# From art to engineering:

# 15 years of standards and tools

# towards digital organisms

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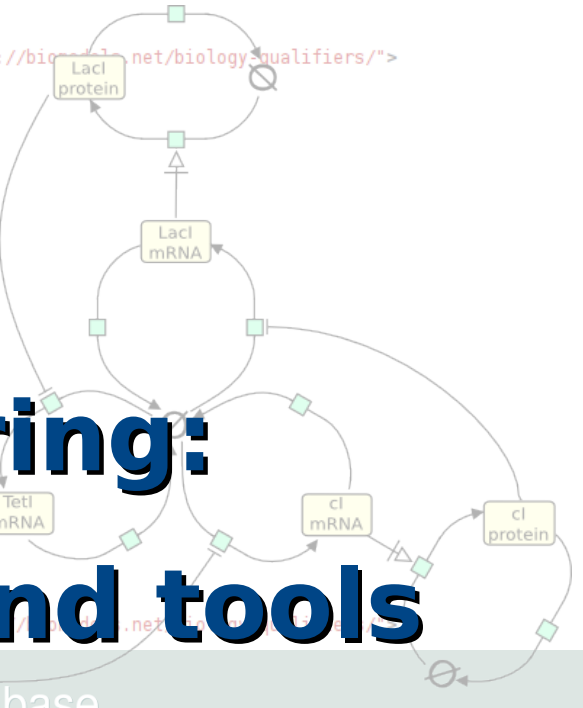
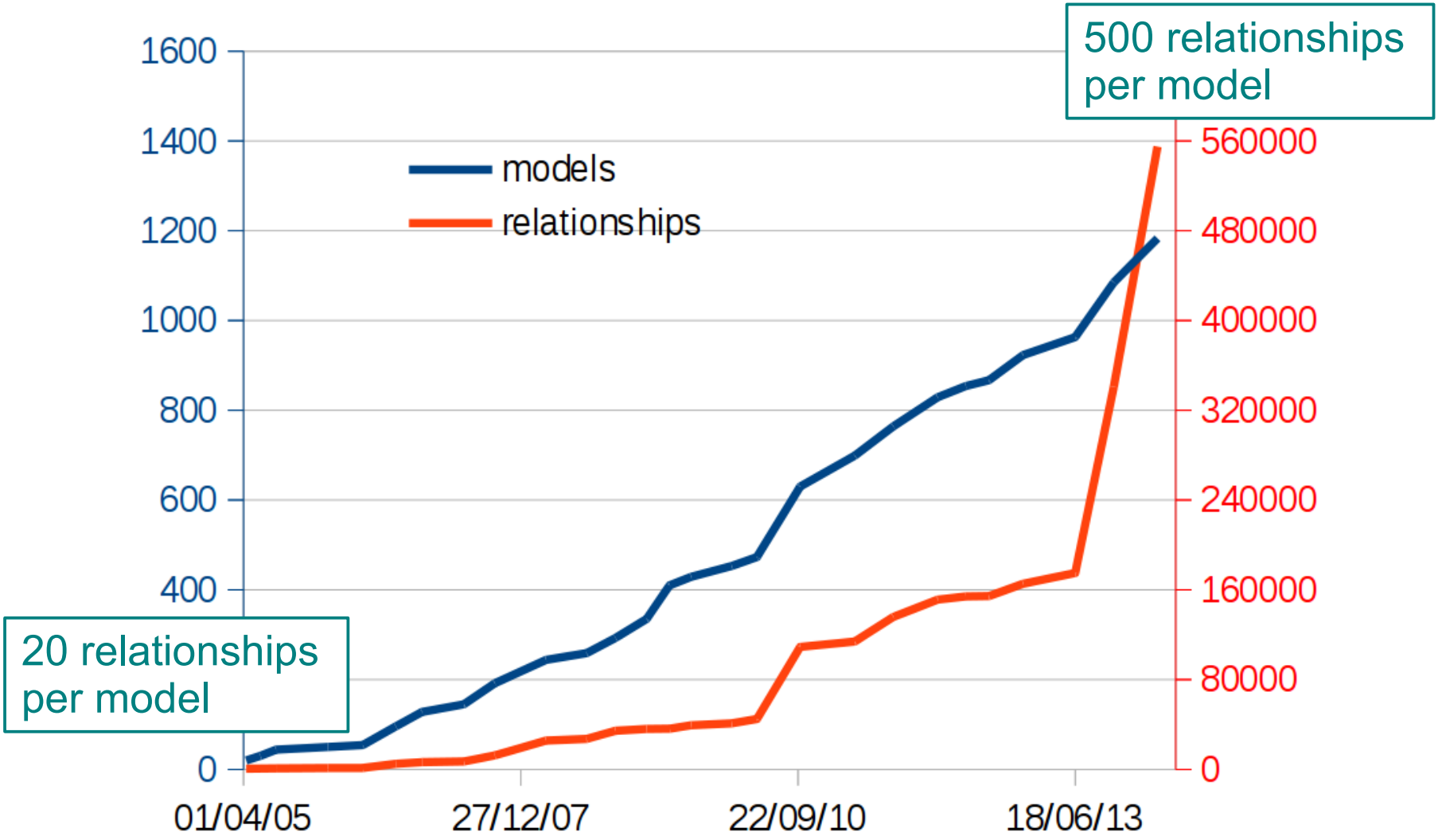
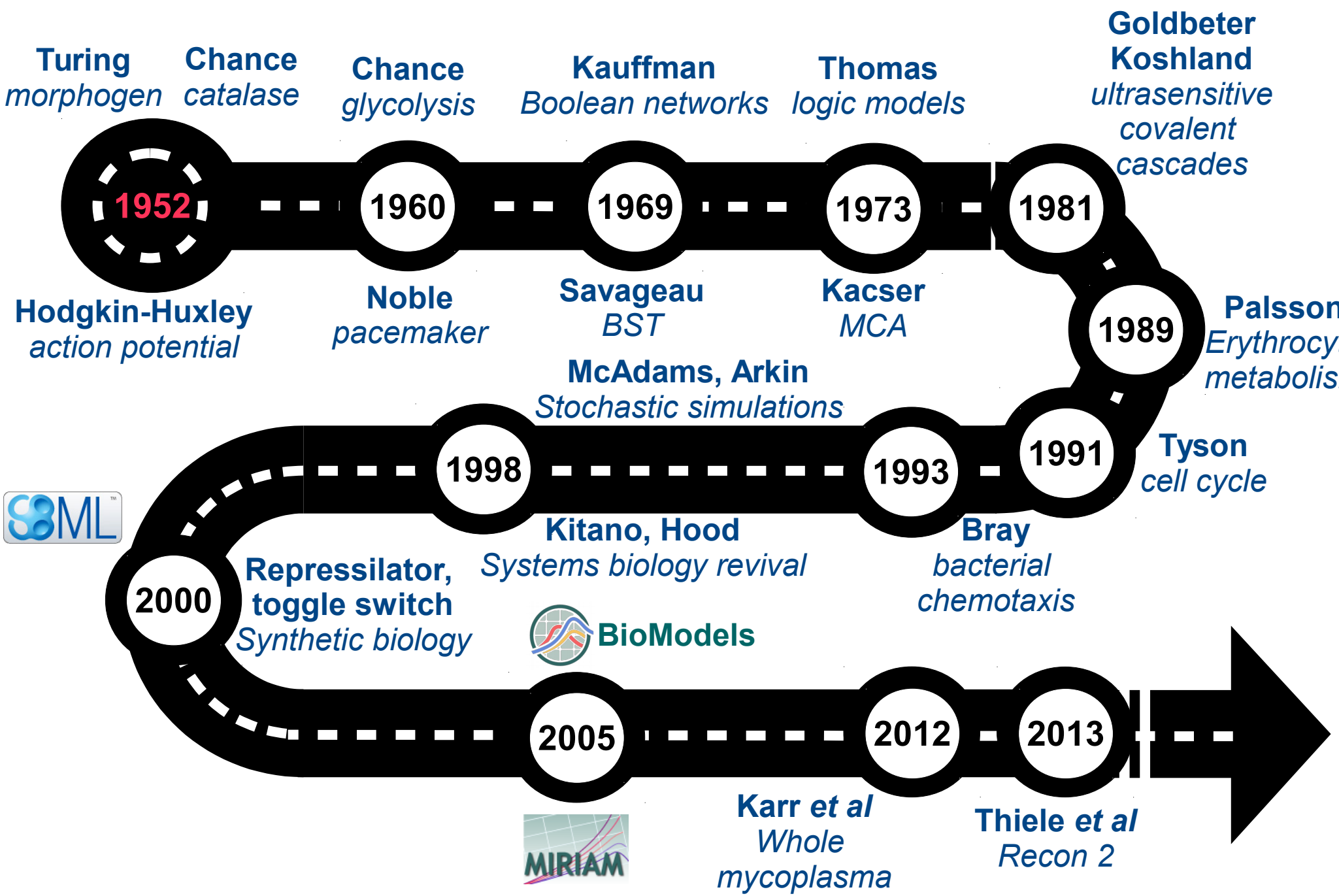
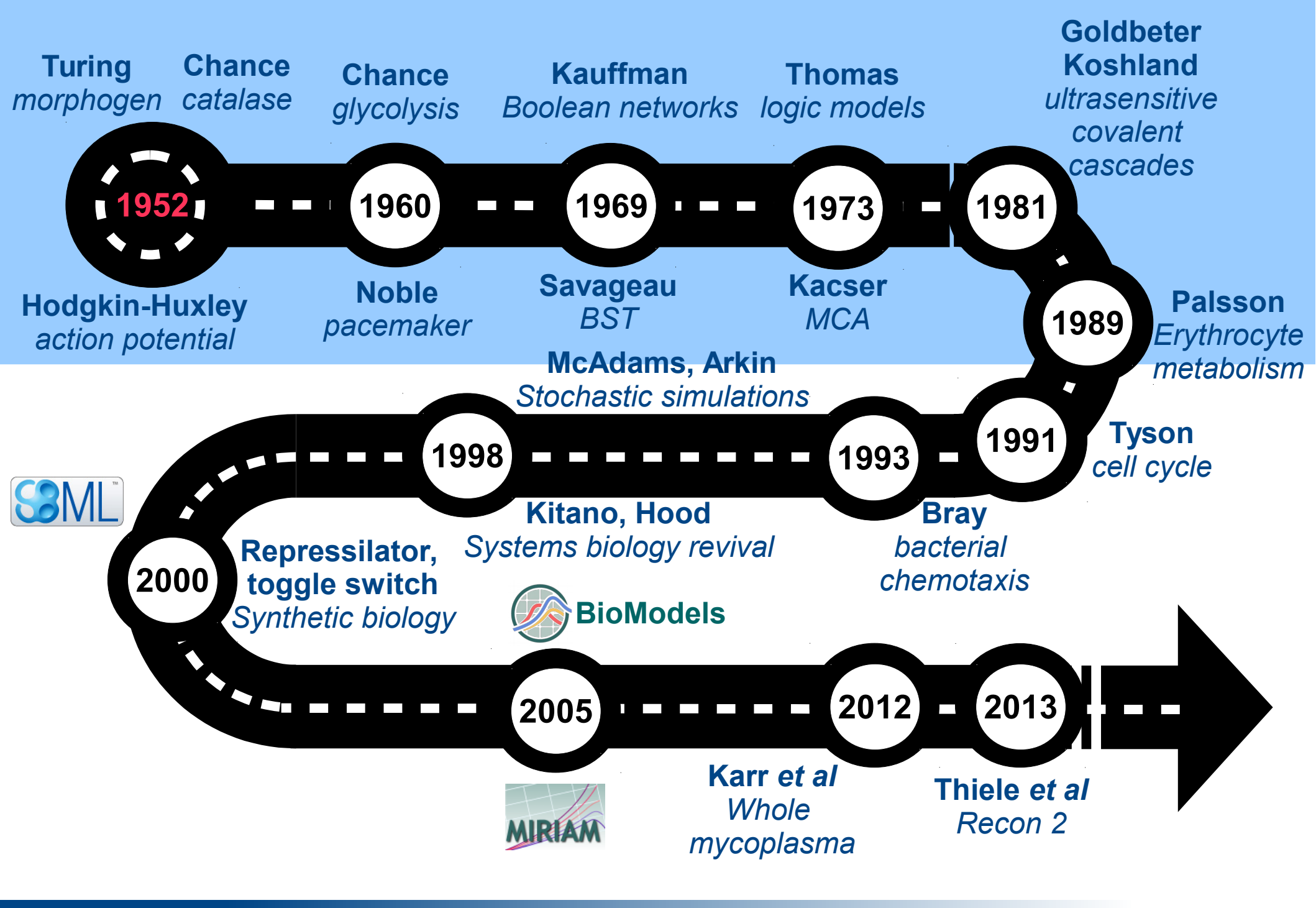



# Computational models on the rise




BioModels Database growth (published models branch) since its creation


Turing
morphogen
Chance
catalase
Chance
glycolysis
Kauffman
Boolean networks
Thomas
logic models
Goldbeter
Koshland
ultrasensitive
covalent
cascades
1952
1960
1969
1973
1981
Hodgkin-Huxley
action potential
Noble
pacemaker
Savageau
BST
Kacser
MCA
1989
Palsson
Erythrocyte
metabolism
McAdams, Arkin
Stochastic simulations
1998
1993
1991
Tyson
cell cycle
SBML
Kitano, Hood
Systems biology revival
Bray
bacterial
chemotaxis
2000
Repressilator,
toggle switch
Synthetic biology
BioModels
2005
2012
2013
MIRIAM
Karr et al
Whole
mycoplasma
Thiele et al
Recon 2


