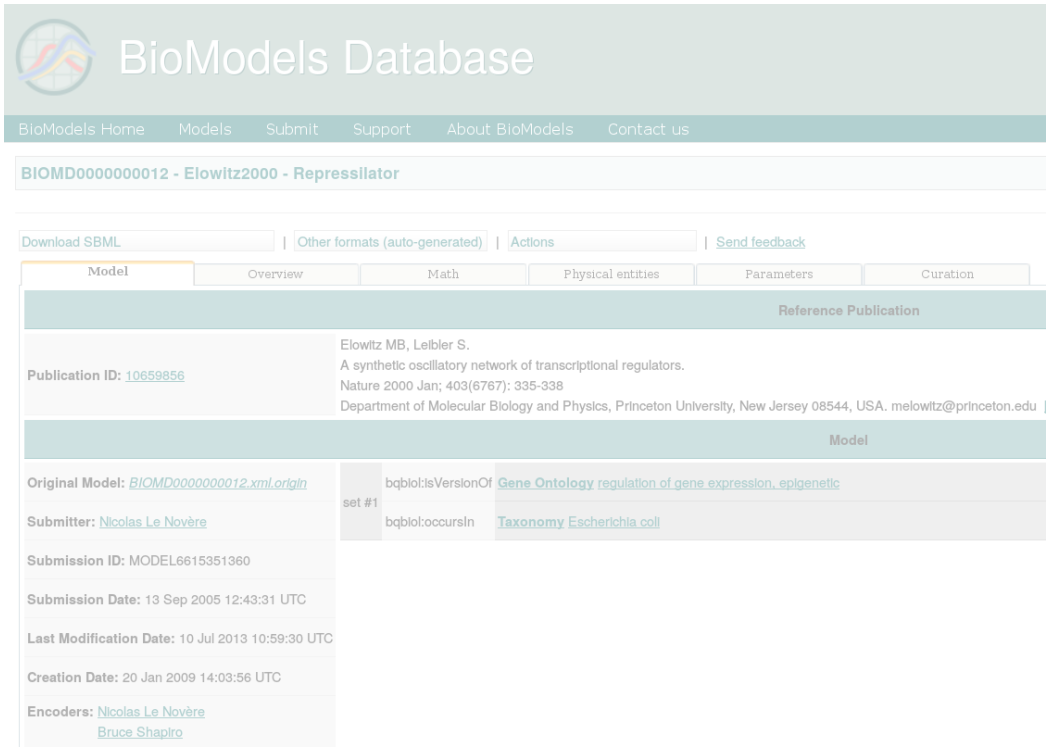
Two decades of model sharing in systems biology

Nicolas Le Novère
The Babraham Institute,
Cambridge, UK
n.lenovere@gmail.com





Who?

Scientific Baccalaureate at *Prytanée National Militaire*

"j'étais en l'une des plus célèbres écoles de l'Europe"
René Descartes – Discours de la méthode

Classes préparatoires aux grandes écoles – Math Bio

Mathematics	Physics Chemistry	Natural sciences

Bachelor physiology and cell biology
Magistere of biology-biochemistry

ENS ÉCOLE NORMALE SUPÉRIEURE

UNIVERSITÉ PARIS SUD Evolution	Molecular biophysics	UPMC SORBONNE UNIVERSITÉS Neuroendocrinology

Who?

Paris

1992 Institut Pasteur 1999

PhD
Nicotinic receptors:
Bioinformatics
Neuroanatomy
Behaviour

2001 Institut Pasteur 2003

CR CNRS
Récepteurs nicotiniques:
Modélisation moléculaire

2014-2015
20%
institutCurie

Chief Data Officer

1999 2001

EMBO post-doc
Bacterial chemotaxy:
Molecular modelling
Mathematical modelling

2003 EMBL-EBI 2012

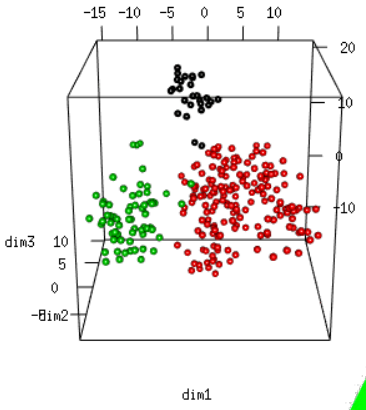
Group leader
Systems biology
Synaptic signalling
Modelling, database
Formal representations

2012- Babraham Institute

Tenure group leader
Signalling 50%
Epigenetics 30%
Lymphocytes 15%
Nuclear Dynamics 5%

Cambridge

What?



Themes

Synaptic plasticity,
Neurodegenerative diseases
Epigenetics, cell differentiation
stem cells

Bioinformatics

NGS: Transcriptomics,
epigenetics (SC)
Metabolomics
(lipidomics)
Network inference
Machine-learning

Modelling

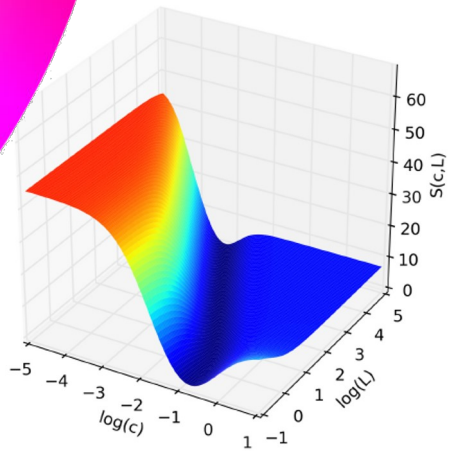
Differential equations
Stochastique process
Steady states, flux
Multi-agent modelling
Rule-based modelling
Reaction-diffusion

Standardisation and sharing

SED ML · SBGN · SBML · pharmML · JSBML · BioModels · MAMO · SBO · KISAO

SYSMOD

combine



Where?

Signalling

Len Stephens
Phil Hawkins
PI3 kinases

Heidy Welch
Rac signalling

Michael Wakelam
Lipidome

Simon Cook
Map kinases

Nick Ktistakis
Auto/mitophagy

Oliver Florey
Endocytosis

Nicolas Le Novère
Calcium signalling

Lymphocytes

Martin Turner
RNA binding proteins

Geoff Butcher
Gimap proteins

Anne Corcoran
Chromatin organisation

Michelle Linterman
Germinal centers

Rahul Roychoudhuri
Immunosuppression

Nicolas Le Novère
Transcriptomics

Epigenetics

Wolf Reik
DNA marks

Gavin Kelsey
Germ cell methylation

Peter Rugg-Gunn
Early lineages

Myriam Hemberger
Trophoblast cells

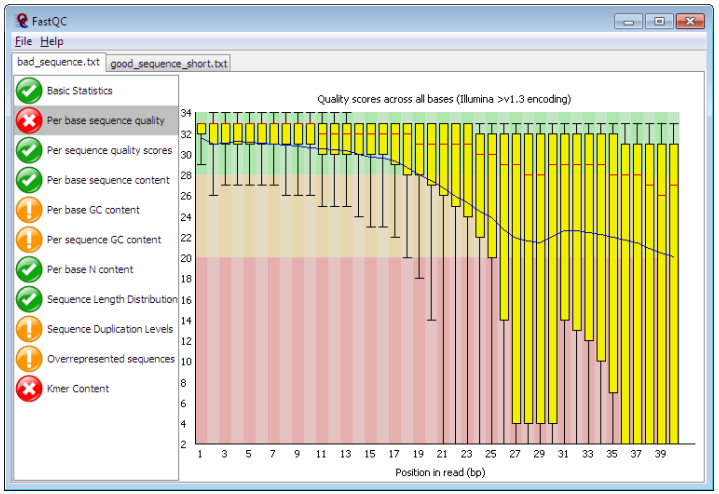
Jon Houseley
Yeast aging

Olivia Casanueva
C elegans aging

Stefan Schoenfelder
3D genome

Nicolas Le Novère
Metabolism

- Animal facility
- Gene targeting
- Flow cytometry
- Chemistry
- Mass spec
- Lipidomics
- Sequencing
- Bioinformatics



FastQC
> 1700 citations

CHiCAGO: robust detection of DNA looping interactions in Capture Hi-C data

Jonathan Cairns †, Paula Freire-Pritchett †, Steven W. Wingett, Csilla Várnai, Andrew Dimond, Vincent Plagnol, Daniel Zerbino, Stefan Schoenfelder, Biola-Maria Javierre, Cameron Osborne, Peter Fraser and Mikhail Spivakov

†Contributed equally

Genome Biology 2016 **17**:127

Bismark: a flexible aligner and methylation caller for Bisulfite-Seq applications

Felix Krueger, Simon R. Andrews

> 1000 citations

Bioinformatics, Volume 27, Issue 11, 1 June 2011, Pages 1571–1572, https://doi.org/10.1093/bioinformatics/btr167
Published: 14 April 2011 **Article history**

Single-cell genome-wide bisulfite sequencing for assessing epigenetic heterogeneity

Sébastien A Smallwood, Heather J Lee, Christof Angermueller, Felix Krueger, Heba Saadeh, Julian Peat, Simon R Andrews, Oliver Stegle, Wolf Reik & Gavin Kelsey

Nature Methods **11**, 817–820 (2014) Received: 28 April 2014

Parallel single-cell sequencing links transcriptional and epigenetic heterogeneity

Christof Angermueller, Stephen J Clark, Heather J Lee, Iain C Macaulay, Mabel J Teng, Tim Xiaoming Hu, Felix Krueger, Sébastien A Smallwood, Chris P Ponting, Thierry Voet, Gavin Kelsey, Oliver Stegle & Wolf Reik

Nature Methods **13**, 229–232 (2016) Received: 29 October 2015

scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells

Stephen J. Clark, Ricard Argelaguet, Chantriolnt-Andreas Kapourani, Thomas M. Stubbs, Heather J. Lee, Celia Alda-Catalinas, Felix Krueger, Guido Sanguinetti, Gavin Kelsey, John C. Marioni, Oliver Stegle & Wolf Reik

Nature Communications **9**, Article number: 781 (2018) Received: 11 December 2017

Where?


Babraham Institute
John Innes Centre
IBERS
Institute of Biological, Environmental and Rural Sciences
BBSRC
bioscience for the future
Earlham Institute
Pirbright INSTITUTE
Quadram Institute
Science Health Food Innovation
ROSLIN
ROTHAMSTED RESEARCH 175

Responsive mode research grants
Responsive mode priorities
Animal health
Bioenergy: generating new replacement fuels for a greener, sustainable future
Combatting antimicrobial resistance
Data driven biology
Food, nutrition and health
Healthy ageing across the lifecourse
Integrative microbiome research
New strategic approaches to industrial biotechnology
Reducing waste in the food chain
The replacement, refinement and reduction (3Rs) in research using animals

Systems approaches to the biosciences

Background

This priority falls under the enabling theme **'Exploiting New Ways of Working'**.

World-class bioscience is critically dependent on new technologies, methodologies and resources. This theme aims to encourage research that will yield the next-generation of these 'new ways of working'. Projects should focus on underpinning and enabling one of our strategic research priorities (food security, industrial biotechnology, bioscience underpinning health) or have potential, generic utility across one or more broad areas of the biosciences.

Aim

The priority aims to encourage the application of systems biology approaches across BBSRC's research portfolio.

Scientific scope

Systems biology is an approach by which biological questions are addressed through integrating data collection activities with computational/ mathematical modelling activities to produce a better understanding of biological systems (or sub-systems).

Methods for integrating data into models should be relevant to the system under investigation but may include a combination of mathematical, statistical and computational modelling, visualisation tools and network inference. Models should capture complex biological behaviour by integrating the necessary components and interactions and thereby simulate the biological system in a way that enables useful predictions to be made. Systems approaches are most relevant when there is a clear biological endpoint. Model development and validation should proceed iteratively, using relevant data to improve the knowledge of the system.

We are particularly interested in encouraging the development and adoption of systems approaches at multiple scales and using multiple approaches, with the ultimate goal being to generate **'digital organisms'**. A digital organism represents all biological processes, pathways and interactions, within a specified organism in the form of mathematical or computational models underpinned by quantitative data. Such tools will enable realistic

Responsive mode research grants
Responsive mode priorities
Animal health
Bioenergy: generating new replacement fuels for a greener, sustainable future
Combatting antimicrobial resistance
Data driven biology
Food, nutrition and health
Healthy ageing across the lifecourse
Integrative microbiome research
New strategic approaches to industrial biotechnology
Reducing waste in the food chain
The replacement, refinement and

Data driven biology

Background

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World-class bioscience is critically dependent on new computational technologies, methodologies and resources. This priority aims to encourage research that will yield the next-generation of these 'new ways of working'. Projects should focus on underpinning and enabling one of our strategic research priorities (agriculture and food security, industrial biotechnology and bioenergy, bioscience for health) or have potential generic utility across one or more broad areas of the biosciences.

Aim

The data driven biology priority aims to encourage the **development of the bioinformatics tools and computational approaches** that are required to extract value and generate new biological understanding from the huge volume and diversity of bioscience data now available and so underpin and enable biological research as it continues to evolve as a data intensive discipline.

Scientific scope

The complexity and scale of biological data is continually increasing and this places demands on the ability of biologists to manage and analyse data. Innovative computational approaches are needed for the integration, analysis and interpretation of new and repurposed biological data to enable bioscientists to gain value and scientific leads from the enormous quantities and diversity of data available.

For a project to address the data driven biology priority a significant focus of the work must involve the initiation or further development of advanced computational tools, resources or methodologies relevant to our remit. Projects may develop entirely new applications, employ cutting-edge computational methods to better exploit data resources, or provide innovative functionality and improvements to an existing computational tool or resource.

Annual calls

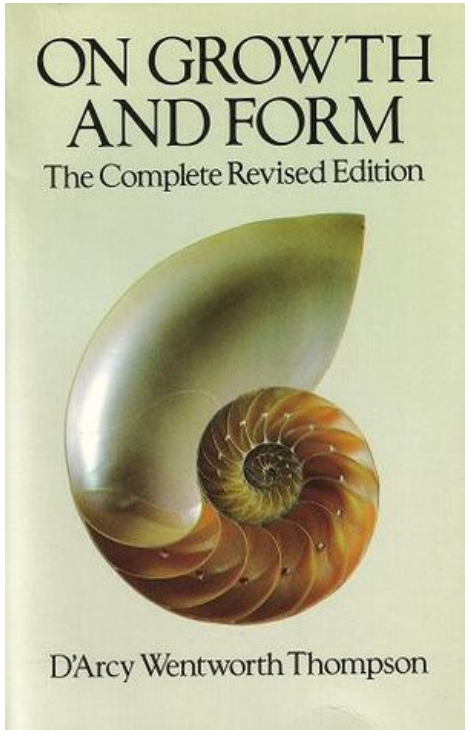
- **Bioinformatics and Biological Resources Fund:**
  The Bioinformatics and Biological Resource Fund was established to tackle a strategic need, identified by BBSRC, to provide 'proper support for resources such as databases, genetic resources and culture collections which require long term maintenance and curation' and plays an important role in enabling data sharing in the biosciences, as mandated by our data sharing policy. The Bioinformatics and Biological Resource Fund launches around February/March each year.

- **Tools and Resources Development Fund:**
  Through the first call of the Tools and Resources Development Fund, which launches annually in June/July, we support small or short-duration, pump-priming projects that enable excellent bioscience, encourage applications that develop novel tools, technologies and methods spanning the breadth of BBSRC research and underpin in the long-run all of our strategic priorities and the wider biosciences.

  The second call of the Tools and Resources Development Fund, launched annually in June/July, supports small or short-duration, pump-priming projects that enable excellent bioscience, encourage the development of novel software tools, technologies and computational methods for research challenges within our remit and help underpin research in the wider biosciences.

What is the goal of using mathematical models?

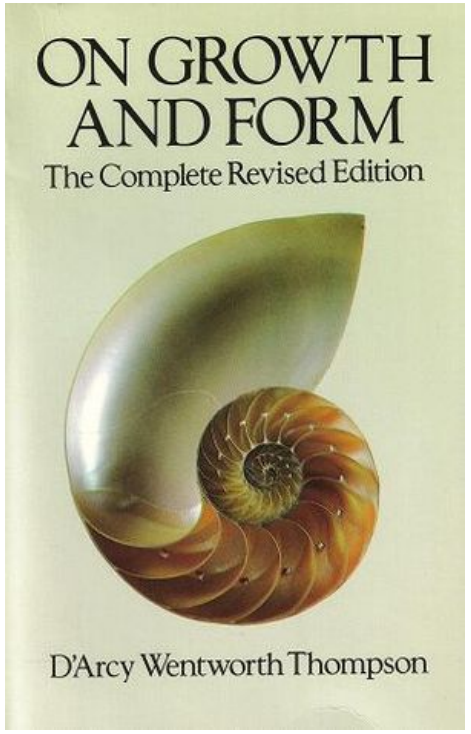
Describe

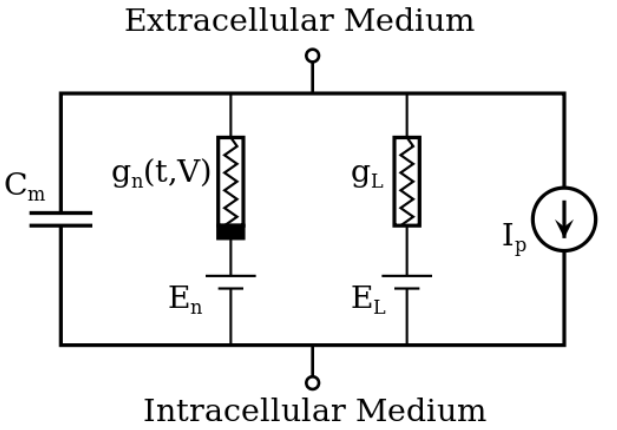


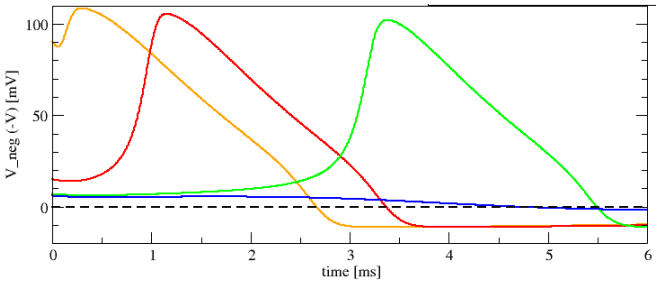
1917

What is the goal of using mathematical models?

Describe	Explain





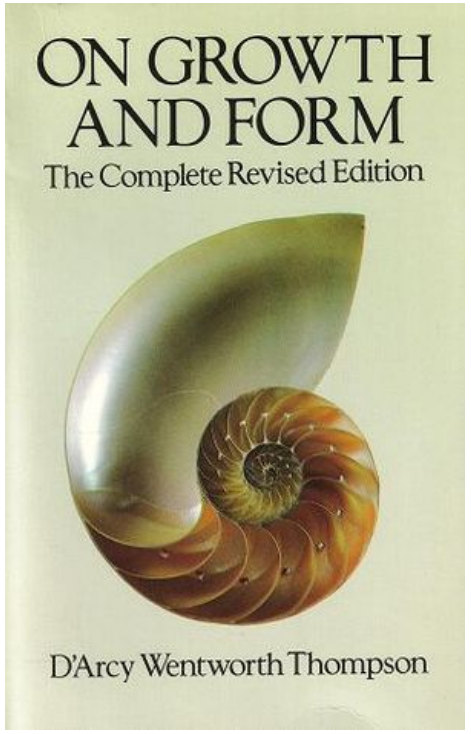


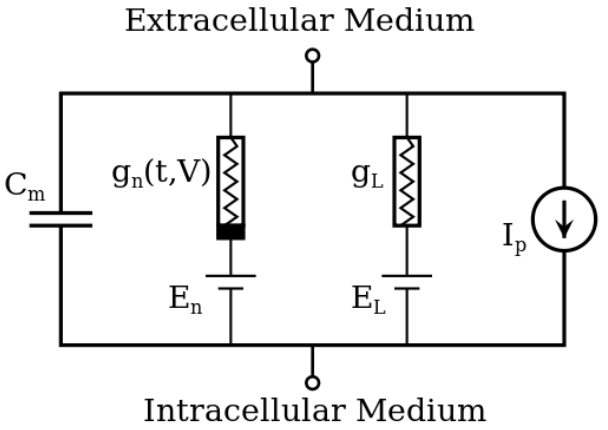
1917

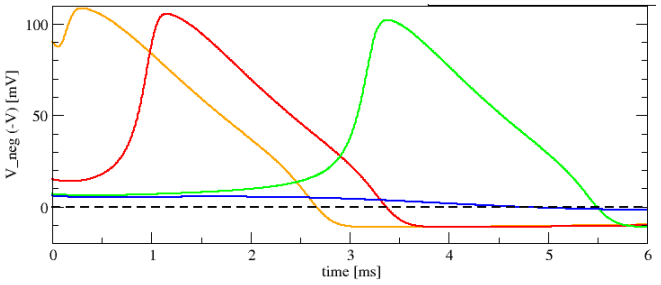
1952

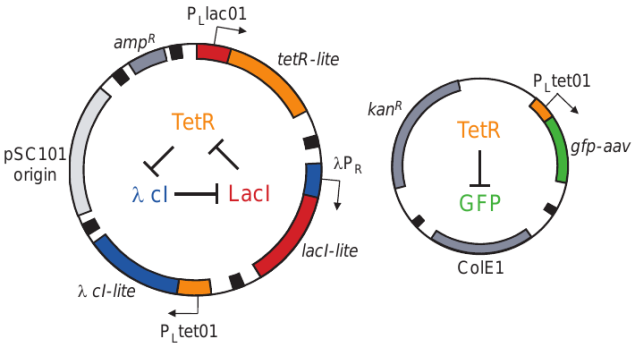
What is the goal of using mathematical models?

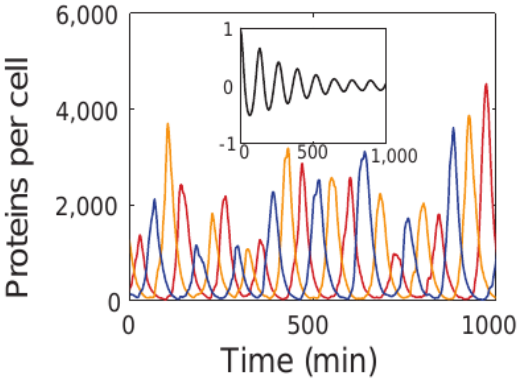
Describe	Explain	Predict











1917 1952 2000

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

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variables
[x]
Vmax
Kd
EC_{50}
length
$t_{1/2}$

What we want to know or compare with experiments

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables
[x]
Vmax
Kd
EC_{50}
length
$t_{1/2}$

relationships

$$K_d = \frac{[A] \cdot [B]}{[AB]}$$

$$d[X]/dt = k \cdot [Y]^2$$

$$\sum_i [X]_i - F(t) = 0$$

$$k(t) \sim N(k, \sigma^2)$$

If $\text{mass}_t > \text{threshold}$
then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$

What we already know or want to test

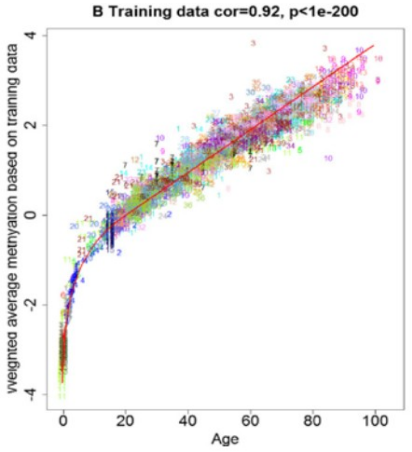
What is a mathematical model?