Turing
morphogen
Chance
catalase
Chance
glycolysis
Kauffman
Boolean networks
Thomas
logic models
Goldbeter
Koshland
ultrasensitive
covalent
cascades
1952
1960
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action potential
Noble
pacemaker
Savageau
BST
Kacser
MCA
1989
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Erythrocyte
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chemotaxis
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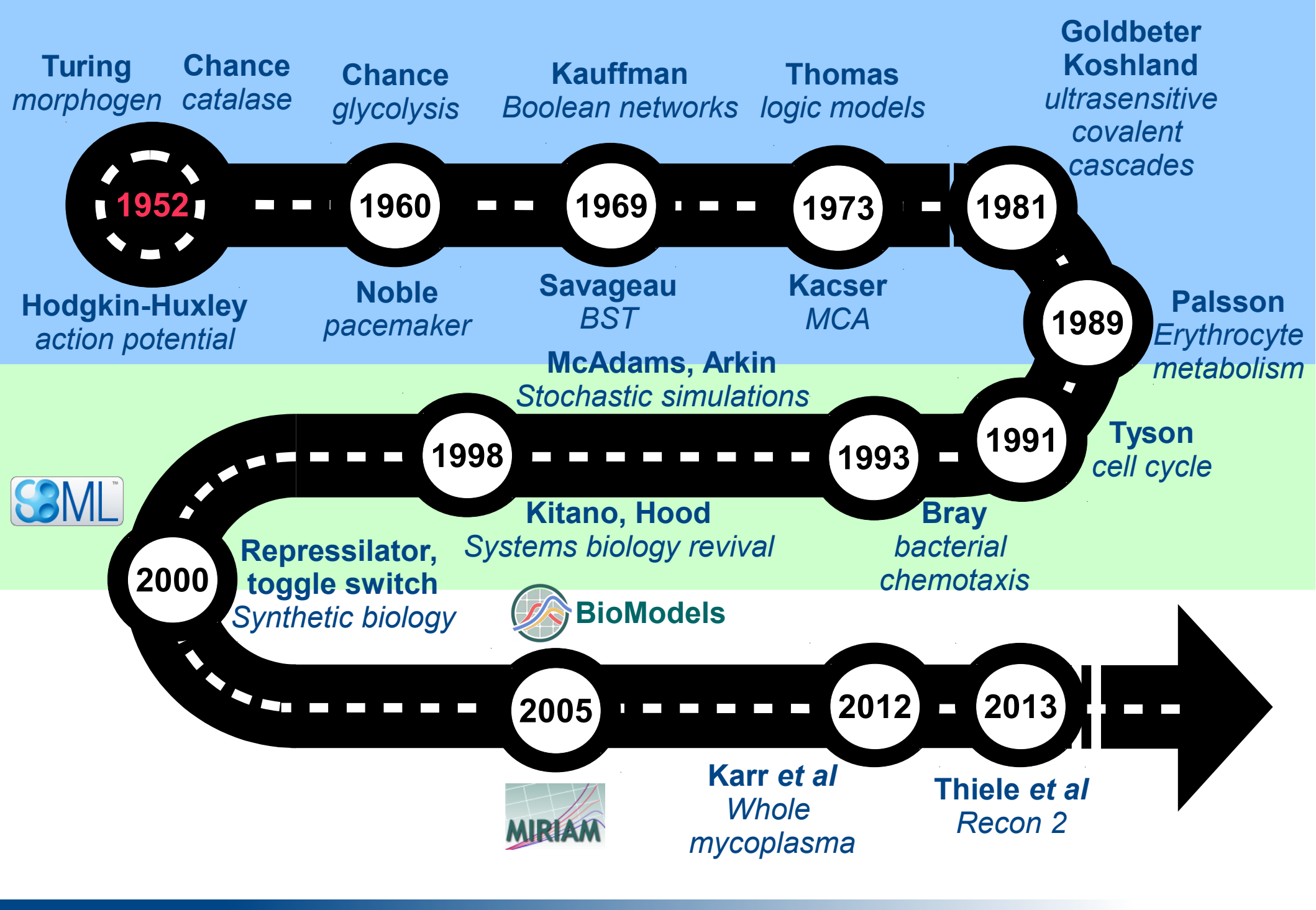
toggle switch
Synthetic biology
BioModels
2005
2012
2013
MIRIAM
Karr et al
Whole
mycoplasma
Thiele et al
Recon 2


Turing
morphogen
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Kauffman
Boolean networks
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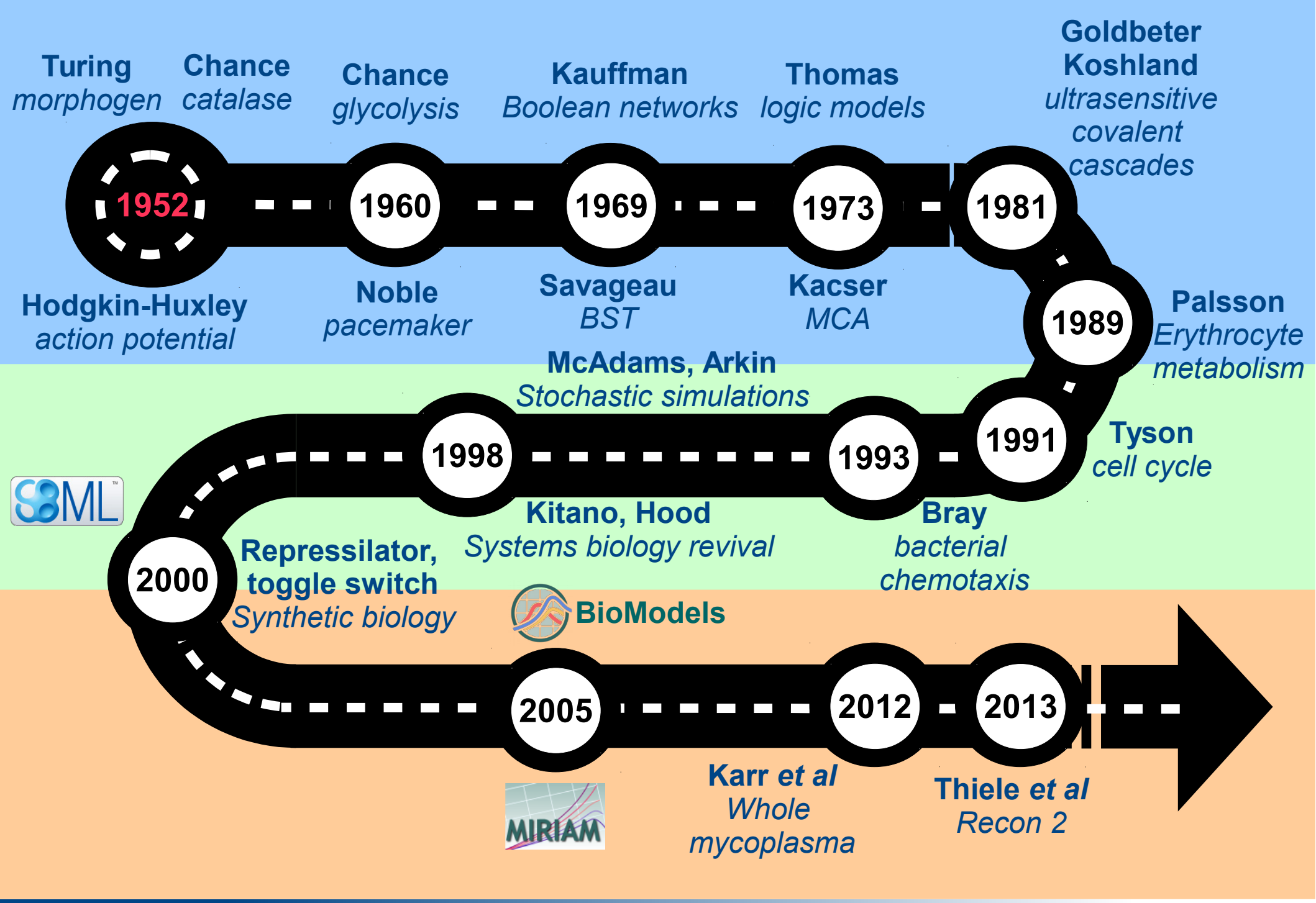
Recon 2


Turing
morphogen
Chance
catalase
Chance
glycolysis
Kauffman
Boolean networks
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logic models
Goldbeter
Koshland
ultrasensitive
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2000
Repressilator,
toggle switch
Synthetic biology
BioModels
2005
2012
2013
MIRIAM
Karr et al
Whole
mycoplasma
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<br>**WHAT** | What to encode in order to share experiments and understand results<br>MIBBI |
| Data-models<br>**HOW** | How to encode the information defined above in a computer-readable manner<br>combine |
| Terminologies | Structured representation of knowledge, with concept definitions and their relationships<br>  <br>OBO foundry |

http://co.mbine.org

combine the computational modeling in biology network

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COMBINE

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- Help
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# Coordinating standards for modeling in biology

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 combine-announce@ebi.ac.uk (Note that the main list of each of the COMBINE standards is already subscriber).

To discuss the goals, organization and operation of COMBINE, subscribe to combine-discuss@ebi.ac.uk.

To report issues about the co.mbine.org website, send a mail to combine-support @ googlegroups.com

## Tweets

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**COMBINE** @combine_coord 25 Feb
Short paper summarizing COMBINE activities
journal.frontiersin.org/article/10.338...
Expand

**COMBINE** @combine_coord 19 Dec
Publication of the OMEX format and the COMBINE archive
biomedcentral.com/1471-2105/15/3...
Expand

# A language to describe computational models in biology

| | Model descriptions |
|---|---|
| Data-models | SBML |

Hucka et al. *Bioinformatics* (2003)