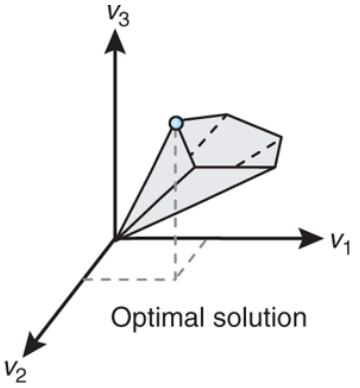
Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables	relationships	constraints
[x]	$K_d = \frac{[A] \cdot [B]}{[AB]}$	[x]≥0
Vmax	$d[X]/dt = k \cdot [Y]^2$	Energy conservation
Kd	$\sum_i [X]_i - F(t) = 0$	Boundary conditions (v < upper limit)
EC_{50}	$k(t) \sim N(k, \sigma^2)$	Objective functions (maximise ATP)
length	If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$	Initial conditions
$t_{1/2}$		

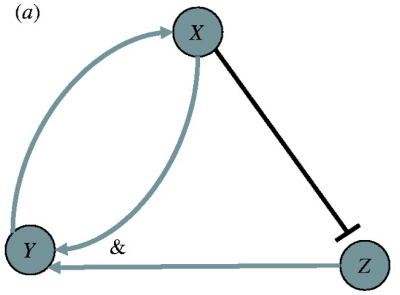
The context or what we want to ignore

Representation of time





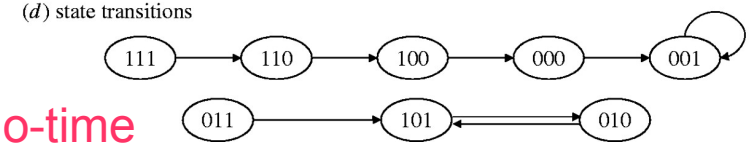
No time: correlations, steady-states



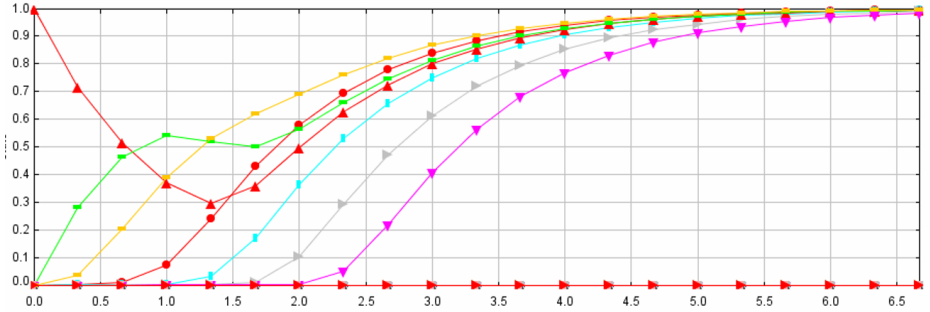
(b) $Y=X \,\&\, Z,\ X=Y,\ Z=\neg X$

(c)

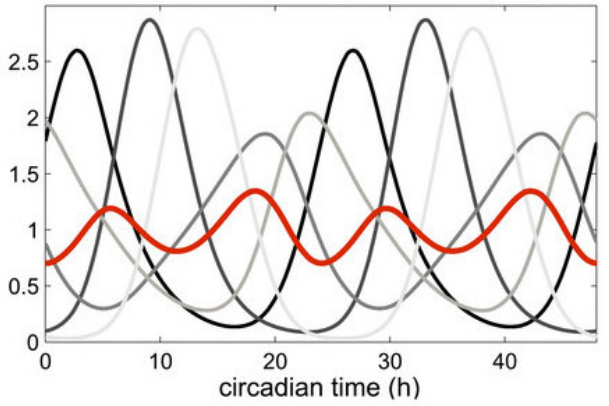
t			$t+1$		
X	Y	Z	X	Y	Z
0	0	0	0	0	1
0	0	1	0	0	1
0	1	0	1	0	1
0	1	1	1	0	1
1	0	0	0	0	0
1	0	1	0	1	0
1	1	0	1	0	0
1	1	1	1	1	0



Pseudo-time
(t4 – t0 is not 2 x t2 -t0): Logic models



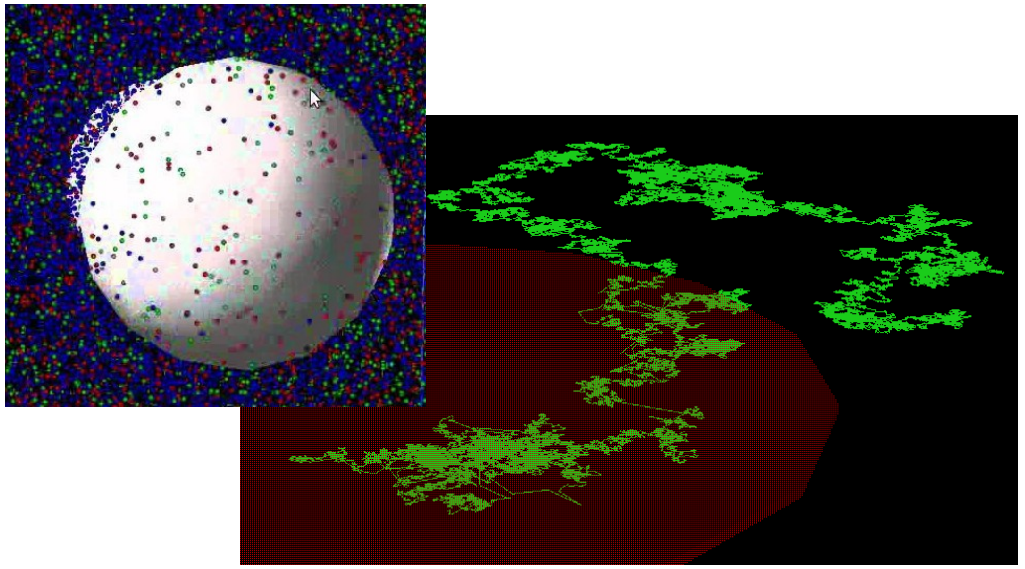
Discrete time



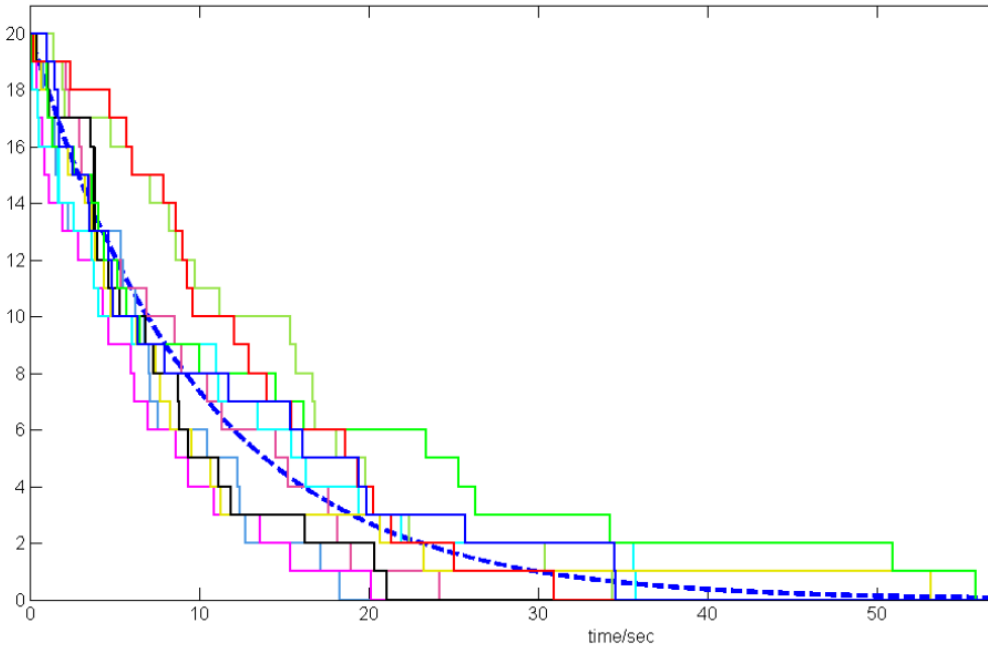
Continuous time

Variable granularity

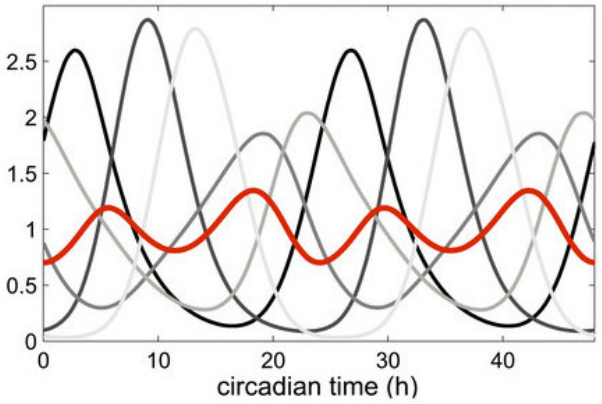
Single particles



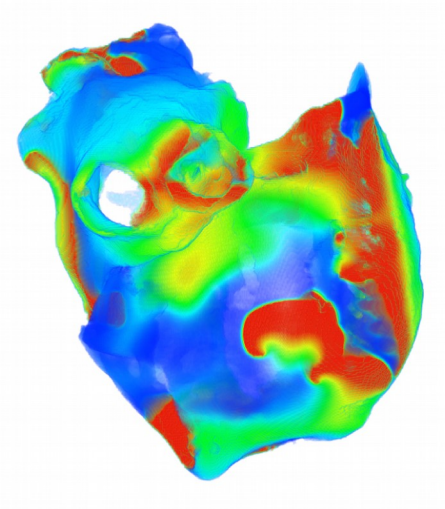
Discrete populations

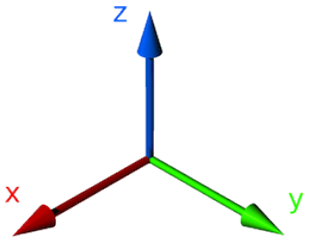


Continuous populations

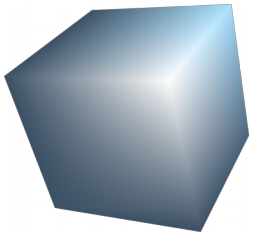


Fields





Spatial representation



No dimension

Homogeneous
(well-stirred, isotropic)

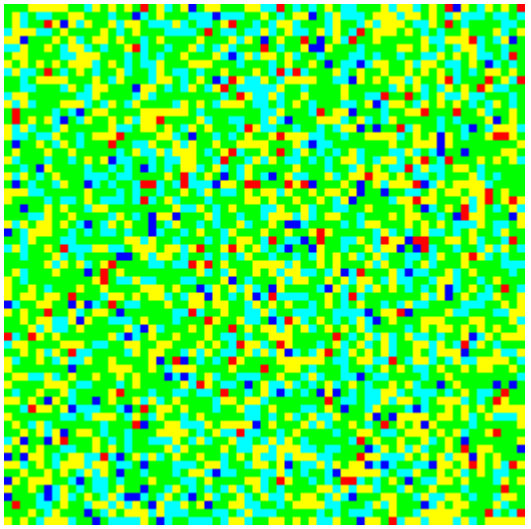
[x]

Compartments

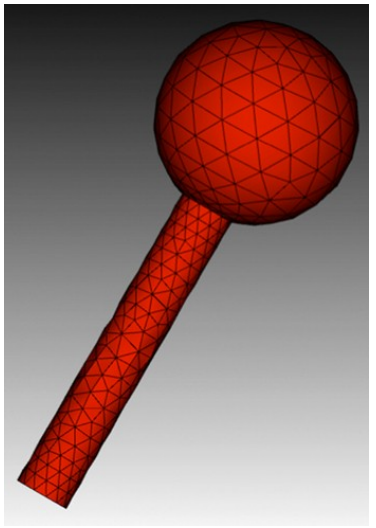
$[x]_A$

$[x]_B$

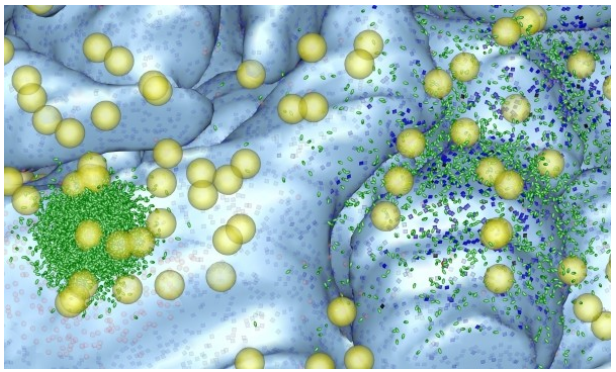
Cellular automata

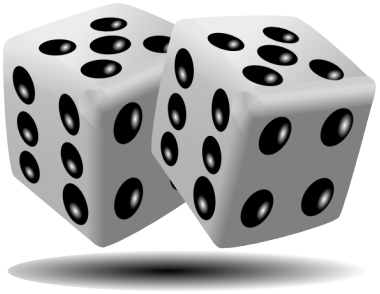


Finite elements



Real space



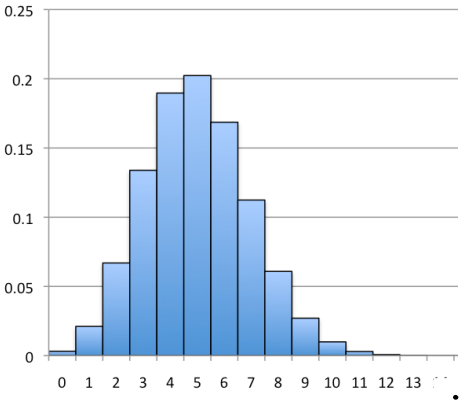


Stochasticity

Deterministic simulation

$$\dot{x}_i = \sum_j n_{ij} k_j \prod_i X_i^{n_{ij}}$$

Ensemble models (distributions)



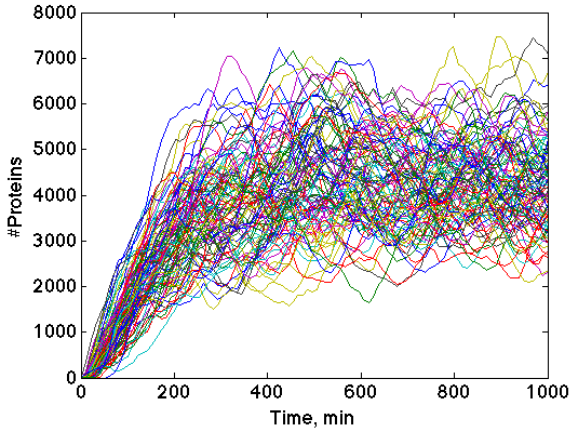
Initial conditions
Parameter values

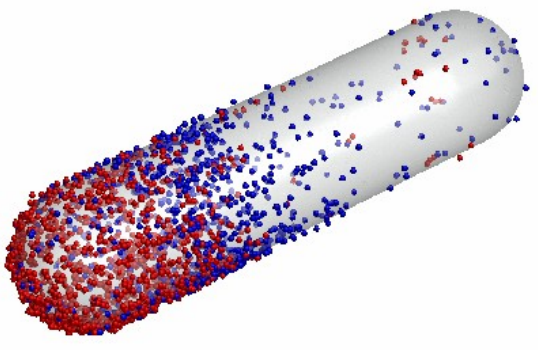
$$\dot{x}_i = \sum_j n_{ij} k_j \prod_i X_i^{n_{ij}}$$

Stochastic differential equations

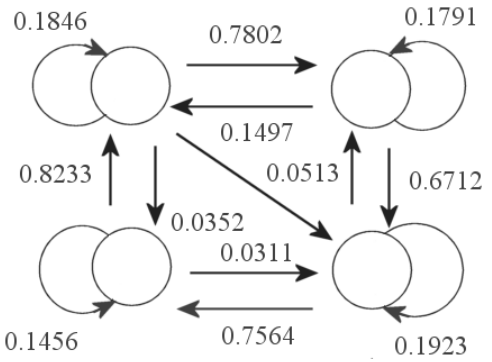
$$\dot{x}_i = f(X) + \sum_j g_j(x_i) n_j(t)$$

Stochastic simulations (SSA, “Gillespie”)

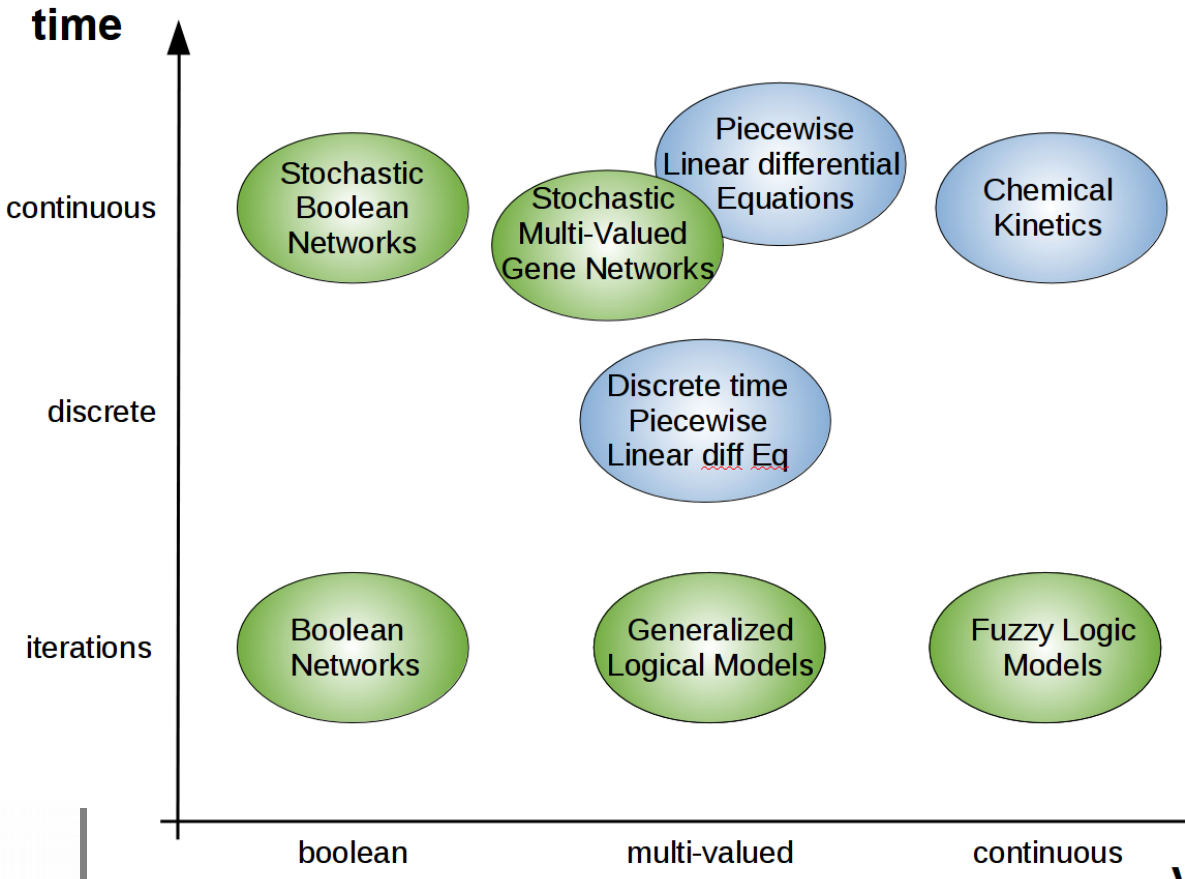


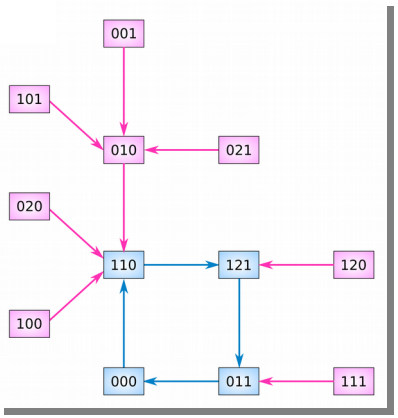


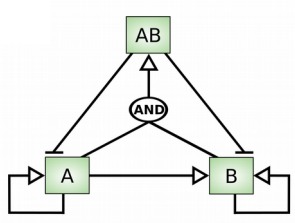
Probabilistic models

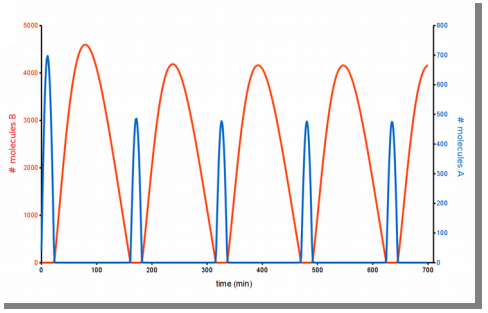


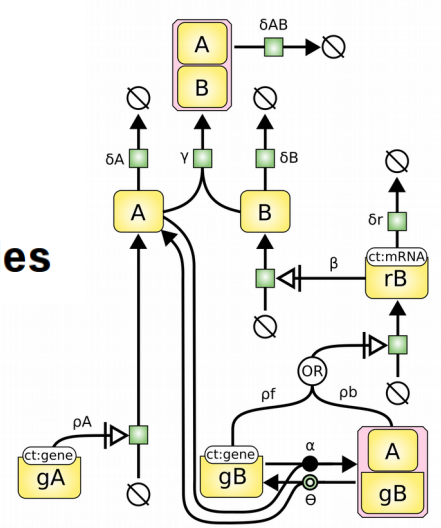
Logic versus numeric





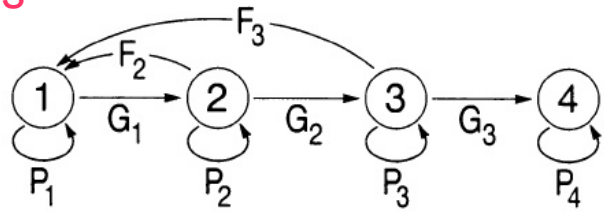




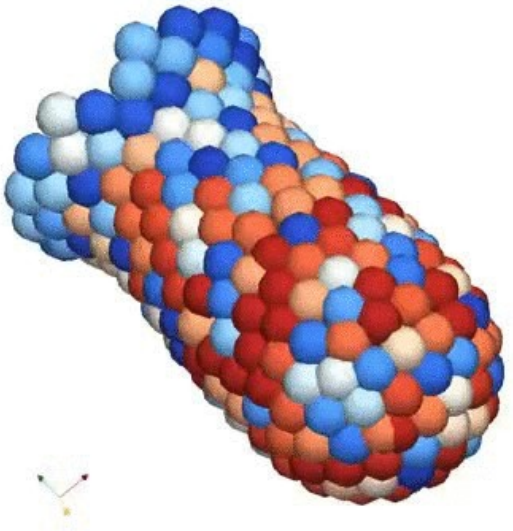


Many other types of models

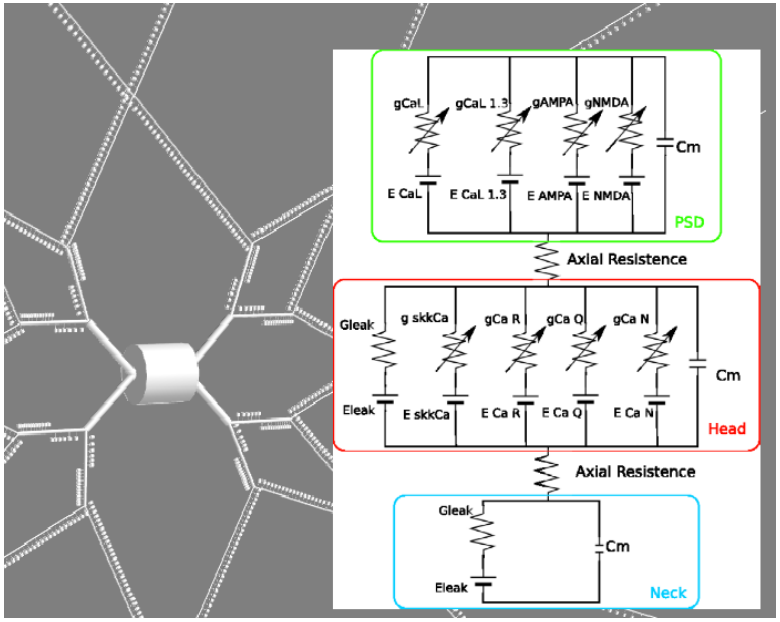
Matrix models



$$\begin{pmatrix} N_1(t+1) \\ N_2(t+1) \\ N_3(t+1) \\ N_4(t+1) \end{pmatrix} = \begin{pmatrix} 0 & F_2 & F_3 & 0 \\ G_1 & P_2 & 0 & 0 \\ 0 & G_2 & P_3 & 0 \\ 0 & 0 & G_3 & P_4 \end{pmatrix} \begin{pmatrix} N_1(t) \\ N_2(t) \\ N_3(t) \\ N_4(t) \end{pmatrix}$$



Multi-agents models (cellular potts)



Cable approximation

The Computational Systems Biology loop

"biological" model

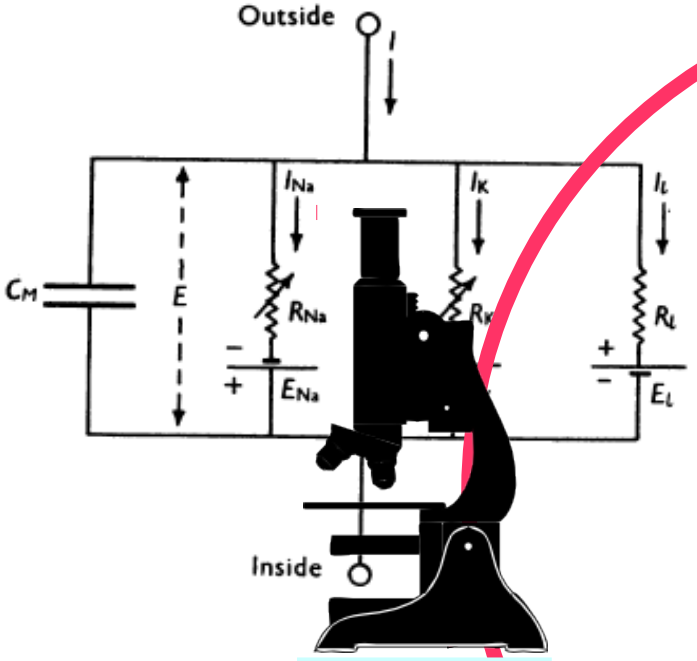
mathematical model

validation

parameterisation

simulation

computational model



$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$dn/dt = \alpha_n (1 - n) - \beta_n n,$$

$$dm/dt = \alpha_m (1 - m) - \beta_m m,$$

$$dh/dt = \alpha_h (1 - h) - \beta_h h,$$

$$\alpha_n = 0{\cdot}01\,(V + 10) \Big/ \left(\exp \frac{V + 10}{10} - 1\right),$$

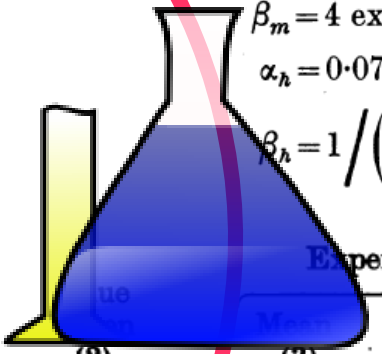
$$\beta_n = 0{\cdot}125 \exp (V/80),$$

$$\alpha_m = 0{\cdot}1\,(V + 25) \Big/ \left(\exp \frac{V + 25}{10} - 1\right),$$