**Born in Caltech 2000**

John Doyle

Hiroaki Kitano

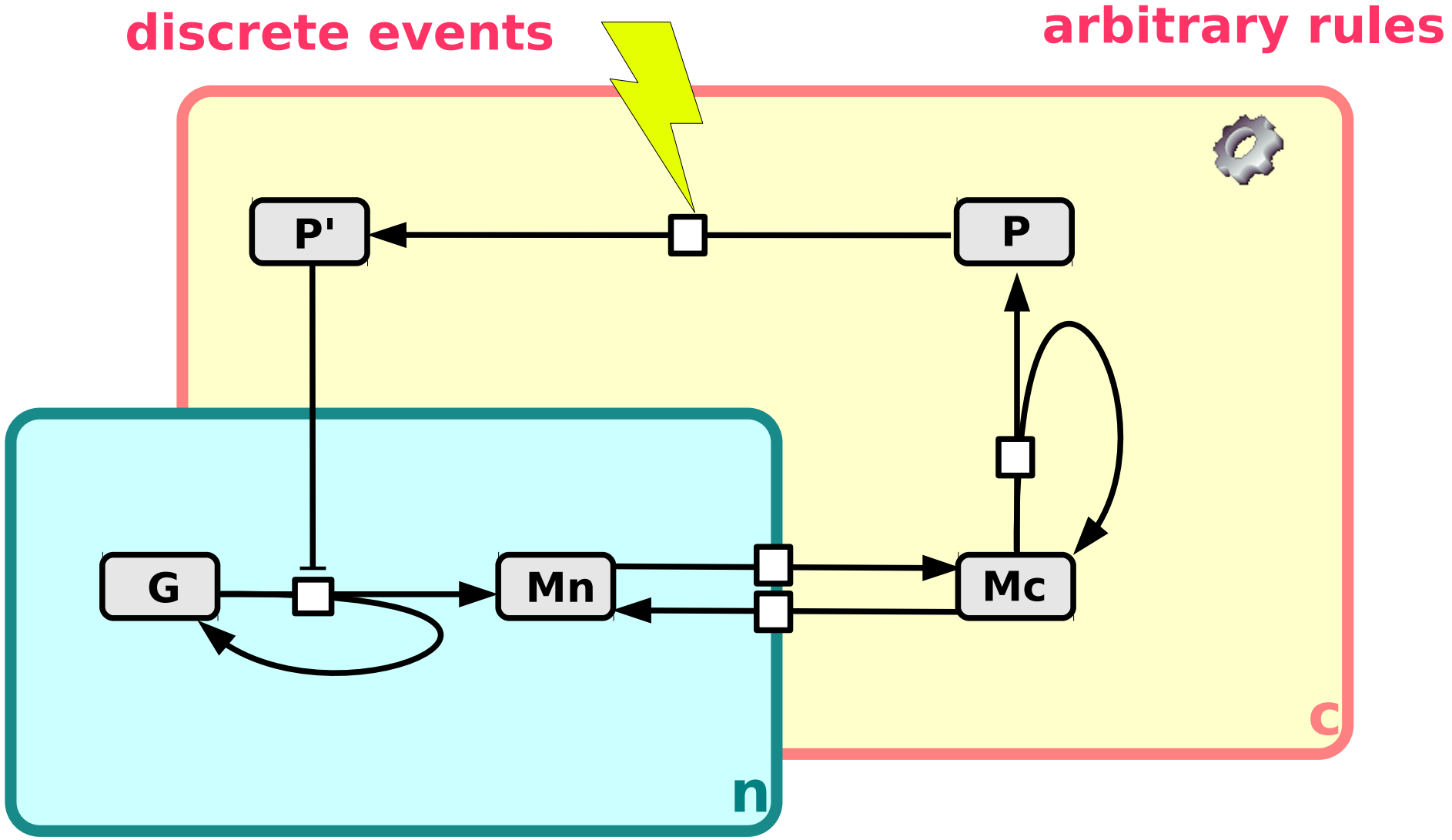
Hamid Bolouri

Mike Hucka

Andrew Finney

Herbert Sauro

# What can we encode in SBML (core)?

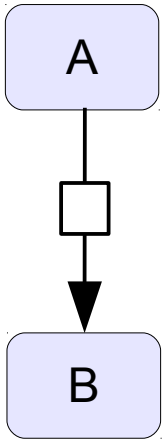


# Structure of SBML

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="3" version="1"·
      xmlns="http://www.sbml.org/sbml/level3/version1/core">
  <model>
    <listOfFunctionDefinitions> <!-- --> </listOfFunctionDefinitions>
    <listOfUnitDefinitions> <!-- --> </listOfUnitDefinitions>
    <listOfCompartments> <!-- --> </listOfCompartments>
    <listOfSpecies> <!-- --> </listOfSpecies>
    <listOfParameters> <!-- --> </listOfParameters>
    <listOfInitialAssignments> <!-- --> </listOfInitialAssignments>
    <listOfRules> <!-- --> </listOfRules>
    <listOfConstraints> <!-- --> </listOfConstraints>
    <listOfReactions> <!-- --> </listOfReactions>
    <listOfEvents> <!-- --> </listOfEvents>
  </model>
</sbml>
```

variables

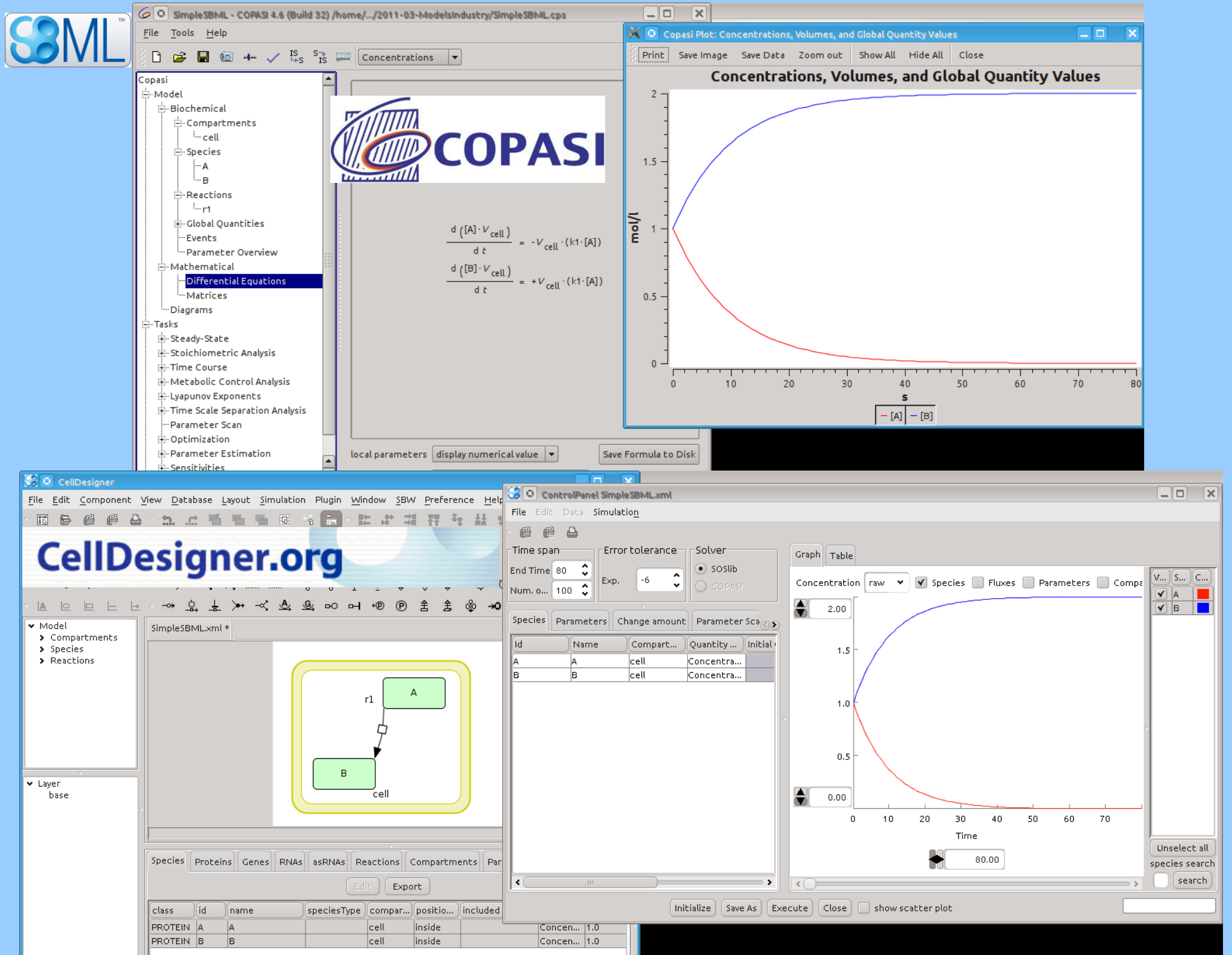
relationships




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

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model name="Simple Model">
    <listOfCompartments>
      <compartment id="cell" size="1" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="1"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="k1" value="0.1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction id="r1" reversible="false">
      <listOfReactants>
          <speciesReference species="A"/>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B"/>
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times/>
              <ci> cell </ci>
              <ci> k1 </ci>
              <ci> A </ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

# A very simple SBML file


SBML
SimpleSBML - COPASI 4.6 (Build 32) /home/.../2011-03-ModelsIndustry/SimpleSBML.cps
File Tools Help
Concentrations
Copasi
Model
Biochemical
Compartments
cell
Species
A
B
Reactions
r1
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
$\frac{d([A] \cdot V_{cell})}{dt} = -V_{cell} \cdot (k1 \cdot [A])$
$\frac{d([B] \cdot V_{cell})}{dt} = +V_{cell} \cdot (k1 \cdot [A])$
local parameters
display numerical value
Save Formula to Disk
Copasi Plot: Concentrations, Volumes, and Global Quantity Values
Print Save Image Save Data Zoom out Show All Hide All Close
Concentrations, Volumes, and Global Quantity Values
mol/l
s
[A] [B]
CellDesigner
File Edit Component View Database Layout Simulation Plugin Window SBW Preference Help
CellDesigner.org
Model
Compartments
Species
Reactions
Layer
base
SimpleSBML.xml *
r1
A
B
cell
Species Proteins Genes RNAs asRNAs Reactions Compartments
Edit Export
class id name speciesType compar... positio... included
PROTEIN A A cell inside Concen... 1.0
PROTEIN B B cell inside Concen... 1.0
ControlPanel SimpleSBML.xml
File Edit Data Simulation
Time span
End Time 80
Num. o... 100
Error tolerance
Exp. -6
Solver
SOSlib
COPASI
Species Parameters Change amount Parameter Sca
Id Name Compart... Quantity ... Initial
A A cell Concentra...
B B cell Concentra...
Graph Table
Concentration raw
Species Fluxes Parameters Compa
2.00
0.00
Time
80.00
V... S... C...
A
B
Unselect all
species search
search
Initialize Save As Execute Close show scatter plot

RESOURCE

# 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/.**

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



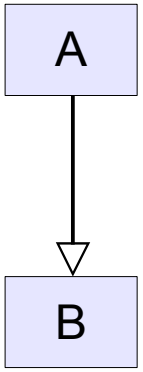
## A not so simple SBML file (Recon2)

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

MODEL1109130000

- Core package – public specification
- Flux balance constraint – public specification
- Qualitative models – public specification
- Model composition – public specification
- Graph Layout – public specification
- Groups – public specification
- Graph rendering – specification finalised
- Complex species – specification finalised
- Spatial diffusion – specification finalised
- Distributions and ranges – draft specification available
- Arrays and sets – draft specification available
- Dynamic structures – draft specification available
- Enhanced metadata – under discussion
- Extended math – under discussion

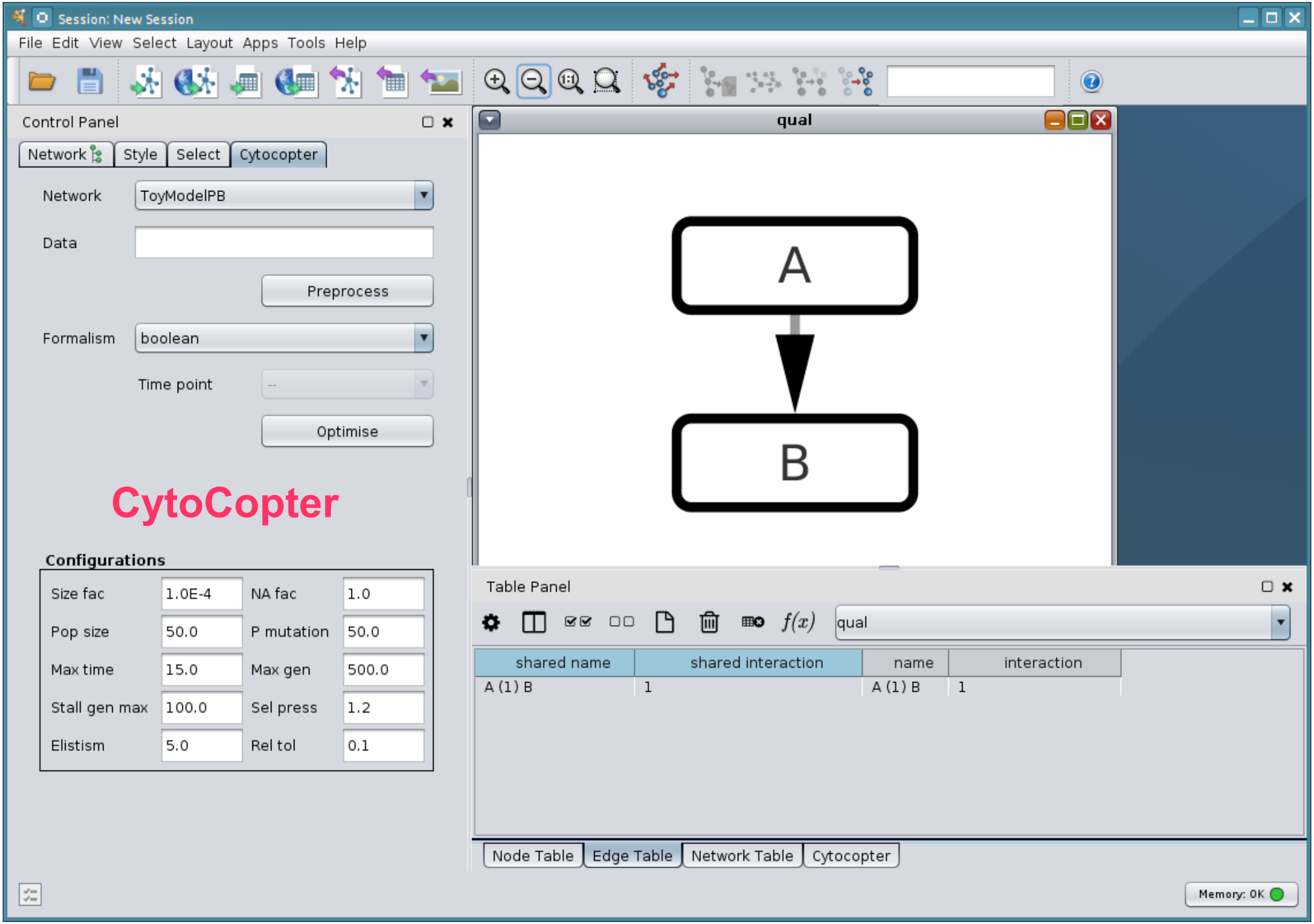
**SBML Level 3 is modular**

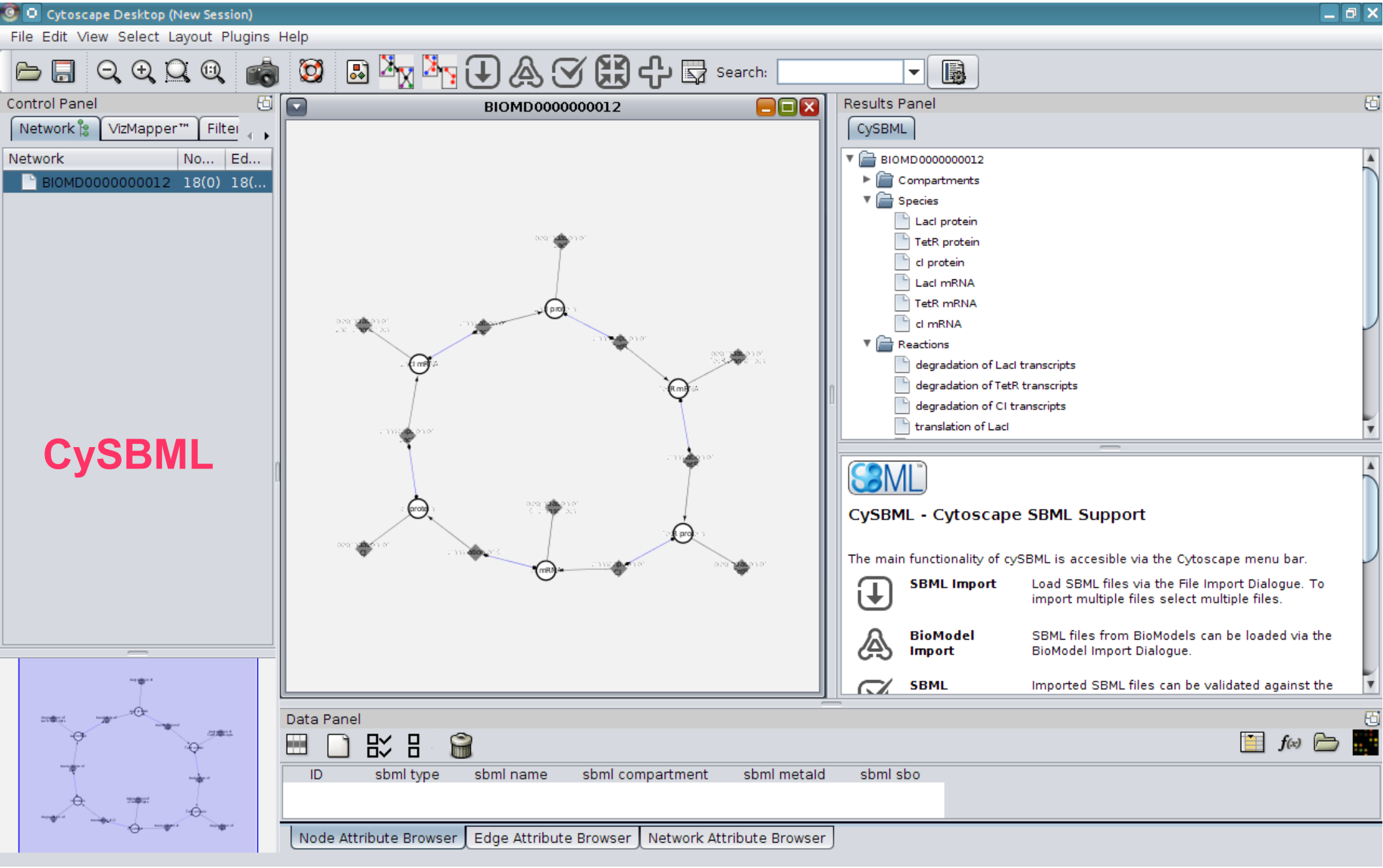



$$A \geqslant 1 \Rightarrow B = 1$$

# Logical model with SBML Qual