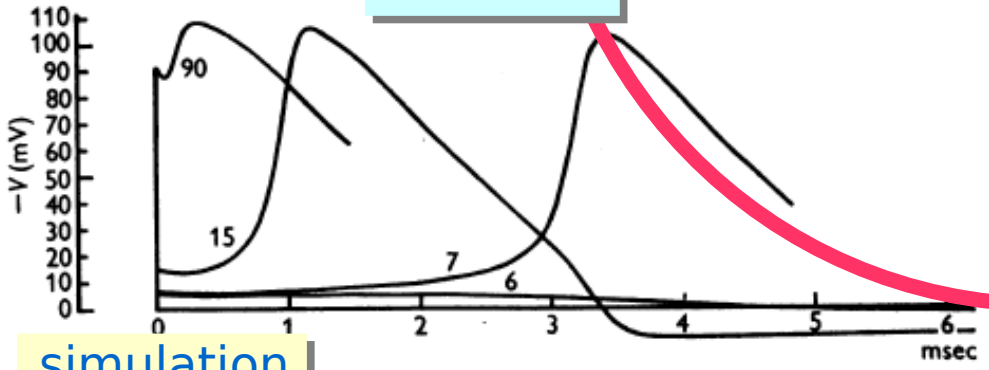
$$\beta_m = 4 \exp (V/18),$$

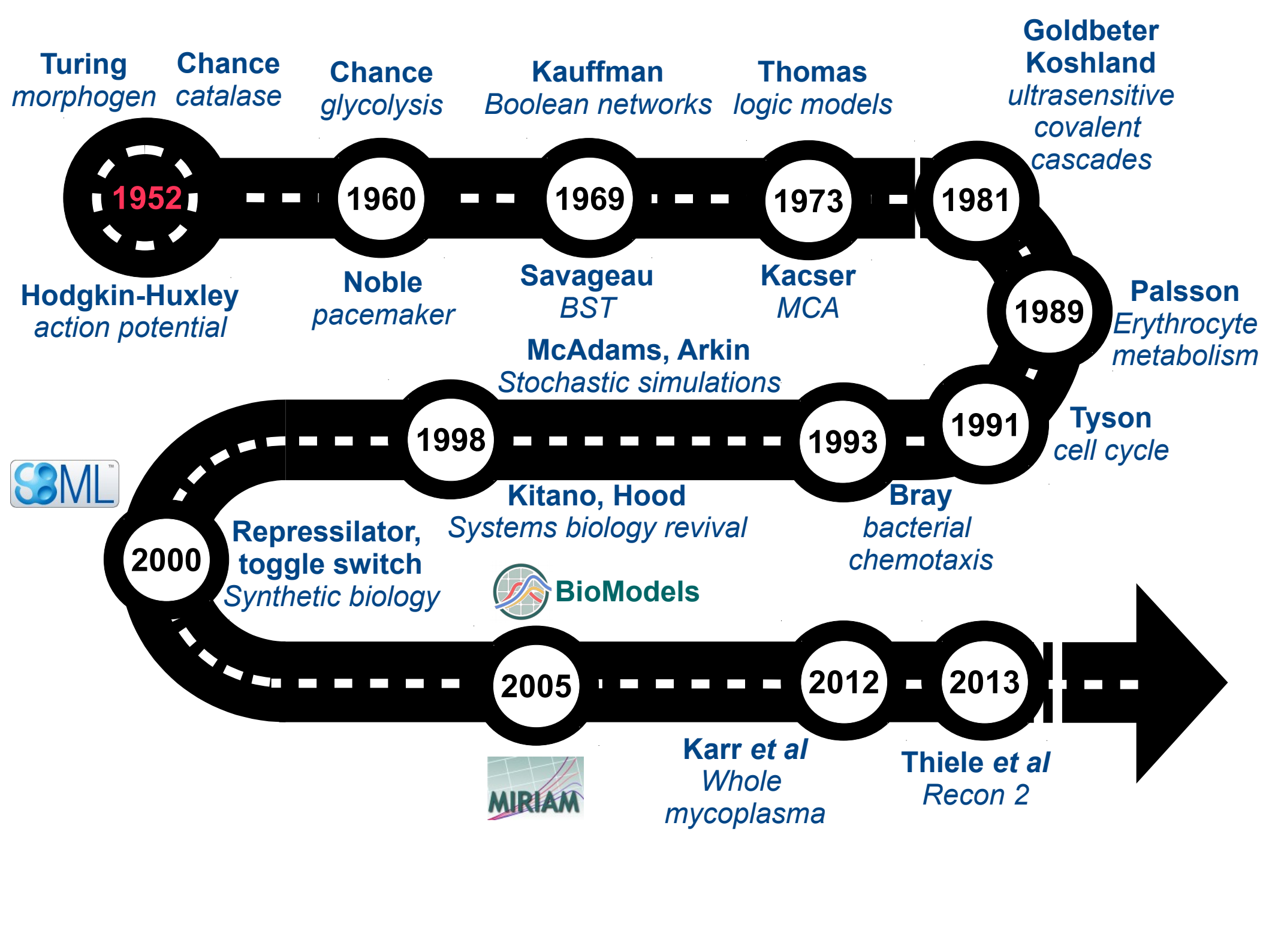
$$\alpha_h = 0{\cdot}07 \exp (V/20),$$

$$\beta_h = 1 \Big/ \left(\exp \frac{V + 30}{10} + 1\right).$$



Constant (1)	Experimental values (2)	(3)	Range (4)
C_M (μF/cm^2)			0·8 to 1·5
V_{Na} (mV)			− 95 to − 119
V_K (mV)			+ 9 to + 14
V_l (mV)	− 10·613	− 11	− 4 to − 22
$\bar{g}_{Na}$ (m.mho/cm^2)	120	80 160	65 to 90 120 to 260
$\bar{g}_K$ (m.mho/cm^2)	36	34	26 to 49
$\bar{g}_l$ (m.mho/cm^2)	0·3	0·26	0·13 to 0·50

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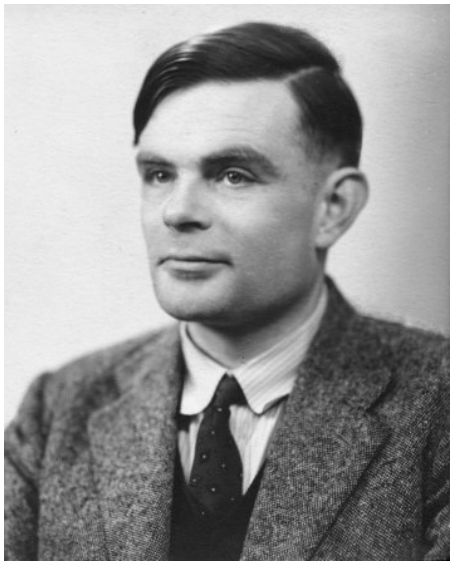
mycoplasma
Thiele et al
Recon 2

Computer simulations Vs. mathematical models



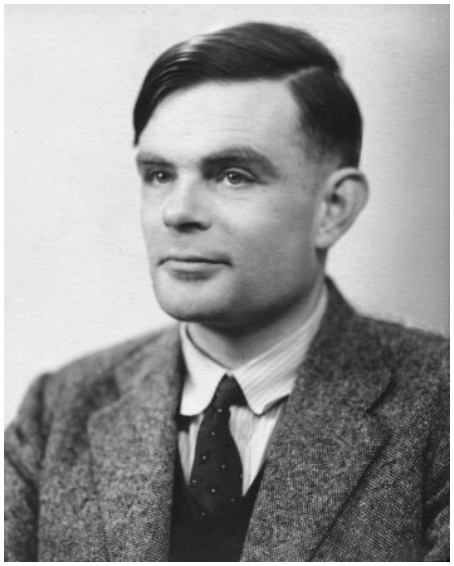
THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two

Computer simulations Vs. mathematical models



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One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.

Birth of Computational Systems Biology

The Mechanism of Catalase Action. [1]

II. Electric Analog Computer Studies

Britton Chance, David S. Greenstein, Joseph Higgins and C. C. Yang

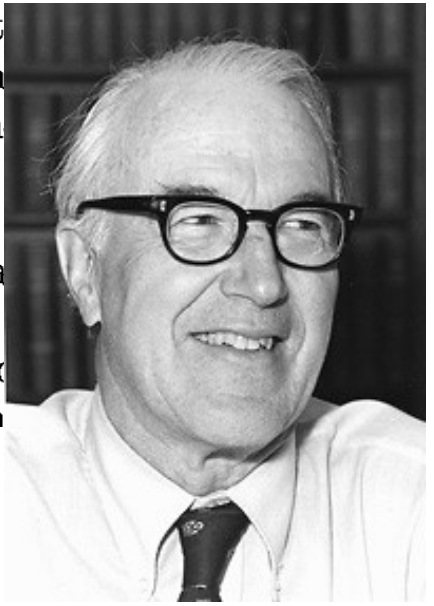
From the Johnson Research Foundation, University of Pennsylvania, Philadelphia, Pennsylvania

Received October 26, 1951

Introduction

In early studies of enzyme reactions only the disappearance of substrate could be measured and only the steady-state operation of the enzyme could be studied. We can now study directly the formation and disappearance of compounds of enzyme and substrate by sensit spectrophotometric methods. Thus not only the steady-state but a the transient portions of the enzyme action are revealed. And th transient portions are very sensitive indicators of the mechanism which the enzyme acts.

Differential equations representing the transient formation a disappearance of an enzyme-substrate complex can readily be set for enzyme reactions that follow the law of mass action, and solutio of these equations are readily obtained for the special and often un



Birth of Computational Systems Biology

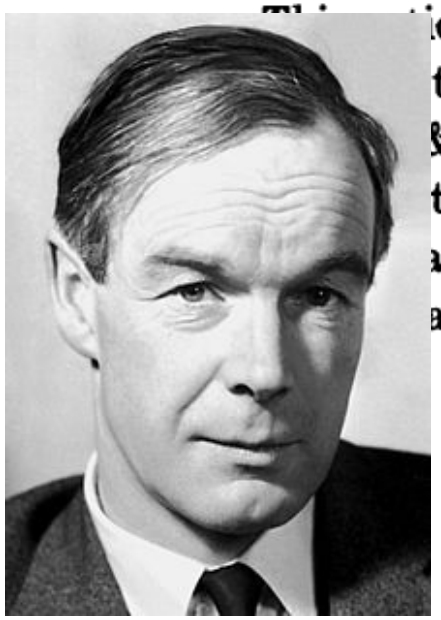
J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

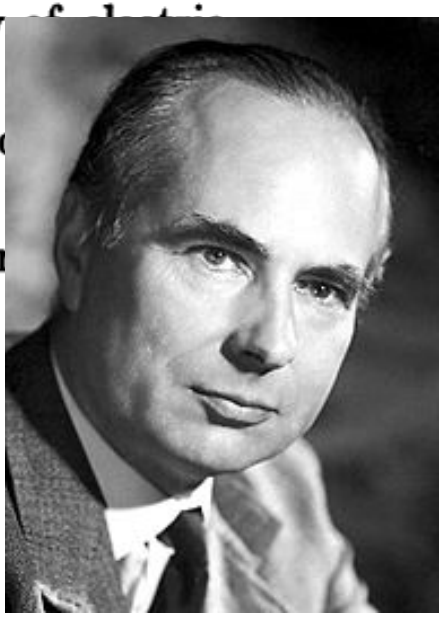
By A. L. HODGKIN and A. F. HUXLEY

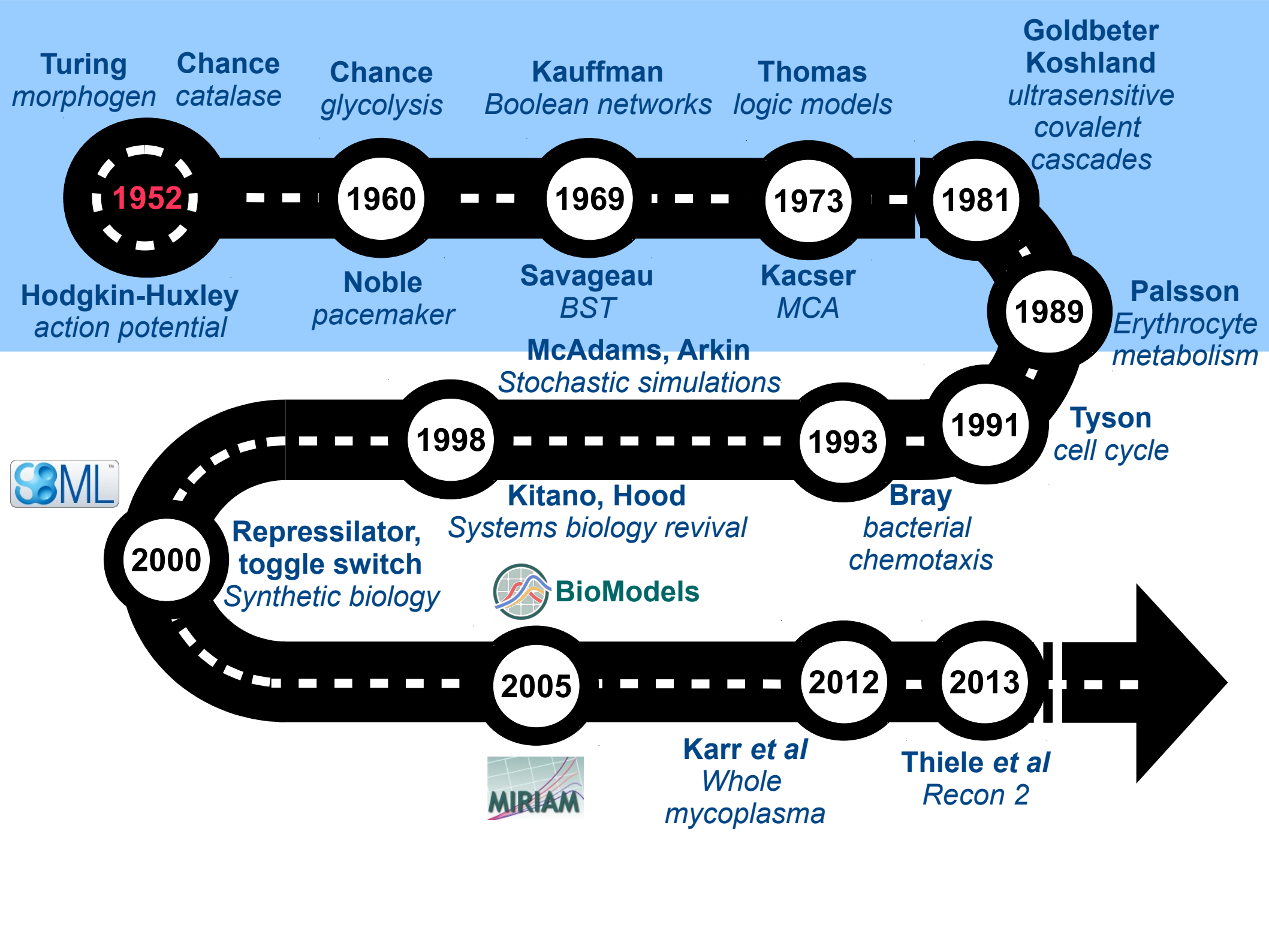
From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)



icle concludes a series of papers concerned with the flow
through the surface membrane of a giant nerve fibre
& Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general
the results of the preceding papers (Part I), to put
atical form (Part II) and to show that they will accou
and excitation in quantitative terms (Part III).

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Synthetic biology
BioModels
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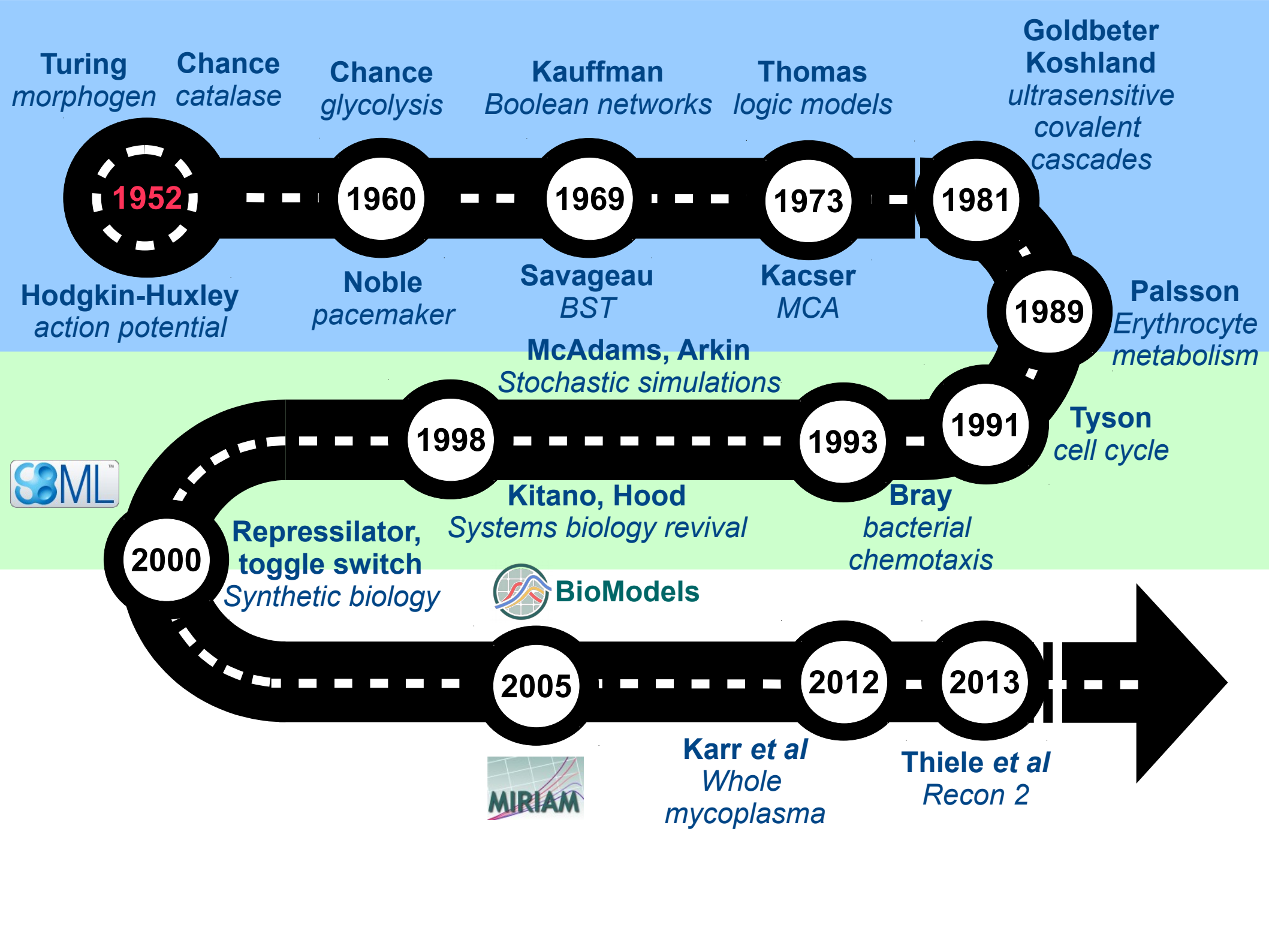
MIRIAM
Karr et al
Whole
mycoplasma
Thiele et al
Recon 2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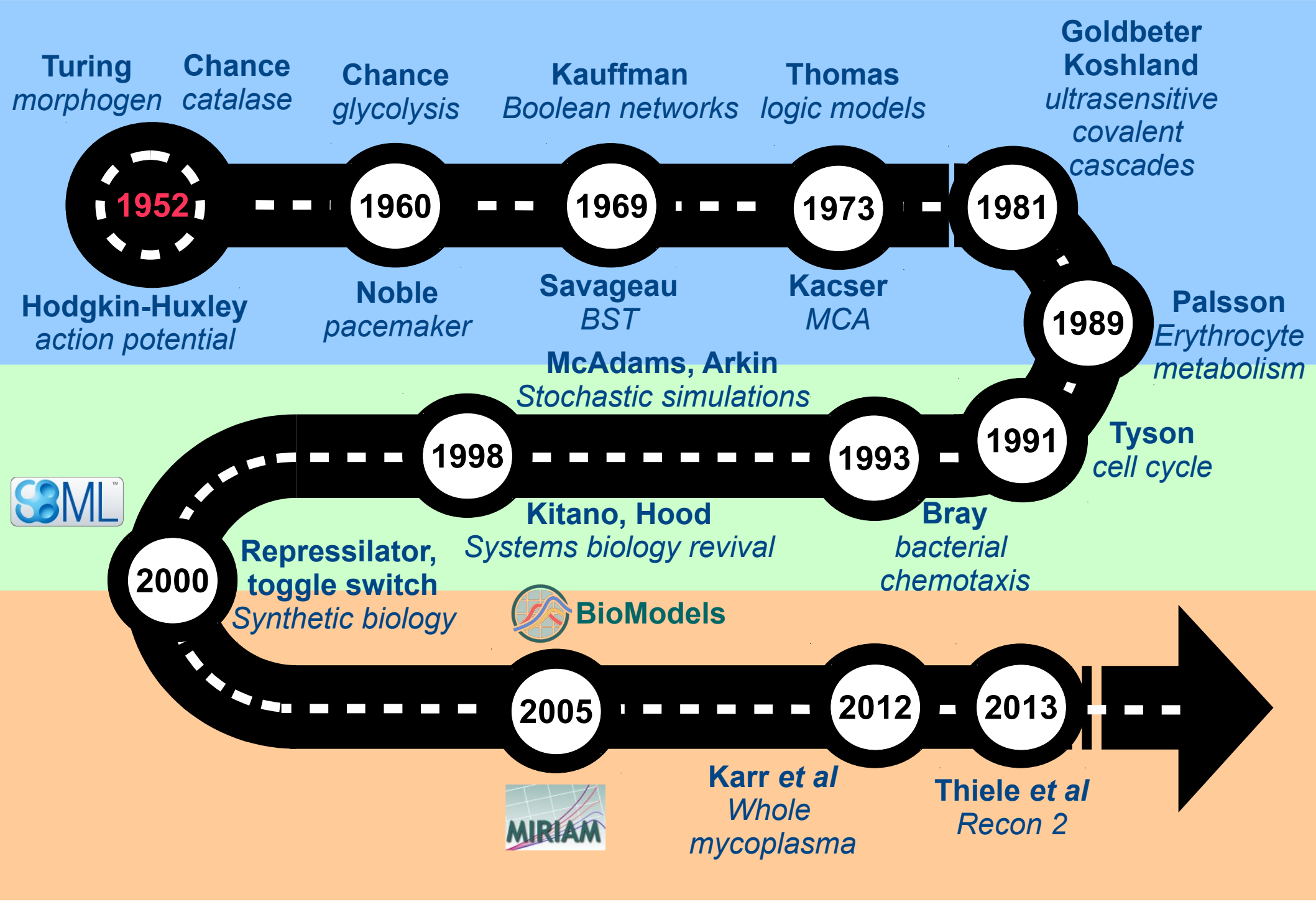
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Thiele et al
Recon 2

Improvised	Designed
One off	Many
Unique	Standard
Manually produced	Automated production
One or few artists	Collaboration
Produced in one go	Workflow
Fragile	Robust

Art.