```
<?xmlversion="1.0" encoding="UTF8"?>
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1"
      xmlns:qual="http://www.sbml.org/sbml/level3/version1/qual/version1" qual:required="true">
  <model id="example">
    <listOfCompartments>
      <compartment id="cytosol" name="cytosol" constant="true"/>
    </listOfCompartments>
    <qual:listOfQualitativeSpecies>
      <qual:qualitativeSpecies qual:compartment="cytosol" qual:constant="false"
                               qual:id="A" qual:maxLevel="2"/>
      <qual:qualitativeSpecies qual:compartment="cytosol" qual:constant="false"
                               qual:id="B" qual:maxLevel="1"/>
    </qual:listOfQualitativeSpecies>
    <qual:listOfTransitions>
      <qual:transition qual:id="tr_B">
        <qual:listOfInputs>
          <qual:input qual:id="theta_B_A" qual:qualitativeSpecies="A" qual:sign="positive"
                      qual:thresholdLevel="1" qual:transitionEffect="none"/>
        </qual:listOfInputs>
        <qual:listOfOutputs>
          <qual:output qual:transitionEffect="assignmentLevel" qual:qualitativeSpecies="B"/>
        </qual:listOfOutputs>
        <qual:listOfFunctionTerms>
          <qual:functionTerm qual:resultLevel="1">
            <math xmlns="http://www.w3.org/1998/Math/MathML">
              <apply>
                <geq/>
                <ci>A</ci>
                <ci>theta_B_A</ci>
              </apply>
            </math>
          </qual:functionTerm>
          <qual:defaultTerm qual:resultLevel="0"/>
        </qual:listOfFunctionTerms>
      </qual:transition>
    </qual:listOfTransitions>
  </model>
</sbml>
```


Session: New Session
File Edit View Select Layout Apps Tools Help
Control Panel
Network Style Select Cytocopter
Network
ToyModelPB
Data
Preprocess
Formalism
boolean
Time point
Optimise
CytoCopter
Configurations
Size fac 1.0E-4
NA fac 1.0
Pop size 50.0
P mutation 50.0
Max time 15.0
Max gen 500.0
Stall gen max 100.0
Sel press 1.2
Elistism 5.0
Rel tol 0.1
qual
A
B
Table Panel
qual
shared name
shared interaction
name
interaction
A (1) B
1
A (1) B
1
Node Table
Edge Table
Network Table
Cytocopter
Memory: OK


Cytoscape Desktop (New Session)
File Edit View Select Layout Plugins Help
Search:
Control Panel
Network
VizMapper™
Network
No...
Ed...
BIOMD0000000012 18(0) 18(...
CySBML
BIOMD0000000012
Results Panel
CySBML
BIOMD0000000012
Compartments
Species
LacI protein
TetR protein
cI protein
LacI mRNA
TetR mRNA
cI mRNA
Reactions
degradation of LacI transcripts
degradation of TetR transcripts
degradation of CI transcripts
translation of LacI
SBML
CySBML - Cytoscape SBML Support
The main functionality of cySBML is accesible via the Cytoscape menu bar.
SBML Import
Load SBML files via the File Import Dialogue. To import multiple files select multiple files.
BioModel Import
SBML files from BioModels can be loaded via the BioModel Import Dialogue.
SBML
Imported SBML files can be validated against the
Data Panel
ID
sbml type
sbml name
sbml compartment
sbml metaId
sbml sbo
Node Attribute Browser
Edge Attribute Browser
Network Attribute Browser

# SBML Software Guide

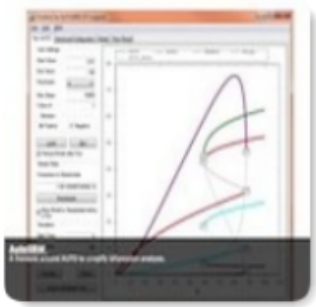
The following pages describe SBML-compatible software packages known to us. We offer different ways of viewing the information, all drawn from the same underlying data collected from the systems' developers via our **software survey**. The *Matrix* provides a table listing all known software and a variety 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: **283**.

**Go to the SBML Software Matrix**

**Go to the SBML Software Summary**

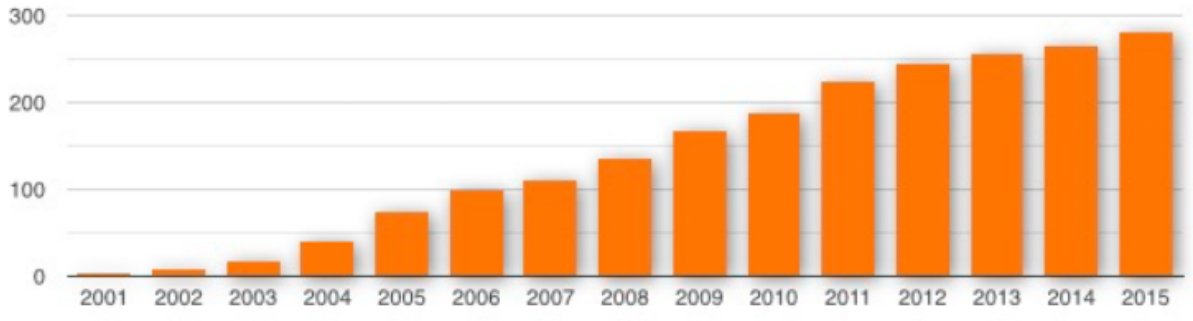
**Go to the SBML Software Showcase**



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

## Historical trend

The following graph shows the total number of known SBML-compatible software packages each year, as counted by the SBML Team. The counts shown are for approximately the middle of each year.



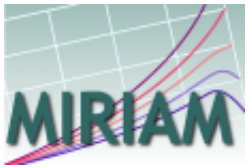
# Adding the semantics to the syntax

| | Model descriptions |
|---|---|
| Minimal requirements | MIRIAM |
| Data-models | SBML |
| Terminologies | SBO |

Born in Heidelberg 2004

Le Novère *et al. Nat Biotechnol* (2005), Courtot *et al. Mol Syst Biol*(2011)

# Minimal Information Required In the Annotation of Models



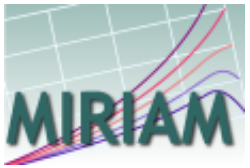

- Encoded in public standard format ☑
- Single reference description ☑
- Reflect biological processes ☑
- Simulatable and reproduce results ☑

- 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 ☑

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

# 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 ☑

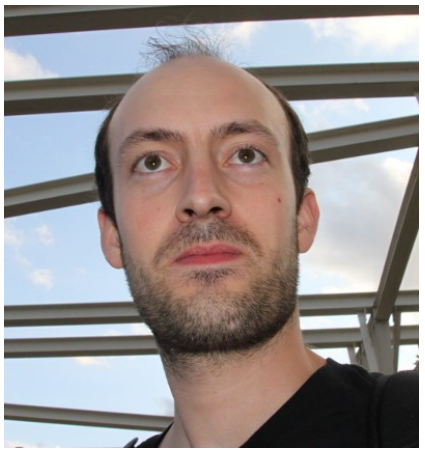
- Model components identified ☑
- Cross reference as triplets {collection, record, qualifier} ☑
- Collection and record in one agreed-upon URI ☑

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

# identifiers.org (aka new MIRIAM URIs)

http://identifiers.org/namespace/identifier

protocol | type of URI | collection | record



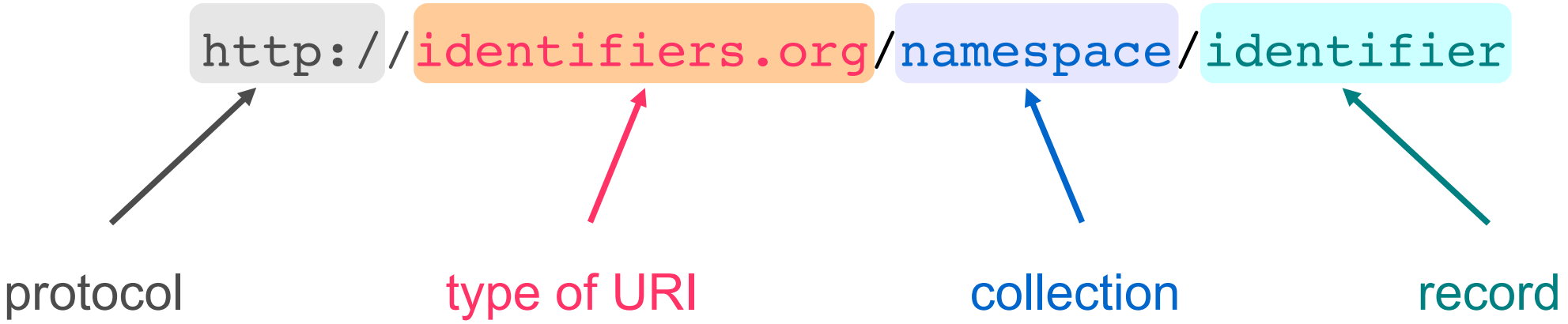
Camille Laibe

Nick Juty

Sarala Wimalaratne

Juty *et al. Nucleic Acid Res.* (2012)

# identifiers.org (aka new MIRIAM URIs)




http://identifiers.org/pubmed/22140103

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

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

# MIRIAM Registry

Search

Examples: ontology, enzyme, Japan, EMBL

Categories & tags

Home | Browse | Download | Web services | Documentation | Contribute | Identifiers.org | About | Feedback

## Persistent identification for life science data

The MIRIAM **Registry** provides a set of online services for the generation of unique and perennial identifiers, in the form of URIs. It provides the core data which is used by Identifiers.org.

The core of the *Registry* is a catalogue of data collections (corresponding to controlled vocabularies, databases, ...), their URIs and the corresponding physical URLs (or resources). These resources are monitored daily to ensure data accessibility and the validity of the resolution mechanism.

Access to the Registry's dataset is made available via exports (XML and RDF) and Web Services (SOAP and REST).

All provided data and services are free for use by all.

### Access data

- Browse by data collection name
- Browse by types of data (categories & tags)