Engineering

We need to

Verify

Re-use

Modify

Build upon

Integrate with

Therefore we need to share

Model descriptions

Simulation descriptions

Parametrisations

Biological meaning

Three types of standards

Minimal requirements **WHAT**	What to encode in order to share experiments and understand results MIBBI
Data-models **HOW**	How to encode the information defined above in a computer-readable manner combine
Terminologies	Structured representation of knowledge, with concept definitions and their relationships  OBO foundry

A language to describe computational models in biology

	Model descriptions
Data-models	SBML™

Born in Caltech 2000

John Doyle

Hiroaki Kitano

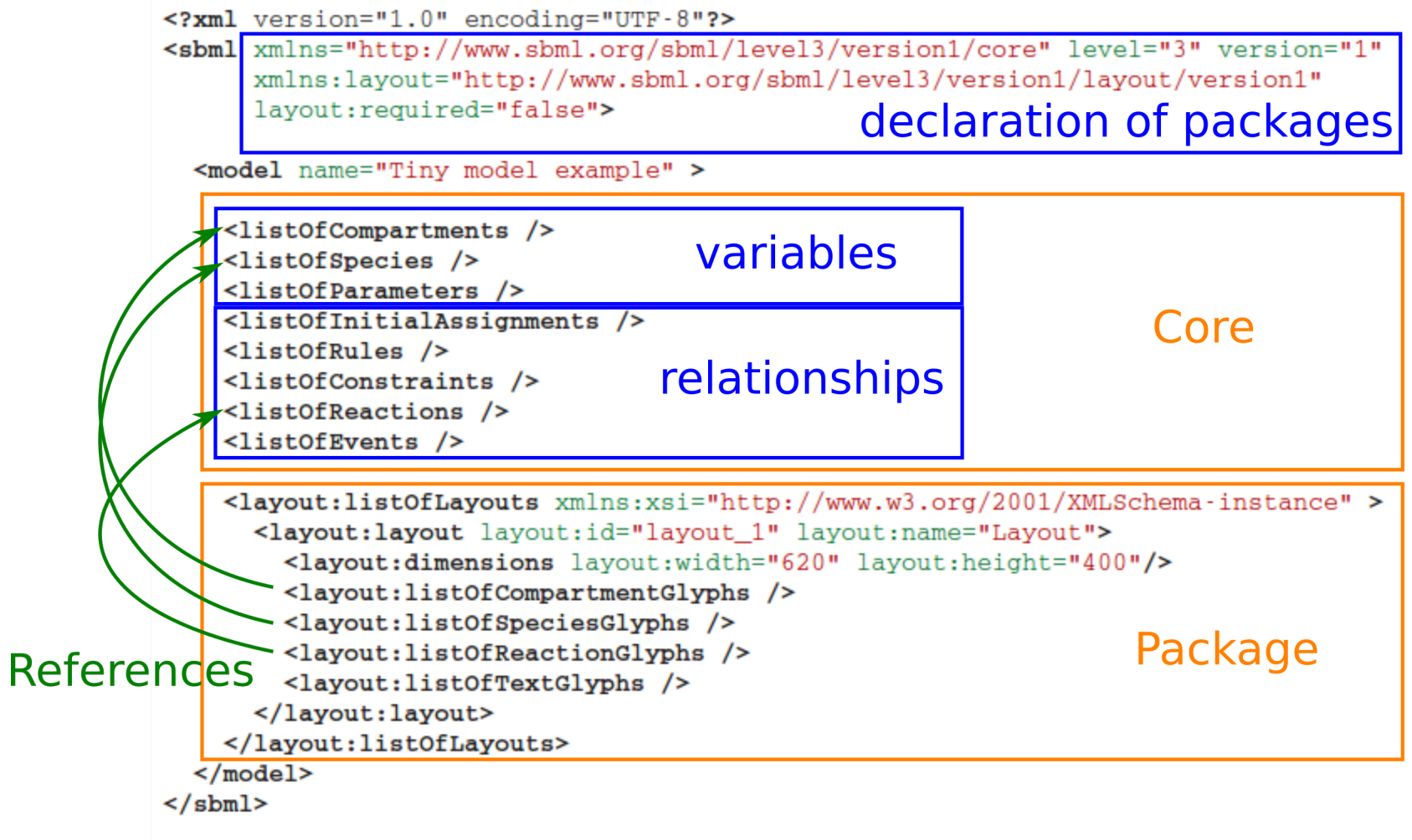
Hamid Bolouri

Mike Hucka

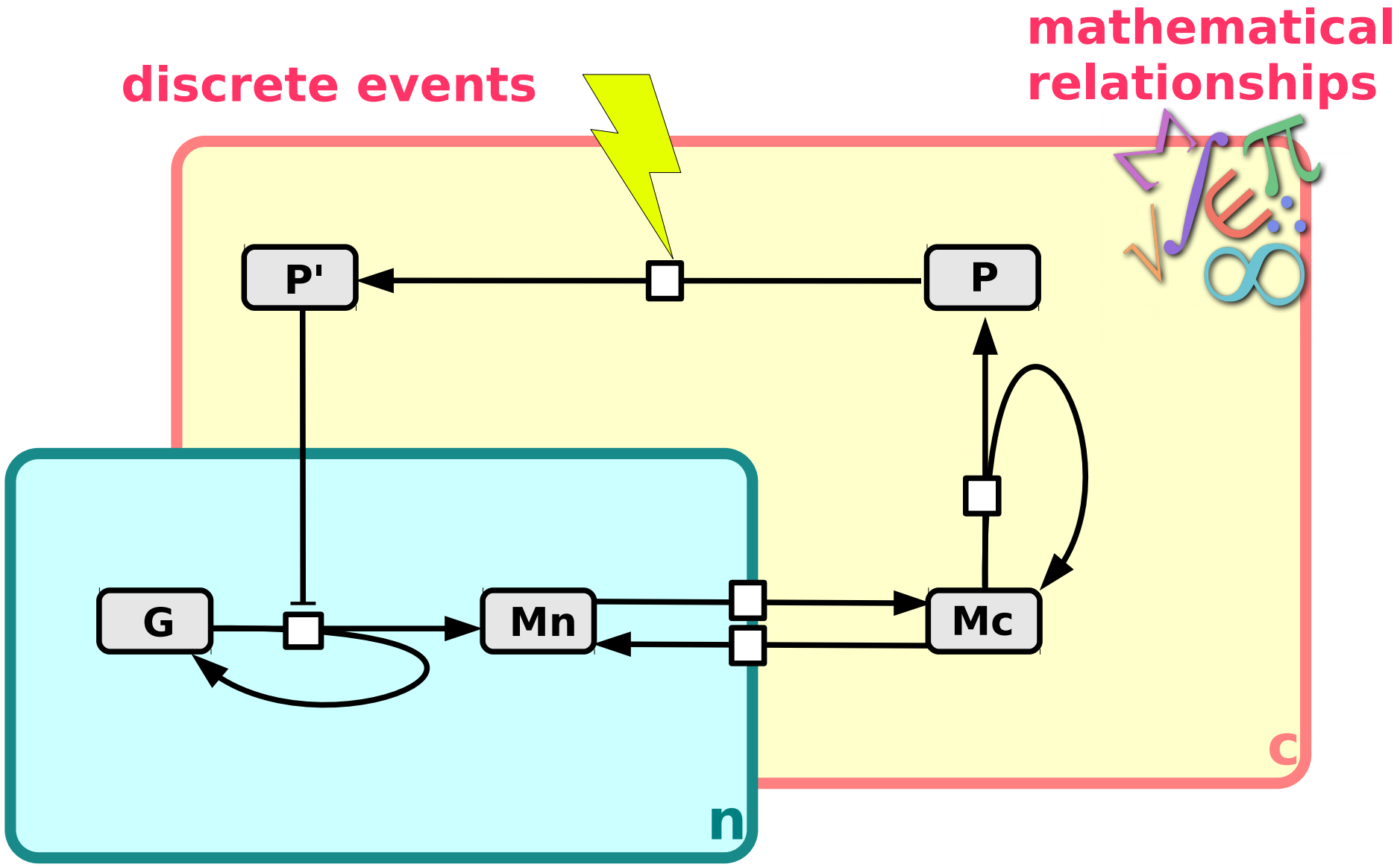
Andrew Finney

Herbert Sauro

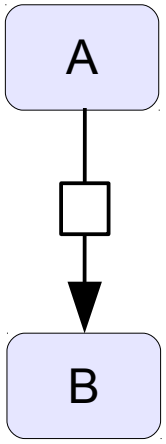
Structure of SBML



What can we encode in SBML Core?



http://sbml.org



$$\frac{d[B]}{dt} = k1 \times [A]$$

```
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      <species id="B" compartment="cell" initialConcentration="1"/>
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          <speciesReference species="B"/>
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              <ci> k1 </ci>
              <ci> A </ci>
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```
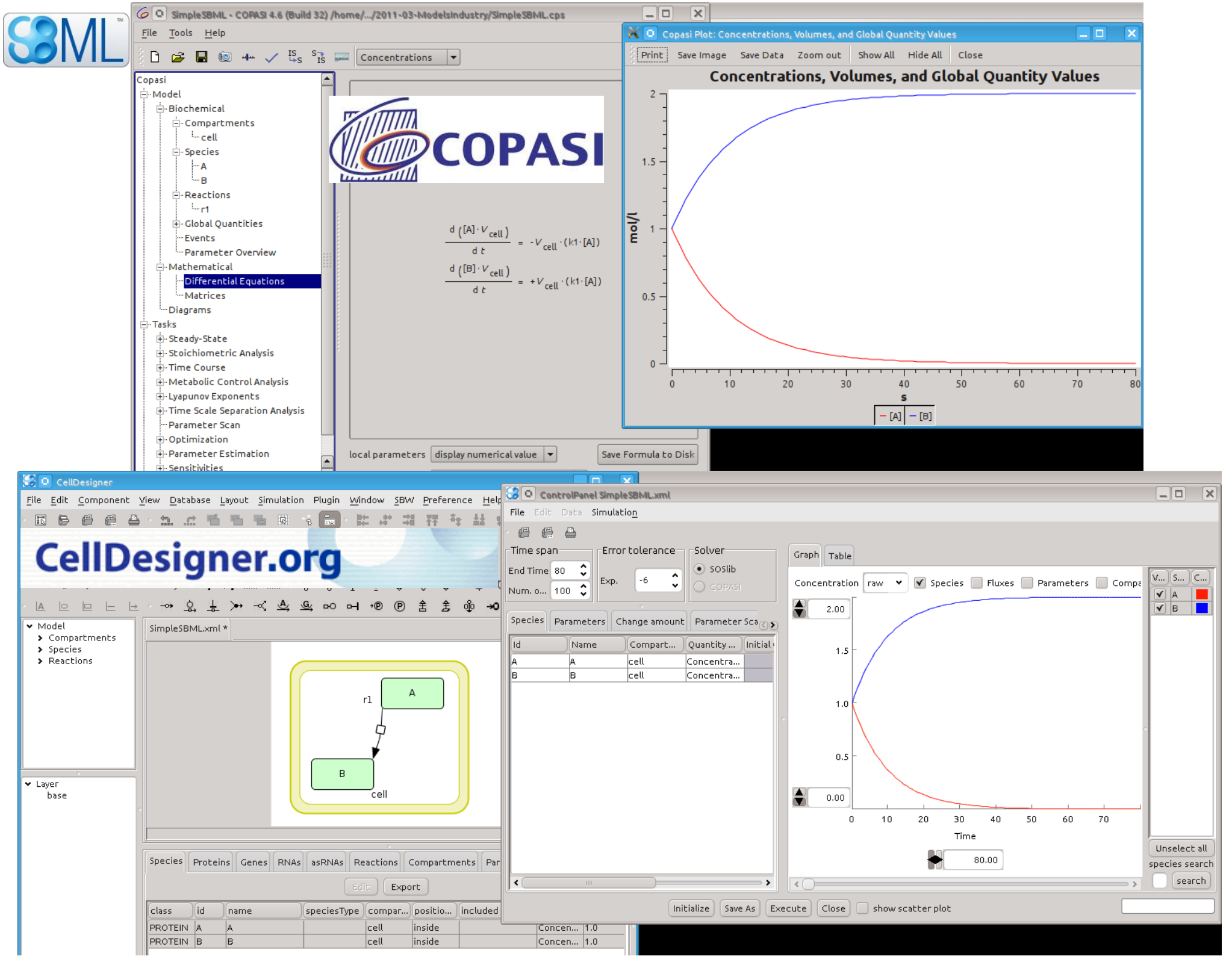

A very simple SBML file


SBML
SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps
File Tools Help
Concentrations
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Global Quantities
Events
Parameter Overview
Mathematical
Differential Equations
Matrices
Diagrams
Tasks
Steady-State
Stoichiometric Analysis
Time Course
Metabolic Control Analysis
Lyapunov Exponents
Time Scale Separation Analysis
Parameter Scan
Optimization
Parameter Estimation
Sensitivities
COPASI
d([A]·V_cell)/dt = -V_cell·(k1·[A])
d([B]·V_cell)/dt = +V_cell·(k1·[A])
local parameters
display numerical value
Save Formula to Disk
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
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Concentrations, Volumes, and Global Quantity Values
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Solver
SOSlib
COPASI
Species Parameters Change amount Parameter Sca
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A A cell Concentra...
B B cell Concentra...
Graph Table
Concentration raw
Species Fluxes Parameters Compa
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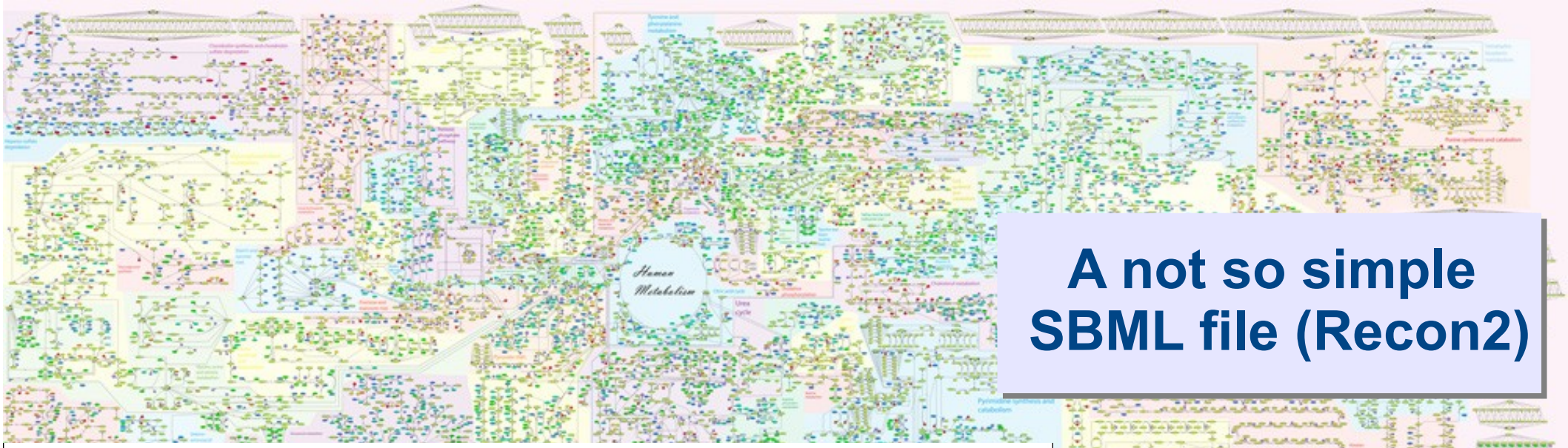
Initialize Save As Execute Close show scatter plot



A not so simple SBML file (Recon2)

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,37], Neil Swainston[3,4,37], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[3,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[3,28,33,34], Douglas B Kell[3,35], Pedro Mendes[3,4,36] & Bernhard Ø Palsson[1,7]

Multiple models of human metabolism have been reconstructed, but each represents only a subset of our knowledge. Here we describe Recon 2, a community-driven, consensus 'metabolic reconstruction', which is the most comprehensive representation of human metabolism that is applicable to computational modeling. Compared with its predecessors, the reconstruction has improved topological and functional features, including ~2× more reactions and ~1.7× more unique metabolites. Using Recon 2 we predicted changes in metabolite biomarkers for 49 inborn errors of metabolism with 77% accuracy when compared to experimental data. Mapping metabolomic data and drug information onto Recon 2 demonstrates its potential for integrating and analyzing diverse data types. Using protein expression data, we automatically generated a compendium of 65 cell type–specific models, providing a basis for manual curation or investigation of cell-specific metabolic properties. Recon 2 will facilitate many future biomedical studies and is freely available at http://humanmetabolism.org/.

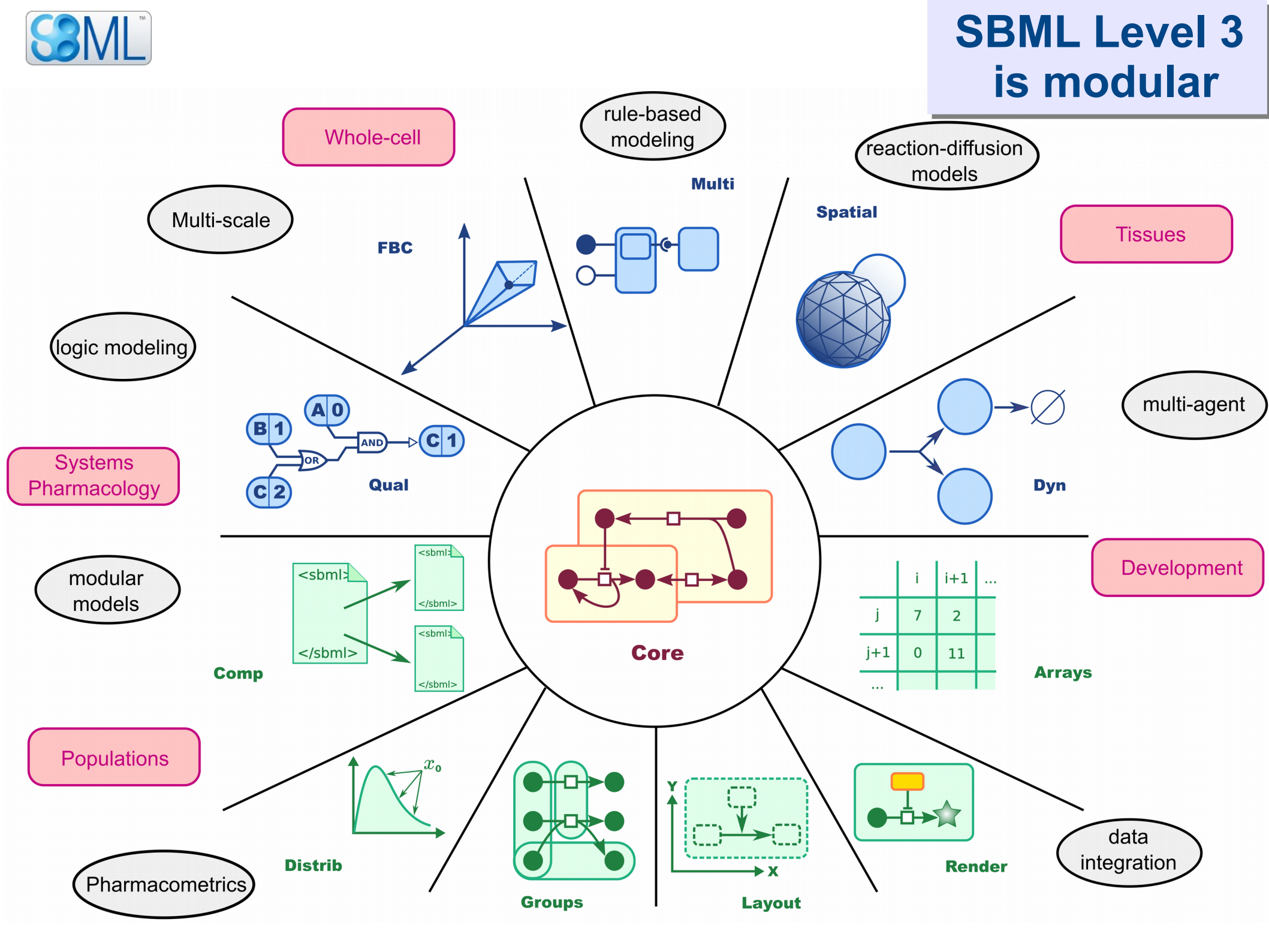
npg

An understanding of metabolism is fundamental to comprehending the phenotypic behavior of all living organisms, including humans, where metabolism is integral to health and is involved in much of human disease. High quality, genome-scale 'metabolic reconstructions' are at the heart of bottom-up systems biology analyses and represent the entire network of metabolic reactions that a given organism is known to exhibit[1]. The metabolic-network reconstruction procedure is now well-established[2] and has been applied to a growing number of model organisms[3]. Metabolic reconstructions allow for the conversion of biological knowledge into a mathematical format and the subsequent computation of physiological states[1,4,5] to address a variety of scientific and applied questions[3,6]. Reconstructions enable network-wide mechanistic investigations of the genotype-phenotype relationship. A high-quality reconstruction of the metabolic network is thus

- 8 compartments
- 5 063 metabolites
- 2 194 proteins
- 7 440 reactions

MODEL1109130000

SBML Level 3 is modular



SBML Software Guide

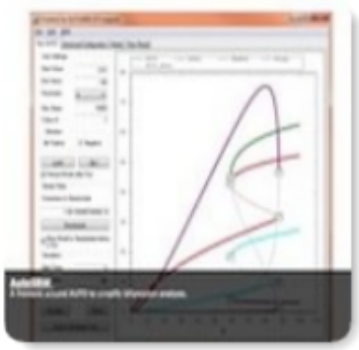
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety of their features; the *Summary* provides general descriptions of most of the software; and the *Showcase* provides a sequential slideshow of a subset of the software.

Number of software packages listed in the matrix today: **290**.

Go to the SBML Software Matrix

Go to the SBML Software Summary

Go to the SBML Software Showcase



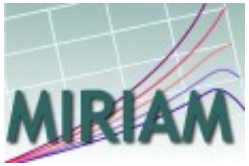
Please **tell us about additions and updates**.

Adding the semantics to the syntax

	Model descriptions
Minimal requirements	MIRIAM
Data-models	SBML
Terminologies	SBO

Born in Heidelberg 2004

Minimal Information Required In the Annotation of Models



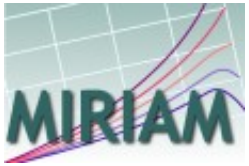
- Encoded in public standard format ☑
- Single reference description ☑
- Reflect biological processes ☑
- Simulatable and reproduce results ☑

- Model creators details ☑
- Time of creation and last modification ☑
- Precise terms of distribution ☑

- Model components identified ☑
- Cross reference as triplets {collection, record, qualifier} ☑
- Collection and record in one agreed-upon URI ☑

https://co.mbine.org/standards/miriam

Minimal Information Required In the Annotation of Models



- Encoded in public standard format ☑
- Single reference description ☑
- Reflect biological processes ☑
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- Model creators details ☑
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- Model components identified ☑
- Cross reference as triplets {collection, record, qualifier} ☑
- Collection and record in one agreed-upon URI ☑

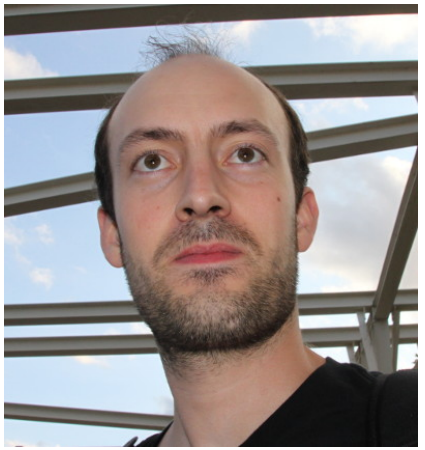
https://co.mbine.org/standards/miriam


Unique
Persistent
Resolvable
Maintained
Homogeneous
“Human readable”

Identifiers.org (aka new MIRIAM URIs)

`https://identifiers.org/namespace/identifier`

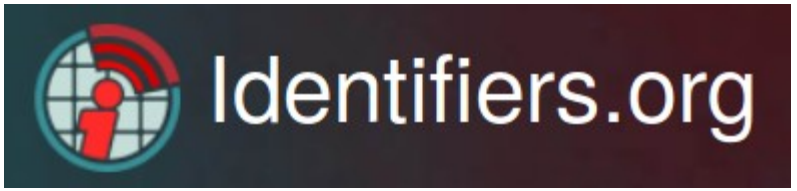
protocol — type of URI — collection — record



Camille Laibe

Nick Juty

Sarala Wimalaratne



(aka new MIRIAM URIs)

https://identifiers.org/pubmed/22140103

https://identifiers.org/ec-code/1.1.1.1

https://identifiers.org/go/GO:0000186

Identifiers.org

Search

Examples: ontology, enzyme, EMBL, Japan

Home | Documentation | Services | About | Request Prefix | Feedback

Registry

The Registry provides the necessary information to allow users to generate unique, perennial and unambiguous identifiers for scientific data.

SPARQL Endpoint

SPARQL endpoint to perform conversions between different URI schemes recorded in the Registry.

Advanced Search

Advanced search to find valid prefixes, identifiers and providers.

Info Service

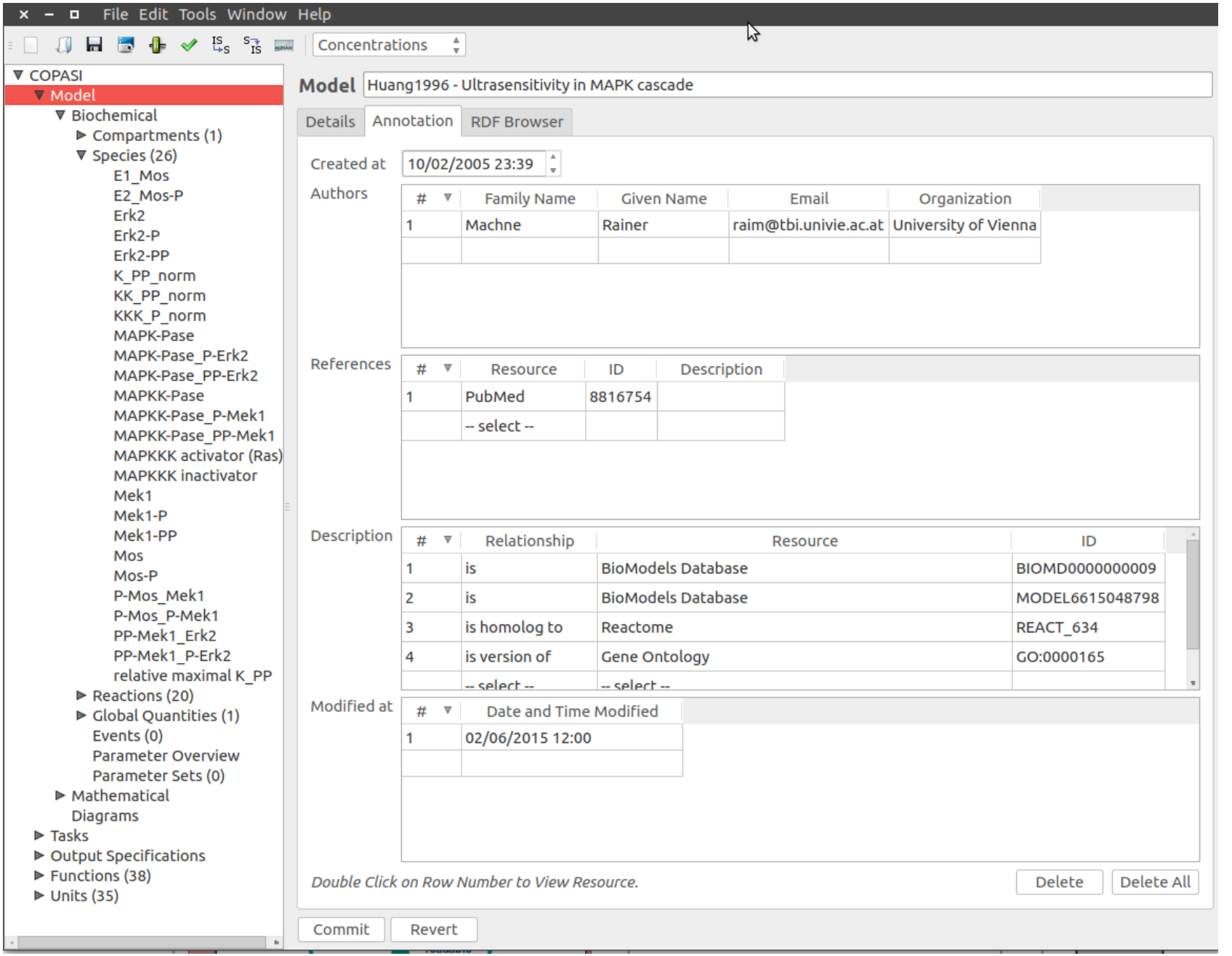
Info service provide access to the Registry's records to identify and retrieve metadata about data entities.

Web services

REST Web Services for programmatic access.

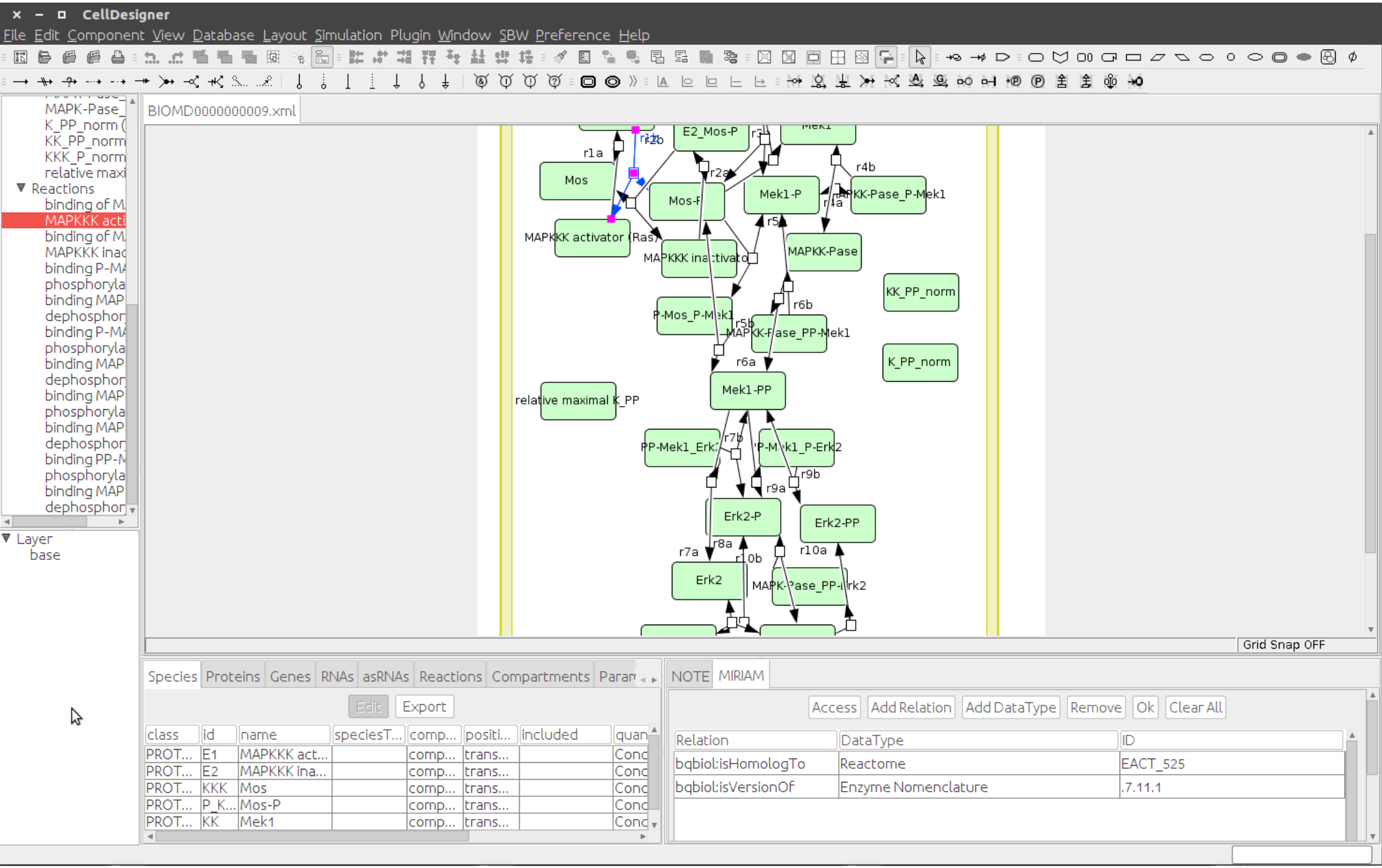
Download

Registry's content in XML is available here.


File Edit Tools Window Help
Concentrations
COPASI
Model
Biochemical
Compartments (1)
Species (26)
E1_Mos
E2_Mos-P
Erk2
Erk2-P
Erk2-PP
K_PP_norm
KK_PP_norm
KKK_P_norm
MAPK-Pase
MAPK-Pase_P-Erk2
MAPK-Pase_PP-Erk2
MAPKK-Pase
MAPKK-Pase_P-Mek1
MAPKK-Pase_PP-Mek1
MAPKKK activator (Ras)
MAPKKK inactivator
Mek1
Mek1-P
Mek1-PP
Mos
Mos-P
P-Mos_Mek1
P-Mos_P-Mek1
PP-Mek1_Erk2
PP-Mek1_P-Erk2
relative maximal K_PP
Reactions (20)
Global Quantities (1)
Events (0)
Parameter Overview
Parameter Sets (0)
Mathematical
Diagrams
Tasks
Output Specifications
Functions (38)
Units (35)
Model
Huang1996 - Ultrasensitivity in MAPK cascade
Details
Annotation
RDF Browser
Created at
10/02/2005 23:39
Authors
Family Name Given Name Email Organization
1 Machne Rainer raim@tbi.univie.ac.at University of Vienna
References
Resource ID Description
1 PubMed 8816754
-- select --
Description
Relationship Resource ID
1 is BioModels Database BIOMD0000000009
2 is BioModels Database MODEL6615048798
3 is homolog to Reactome REACT_634
4 is version of Gene Ontology GO:0000165
-- select -- -- select --
Modified at
Date and Time Modified
1 02/06/2015 12:00
Double Click on Row Number to View Resource.
Delete
Delete All
Commit
Revert

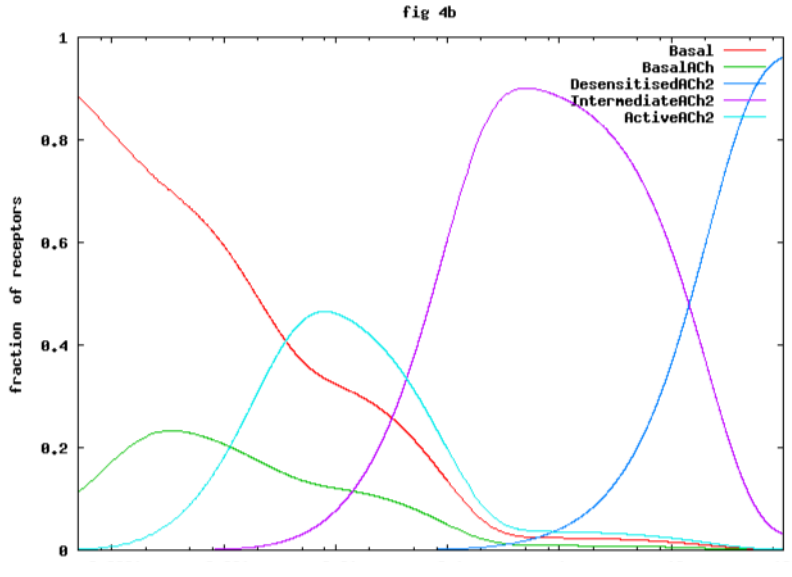
CellDesigner

File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help

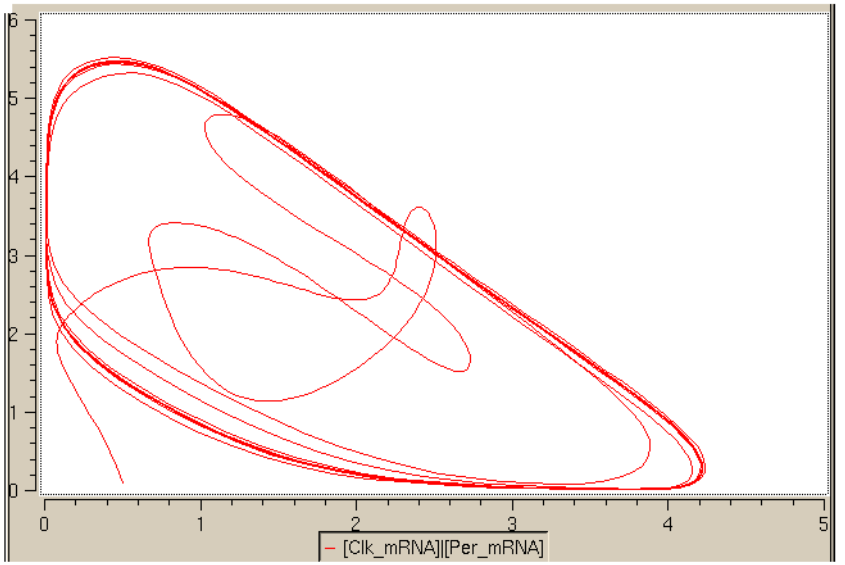


Surely, this is enough?

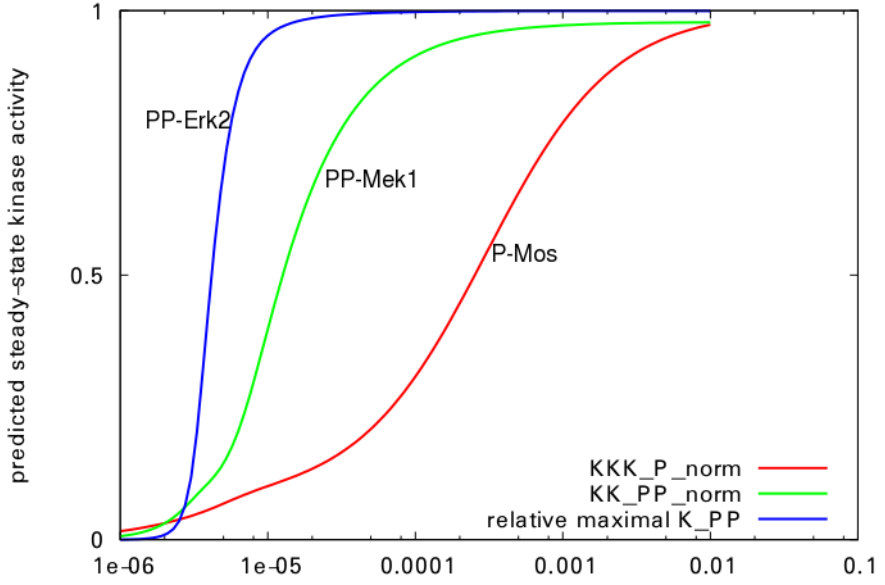
Simulation experiment = model + what to do with it



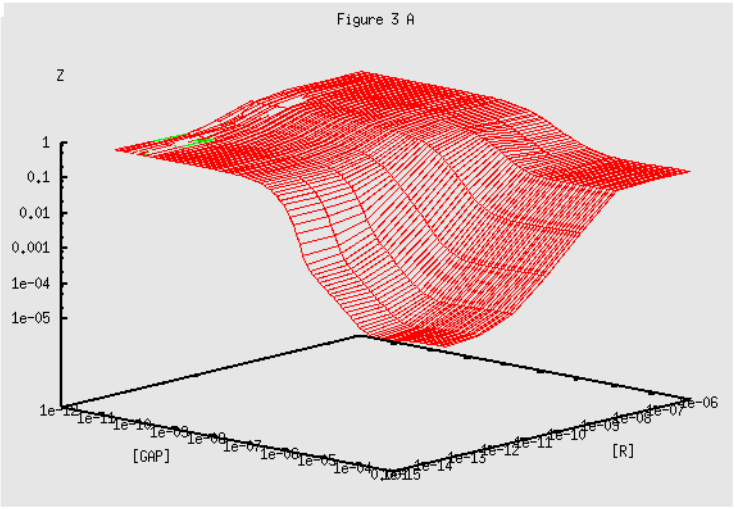
Edelstein et al 1996 (BIOMD0000000002)



Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)

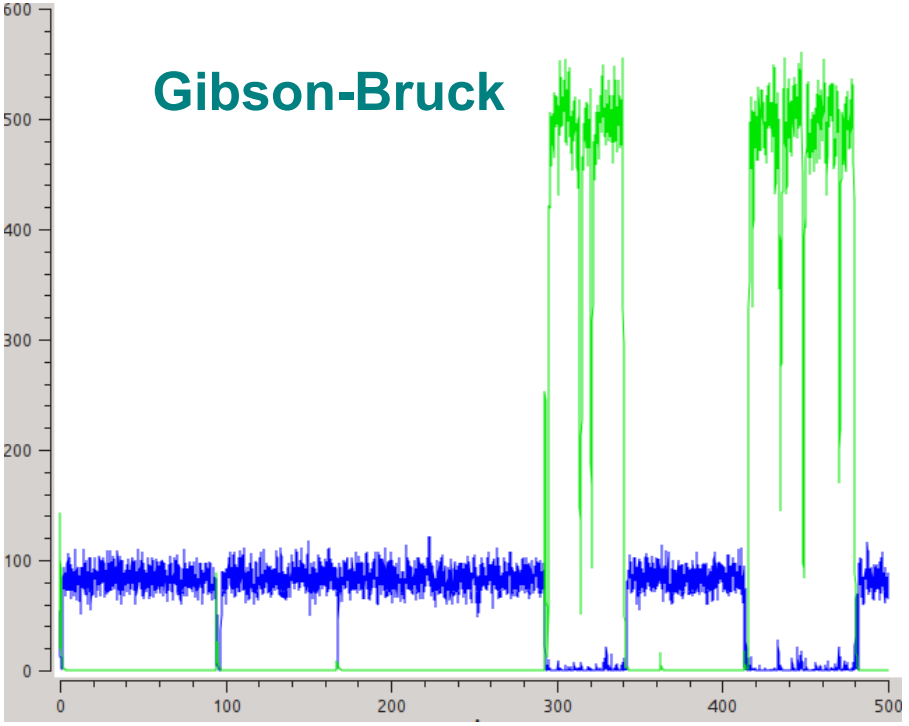


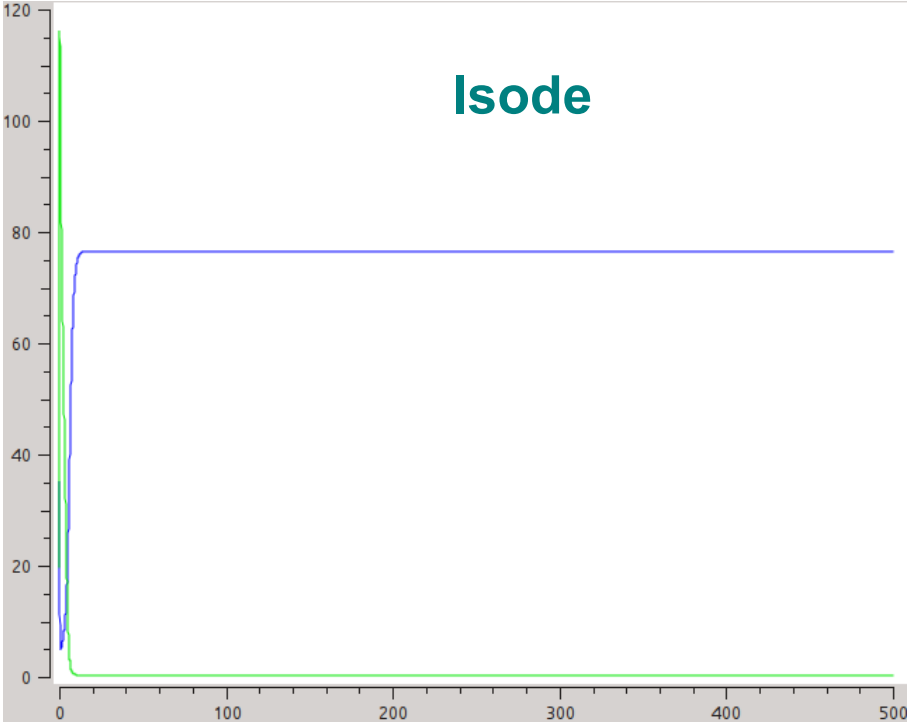
Huang & Ferrell (BIOMD0000000009)

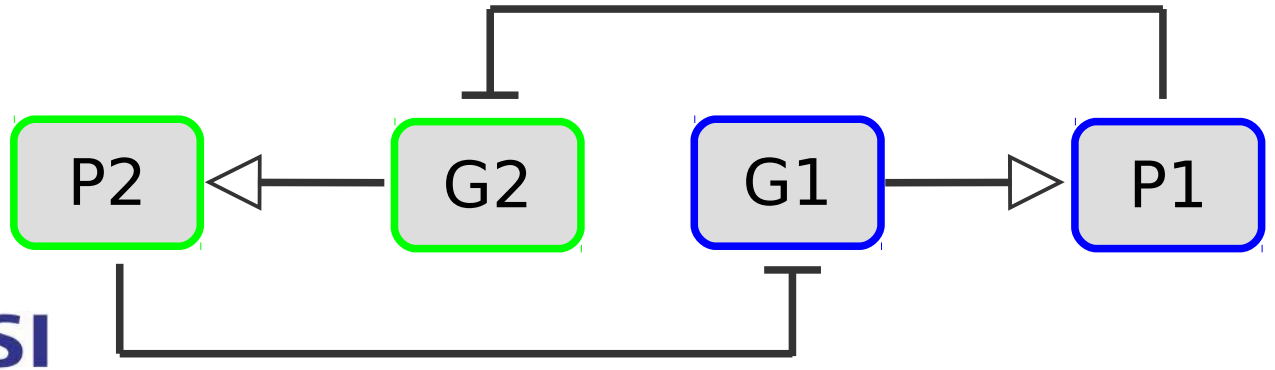


Bornheimer et al 2004 (BIOMD0000000086)

Choice of algorithm affects behaviour







COPASI

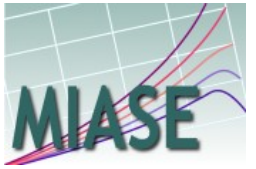
Description of simulations and analyses

	Model descriptions	Simulations and analysis
Minimal requirements	MIRIAM	MIASE
Data-models	SBML, SBGN	SED-ML
Terminologies	SBO	KISAO

Dagmar Waltemath

Born in Hinxton 2007

Minimal Information About a Simulation Experiment



- Provide models or mean of access ☑
- Equations, parameter values and necessary conditions ☑
- Standard formats, code available or full description ☑
- Modifications required before simulation ☑

- Simulation steps, algorithms, order, processing ☑
- Information for correct implementation of all steps ☑
- If not open source, all information to rewrite ☑
- If dependent on platform, how to use this platform ☑

- Post-processing steps to generate final results ☑
- How to compare results to get insights ☑

https://co.mbine.org/standards/miase

Simulation Experiment Description Markup Language

```
<?xml version="1.0" encoding="utf-8"?>
<sedML xmlns="http://sed-ml.org/"
       xmlns:math="http://www.w3.org/1998/Math/MathML"
       level="1" version="1">
  <listOfSimulations><!-- --> </listOfSimulations>
  <listOfModels>
    <model id="" source="">
      <listOfChanges><!-- --></listOfChanges>
    </model>
  </listOfModels>
  <listOfTasks><!-- --></listOfTasks>
  <listOfDataGenerators><!-- --></listOfDataGenerators>
  <listOfOutputs>
    <plot2D />
    <plot3D />
    <report />
  </listOfOutputs>
</sedML>
```

http://sed-ml.org

Flexible model use in SED-ML

Any XML