- Web services
- Download complete dataset (XML)
- Identifiers.org

### Contribute

- Contact the team and community
- Edit existing data collection
- Request new data collection(s)
- Provide feedback

### Learn & discover

- Getting started with the Registry
- Frequently Asked Questions
- Publications, presentations, posters, ...
- Review of URI based identification systems
- Documentation
- About the Registry

### Latest publication

**Identifiers.org and MIRIAM Registry: community resources to provide persistent identification.**

Juty N., Le Novère N., Laibe C.
*Nucleic Acids Research*. 2012; 40 (Database issue): [
[Europe PMC] [Oxford Journals]

### Registry statistics

**Published**

| | |
|---|---|
| Data collections: | 560 (575) |
| Resources: | 699 (767) |
| Last update: | Jun 24, 2016 |

**Under curation**

| | |
|---|---|
| Data collections: | 414 |
| Resources: | 419 |
| Last update: | May 23, 2016 |

### News

**Dataset descriptor and RDF representations**

*August 2013*

The Registry now provides a dataset descriptor and RDF representations of the whole Registry and individual data collections (in RDF/XML and Turtle formats). Read more...

**Primary resources**

*July 2013*

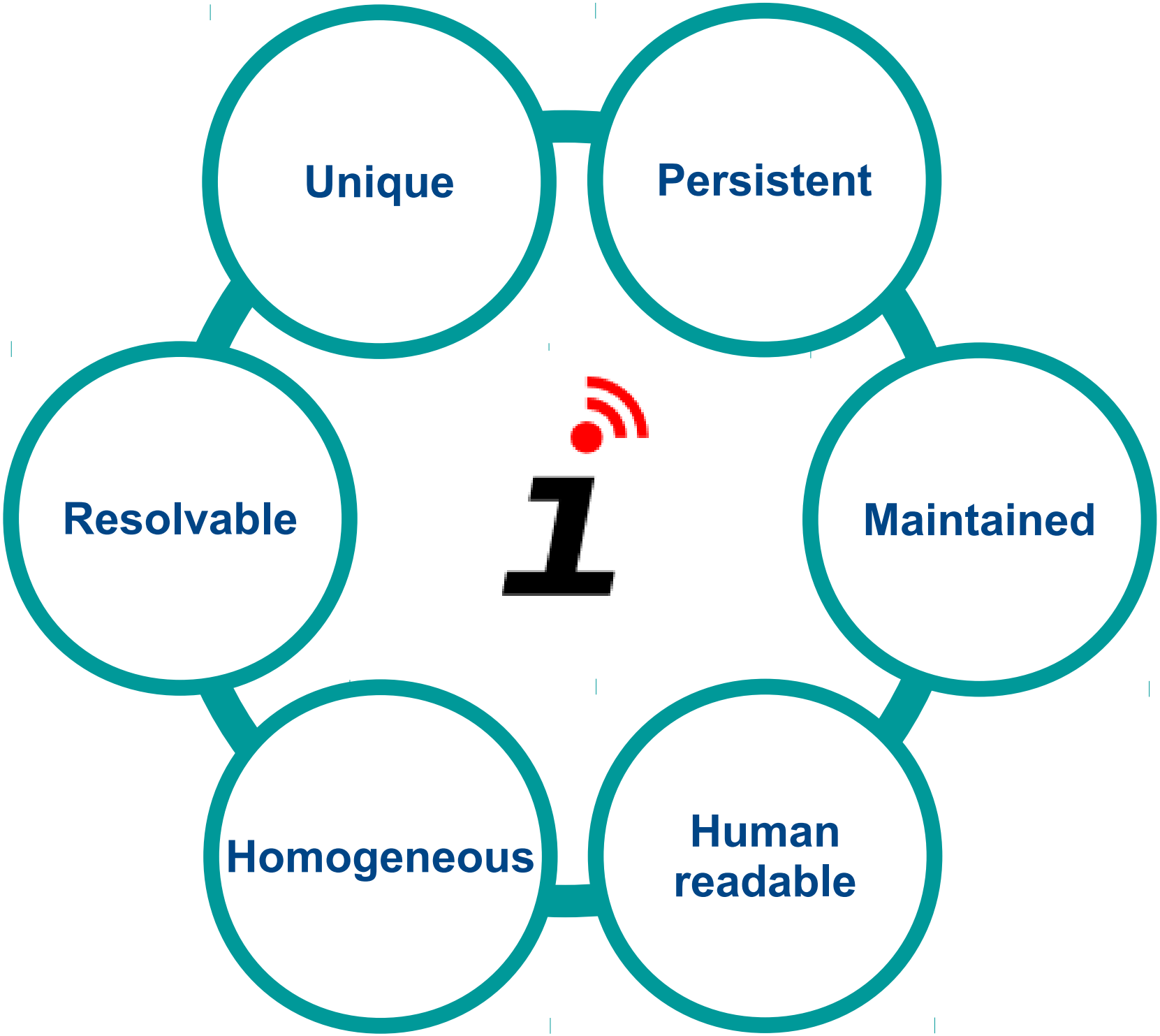
Identifiers.org and its Registry now highlight the "primary resource" for data collections. Read more...

**Presentation at BioHackathon 2013**

*June 2013*

Presentation "Identifiers.org: practical integration tool for heterogeneous ...s" at the BioHackathon 2013 ...ium in Tokyo, Japan (slides, PDF)

**http://www.ebi.ac.uk/miriam/**
**http://identifiers.org/registry**


Unique
Persistent
Resolvable
Maintained
Homogeneous
Human readable

# The Systems Biology Graphical Notation

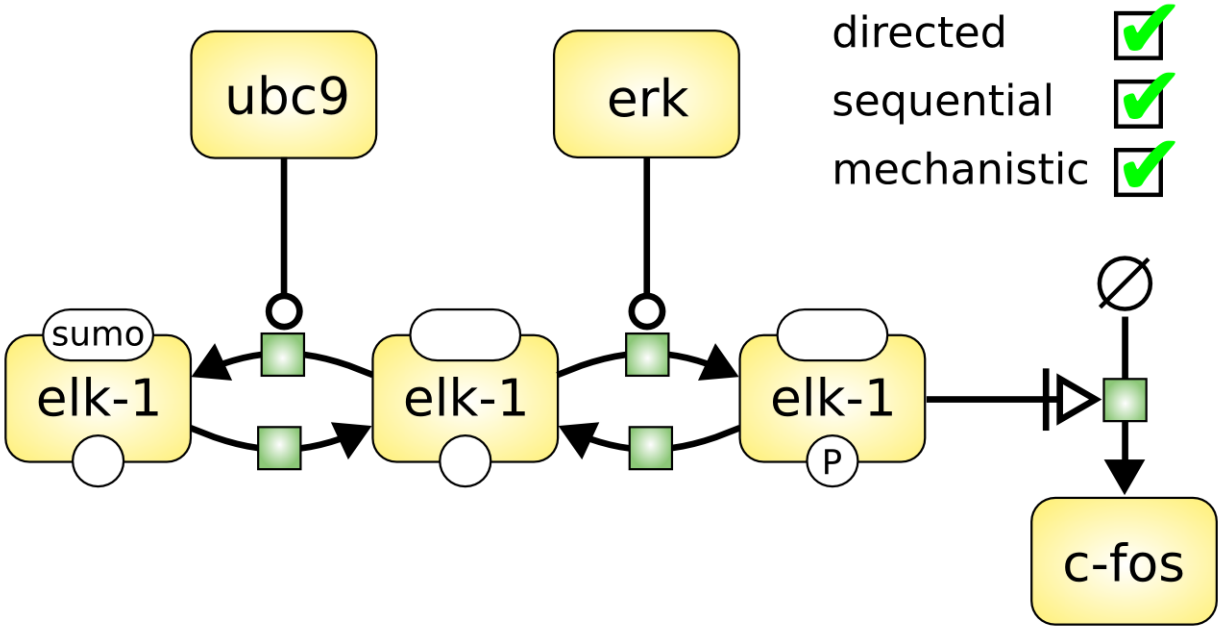

**http://sbgn.org/**

*Le Novère et al (2009)*

# Unambiguous consensual visual notation

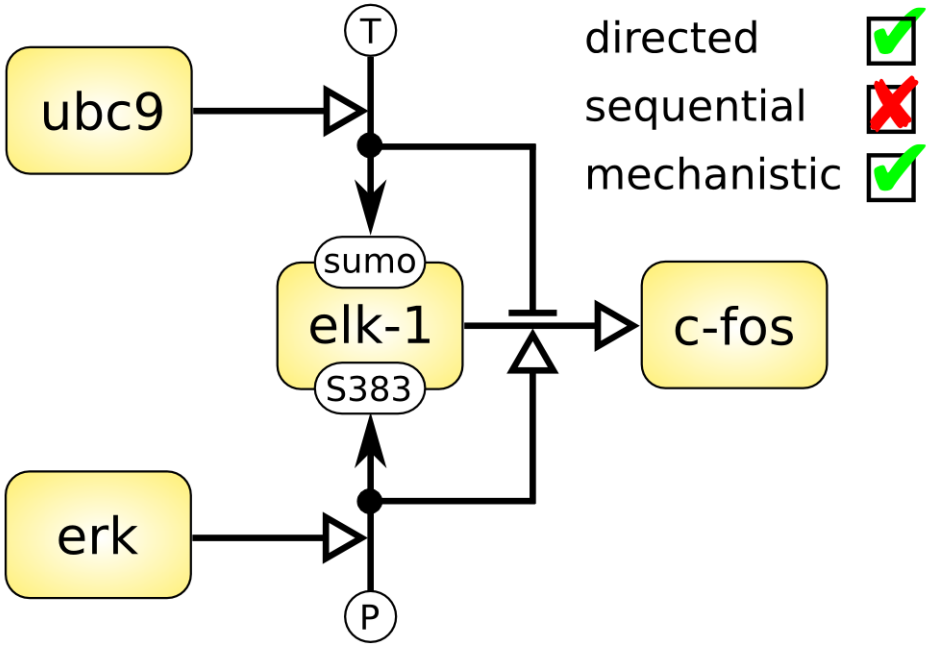
- An unambiguous way of graphically describing and interpreting biochemical and cellular events
- Limited amount of symbols
  Re-use existing symbols
  ☞ Smooth learning curve
- Can represent logical or mechanistic models, biochemical pathways, at different levels of granularity
- Detailed technical specification, precise data-models, standard API and growing software support
- Developed over ten years by a diverse community, including biologists, modellers, computer scientists etc.

# Process Descriptions




- Process modelling
- Biochemistry, Metabolic networks
- Generally within “closed world”
- Subjected to combinatorial explosion

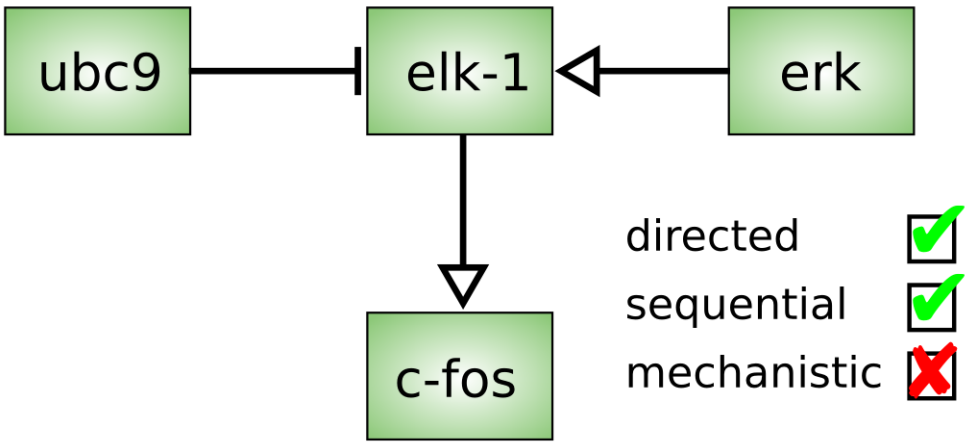
# Entity Relationships




- Rule-based modelling
- Molecular Biology
- “Open world”
- Independent rules: no explosion

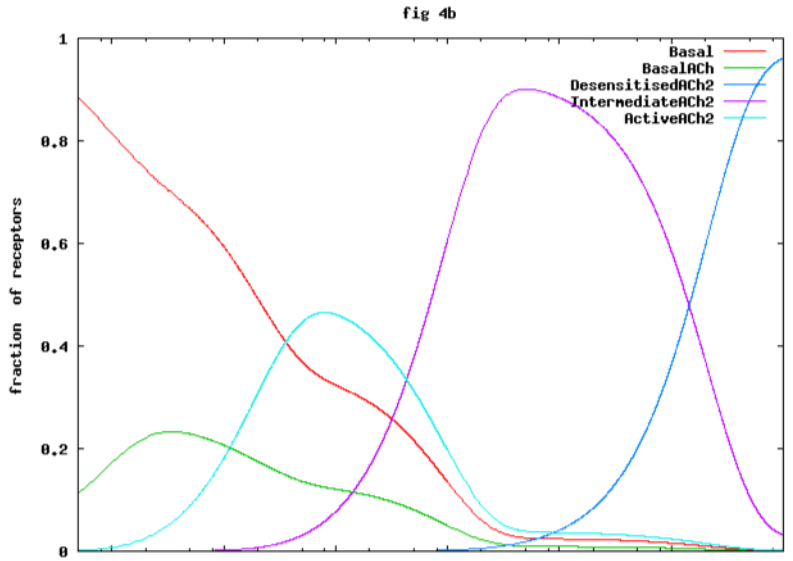
# Activity Flows

- Logical modelling
- Signalling pathways, gene regulatory networks

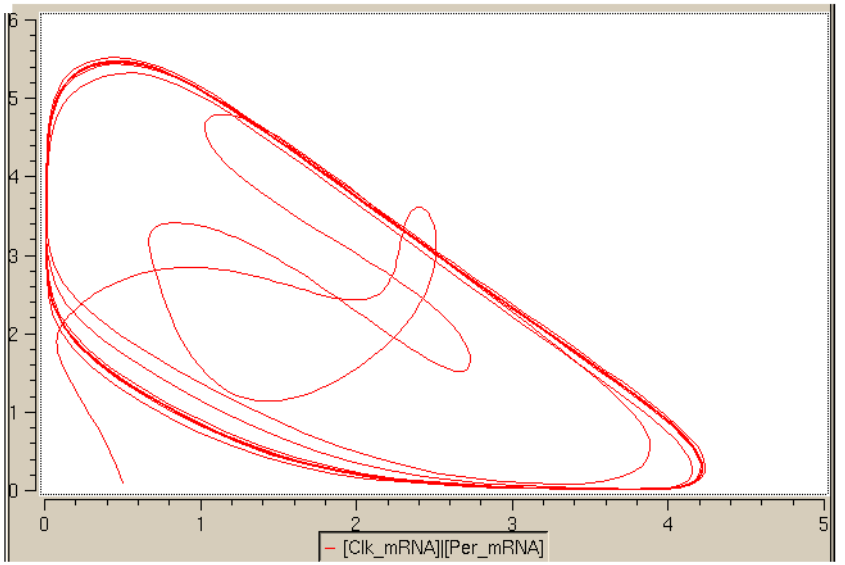


# Surely, this is enough?

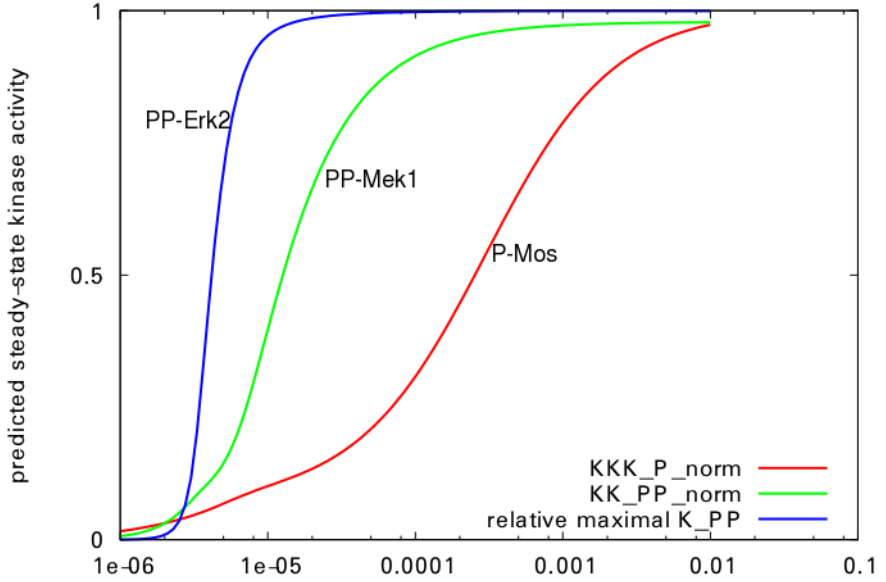
# Simulation experiment = model + what to do with it



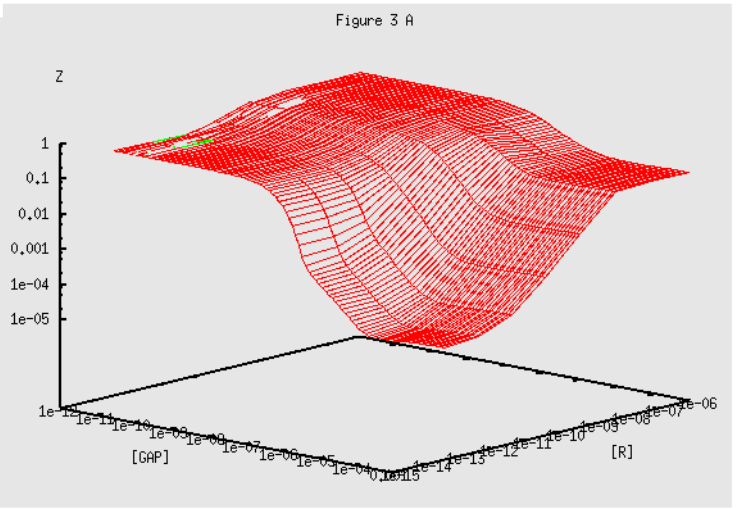

Edelstein et al 1996 (BIOMD0000000002)




Ueda, Hagiwara, Kitano 2001 (BIOMD0000000022)

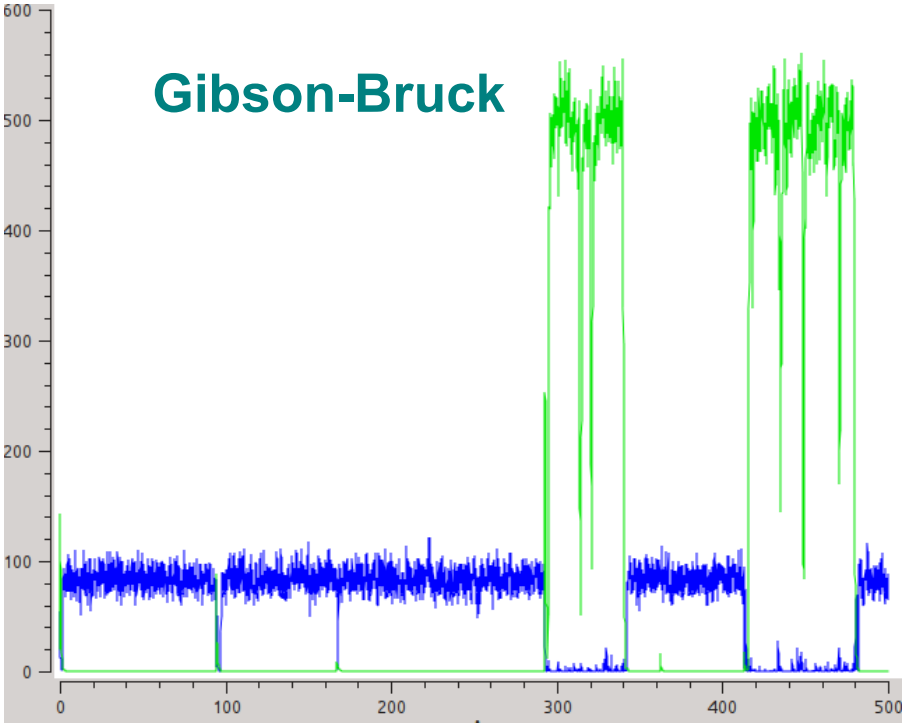