```
<listOfModels>
  <model id="model1"
         name="Regular_Spiking"
         language="http://identifiers.org/combine.specifications/sbml.level-2.version-4.release-1"
         source="http://identifiers.org/biomodels.db/BIOMD0000000127" />
  <model id="model2"
         name="chattering"
         source="model1">
    <listOfChanges>
      <changeAttribute target=
           "/sbml/model/listOfParameters/parameter[@id='c']/@value" newValue="-50">
      </changeAttribute>
      <changeAttribute target=
           "/sbml/model/listOfParameters/parameter[@id='d']/@value" newValue="42">
      </changeAttribute>
    </listOfChanges>
  </model>
</listOfModels>
```

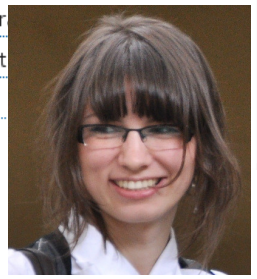
Remote access

Modifications before simulations

Controlled terminologies

MAthematical Modelling Ontology

- model
  - domain model
  - mathematical model
    - Bayesian model
    - Markov model
    - Petri net
    - computational model
    - differential equation model
    - interacting state machine
    - logical model
      - boolean model
      - fuzzy logic model
      - multi-value logic model
    - population model
    - process algebra
    - rule-based model
    - statistical model
    - steady-state model
      - constraint-based model
- modelling entity feature
- readout
  - phase portr
  - steady stat
  - timecourse
- variable



Anna Zhukova

Systems Biology Ontology

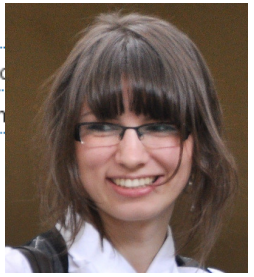
- systems biology representation
  - mathematical expression
  - metadata representation
  - modelling framework
  - occurring entity representation
    - biological activity
    - process
      - biochemical or transport reaction
      - biological effect of a perturbation
      - composite biochemical process
      - encapsulating process
      - molecular or genetic interaction
      - or
      - phenotype
      - state variabl
      - uncertain pr
    - relationship
  - participant role
    - functional comp
    - modifier
      - dual-activity
      - inhibitor
      - modifier of u
      - stimulator
    - neutral participa
    - product
    - promoter
    - reactant

Mélanie Courtot

Varun Kothamachu

KInetics Simulation Algorithm Ontology

- modelling and simulation algorithm
  - Bayesian inference algorithm
  - CVODE-like method
    - CVODE
    - PVODE
  - algorithm using adaptive timesteps
  - algorithm using continuous variables
  - algorithm using deterministic rules
  - algorithm using discrete variables
  - algorithm using fixed timesteps
  - algorithm using spatial description
  - algorithm using stochastic rules
  - hybrid method
  - iterative method for linear system
  - one-step method
  - optimization algorithm
  - preconditioning technique
- modelling and simulation algorithm characteristic
- modelling and simulation algorithm parameter
  - clusterization parameter
  - error control parameter
  - granularity control parameter
  - half-bandwith parameter
  - integration method
  - interpolate solution
  - iteration type
  - linear solver
  - method switching contro
  - minimum damping
  - number of N-way partial
  - number of partial least s
  - partitioning control paran
  - preconditioner
  - seed
  - type of validation
  - variables preprocessing parameter



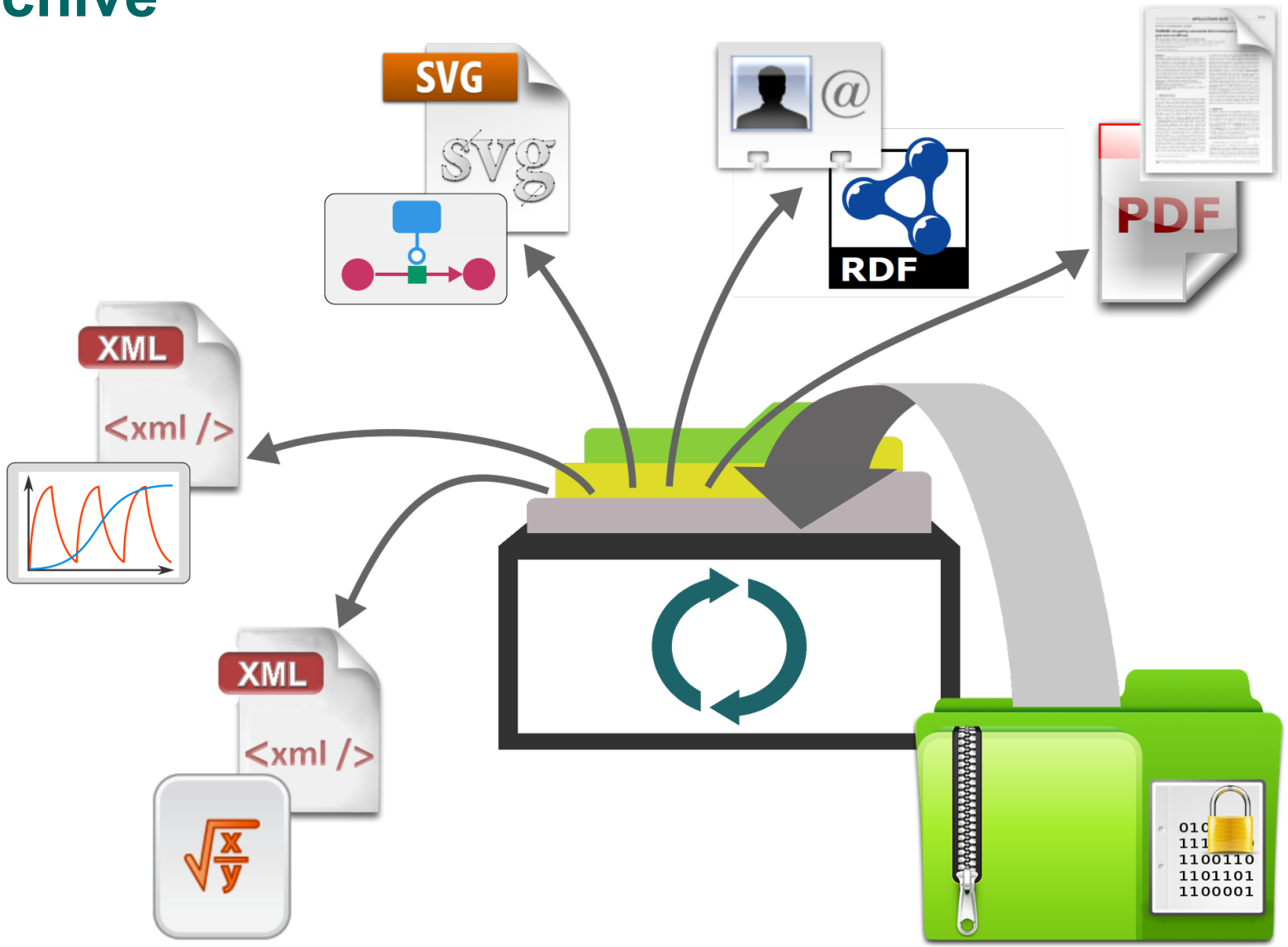
TErminology for the Description of DYnamics

- TEDDY entity
  - _obsolete
  - behaviour characteristic
    - curve characteristic
    - stability characteristic
  - behaviour diversification
    - bifurcation
      - global bifurcation
      - local bifurcation
    - bursting
    - perturbation response
      - bistable perturbation response
      - excitability
      - monostable perturbation response
      - multistable perturbation response
  - functional motif
    - feed-forward loop
      - multi-output feed-forward loop
      - three-node feed-forward loop
        - coherent three-node feed-forward loop
        - incoherent three-node feed-forward loop
    - feedback loop
    - integrator
    - switch
  - temporal behaviour
    - fixed point
    - limit behaviour
    - non-periodic orbit
    - periodic orbit

Christian Knüpfer

combine

archive



https://co.mbine.org/standards/omex

Bergman *et al. BMC Syst Biol (2014)*

combine the computational modeling in biology network

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lenov

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  - HTML Page
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  - Panel
  - Poll
  - URL aliases Admin
- Recent posts
- Administer
- Help
- Log out
- Junk

Coordinating standards for modeling in biology

View | Edit | Revisions | Access control | Delete

The 'COmputational Modeling in BIology' NEtwork (COMBINE) is an initiative to coordinate the development of the various community standards and formats for computational models. By doing so, it is expected that the federated projects will develop a set of interoperable and non-overlapping standards covering all aspects of modeling in biology.

Building on the experience of mature projects, which already have stable specifications, software support, user-base and community governance, COMBINE will help foster or support fledgling efforts aimed at filling gaps or new needs. As those efforts mature, they may become part of the core set of COMBINE standards.

One of the initial activities of COMBINE is to coordinate the organization of scientific and technical events common to several standards. Those events, as others related to our field of research are gathered in a calendar.

To receive announcements from COMBINE, subscribe to the twitter [https://twitter.com/combine_coord COMBINE news]

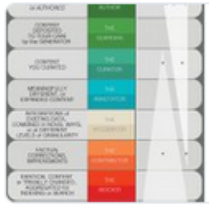
To discuss the goals, organization and operation of COMBINE, subscribe to [https://groups.google.com/forum/?hl=en-GB#!forum/combine-discuss COMBINE discuss]. To report issues about the co.mbine.org website, send a mail to combine-support @ googlegroups.com

https://co.mbine.org

Tweets by @combine_coord

COMBINE @combine_coord

Best practises in building and using identifiers. Identifiers.org can help journals.plos.org/plosbiology/ar…



Identifiers for the 21st century: …

In many disciplines, data are highly decentralized across thousands of

journals.plos.org

2h

COMBINE @combine_coord

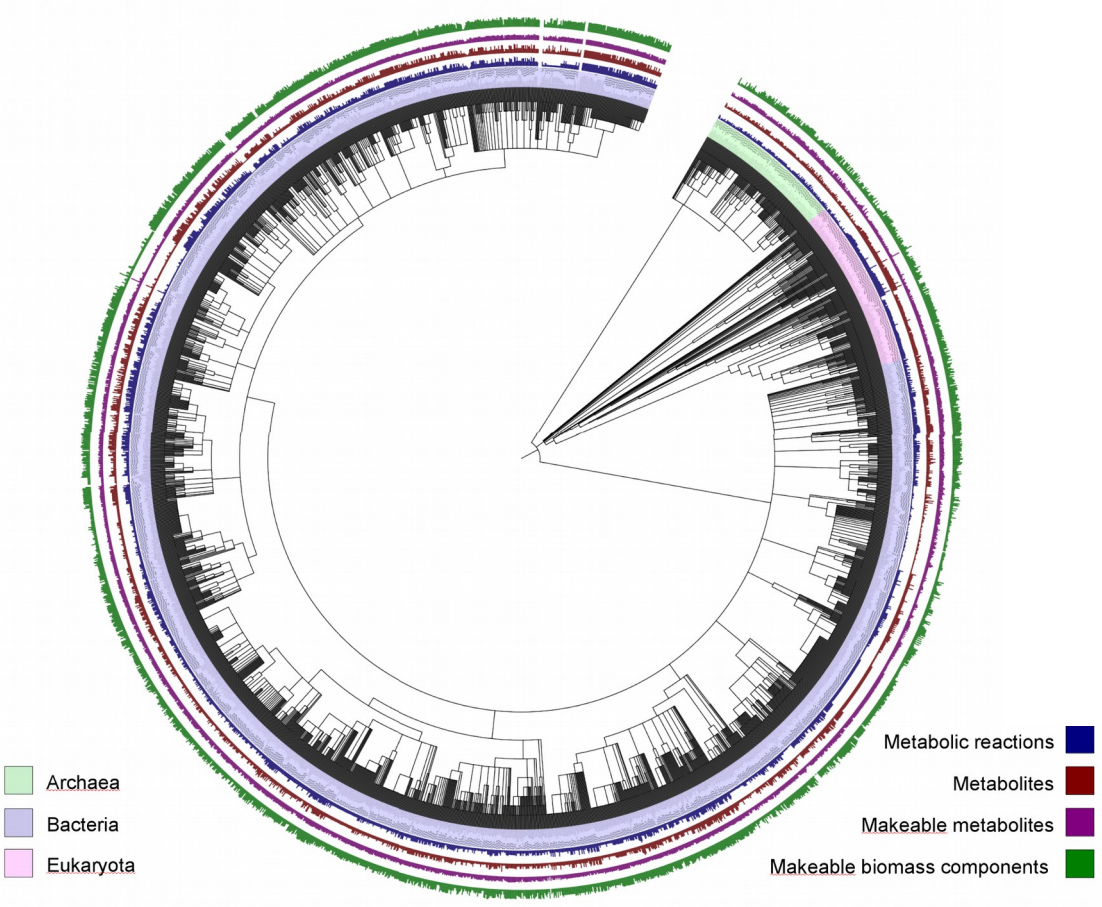
COMBINE 2017, 9-13 Oct, Milano. Register before Aug 1st co.mbine.org/events/COMBINE… #SBML #SBGN #BioPAX #SBOL #SEDML #NeuroML #CellML

06 Jul

Was it worth it?

Build

Automated reconstruction
>2600 species



Büchel et al. BMC Systems Biology 2013, 7:116
http://www.biomedcentral.com/1752-0509/7/116

BMC Systems Biology

RESEARCH ARTICLE Open Access

Path2Models: large-scale generation of computational models from biochemical pathway maps

Finja Büchel[1,2†], Nicolas Rodriguez[1,3†], Neil Swainston[4†], Clemens Wrzodek[2†], Tobias Czauderna[5], Roland Keller[2], Florian Mittag[1,2], Michael Schubert[1], Mihai Glont[1], Martin Golebiewski[6], Martijn van Iersel[1], Sarah Keating[1], Matthias Rall[2], Michael Wybrow[7], Henning Hermjakob[1], Michael Hucka[8], Douglas B Kell[4,9], Wolfgang Müller[6], Pedro Mendes[4,10,11], Andreas Zell[2], Claudine Chaouiya[12], Julio Saez-Rodriguez[1], Falk Schreiber[5,13], Camille Laibe[1], Andreas Dräger[2,14] and Nicolas Le Novère[1,3*]

Abstract

Background: Systems biology projects and omics technologies have led to a growing number of biochemical pathway models and reconstructions. However, the majority of these models are still created *de novo*, based on literature mining and the manual processing of pathway data.

Results: To increase the efficiency of model creation, the Path2Models project has automatically generated mathematical models from pathway representations using a suite of freely available software. Data sources include KEGG, BioCarta, MetaCyc and SABIO-RK. Depending on the source data, three types of models are provided: kinetic, logical and constraint-based. Models from over 2 600 organisms are encoded consistently in SBML, and are made freely available through BioModels Database at http://www.ebi.ac.uk/biomodels-main/path2models. Each model contains the list of participants, their interactions, the relevant mathematical constructs, and initial parameter values. Most models are also available as easy-to-understand graphical SBGN maps.

Conclusions: To date, the project has resulted in more than 140 000 freely available models. Such a resource can tremendously accelerate the development of mathematical models by providing initial starting models for simulation and analysis, which can be subsequently curated and further parameterized.

Keywords: Modular rate law, Constraint based models, Logical models, SBGN, SBML

Background

Since the discovery of the set of biochemical transformations known as the Embden-Meyerhof-Parnas glycolysis pathway in the early twentieth century, the concepts of pathways and networks have become useful and ubiquitous tools in the understanding of biochemical processes. Biochemical pathways provide a qualitative representation of chains of molecular interactions and chemical reactions that are known to take place in cells. Such interactions result in changes in the concentration, state or location of chemical entities. Pathways aim at providing a detailed representation of this biochemical reality, based on observations of the reactions. As such, the elucidation of biochemical pathways is being dramatically sped up with the efforts of molecular biology and biochemistry research, and particularly with the recent appearance of high-throughput omics technologies.

The definition of biochemical pathways is largely arbitrary, as in practice they are interlinked and interdependent in the functioning cell. Nevertheless, it is convenient to partition these pathways into different types such as signaling pathways, metabolic networks, gene regulatory networks, etc. With the growing number and complexity of biochemical pathways, a number of public databases

* Correspondence: lenov@babraham.ac.uk
†Equal contributors
[1]European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
[3]Babraham Institute, Babraham Research Campus, Cambridge, UK
Full list of author information is available at the end of the article

Signalling Pathways

+

Logic models
of individual signalling pathways

Core + Qual

Signalling Pathways

+

Logic models
of individual signalling pathways

Core + Qual

Metabolic Networks

Chemical kinetics models
of individual metabolic pathways

Core

Signalling Pathways

+

→

Logic models
of individual signalling pathways

Core + Qual

Metabolic Networks

→

Chemical kinetics models
of individual metabolic pathways

Core

Metabolic Networks

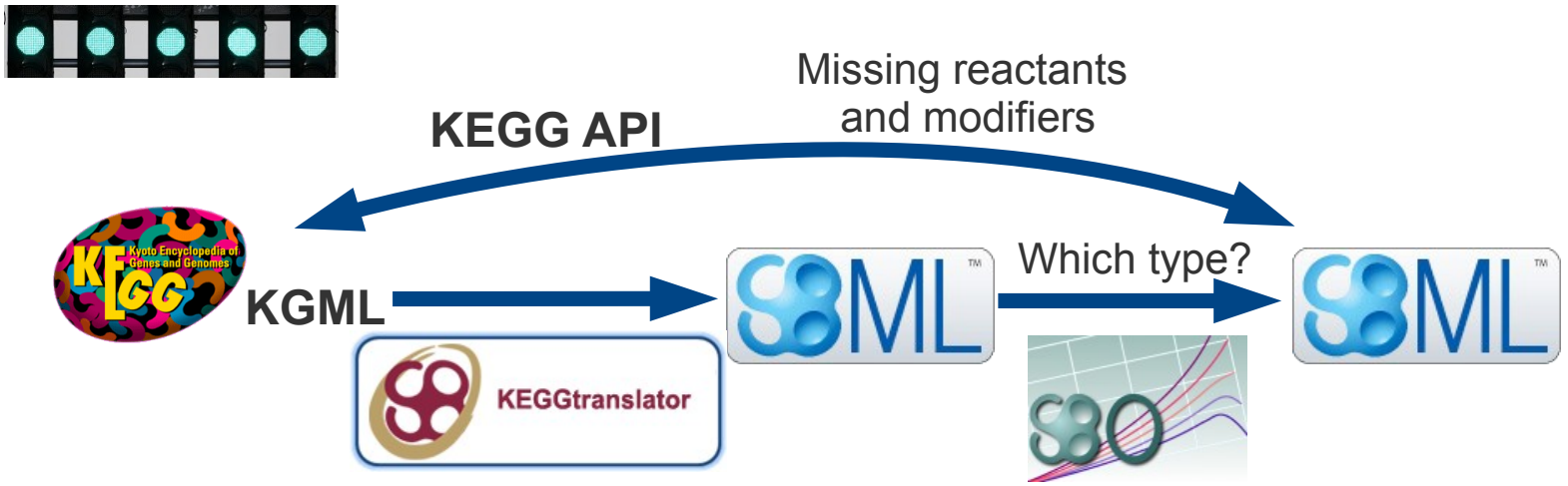
+

→

Flux Balance Analysis
of whole genome reconstructions

Core + FBC


KEGG
Kyoto Encyclopedia of Genes and Genomes
KGML
SBML
KEGGtranslator


KEGG API
Missing reactants
and modifiers
KGML
Which type?
KEGGtranslator

KEGG API

Missing reactants and modifiers

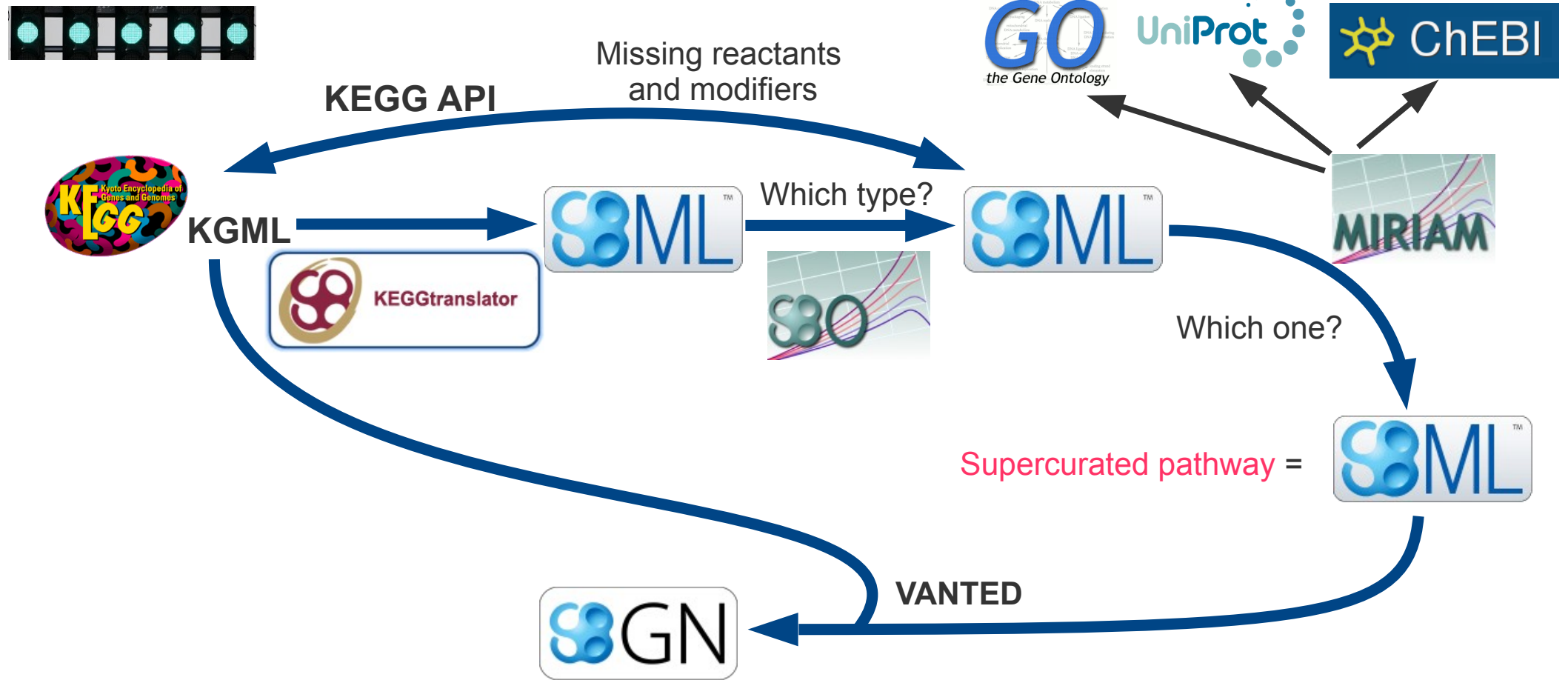
KGML

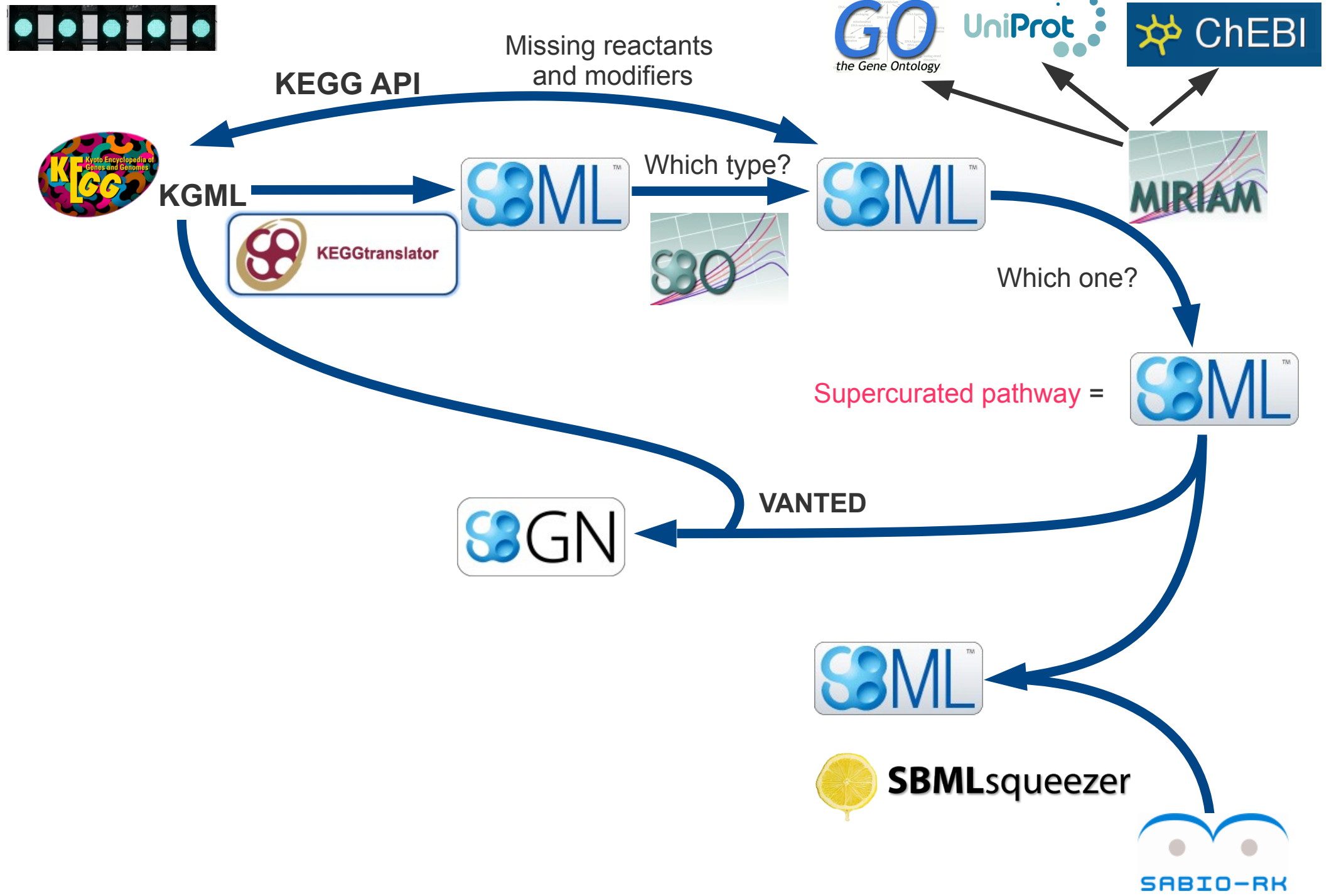
KEGGtranslator

Which type?

Which one?

Supercurated pathway =


KEGG API
Missing reactants
and modifiers
GO
the Gene Ontology
UniProt
ChEBI
KGML
KEGGtranslator
Which type?
MIRIAM
Which one?
Supercurated pathway =
VANTED


KEGG API
Missing reactants
and modifiers
KGML
KEGGtranslator
Which type?
Which one?
Supercurated pathway =
VANTED
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the Gene Ontology
UniProt
ChEBI
MIRIAM
SBGN
SBMLsqueezer
SABIO-RK

KEGG API

Missing reactants and modifiers

GO the Gene Ontology

UniProt

ChEBI

KGML

KEGGtranslator

Which type?

Which one?

Supercurated pathway =

VANTED

Ab initio kinetics

=

Chemical kinetics model

SBMLsqueezer

SABIO-RK

KEGG API

Missing reactants and modifiers

KGML

KEGGtranslator

Which type?

Which one?

Supercurated pathway =

VANTED

Ab initio kinetics

=

Chemical kinetics model

SBMLsqueezer

SABIO-RK

Welcome to BioModels

BioModels is a repository of mathematical models of biological and biomedical systems. It hosts a vast selection of existing literature-based physiologically and pharmaceutically relevant mechanistic models in standard formats. Our mission is to provide the systems modelling community with reproducible, high-quality, freely-accessible models published in the scientific literature. More information about BioModels can be found in the FAQ.

Recently published

- Tiemann2011_PhenotypeTransitions
- Figure4C
- Figure4D
- Sier2017_E2_combined
- Signaling_class_5
- Sier2017_estrogen_PBPK_GSMN
- Sier et al_2017_estrogen PBPK_simple

Recently accessed

- Tiemann2011_PhenotypeTransitions
- Mufudza2012 - Estrogen effect on the dynamics of breast cancer
- Singh2006_TCA_mtu_model1
- Switching behaviour of PP2A inhibition by ARPP-16 - mutual inhibitions
- DeCaluwe2016 - Circadian Clock
- Uhlén2017 - TCGA-F2-6879-01A - Pancreatic Adenocarcinoma (male, 58 years)
- Araujo2016 - Positive feedback in Cdk1 signalling keeps mitotic duration short and constant

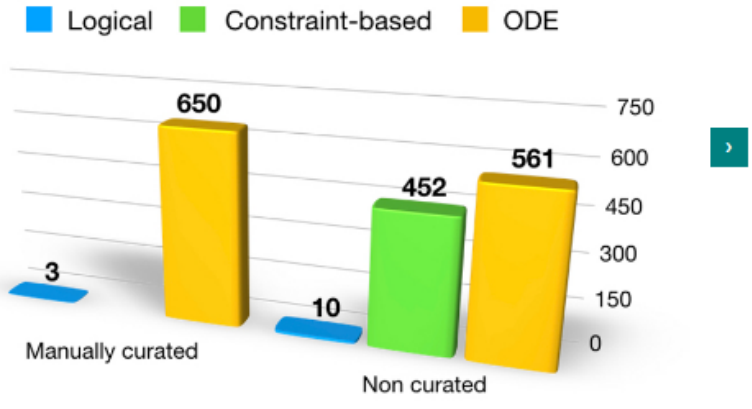
Features

What is available in BioModels?

Two branches
- ☑ Manually curated
- ☑ Non curated

Model formats
- ☑ SBML
- ☑ CellML
- ☑ Matlab
- ☐ ...

Modelling approaches
- ☑ Ordinary Differential Equation
- ☑ Logical
- ☑ Constraint-based
- ☐ ...

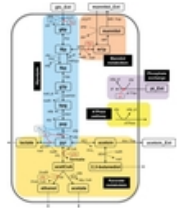


Acknowledgements

EMBL | BBSRC bioscience for the future | AgedBrainSYSBIO | imi | SEVENTH FRAMEWORK PROGRAMME | elixir

Model of the month

May, 2018



Lactococcus lactis has been genetically modified to increase the yield of mannitol and 2,3-butanediol. Costa et al. (2014) presented a mathematical model that provided new targets to further improve metabolite yield.

Access this model of the month | View all Model of the Month entries

News

Patient-derived genome-scale metabolic models

BioModels now hosts 6753 models derived from biological samples collected from patients.
21 Aug 2017 at 10:00

31st release of BioModels

We are extremely happy to announce the 31st release of BioModels!
26 Jun 2017 at 02:20

Metabolic networks and logical models have been published

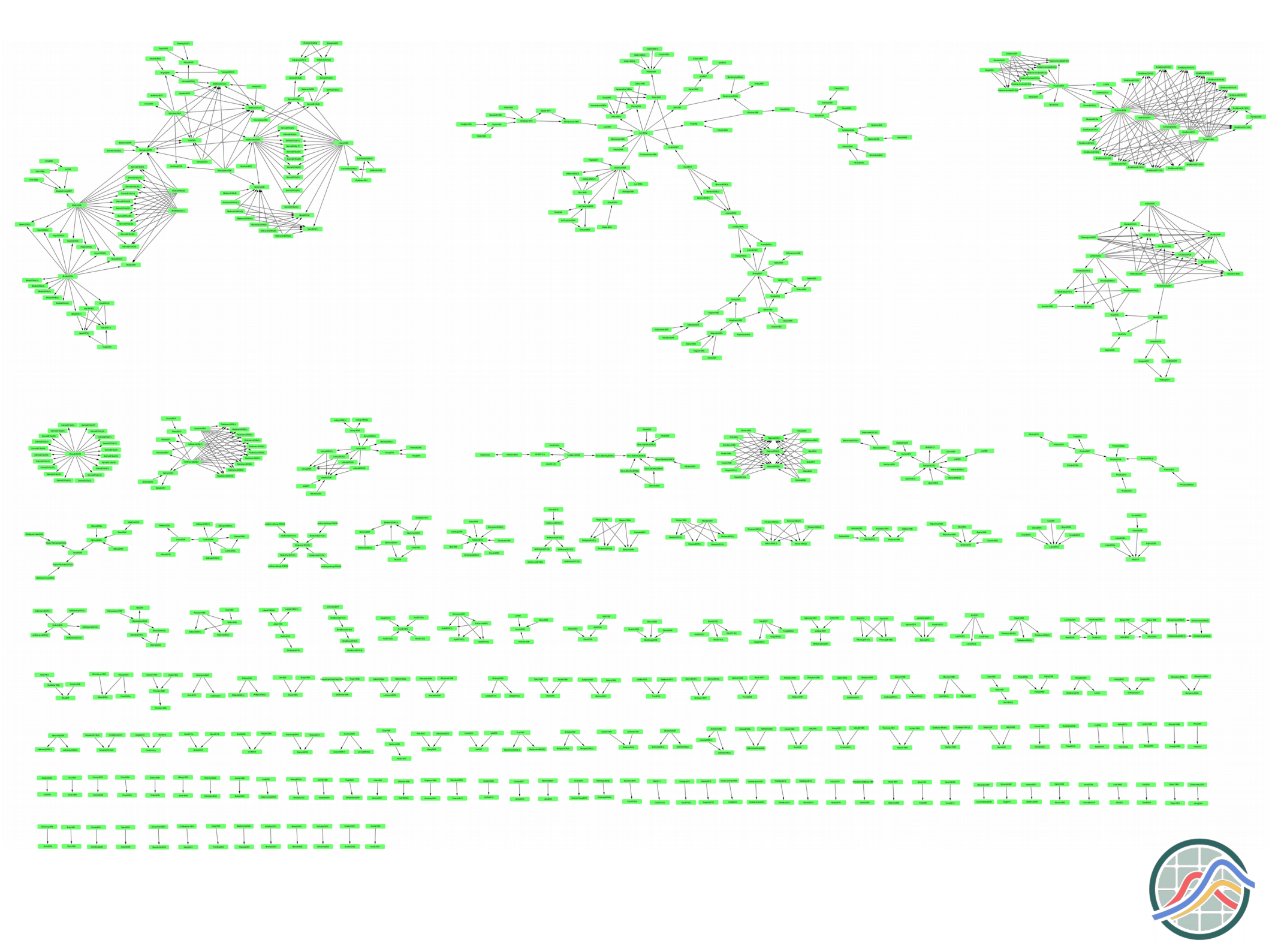
The metabolic network and logical models hosted in the literature-based branch of BioModels can now be downloaded from our FTP server.
16 Jan 2017 at 04:15

Mechanistic models on neurodegenerative dise[illegible] processes published

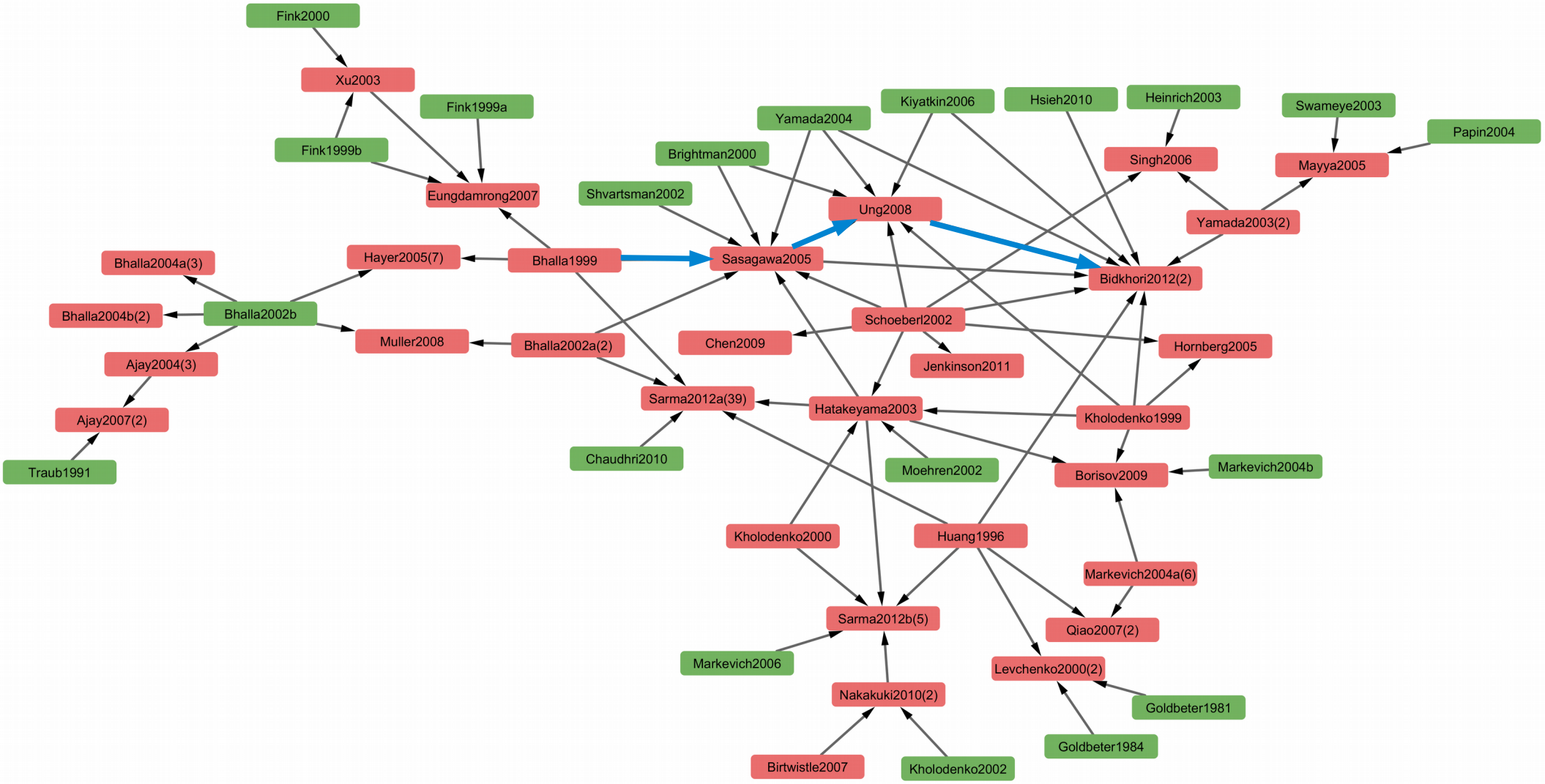
[illegible] paper, entitled Mechanistic models on neurodegenerative disease processes, available from CPT:PSP
09 Jan 2017 at 09:03

Help

Reuse

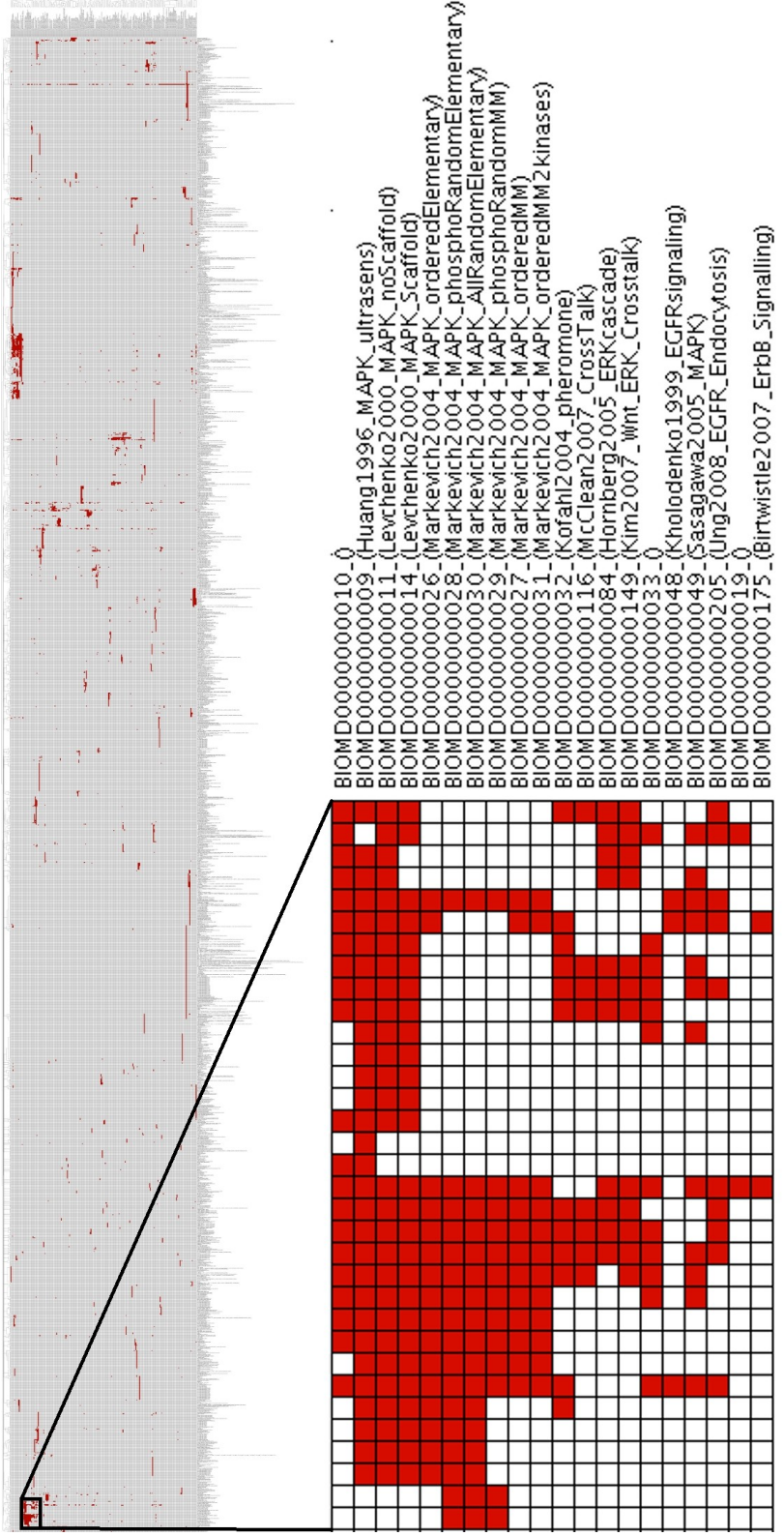


Erb receptor signalling



Discover

Clustering models (and data) based on metadata



Molecular Systems Biology 7; Article number 512; doi:10.1038/msb.2011.41
Citation: ***Molecular Systems Biology*** **7:512**

www.molecularsystemsbiology.com

molecular systems biology

PERSPECTIVE

Retrieval, alignment, and clustering of computational models based on semantic annotations

Marvin Schulz[1], Falko Krause[1], Nicolas Le Novère[2], Edda Klipp[1,*] and Wolfram Liebermeister[1,3]

in mathematical models, which statically or dynamically describe the interconversion of biochemical compounds within reaction networks. A wealth of models, picturing

Ranking and retrieval of models

Model	BioModel	Similarity	*P*-value	Overlap	*P*-value
Huang1996_MAPK_ultrasens	BIOMD0000000009	1.000	<=1e-3	30	0.0e+00
Levchenko2000_MAPK_noScaffold	BIOMD0000000011	0.930	<=1e-3	28	0.0e+00
Levchenko2000_MAPK_Scaffold	BIOMD0000000014	0.874	<=1e-3	26	0.0e+00
Kholodenko2000_MAPK_feedback	BIOMD0000000010	0.830	<=1e-3	20	0.0e+00
Markevich2004_MAPK_orderedElementary	BIOMD0000000026	0.749	<=1e-3	16	2.9e-15
Markevich2004_MAPK_phosphoRandomElementary	BIOMD0000000028	0.692	<=1e-3	15	9.1e-14
Markevich2004_MAPK_AllRandomElementary	BIOMD0000000030	0.692	<=1e-3	15	9.1e-14
Markevich2004_MAPK_orderedMM	BIOMD0000000027	0.691	<=1e-3	12	9.8e-10
Markevich2004_MAPK_orderedMM2kinases	BIOMD0000000031	0.691	<=1e-3	12	9.8e-10
Markevich2004_MAPK_phosphoRandomMM	BIOMD0000000029	0.626	<=1e-3	11	1.6e-08
Hornberg2005_ERKcascade	BIOMD0000000084	0.523	<=1e-3	9	2.7e-06
McClean2007_CrossTalk	BIOMD0000000116	0.453	<=1e-3	8	2.7e-05
Kofahl2004_pheromone	BIOMD0000000032	0.441	<=1e-3	12	9.8e-10
Goldbeter1991_MinMitOscil_ExplInact	BIOMD0000000004	0.389	<=1e-3	3	1.5e-01
Brown2004_NGF_EGF_signaling	BIOMD0000000033	0.371	<=1e-3	9	2.7e-06
Ung2008_EGFR_Endocytosis	BIOMD0000000205	0.363	<=1e-3	8	2.7e-05
Kim2007_Wnt_ERK_Crosstalk	BIOMD0000000149	0.355	<=1e-3	10	2.2e-07
Goldbeter1991_MinMitOscil	BIOMD0000000003	0.349	<=1e-3	3	1.5e-01
Sasagawa2005_MAPK	BIOMD0000000049	0.339	<=1e-3	9	2.7e-06
Swat2004_Mammalian_G1_S_Transition	BIOMD0000000228	0.317	<=1e-3	2	4.0e-01