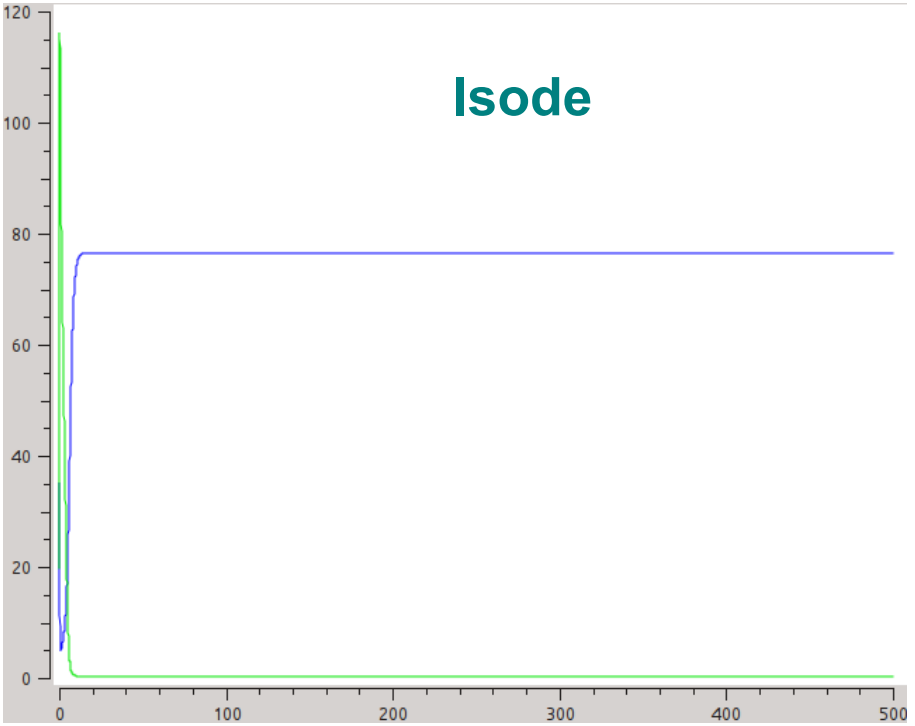

Huang & Ferrell (BIOMD0000000009)

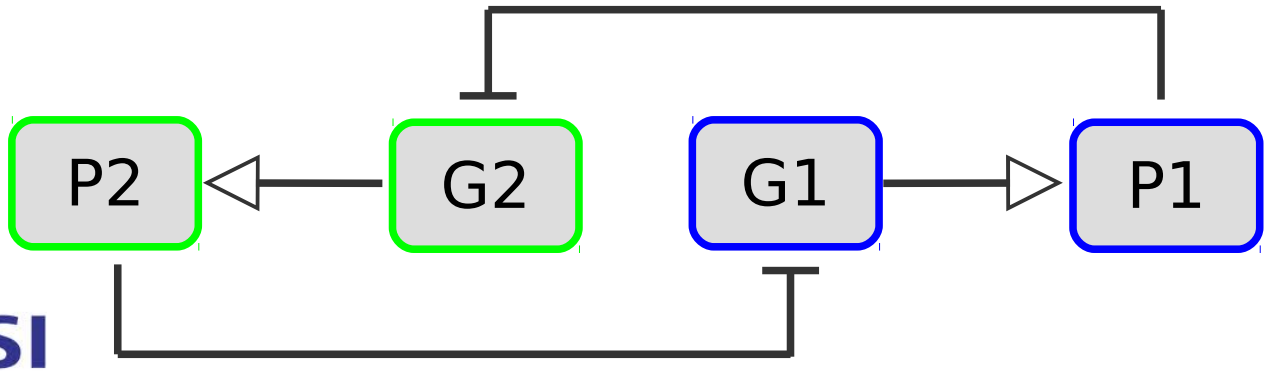



Bornheimer et al 2004 (BIOMD0000000086)

# Choice of algorithm affects behaviour



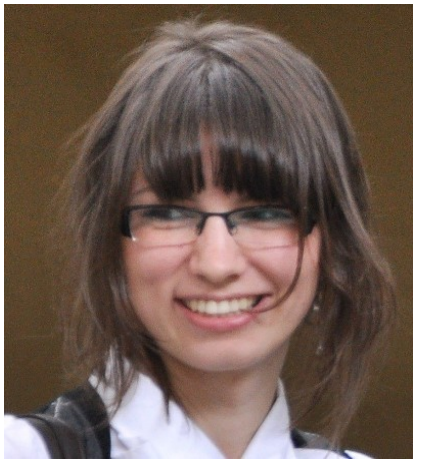




COPASI

# 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

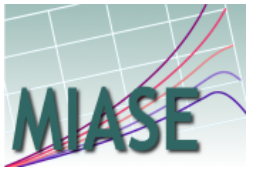


Anna Zhukova

**Born in Hinxton 2007**

Waltemath *et al. PloS Comput Biol* (2011), *BMC Syst Biol* (2011), Courtot *et al. Mol Syst Biol* (2011)

# 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 ☑

http://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

# Etc.

| | Model descriptions | Simulations and analysis | Numerical |
|---|---|---|---|
| Minimal requirements | MIRIAM | MIASE |  Christian Knüpfer |
| Data-models | SBML, SBGN | SED ML | NuML |
| Terminologies | SBO | KISAO | TEDDY |

# 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 portrait
  - steady state value
  - timecourse
- variable

## 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
      - omitted process
      - phenotype
      - state variable assignment
      - uncertain process
    - relationship
  - participant role
    - functional compartment
    - modifier
      - dual-activity modifier
      - inhibitor
      - modifier of unknown activity
      - stimulator
    - neutral participant
    - product
    - promoter
    - reactant

## KInetics Simulation Algorithm Ontology

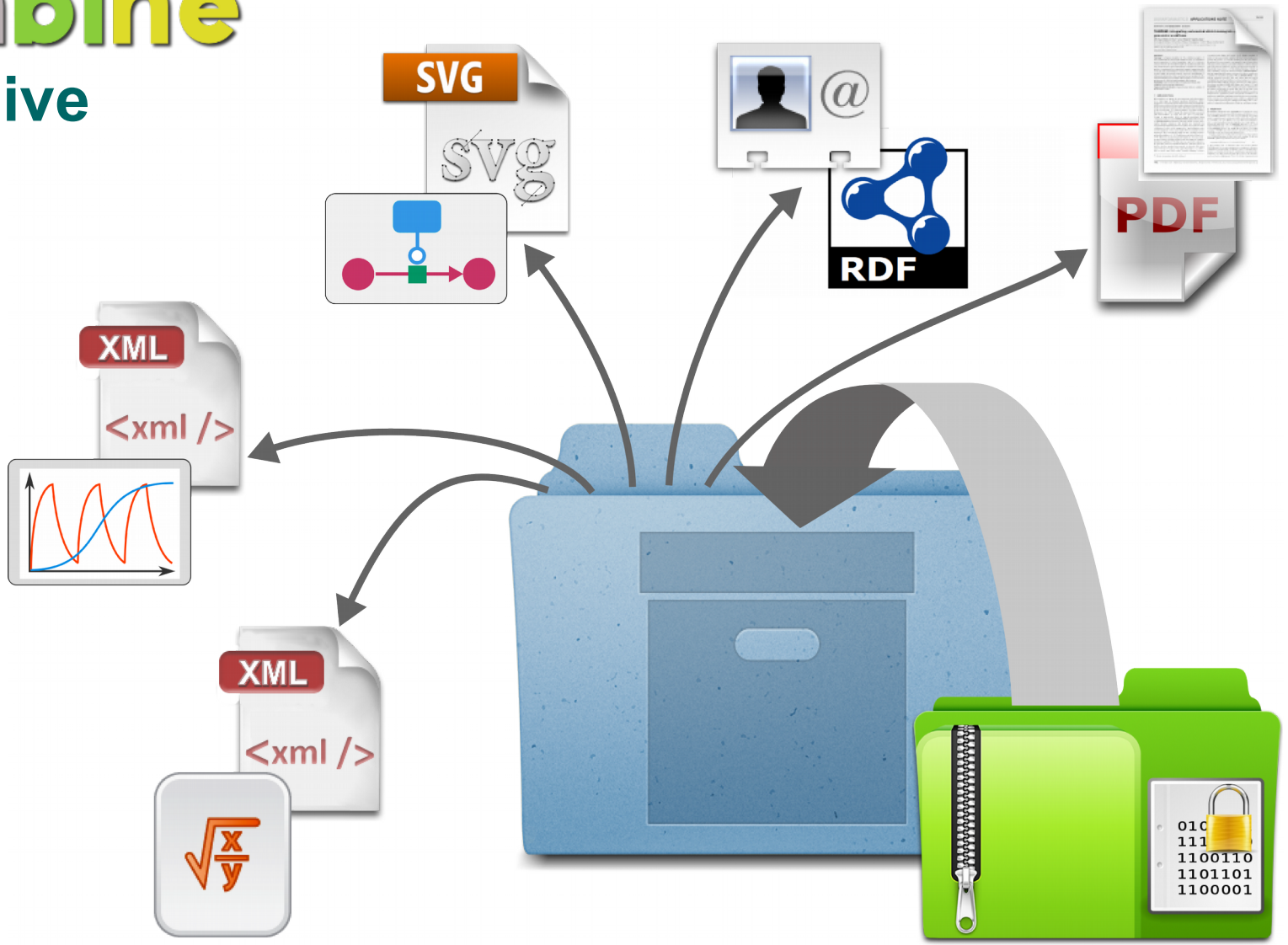
- modelling and simulation algorithm
  - Bayesian inference algorithm
  - CVODE-like method
    - CVODE
    - PVODE
  - algorithm using adaptive timesteps
  - algorithm using continuous variables
  - algorithm using deterministic rules
  - algorithm using discrete variables
  - algorithm using fixed 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 control parameter
  - minimum damping
  - number of N-way partial least squares regressi
  - number of partial least squares components
  - partitioning control parameter
  - 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

Courtot *et al. Mol Syst Biol (2011)*

combine archive




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

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

**That looks very useful.**
**Where can I find those?**

# BioModels Database

Search

Advanced

BioModels Home | Models | Submit | Support | About BioModels | Contact us

BioModels Database is a repository of computational models of biological processes. Models described from literature are manually curated and enriched with cross-references. All models are provided in the Public Domain. More information about BioModels Database can be found in the FAQ.

Models published in the literature

*Browse*

Manually curated
(612 models)

Non curated
(873 models)

*Alternative access*

Gene Ontology classification

Gene Ontology tree

Advanced search

Models automatically generated from pathway resources (Path2Models)

*Browse*

Metabolic (112,898 models)
Non-metabolic (27,531 models)
Whole genome metabolism (2,641 models)

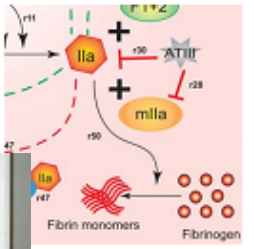
*Alternative access*

Taxonomy

Model of the month

June, 2016

A systems model by Nayak et al., (2015) that describes the effect of modulating




this network
eatment is

Marco Donizelli

Release

We are extremely happy to announce the 30th release of BioModels, which now provides access to 1483 literature-based models and 143,070
pathway
ed features.

Viji Chelliah

Mihai Glont

**http://www.ebi.ac.uk/biomodels**

Le Novère *et al. Nucleic Acid Res* (2006), Li *et al BMC Syst Biol* (2010), Juty *et al. Nucleic Acid Res (2015)*

Acknowledgements: EMBL BBSRC

# Was it worth it?

"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."

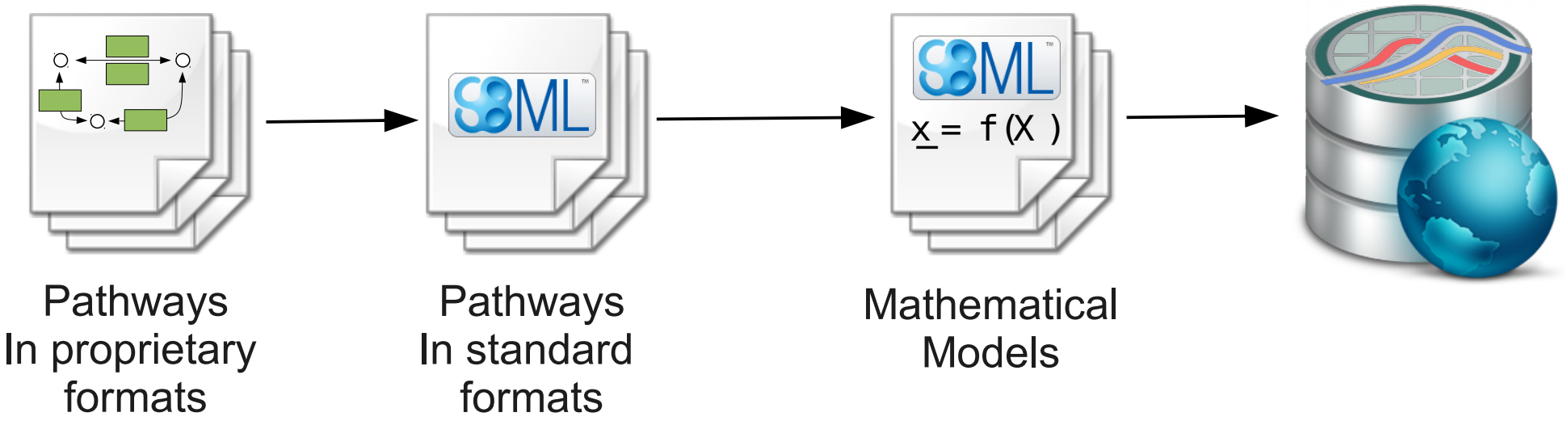
*Biomathematician, 2007*

"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*

# From pathways to models … path2models

- Provide pathways in a standard format
- Re-use existing pathway data to generate biochemically based models
- Provide starting points to build more quantitative models




Büchel *et al. BMC Syst Biol* (2013)


Signalling Pathways

+



**Logical models**
**of individual signalling pathways**


Signalling Pathways

+



**Logical models**
**of individual signalling pathways**


Metabolic Networks

**Chemical kinetics models**
**of individual metabolic pathways**


Signalling Pathways

+



**Logical models**
**of individual signalling pathways**


Metabolic Networks

**Chemical kinetics models**
**of individual metabolic pathways**


Metabolic Networks

+

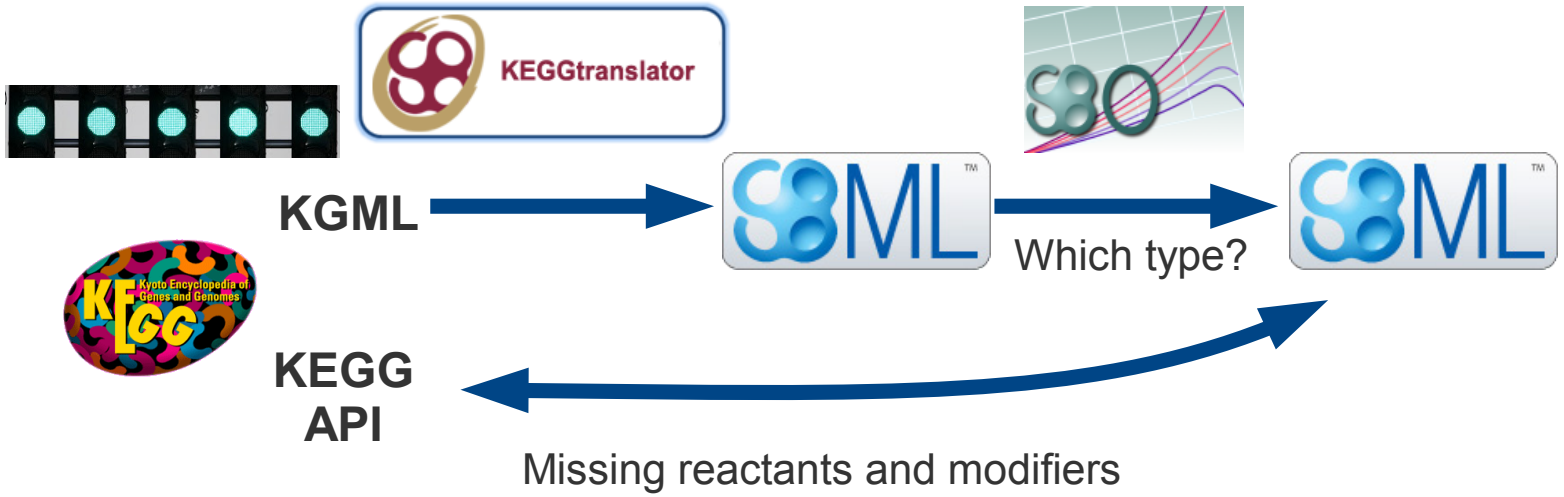

**Flux Balance Analysis**
**of whole genome reconstructions**

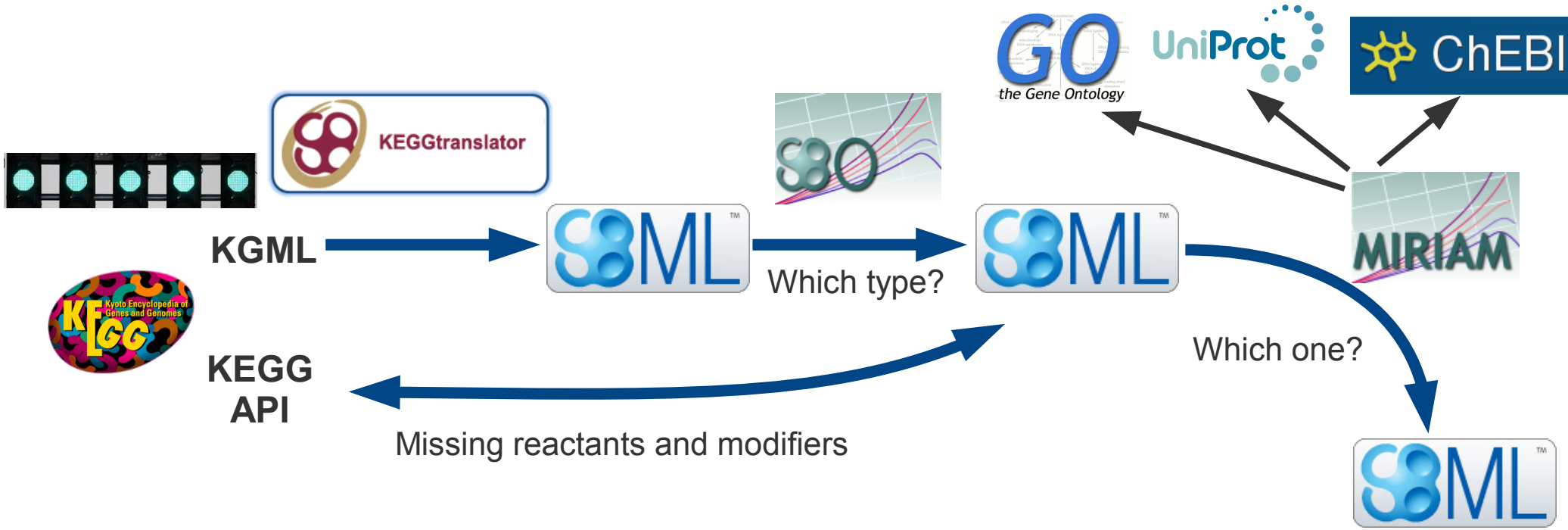
KEGGtranslator

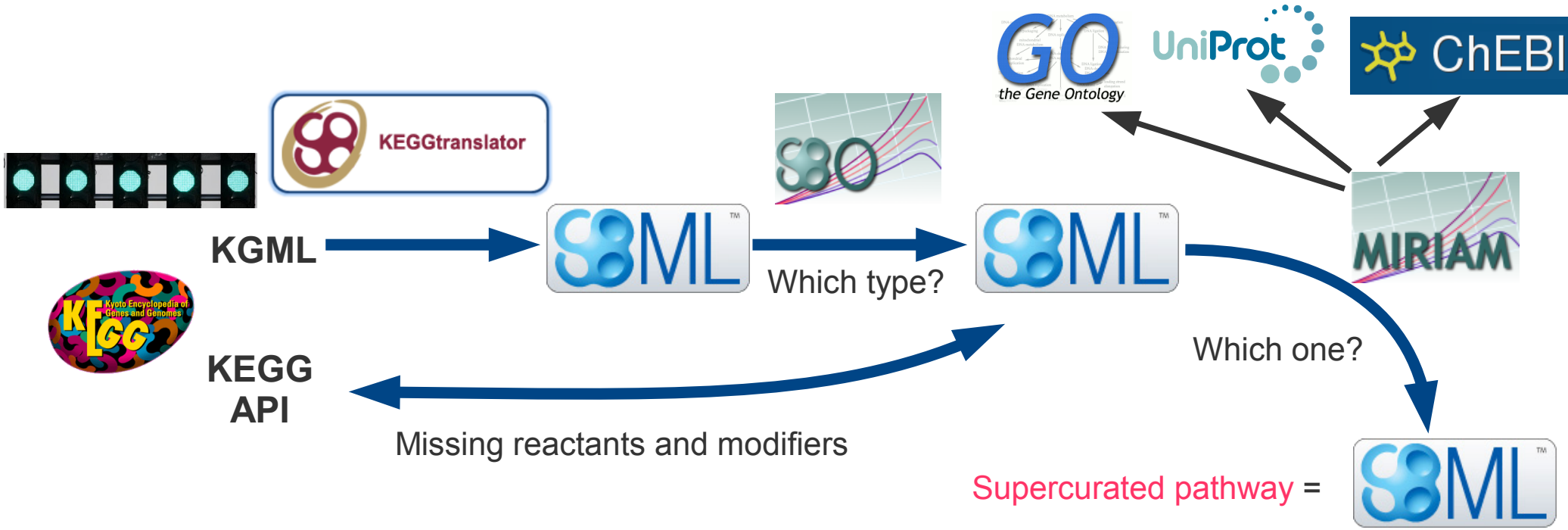
KGML → SBML

Kyoto Encyclopedia of Genes and Genomes


KEGGtranslator
KGML
SBML
Which type?
SBML
KEGG
Kyoto Encyclopedia of Genes and Genomes


KEGGtranslator
KGML
Which type?
KEGG
API
Missing reactants and modifiers


GO
the Gene Ontology
UniProt
ChEBI
KEGGtranslator
SBO
KGML
SBML
Which type?
SBML
MIRIAM
KEGG
Kyoto Encyclopedia of Genes and Genomes
KEGG API
Missing reactants and modifiers
Which one?
SBML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KGML
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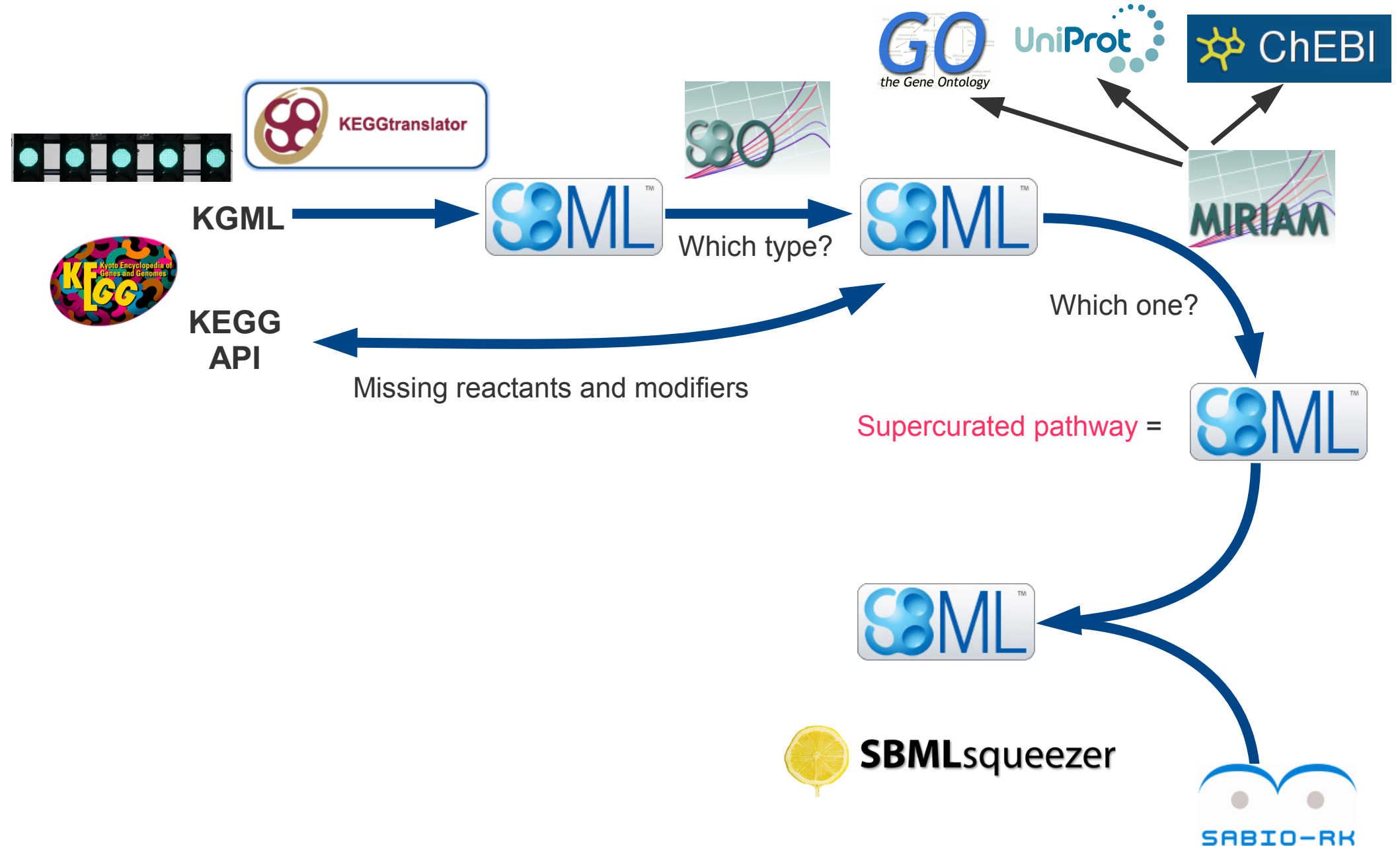
API
Missing reactants and modifiers
Supercurated pathway =
the Gene Ontology
UniProt
ChEBI
MIRIAM


GO
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Kyoto Encyclopedia of Genes and Genomes
KEGG API
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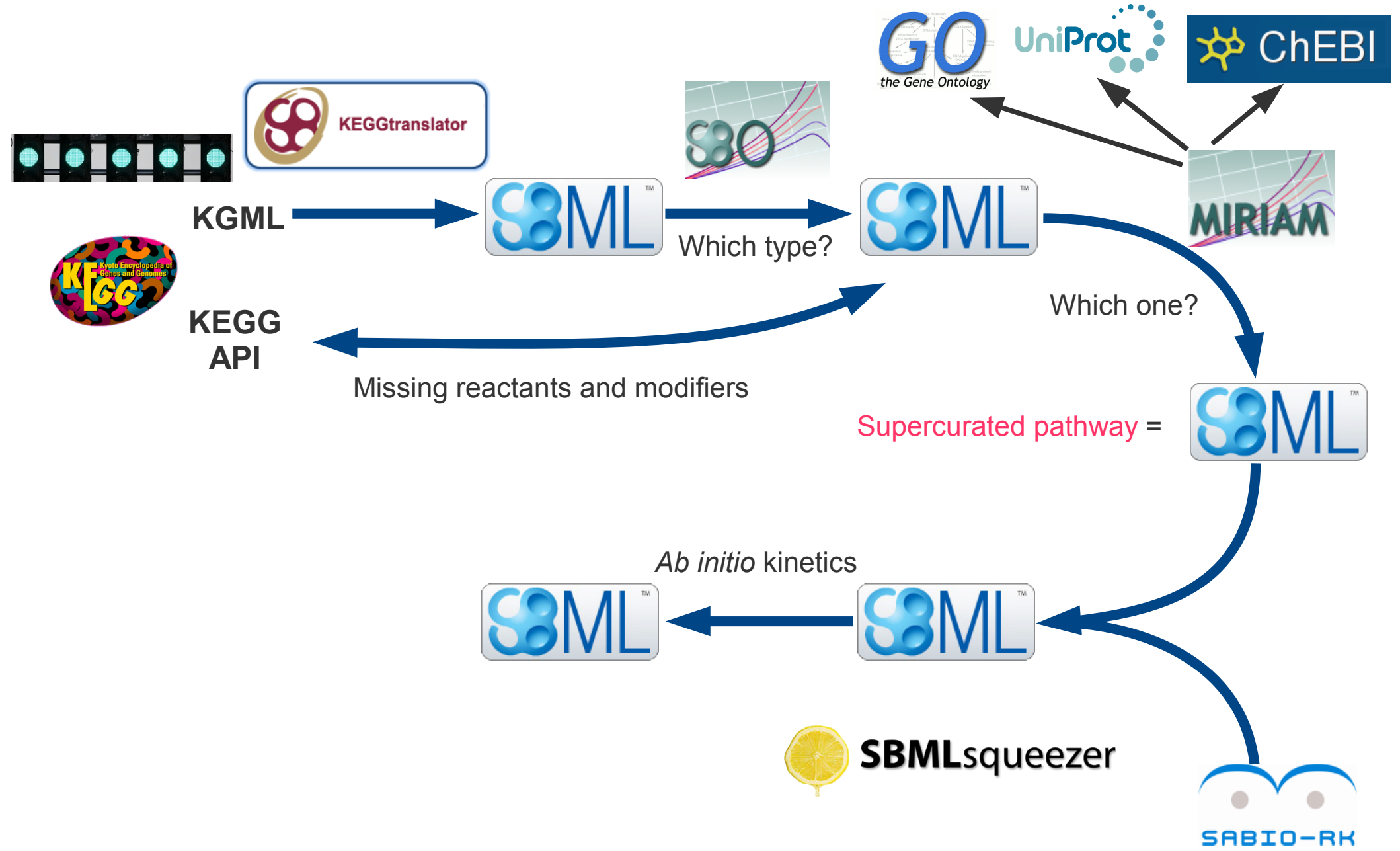
Missing reactants and modifiers
Supercurated pathway =
SBML
SBML
SBMLsqueezer
SABIO-RK


GO
the Gene Ontology
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ChEBI
KEGGtranslator
SBO
MIRIAM
KGML
SBML
Which type?
SBML
Which one?
KEGG
API
Missing reactants and modifiers
Supercurated pathway =
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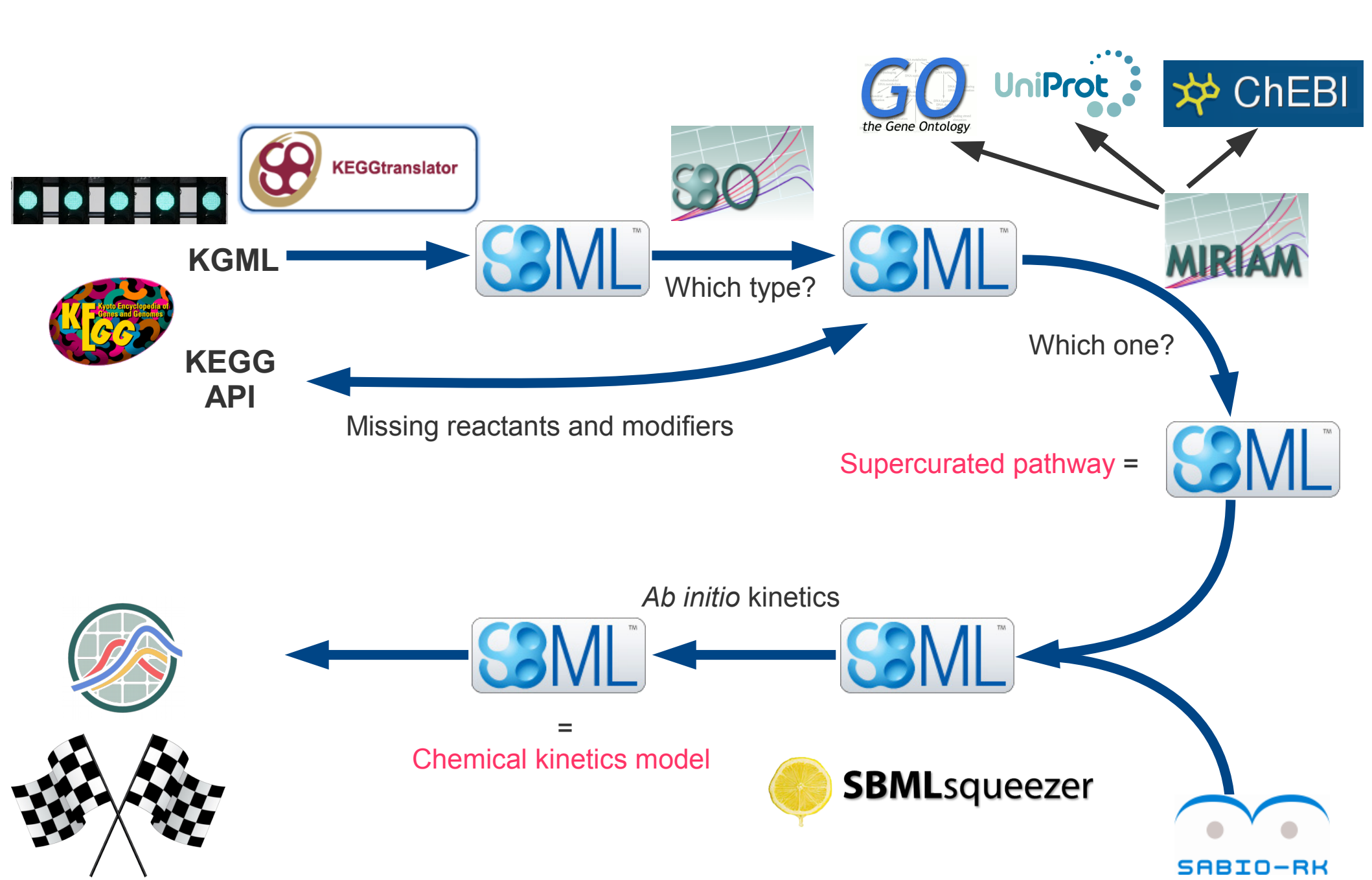
Ab initio kinetics
SBML
SBML
SBMLsqueezer
SABIO-RK


GO
the Gene Ontology
UniProt
ChEBI
KEGGtranslator
SBO
KGML
SBML
Which type?
SBML
MIRIAM
KEGG
API
Which one?
Missing reactants and modifiers
Supercurated pathway =
SBML
Ab initio kinetics
SBML
SBML
=
Chemical kinetics model
SBMLsqueezer
SABIO-RK