Tyson1991_CellCycle_6var	BIOMD0000000005	0.304	<=1e-3	4	4.2e-02
Goldbeter1995_CircClock	BIOMD0000000016	0.274	<=1e-3	4	4.2e-02
Novak1997_CellCycle	BIOMD0000000007	0.259	<=1e-3	1	7.6e-01
Novak2001_FissionYeast_CellCycle	BIOMD0000000111	0.255	<=1e-3	2	4.0e-01
Leloup1999_CircClock	BIOMD0000000021	0.246	<=1e-3	4	4.2e-02
Birtwistle2007_ErbB_Signalling	BIOMD0000000175	0.236	<=1e-3	1	7.6e-01
Neves2008_Cell_Shape	BIOMD0000000182	0.222	<=1e-3	6	1.6e-03
Leloup1998_CircClock_LD	BIOMD0000000171	0.219	<=1e-3	4	4.2e-02
Veening2008_DegU_Regulation	BIOMD0000000240	0.211	4.0e-03	2	4.0e-01
Chen2004_CellCycle	BIOMD0000000056	0.209	4.0e-03	4	4.2e-02
Fernandez2006_ModelA	BIOMD0000000152	0.207	5.0e-03	2	4.0e-01
Fisher2006_NFAT_Activation	BIOMD0000000123	0.199	7.0e-03	2	4.0e-01
Hatakeyama2003_MAPK	BIOMD0000000146	0.198	7.0e-03	1	7.6e-01

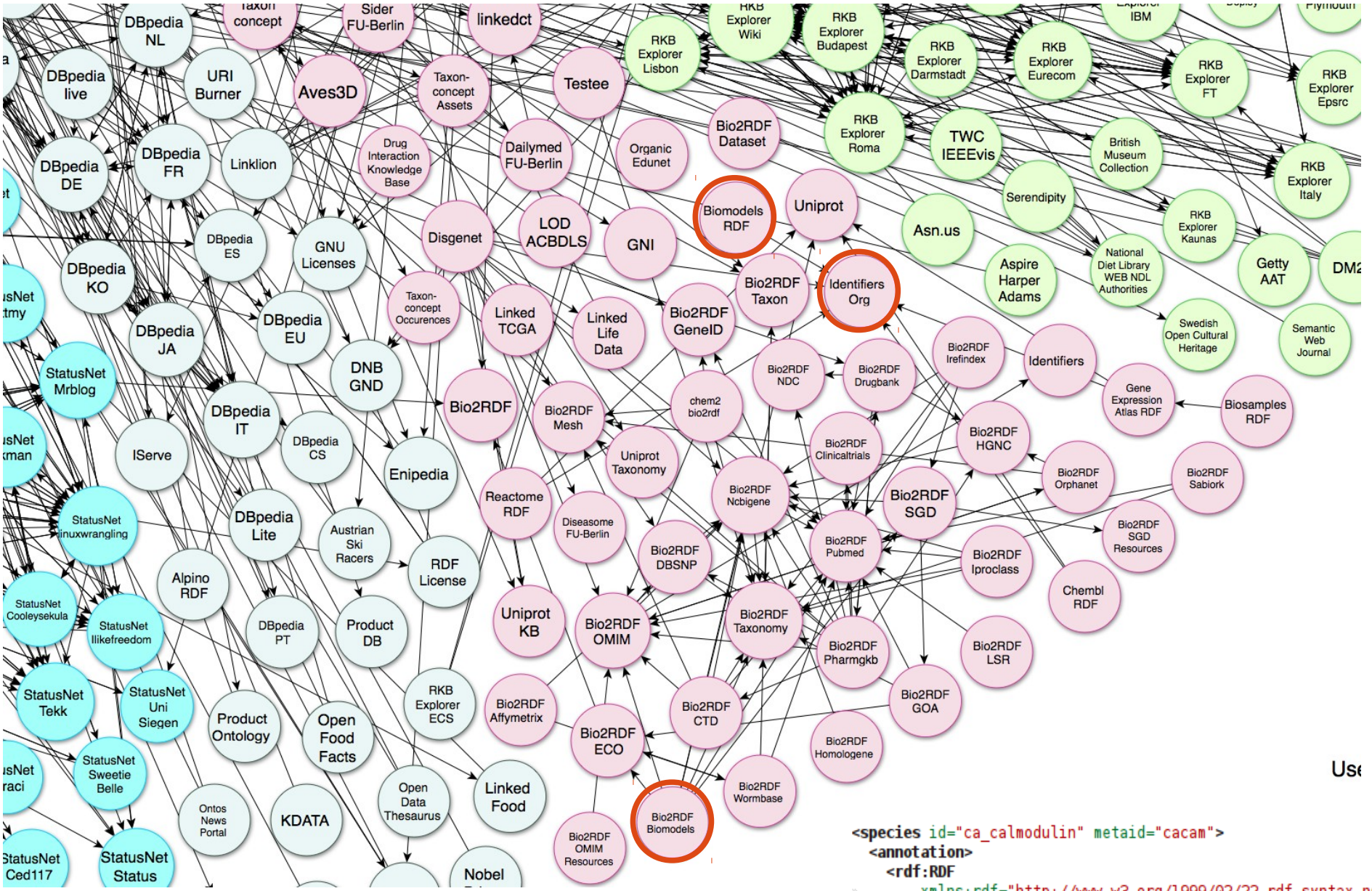
MAPK

Using the model from Huang and Ferrell 1996

Retrieval of models using gene expression

Model	BioModel	Similarity	*P*-value	Overlap	*P*-value
Wolf2001 respiratory oscillations	BIOMD0000000090	0.207	<=1e-3	6	6.6e-09
Chassagnole2001_Threonine Synthesis	BIOMD0000000066	0.184	<=1e-3	4	1.5e-05
Curien2009_Aspartate_Metabolism	BIOMD0000000212	0.170	<=1e-3	5	3.6e-07
Curien2003_MetThr_synthesis	BIOMD0000000068	0.141	<=1e-3	2	1.0e-02
Proctor2007_ubiquitine	BIOMD0000000105	0.098	2.0e-03	1	1.4e-01
Curto1998_purineMetabol	BIOMD0000000015	0.063	1.1e-02	2	1.0e-02
Ibrahim2008_Spindle_Assembly_Checkpoint_dissociation	BIOMD0000000186	0.057	1.8e-02	0	1.0e+00
Ibrahim2008_Spindle_Assembly_Checkpoint_convey	BIOMD0000000187	0.057	1.8e-02	0	1.0e+00
Rodriguez-Caso2006_Polyamine_Metabolism	BIOMD0000000190	0.040	7.1e-02	1	1.4e-01
Nijhout2004_Folate_Cycle	BIOMD0000000213	0.032	1.1e-01	1	1.4e-01
Morrison1989_FolateCycle	BIOMD0000000018	0.030	1.3e-01	1	1.4e-01
Zatorsky2006_p53_Model3	BIOMD0000000154	0.023	2.5e-01	0	1.0e+00
Zatorsky2006_p53_Model6	BIOMD0000000155	0.023	2.5e-01	0	1.0e+00
Hunziker2010_p53_StressSpecificResponse	BIOMD0000000252	0.023	2.5e-01	0	1.0e+00
Zatorsky2006_p53_Model5	BIOMD0000000156	0.022	2.7e-01	0	1.0e+00
Zatorsky2006_p53_Model4	BIOMD0000000157	0.022	2.7e-01	0	1.0e+00
Zatorsky2006_p53_Model2	BIOMD0000000158	0.022	2.7e-01	0	1.0e+00
Zatorsky2006_p53_Model1	BIOMD0000000159	0.022	2.7e-01	0	1.0e+00
Proctor2008_p53_Mdm2_ATM	BIOMD0000000188	0.013	4.3e-01	0	1.0e+00
McClean2007_CrossTalk	BIOMD0000000116	0.012	4.7e-01	0	1.0e+00
Proctor2008_p53_Mdm2_ARF	BIOMD0000000189	0.012	4.9e-01	0	1.0e+00
Haberichter2007_cellcycle	BIOMD0000000109	0.011	5.0e-01	0	1.0e+00
Sasagawa2005_MAPK	BIOMD0000000049	0.006	5.5e-01	0	1.0e+00

Using differential gene expression suring metabolic oscillations in yeast

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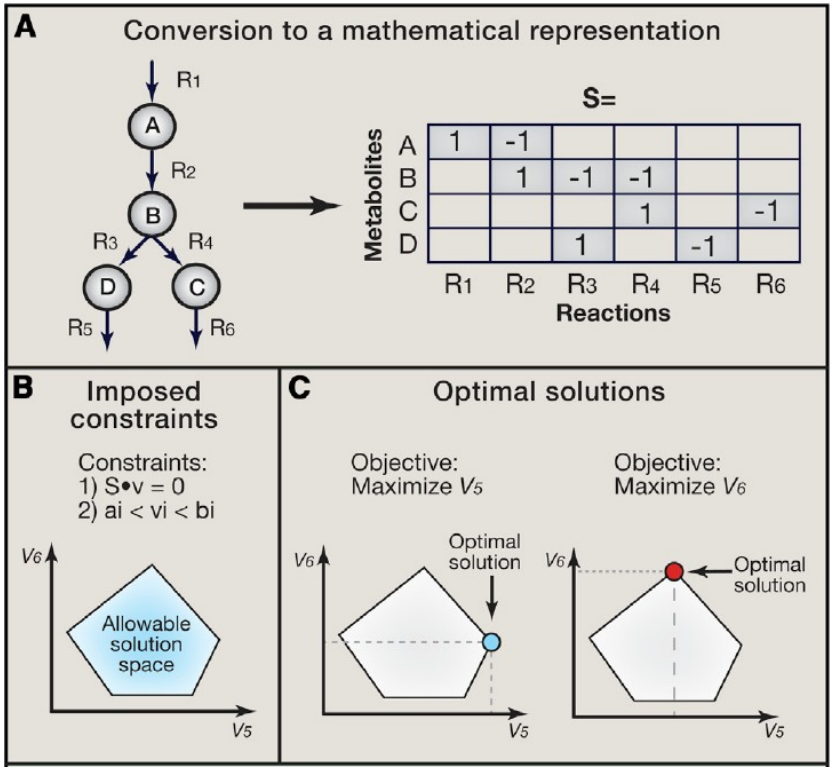
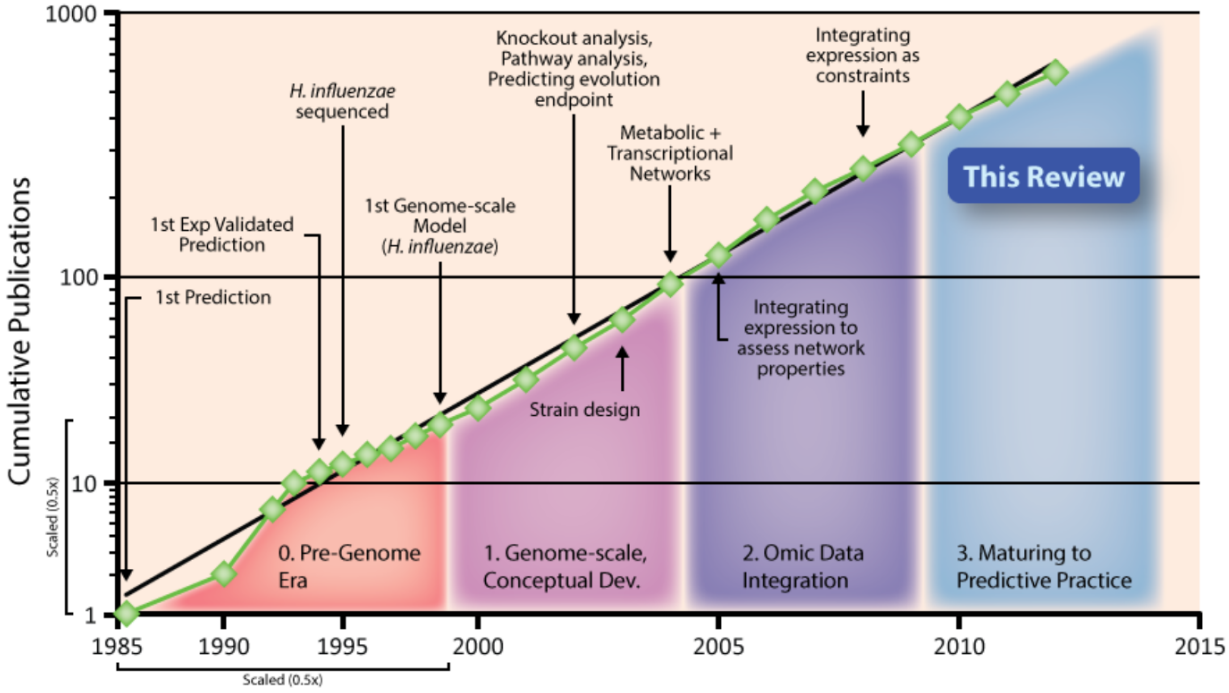
W3C Semantic Web

Validate





Do genome-scale models need exact solvers or clearer standards?

Ali Ebrahim, Eivind Almaas, Eugen Bauer, Aarash Bordbar, Anthony P Burgard, Roger L Chang, Andreas Dräger, Iman Famili, Adam M Feist, Ronan MT Fleming, Stephen S Fong, Vassily Hatzimanikatis, Markus J Herrgård, Allen Holder, Michael Hucka, Daniel Hyduke, Neema Jamshidi, Sang Yup Lee, Nicolas Le Novère, Joshua A Lerman, Nathan E Lewis, Ding Ma, Radhakrishnan Mahadevan, Costas Maranas, Harish Nagarajan, Ali Navid, Jens Nielsen, Lars K Nielsen, Juan Nogales, Alberto Noronha, Csaba Pal, Bernhard O Palsson, Jason A Papin, Kiran R Patil, Nathan D Price, Jennifer L Reed, Michael Saunders, Ryan S Senger, Nikolaus Sonnenschein, Yuekai Sun, Ines Thiele

Author Affiliations

DOI 10.15252/msb.20156157 | Published online 14.10.2015
Molecular Systems Biology (2015) 11, 831

SBML Level 3 Package Specification

SBML Level 3 Package: Flux Balance Constraints ('fbc')

Brett G. Olivier
b.g.olivier@vu.nl
Systems Bioinformatics
VU University Amsterdam
Amsterdam, NH, The Netherlands

Frank T. Bergmann
fbergmann@caltech.edu
Computing and Mathematical Sciences
California Institute of Technology
Pasadena, CA, US

Version 2, Release 1

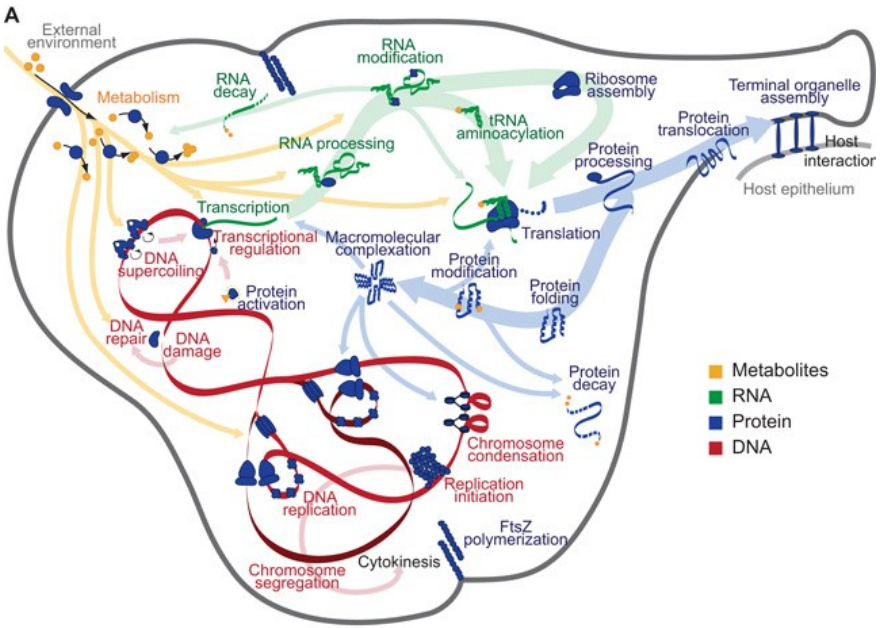
September 12, 2015

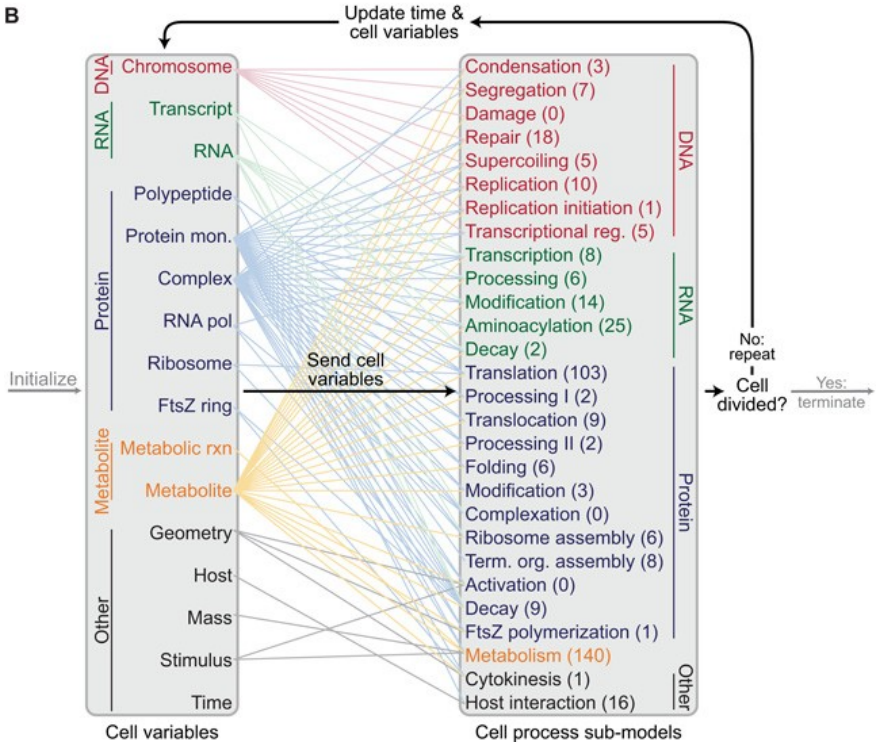
“You should not develop standards and easy to use modelling software. This allows biologists to write models, and they don't know how to do it properly.”

Biomathematician, 2007

“By developing BioModels you harmed the cause of modelling in biology. My students do not learn how to make a model any more, instead, they download it ready to use.”

Theoretical biologist, 2006





Theory

2012 Jul 20

Cell

A Whole-Cell Computational Model Predicts Phenotype from Genotype

Jonathan R. Karr,[1,4] Jayodita C. Sanghvi,[2,4] Derek N. Macklin,[2] Miriam V. Gutschow,[2] Jared M. Jacobs,[2] Benjamin Bolival, Jr.,[2] Nacyra Assad-Garcia,[3] John I. Glass,[3] and Markus W. Covert[2,*]

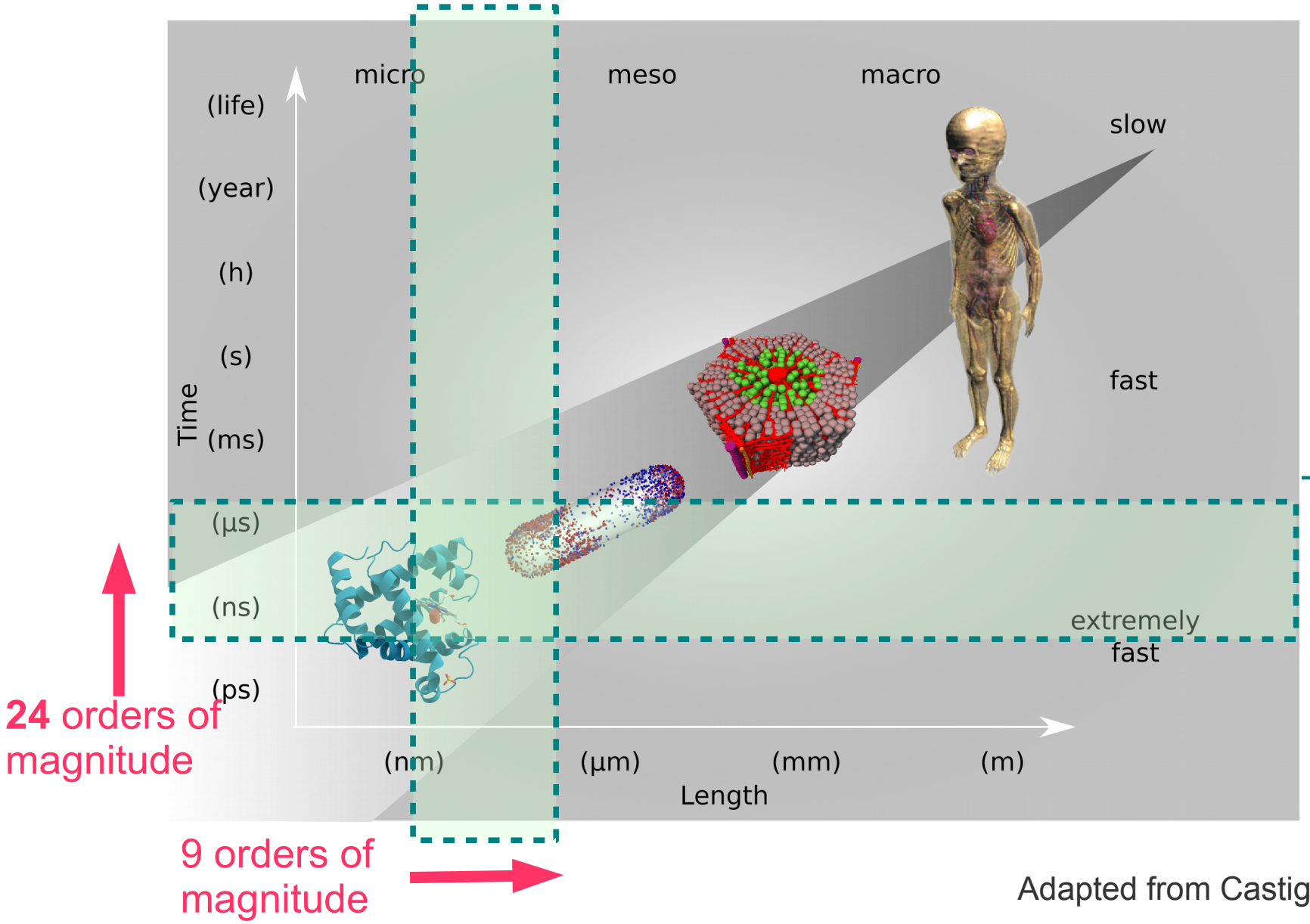
[1]Graduate Program in Biophysics
[2]Department of Bioengineering
Stanford University, Stanford, CA 94305, USA
[3]J. Craig Venter Institute, Rockville, MD 20850, USA
[4]These authors contributed equally to this work
*Correspondence: mcovert@stanford.edu
http://dx.doi.org/10.1016/j.cell.2012.05.044

SUMMARY

Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen *Mycoplasma genitalium* that includes all of its molecular components and their interactions. An integrative approach to modeling that combines diverse mathematics enabled the simultaneous inclusion of fundamentally different cellular processes and experimental measurements. Our whole-cell model accounts for all annotated gene functions and was validated against a broad range of data. The model provides insights into many previously unobserved cellular behaviors, including in vivo rates of protein-DNA association

First, until recently, not enough has been known about the individual molecules and their interactions to completely model any one organism. The advent of genomics and other high-throughput measurement techniques has accelerated the characterization of some organisms to the extent that comprehensive modeling is now possible. For example, the mycoplasmas, a genus of bacteria with relatively small genomes that includes several pathogens, have recently been the subject of an exhaustive experimental effort by a European consortium to determine the transcriptome (Güell et al., 2009), proteome (Kühner et al., 2009), and metabolome (Yus et al., 2009) of these organisms.

The second limiting factor has been that no single computational method is sufficient to explain complex phenotypes in terms of molecular components and their interactions. The first approaches to modeling cellular physiology, based on ordinary differential equations (ODEs) (Atlas et al., 2008; Browning et al., 2004; Castellanos et al., 2004, 2007; Domach et al., 1984; Tomita et al., 1999), were limited by the difficulty in obtaining the necessary model parameters. Subsequently, alternative



Coupled multi-scale models

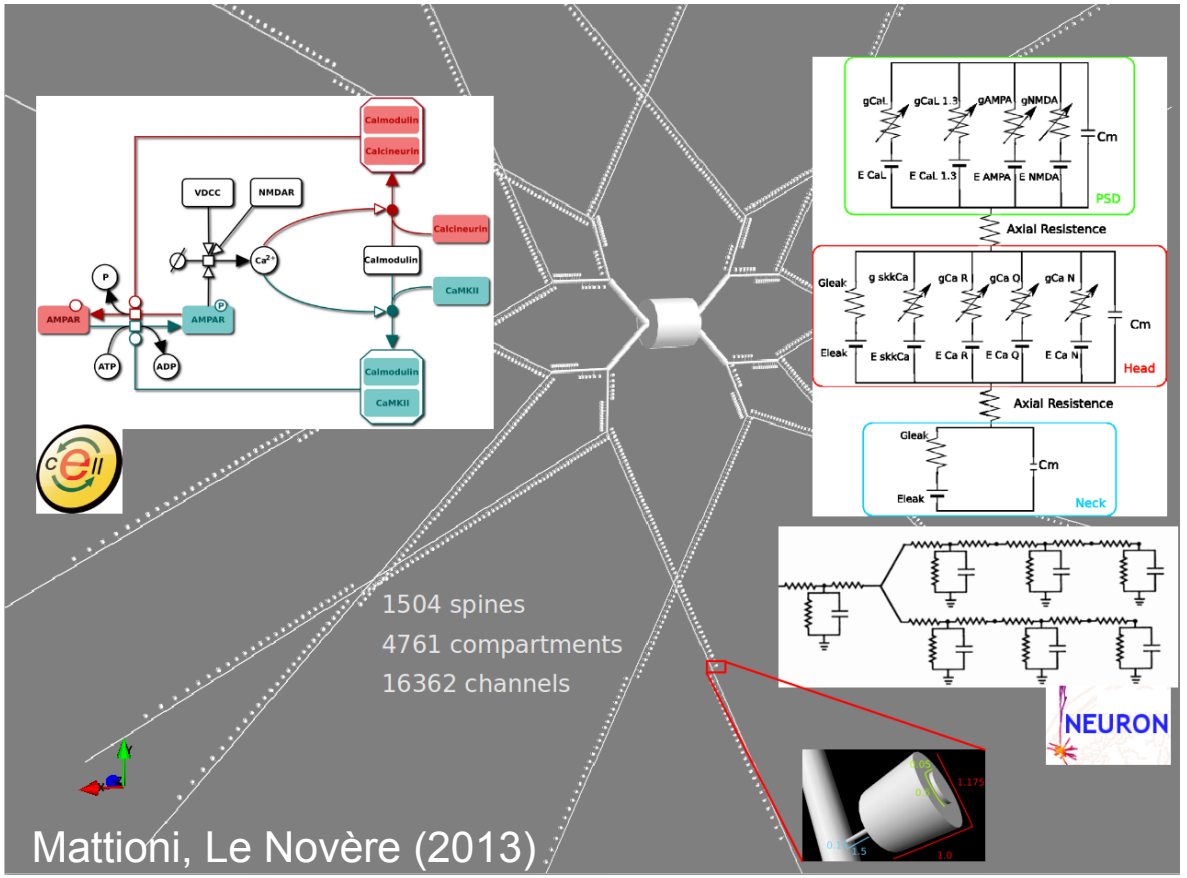
Theoretical and Computational roadblockers

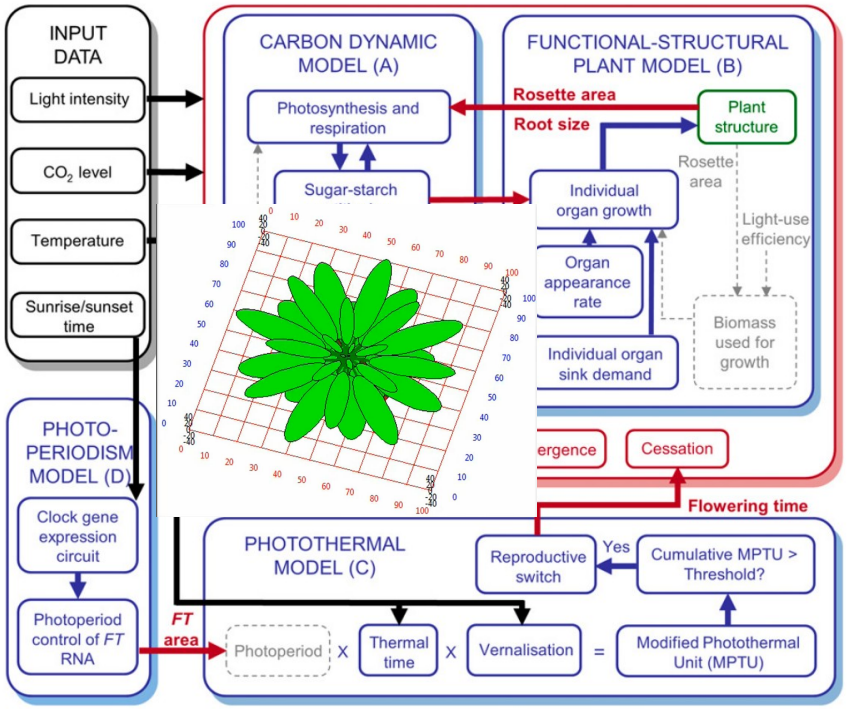
24 orders of magnitude

9 orders of magnitude

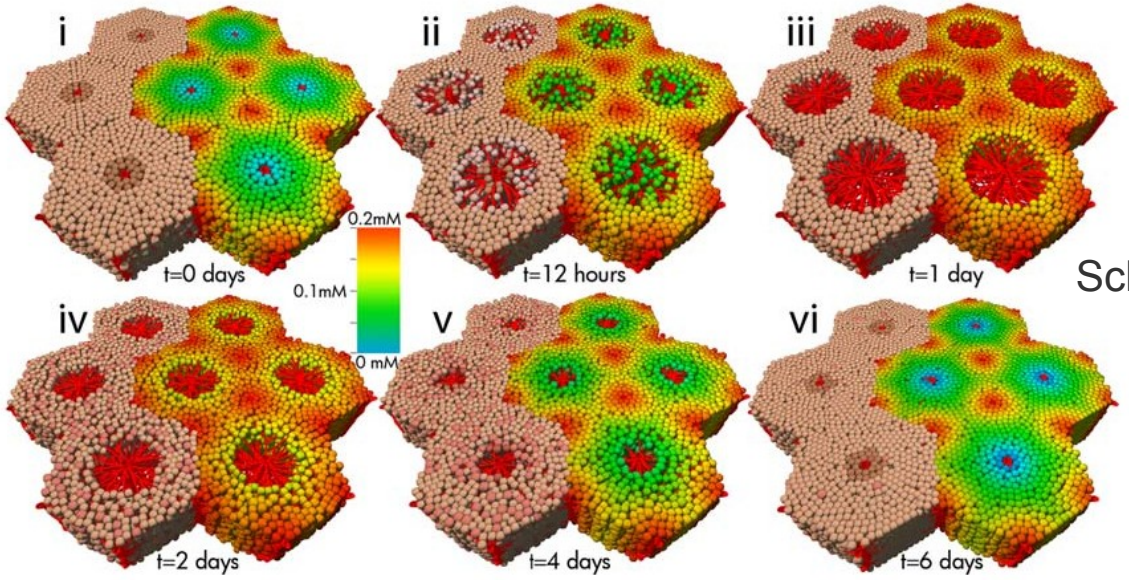
Adapted from Castiglione *et al.* (2014)

Multi-scale coupling





Chew *et al.* (2014)



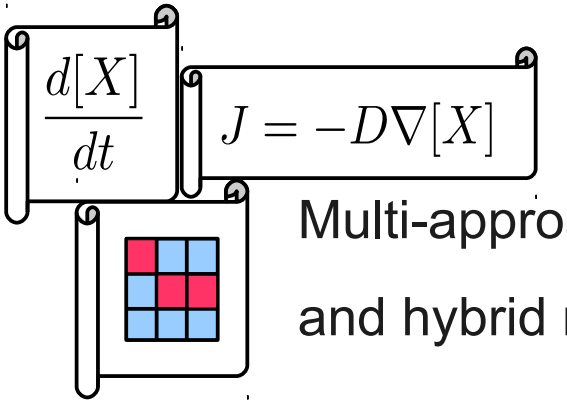
Schliess *et al.* (2014)

Modular

Collaborative

Built on

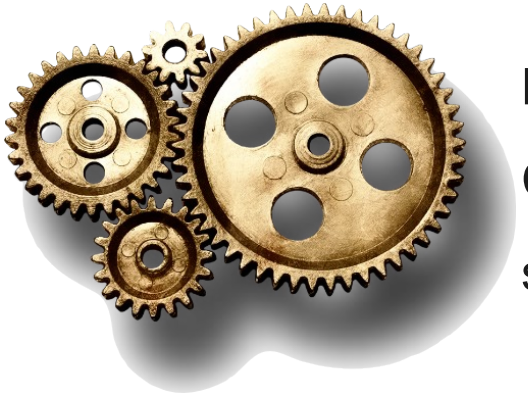
knowledge-bases



Multi-approach

and hybrid models

Versioned



Multi-software

Coupled

simulations

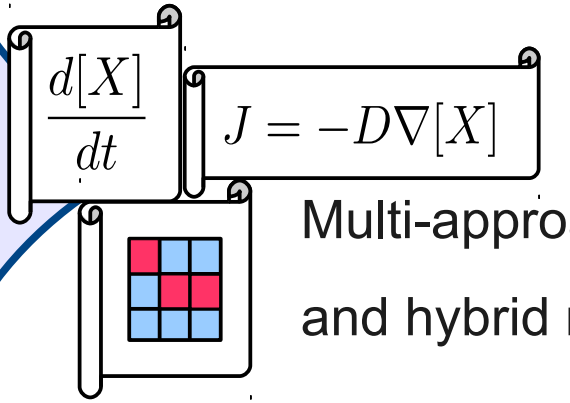
Modular

Collaborative

Standards!

Built on

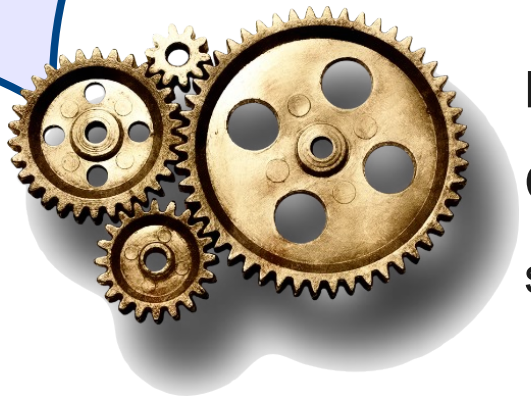
knowledge-bases



Multi-approach

and hybrid models

Versioned



Multi-software

Coupled

simulations

Bridging Bioinformatics and Systems Biology

Big historical divide: Origin of scientists (math/bio Vs eng/physics), journals, conferences, scientific societies etc.

Frontiers tend to blur: Network inference from omics data, parametrisation of models, optimisation (e.g. whole-genome metabolic models), precision medicine (perturbations and drugs explained in mechanistic context)

SysMod attempts to bring back systems modelling to ISCB (society) and ISMB (conference)

Improve the conversation between communities of bioinformatics/genomics and modelling

Annual meeting (Chicago, 07 July 2018)

sysmod@googlegroups.com

@cosi_sysmod

http://sysmod.info

Pecunia est nervus belli